

## REVIEW ARTICLE

# Overview of Alzheimer's Disease Neuroimaging Initiative and future clinical trials

Michael W. Weiner<sup>1,2,3,4,5,6</sup>  | Shaveta Kanoria<sup>1,6</sup> | Melanie J. Miller<sup>1,6</sup> | Paul S. Aisen<sup>7</sup> | Laurel A. Beckett<sup>8</sup> | Catherine Conti<sup>1,6</sup> | Adam Diaz<sup>1,6</sup> | Derek Flenniken<sup>6</sup> | Robert C. Green<sup>9</sup> | Danielle J. Harvey<sup>8</sup> | Clifford R. Jack Jr.<sup>10</sup> | William Jagust<sup>11</sup> | Edward B. Lee<sup>12</sup> | John C. Morris<sup>13,14,15</sup> | Kwangsik Nho<sup>16,17</sup> | Rachel Nosheny<sup>1,4</sup> | Ozioma C. Okonkwo<sup>18</sup> | Richard J. Perrin<sup>13,14,15</sup> | Ronald C. Petersen<sup>19</sup> | Monica Rivera-Mindt<sup>20,21</sup> | Andrew J. Saykin<sup>16,22</sup> | Leslie M. Shaw<sup>23</sup> | Arthur W. Toga<sup>24</sup> | Duygu Tosun<sup>1,2</sup> | Dallas P. Veitch<sup>1,6</sup> | for the Alzheimer's Disease Neuroimaging Initiative

<sup>1</sup>Department of Veterans Affairs Medical Center, Center for Imaging of Neurodegenerative Diseases, San Francisco, California, USA

<sup>2</sup>Department of Radiology and Biomedical Imaging, University of California San Francisco, San Francisco, California, USA

<sup>3</sup>Department of Medicine, University of California San Francisco, San Francisco, California, USA

<sup>4</sup>Department of Psychiatry and Behavioral Sciences, University of California San Francisco, San Francisco, California, USA

<sup>5</sup>Department of Neurology, University of California San Francisco, San Francisco, California, USA

<sup>6</sup>Northern California Institute for Research and Education (NCIRE), San Francisco, California, USA

<sup>7</sup>Alzheimer's Therapeutic Research Institute, University of Southern California, San Diego, California, USA

<sup>8</sup>Division of Biostatistics, Department of Public Health Sciences, University of California, Medical Sciences 1C, Davis, California, USA

<sup>9</sup>Division of Genetics, Department of Medicine, Brigham and Women's Hospital, Broad Institute Ariadne Labs and Harvard Medical School, Boston, Massachusetts, USA

<sup>10</sup>Department of Radiology, Mayo Clinic, Rochester, Minnesota, USA

<sup>11</sup>Helen Wills Neuroscience Institute, University of California Berkeley, Berkeley, California, USA

<sup>12</sup>Translational Neuropathology Research Laboratory, Department of Pathology and Laboratory Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, USA

<sup>13</sup>Knight Alzheimer's Disease Research Center, Washington University School of Medicine, Saint Louis, Missouri, USA

<sup>14</sup>Department of Neurology, Washington University School of Medicine, Saint Louis, Missouri, USA

<sup>15</sup>Department of Pathology and Immunology, Washington University School of Medicine, St. Louis, Missouri, USA

<sup>16</sup>Department of Radiology and Imaging Sciences and the Indiana Alzheimer's Disease Research Center, Indiana University School of Medicine, Indianapolis, Indiana, USA

<sup>17</sup>Center for Computational Biology and Bioinformatics, Indiana University School of Medicine, Indianapolis, Indiana, USA

<sup>18</sup>Wisconsin Alzheimer's Disease Research Center and Department of Medicine, University of Wisconsin School of Medicine and Public Health, Clinical Science Center, Madison, Wisconsin, USA

<sup>19</sup>Department of Neurology, Mayo Clinic, Rochester, Minnesota, USA

<sup>20</sup>Department of Psychology, Latin American and Latino Studies Institute, African and African American Studies, Fordham University, Bronx, New York, USA

<sup>21</sup>Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, New York, USA

<sup>22</sup>Department of Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, Indiana, USA

<sup>23</sup>Department of Pathology and Laboratory Medicine and the PENN Alzheimer's Disease Research Center, Center for Neurodegenerative Research, Perelman School of Medicine, University of Pennsylvania, Philadelphia, USA

<sup>24</sup>Laboratory of Neuro Imaging, Institute of Neuroimaging and Informatics, Keck School of Medicine of the University of Southern California, San Diego, California, USA

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial](https://creativecommons.org/licenses/by-nc/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2024 The Author(s). *Alzheimer's & Dementia* published by Wiley Periodicals LLC on behalf of Alzheimer's Association.

**Correspondence**

Michael W. Weiner, Department of Veterans Affairs Medical Center, Center for Imaging of Neurodegenerative Diseases, 4150 Clement St, San Francisco, CA 94121, USA.  
Email: [michael.weiner@ucsf.edu](mailto:michael.weiner@ucsf.edu)

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database ([adni.loni.usc.edu](http://adni.loni.usc.edu)). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data. Some ADNI investigators participated in analysis or writing of this report.

A complete listing of ADNI investigators can be found at: [http://adni.loni.usc.edu/wp-content/uploads/how\\_to\\_apply/ADNI\\_Acknowledgement\\_List.pdf](http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf)

**Funding information**

NIH, Grant/Award Number: U19 -AG 024904; National Institute on Aging, Grant/Award Number: U19AG024904

**Abstract**

The overall goal of the Alzheimer's Disease Neuroimaging Initiative (ADNI) is to optimize and validate biomarkers for clinical trials while sharing all data and biofluid samples with the global scientific community. ADNI has been instrumental in standardizing and validating amyloid beta (A $\beta$ ) and tau positron emission tomography (PET) imaging. ADNI data were used for the US Food and Drug Administration (FDA) approval of the Fujirebio and Roche Elecsys cerebrospinal fluid diagnostic tests. Additionally, ADNI provided data for the trials of the FDA-approved treatments aducanumab, lecanemab, and donanemab.

More than 6000 scientific papers have been published using ADNI data, reflecting ADNI's promotion of open science and data sharing. Despite its enormous success, ADNI has some limitations, particularly in generalizing its data and findings to the entire US/Canadian population. This introduction provides a historical overview of ADNI and highlights its significant accomplishments and future vision to pioneer "the clinical trial of the future" focusing on demographic inclusivity.

**KEYWORDS**

Alzheimer's disease, Alzheimer's disease biomarkers, Alzheimer's disease clinical trials, Alzheimer's Disease Neuroimaging Initiative, Alzheimer's disease progression, amyloid, Laboratory of Neuro Imaging, magnetic resonance imaging, neurodegeneration, positron emission tomography, post-traumatic stress disorder, tau, underrepresented populations

**Highlights**

- The Alzheimer's Disease Neuroimaging Initiative (ADNI) introduced a novel model for public-private partnerships and data sharing.
- It successfully validated amyloid and Tau PET imaging, as well as CSF and plasma biomarkers, for diagnosing Alzheimer's disease.
- ADNI generated and disseminated vital data for designing AD clinical trials.

**1 | INTRODUCTION**

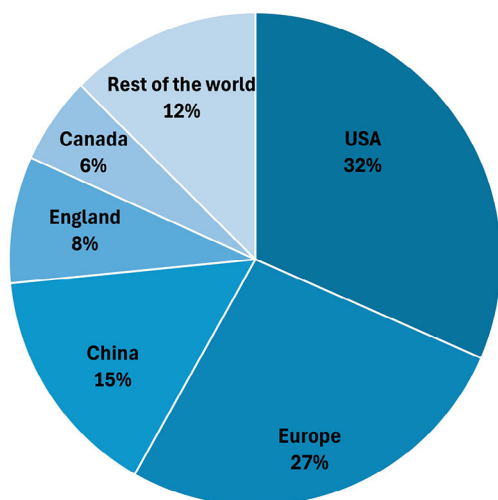
As the Alzheimer's Disease Neuroimaging Initiative (ADNI) reaches its 20-year milestone, it is helpful to reflect on the goals, accomplishments, and future directions of this study. ADNI, with its goals of improving clinical trials in the arena of Alzheimer's disease (AD) by optimizing and validating biomarkers while freely sharing its data and biofluid samples with the worldwide scientific community, has achieved unprecedented success. ADNI has focused on AD and has not included vascular cognitive impairment dementia, frontotemporal degeneration, Lewy body disease, or other causes of dementia. The study has standardized and validated amyloid and tau positron emission tomography (PET) imaging, magnetic resonance imaging (MRI), and cerebrospinal fluid (CSF) biomarkers for AD diagnosis.<sup>1-3</sup> The data generated by ADNI were used to design the clinical trials by pharmaceutical companies, including Biogen (for aducanumab),<sup>4</sup> Eisai (for lecanemab),<sup>5</sup> Lilly (for donanemab<sup>6</sup> and solanezumab<sup>7</sup>), Merck (for verubecestat),<sup>8</sup> Genentech (for crenezumab),<sup>9</sup> and Roche (for gantenerumab).<sup>10</sup> ADNI has been featured in multiple special issues in journals in the past,<sup>11-13</sup> and

its data have been used in > 6000 research articles to date. This introduction summarizes the history, major accomplishments, limitations, and future directions of this groundbreaking study.

**2 | MAJOR ACCOMPLISHMENTS OF ADNI IN THE LAST 20 YEARS****2.1 | Data and sample sharing**

From the outset, ADNI emphasized the importance of data sharing by making all ADNI data available to the scientific community without any restrictions. Considering the scale of ADNI's study, this was a novel and radical concept in the early 2000s. To facilitate this, the Informatics Core via the Laboratory of Neuro Imaging (LONI), developed the Image and Data Archive (IDA) to house ADNI data. This data can be accessed through the ADNI LONI website.<sup>14</sup> The success of this initiative is discussed extensively by Arthur W. Toga et al.<sup>15</sup> elsewhere in this Special Issue, focusing on the Informatics Core. Further,

## Geographic Distribution of Authors in ADNI Publications



**FIGURE 1** Geographic distribution of authors contributing to ADNI publications. Researchers from the United States account for the largest share of publications (32%), followed by those from Europe (27%), China (15%), England (8%), and Canada (6%). The remaining 12% of publications are authored by researchers from other countries around the world. ADNI, Alzheimer's Disease Neuroimaging Initiative; USA, United States of America.

researchers can request biospecimen samples (such as plasma, serum, genetic material, and more) through the Resource Allocation Review Committee (RARC) and Biospecimen Review Committee (BRC), which are independent review committees overseen by the National Institute on Aging (NIA). More than 40 sample requests have been approved, and the resulting data have been shared with the larger research community through the LONI IDA.<sup>16</sup> To further facilitate collaboration among data users, a publicly accessible list of individuals with access to the ADNI-generated data and their ongoing projects is available at the following web link: <https://adni.loni.usc.edu/study-design/ongoing-investigations/>.

ADNI's early adoption of "open access" data and sample sharing has led to thousands of scientific publications using ADNI data and/or samples.

As of mid-2024, > 6000 studies from groups worldwide using ADNI data were published in peer-reviewed journals, with an average of  $\approx$  700 publications annually in recent years, highlighting ADNI's substantial impact on AD research. ADNI data have been downloaded by investigators in many countries. The majority of the ADNI publications have been authored by researchers in the United States (32%), followed by Europe (27%), China (15%), England (8%), and Canada (6%). Authors from the rest of the world contributed 12% of the publications (Figure 1). In total, 105 manuscripts using ADNI data were published in journals with an impact score > 20, 949 in journals with impact scores between 11 and 20, 1945 in journals with impact scores between 5 and 10, and 2514 in journals with impact factor of  $\leq$  5 (Table 1). The h index of 171 for ADNI publications and an average of 32 citations per

**TABLE 1** Distribution of manuscripts by journal impact factor range.

Journal impact factor Range	Number of manuscripts
0-5	2514
5-10	1945
11-20	949
21-30	80
30+	25
<sup>a</sup> N/A	537

<sup>a</sup>Impact factor information was not available for the journals in which 537 manuscripts were published.

ADNI publication, totaling  $\approx$  123,703 citations, further highlights the significance of ADNI's contributions in advancing AD research.

Besides the Human Genome Project, this is the only project we know of resulting in so many publications. Remarkably, there are no other research studies with comparable achievements in AD and neurology. We encourage other projects to adopt a similar approach of open data access for the scientific community. Sharing data does not prevent the ADNI project investigators from publishing their scientific findings. Approximately 10% of all publications using ADNI data are authored by ADNI investigators. Our commitment to free data sharing has greatly magnified the overall impact of ADNI on AD research.

We have adopted a comprehensive system-wide approach to safeguard patients' privacy. Recent advances in MRI and PET imaging have led to higher-resolution images that can be constructed to yield identifiable face images. To address this privacy concern, we are using Christopher Schwarz's defacing algorithm<sup>17</sup> and thoroughly reviewing each data request to ensure that data are only shared with individuals with legitimate interests.

## 2.2 | Validation, comparison, and standardization of biomarkers

The validation, comparison, and standardization of biomarkers have always been the primary goals of ADNI. Prior to the widespread use of amyloid PET, there was no reliable method to diagnose AD pathology with certainty before death, except through brain biopsy. A diagnosis of AD required an autopsy confirmation for the presence of neurofibrillary tangles and plaques due to abnormal tau filaments and extracellular deposits of amyloid beta ( $A\beta$ ) fibrils, which together led to neurodegeneration.<sup>18-21</sup> Although the first ADNI study that related CSF  $A\beta$ 42 and tau proteins to AD diagnosis included an ADNI-independent cohort with autopsy diagnosis for disease detection, the clinical diagnosis of cognitively unimpaired (CU), mild cognitive impairment (MCI), and AD was the major approach to validation at the time aided by the fact that AD neuropathology remains the leading cause of dementia within the age range of the ADNI cohort.<sup>3</sup> During ADNI1, extensive data were collected using T1 and T2 MRI and

fluorodeoxyglucose (FDG) PET,<sup>22</sup> with many publications demonstrating baseline differences and rates of change of these biomarkers at different stages of disease progression.<sup>23</sup>

In the early stages of ADNI, there was a great interest in determining the optimum MRI and FDG PET processing methods to track the progression of neurodegeneration. At the time, many studies suggested that alterations in brain structure detected through MRI or in brain glucose metabolism detected through FDG PET had lower variability and much greater statistical power than clinical diagnosis to detect cognitive decline and therefore these were more promising for use in clinical trials.<sup>24</sup> CSF analysis by the Biomarker Core using the Roche Elecsys Platform helped Roche obtain US Food and Drug Administration (FDA) approval for their CSF A $\beta_{1-42}$  measures.<sup>25-28</sup> Similarly, the Fujirebio Lumipulse system analysis facilitated FDA approval.<sup>29,30</sup> During ADNI2 and ADNI3, extensive data were obtained on Flortbetapir and Flortaucipir and additional tracers are included in ADNI4.<sup>31</sup>

### 2.3 | Clinical trial successes

The most dramatic and impactful events in our field have been the recent demonstration that the monoclonal antibodies against amyloid including aducanumab, lecanemab, and donanemab lead to marked reduction of amyloid plaques and slow cognitive decline by up to 30% to 40% in amyloid positive (i.e., they have AD pathology) patients with MCI and mild dementia.<sup>5,32</sup>

Companies that successfully tested these antibodies, Biogen, Roche, Eisai, and Lilly, have designed their clinical trials based on data downloaded from ADNI, in accordance with ADNI's purpose of providing data to the pharmaceutical industry and academic investigators planning AD clinical trials.

Representatives of these companies have frequently acknowledged the many contributions from ADNI to their efforts; this is the single most impactful accomplishment of ADNI. ADNI data have also been widely used to help design secondary prevention trials such as Anti-Amyloid Treatment in Asymptomatic Alzheimer's (A4)<sup>7</sup> and AHEAD.<sup>33</sup> The ADNI team is frequently asked by academics and industry representatives of biotech and pharma how our data can be accessed and used to facilitate clinical trial design.

### 2.4 | Providing a new model for longitudinal observational studies

At the time ADNI was first proposed, despite many ongoing multi-site clinical trials for cognition-enhancing drugs, there were no large public-private partnerships conducting multisite longitudinal observational studies and openly sharing the resulting data. Immediately, ADNI was recognized as a "new model" for collaborative research by many investigators, companies, and non-profit and government organizations. The ADNI leadership has been contacted numerous times by investigators in various fields of neurological, psychiatric, and even cancer research regarding various aspects of our model. Kenneth

Marek, MD, who previously worked at Yale University, sought to create an ADNI-like project for Parkinson's disease, attending several ADNI Steering Committee meetings and seeking funding from various sources. Eventually, the Michael J. Fox Foundation launched the Parkinson's Progression Markers Initiative (PPMI) using several Core leaders from ADNI, with LONI as the data-sharing repository.<sup>34</sup>

Takeshi Iwatsubo, MD, PhD, created Japanese ADNI using specific methods and budgets in our grant as a model.<sup>35</sup> Giovanni Frisoni, MD, launched European ADNI.<sup>36</sup> There were similar efforts in Korea (Korean Brain Aging Study for the Early Diagnosis and Prediction of AD [KBASE]),<sup>37,38</sup> China (China-ADNI),<sup>39</sup> and South America.<sup>40</sup> The Alzheimer's Association created Worldwide ADNI,<sup>41,42</sup> a consortium of all these efforts. The following projects in the AD field were either inspired and/or modeled on ADNI: Dominantly Inherited Alzheimer Network (DIAN) studies,<sup>43</sup> Alzheimer's Disease Research Consortium (ADRC) Consortium for Clarity in ADRD Research Through Imaging (CLARITI),<sup>44</sup> Longitudinal Early-Onset Alzheimer's Disease Study (LEADS),<sup>45</sup> Australian Imaging Biomarker & Lifestyle Flagship Study of Ageing (AIBL),<sup>46</sup> ARTFL LEFFTDS Longitudinal Frontotemporal Lobar Degeneration (ALLFTD),<sup>47</sup> Diverse Vascular Contributions to Cognitive Impairment and Dementia (VCID),<sup>48</sup> and Biomarkers for Vascular Contributions to Cognitive Impairment and Dementia (MarkVCID).<sup>49</sup> Population-based studies, such as the Mayo Clinic Study of Aging have provided data to parallel ADNI as a real-world comparison.<sup>50</sup>

### 2.5 | Genetics, systems biology, and artificial intelligence offshoots of ADNI

The Genetics Core, collaborating with the Biomarker, Neuropathology, and other ADNI cores, along with external collaborators, is actively co-leading efforts to advance a systems biology approach to AD in support of precision medicine. One major initiative is the AD Metabolomics Consortium (ADMC)<sup>51</sup> led by Rima Kaddurah-Daouk, PhD, which has been working with ADNI for the past decade to perform longitudinal studies to characterize the metabolome and lipidome in individuals with MCI and AD. More recently, a new U19 project called Centrally-Linked Longitudinal Peripheral Biomarkers of AD in Multi-Ethnic Populations (CLEAR-AD),<sup>52</sup> funded by the NIA, aims to expand our understanding of AD at a systems biology level using samples and data from ADNI, ADRC, and Mayo Clinic Study of Aging. CLEAR-AD integrates data from various ADNI Cores to link cell-specific gene expression patterns from different brain regions with molecular signatures obtained from multi-omics analysis of blood samples.

Another important collaborator is the NIA-funded AD Sequencing Project (ADSP),<sup>53</sup> which has conducted whole genome sequencing of ADNI data in multiple phases and is harmonizing the ADNI phenotypic data with those from other relevant National Institutes of Health aging and dementia studies. Notably, ADNI was the first to provide whole genome sequencing data to ADSP, which now encompasses  $\approx$  40 cohorts and > 36,000 genomes. The growing abundance of complex and high-dimensional data, including multimodal neuroimaging, whole genome sequencing, and multi-omics panels, has necessitated

innovative analytical approaches, particularly strategies leveraging advancements in artificial intelligence (AI), especially deep learning techniques.

The U01 program, Ultrascale Machine Learning to Empower Discovery in Alzheimer's Disease Biobanks, which includes Artificial Intelligence for Alzheimer's Disease (AI4AD),<sup>54</sup> is supported by NIA under the ADSP and involves many ADNI investigators and collaborators. Current AI4AD analyses of ADNI data encompass various aspects, including efficient variant discovery from whole genome sequencing data and enhanced analysis of AD phenotypes, such as improved feature extraction from tau PET scans.<sup>55,56</sup> Additionally, Gyungah Jun, PhD, et al. are conducting drug repurposing analyses using a "Profiling predictor, signature, biomarker, and outcome (PreSiBO)" approach, combining data from ADNI and Accelerating Medicines Partnership program for Alzheimer's disease (AMP-AD).<sup>57</sup>

### 3 | ADNI HISTORY: GENESIS AND DEVELOPMENT OF THE STUDY

A brief version of the history of ADNI is presented here. A much more complete and detailed version is provided in Appendix 1.

#### 3.1 | State of the field before ADNI

In the years prior to 2001, when ADNI was first conceived, AD was histologically defined by its core neuropathology of A $\beta$  plaques and neurofibrillary tangles composed of abnormally phosphorylated tau (p-tau) amyloid fibrils, leading to the loss of synapses and neurodegeneration, causing memory loss, cognitive impairment, and dementia.<sup>58-61</sup> Clinical trials for cognitive enhancement therapeutics, including donepezil and similar compounds, were underway and demonstrated some clinical efficacy. However, none of these treatments could slow the progression of cognitive decline. Selkoe and Hardy proposed the "amyloid hypothesis" positing that amyloid accumulation was the proximate cause of AD symptoms.<sup>62</sup> In a seminal report, Dale Schenk, PhD, et al. at Athena Neurosciences (which later became a part of Elan Pharmaceuticals) demonstrated that injection of A $\beta$  into transgenic mice with amyloid plaques led to the generation of antibodies that removed the plaques in their brains.<sup>63</sup> This stimulated many academic laboratories and the biotech/pharmaceutical industry to work toward finding an amyloid-targeted treatment for AD. However, at the time when ADNI was first conceived, it was not possible to definitively diagnose the presence of AD pathology in living people. The Alzheimer's Imaging Consortium (AIC) was founded in 1998 primarily focusing on MRI and PET studies.

#### 3.2 | What led to the proposal of ADNI?

In the early 2000s, several pharmaceutical companies organized advisory boards to discuss how "disease-modifying" clinical trials, partic-

ularly targeting amyloid accumulation using secretase inhibitors and immunotherapy and other approaches, should be designed. During these meetings, a variety of biomarkers were discussed as potential diagnostics and for therapy monitoring. It was apparent that there were no "standard" methods. This led to a proposal by Michael W. Weiner, MD, at the University of California San Francisco (UCSF), including Leon Thal at University of California San Diego for a multisite MRI study aiming to standardize MRI acquisition and processing to compare different methods of tracking longitudinal change. In August 2001, Weiner and Thal contacted Neil Buckholtz, PhD, director of the AD branch of the NIA. Later, a meeting at the NIA, inviting the directors of neuroscience of all the major pharmaceutical companies was held to plan a substantial multisite study enrolling individuals with dementia due to AD, a large cohort of individuals with MCI, and some CU elderly, all of whom would be followed longitudinally. The assessment parameters would include the clinical assessments and neuropsychological tests currently in use for AD clinical trials (of cognitive enhancement compounds) as well as MRI, FDG PET, a lumbar puncture to obtain CSF, and a blood sample for genetic profiling. This enabled the development of public/private partnerships using pooled funds. The needs of the companies for data led to the general concept that all data would be released to the entire scientific community, without any embargo, through a website.

Weiner and Thal organized a team of Core leaders to write the first grant application (called the "Alzheimer's Disease Neuroimaging Initiative" or ADNI), with Weiner as the principal investigator (PI), and the grant was awarded to Weiner at the Northern California Institute of Research and Education (NCIRE) in 2004.

#### 3.3 | ADNI1

The Foundation of the National Institutes of Health (FNIH) was a critical innovation that established contracts with major pharmaceutical and diagnostic companies in this field, allowing funding from the companies to flow through the FNIH to the NIA. A major advancement was the Private Partner Scientific Board (PPSB), comprising the contributing members convened by the FNIH.<sup>64</sup> The PPSB is discussed in another publication in this Special Issue. Growing out of this infrastructure, the FNIH subsequently established the Biomarker Consortium. The first ADNI grant used the multisite infrastructure, assessment battery, and data capture system developed by the ADCS for the MCI trial.<sup>65</sup> A total of  $\approx$  60 clinical sites were recruited to join ADNI. The MRI Core, led by Clifford Jack, MD, at the Mayo Clinic, spearheaded the development of standardized MRI acquisition and processing protocols.<sup>66</sup> The PET Core, led by William Jagust, MD, at the University of California Berkeley, was similarly responsible for the standardization and analysis of FDG PET scanning with various scanners, each with different resolutions.<sup>22</sup> Robert Koeppe, PhD, at the University of Michigan, oversaw site qualification and quality control of PET scans. The fluid Biomarker Core was led by John Trojanowski, PhD, MD, together with Leslie Shaw, PhD, at the University of Pennsylvania. This core received samples of CSF, plasma, serum, and urine,

which were aliquoted and banked. CSF was analyzed for amyloid and tau by a multiplex immunoassay.<sup>3</sup> The Biostatistics Core led by Laurel Beckett, PhD, at the University of California Davis, provided guidance on harmonizing study design and analysis. Arthur W. Toga, PhD, then at the University of California Los Angeles, led the highly innovative Informatics Core, which received and archived all data from each of the cores and developed a website through which any investigator from anywhere in the world could request and receive all available ADNI data. To date, ADNI data have been requested by 47,735 users. After the launch of ADNI1, Andrew J. Saykin, PsyD, then ADNI site PI at Dartmouth Medical School, joined the Core team as PI of the Genetics Working Group, which later became the Genetics Core in subsequent ADNI renewals. John C. Morris, MD, at Washington University in St. Louis, proposed the formation of a Neuropathology Core to follow ADNI participants to autopsy. Finally, in the early days of ADNI, Chet Mathis, PhD, and William E. Klunk, MD, PhD, reported the development of an amyloid PET tracer called Pittsburgh compound-B (PiB).<sup>67</sup> Remarkably, the Alzheimer's Association provided funding to launch these pioneering efforts, with PiB as a "proof of concept" that subsequently led to a larger study with <sup>18</sup>F ligands in the next phases of ADNI. ADNI1 ultimately enrolled and longitudinally followed 819 participants, including 229 CU older adult controls, 402 MCI, 188 AD patients, and 90% were non-Latinx White older adults.<sup>2</sup>

### 3.4 | ADNI-GO

The ADNI Grand Opportunities (ADNI-GO) had the goal of enrolling participants with early MCI (EMCI), who according to the Petersen/Winblad criteria,<sup>68</sup> have objective or subjective signs of cognitive decline but are notably not demented or functionally impaired, to examine biomarkers at an earlier stage of the disease, leading to the enrollment of 131 new participants with EMCI of whom 86% were non-Latinx White older adults. In ADNI-GO, amyloid PET scans using the <sup>18</sup>F-AV-45 (later Flortaucipir) ligand developed by AVID Pharmaceuticals began,<sup>69</sup> with all rollovers from ADNI1 and all new EMCI participants completing an <sup>18</sup>F-AV-45 PET scan as standard.

### 3.5 | ADNI2

ADNI2 had several significant changes, especially the inclusion of longitudinal amyloid PET scans for all participants using Flortaucipir.<sup>69</sup> AVID very generously provided the tracer to all ADNI sites without cost. A competitive supplement introducing tau PET via [<sup>18</sup>F]-AV-1451 (Flortaucipir) began in 2015. A new group called "significant memory concerns" (SMC), comprising CU participants reporting subjective concerns with memory, was added to CU, EMCI, late MCI (LMCI), and mild dementia groups. Because many MRI sites were upgrading to 3T scanners, the MRI Core developed new protocols for 3T.<sup>66,70</sup> The Neuropathology Core and Genetics Core were instituted in this phase. ADNI2 enrolled 188 new participants into the CU cohort with 106 of them in the SMC group, as well as 188 new EMCI participants who

were added to 131 enrolled in ADNI-GO. The cohort also included 164 participants with LMCI and 151 with mild dementia.<sup>71</sup> Remarkably, by the end of ADNI2, 600 peer-reviewed articles had been published using ADNI data.<sup>72</sup>

### 3.6 | ADNI3

The second competitive renewal of ADNI (ADNI3) included a number of major changes. By this time, all MRI scanners were 3T. Tau PET was implemented with Flortaucipir,<sup>73,74</sup> developed by AVID. During ADNI3, the schedule for obtaining Flortaucipir PET was modified so that patients with AD were scanned at baseline and two subsequent annual visits, while CU and MCI patients all received Flortaucipir PET at baseline and 4 years later. The <sup>18</sup>F amyloid PET ligand Florbetaben (provided by Piramal) was implemented in addition to the continued use of Flortaucipir. The early and late MCI groups were merged to form one MCI group and the SMC group was folded into the CU group. The COVID-19 pandemic dramatically reduced enrollment and in-clinic visits. Toward the end of ADNI-3, > 4000 peer-reviewed studies had been published by researchers from all over the world.<sup>75</sup>

The lack of inclusion of individuals from historically underrepresented populations (URPs) in the previous phases of the study led to a rethinking of ADNI's inclusion and engagement efforts and to the establishment of the "Diversity Task Force" (DVTF) co-led by Ozioma Okonkwo, PhD, at the University of Wisconsin-Madison and Monica Rivera-Mindt, PhD, from Fordham University and the Icahn School of Medicine at Mount Sinai. Thirteen selected sites used a vigorous digital marketing campaign by Alaniz Marketing and focused site-specific local efforts to pilot culturally informed, community-engaged research (CI-CER) efforts promoting inclusive enrollment of URPs into ADNI3. As a result of these efforts, 86 individuals from URPs were enrolled during the last 2 years of ADNI3, ultimately leading to a total enrollment of 1084 participants (561 CU, 336 MCI, 119 AD), with 29% of newly enrolled participants identifying as being from a URP background.<sup>76</sup> Based on this success, Okonkwo and Rivera-Mindt were invited to become the co-PIs of the new Engagement Core for ADNI4.

### 3.7 | ADNI4

ADNI4 was fully funded by the NIA in 2022 for \$145 million. The Alzheimer's Association has continued to convene the PPSB. A major focus of ADNI4 is increasing the inclusive enrollment and engagement of URPs. These groups encompass individuals from diverse ethnic and cultural backgrounds, such as Black/African American, Latinx, Asian, American Indian, Native Hawaiian, Native Alaskan and other Indigenous groups, and Pacific Islander adults. Additionally, URPs include those from lower socioeconomic backgrounds, using education as a proxy ( $\leq 12$  years of education), and individuals residing in rural areas, considering the health risks associated with such environments.<sup>77,78</sup> The primary task of the Engagement Core is to ensure that 50% to

60% of all new participants in ADNI4 are recruited from URPs and the Health Equity Scholars Program (HESP; see Amaza et al. in this Special Issue).

Collaborating with Alaniz Marketing, online social media-based advertising campaigns have been developed, featuring culturally relevant imagery and messaging, guiding interested individuals to join ADNI's Remote Digital cohort by completing a web-based screener that determines eligibility for the study. This collects demographic information and a brief medical history and includes a subjective cognitive decline questionnaire (Everyday Cognition Scale 12-item) and a novel speech-based test (Novoic Ltd.'s Storyteller) to help distinguish CU and MCI individuals<sup>79</sup> (see Miller et al.<sup>80</sup> in this Special Issue for more details). A subset of participants (the Remote Blood Cohort) are invited to provide a blood sample at a local Quest Diagnostics phlebotomy center for plasma AD analysis for biomarkers including A $\beta_{42/40}$ , p-tau<sub>217</sub>, p-tau<sub>181</sub>, neurofilament light (NfL), and glial fibrillary acidic protein (GFAP).<sup>75</sup> This represents a new recruitment pathway to in-clinic ADNI enrollment.<sup>75</sup> Engagement Core efforts are described by Rivera-Mindt et al. in this Special Issue.

For the ADNI4 in-clinic study, new analyses include collecting novel assessments of sociocultural determinants of health and introducing a new amyloid PET tracer, Flutafuranol, and two new tau PET tracers, MK6240 and PI2620. Existing PET tracers, Flortetaben (Neuraceq), Flortetapir (Amyvid), and Flortaucipir (Tauvid) continue to be used. Visual reads of amyloid PET scans will also be conducted, allowing participants to learn about their amyloid status.<sup>81</sup>

To safeguard privacy, a "defacing program" developed by Christopher Schwarz, PhD, at Mayo Clinic, obscures the face on high-resolution MRI and PET scans. Duygu Tosun, PhD, at UCSF, became the PI of Project 1, focusing on integrating ADNI biomarker data across all phases and developing a clinical trial simulation platform. The fluid Biomarker Core is implementing various mass spectroscopy and immune assays for plasma amyloid and tau species.<sup>82</sup> Enrollment in ADNI4 is ongoing.

### 3.8 | ADNI "SPIN-OFF" STUDIES

In addition to the main ADNI study, two related "spinoff" projects have used ADNI participants, methodologies, and infrastructure. Scott Mackin, PhD, at UCSF, recognized that people with major depression were excluded from ADNI despite depression being suggested as an AD risk factor<sup>83,84</sup> and proposed the ADNI Depression project (ADNI-D).<sup>84</sup>

The Department of Defense-ADNI (DOD-ADNI) project enrolled a large number of veterans and tested them for all the ADNI biomarkers, including amyloid PET, CSF amyloid and tau, and MRI, with plasma saved for future analysis.<sup>85,86</sup> The major finding was an absence of any relationship between post-traumatic stress disorder and traumatic brain injury with the development of brain amyloid or other AD biomarkers.<sup>87</sup> Other ADNI-related projects inspired or modeled on ADNI were discussed in section 2.4.

## 4 | LIMITATIONS OF ADNI

From the outset of ADNI, the leadership has strived to understand our weaknesses and limitations. In this discussion, we acknowledge major limitations while recognizing that these may not be comprehensive. We emphasize that ADNI is very open to hearing criticism and suggestions for improvement. This can be done through the LONI website or by contacting the PI (corresponding author of this paper).

### 4.1 | Lack of diversity and generalizability

The primary challenge with ADNI, like in all clinical studies, is recruitment, and engaging individuals from URPs adds another dimension to that challenge! The primary obstacle has been the stringent inclusion and exclusion criteria of the recruitment protocol, which was designed to enroll people with relatively "pure" AD or healthy controls, excluding those with comorbidities that affect cognition. This approach aims to study AD pathology without any confounding factors and helps to reduce the variance in the baseline and longitudinal cognitive change, thereby enhancing the efficiency of our studies on biomarkers and treatments in AD clinical trials. However, there is a downside to this approach: by excluding people with comorbidities and other factors that prevent optimum data collection (e.g., claustrophobia, which prevents MRI scanning), we exclude a substantial proportion of the elderly population. This reduces the generalizability of the study.

Furthermore, people from historically URPs, including people of color and people with low socioeconomic status and low education, are well known to have more comorbidities.<sup>76</sup> Therefore, the exclusion criteria of ADNI have not only made inclusive enrollment and participation more difficult but also prevented greater enrollment of URPs. Exacerbating these effects of stringent exclusion criteria are the structural and systemic barriers that limit opportunities for individuals from URPs to seek treatment in academic AD centers<sup>76</sup> and to have a greater belief that late-life cognitive decline is "normal aging."<sup>76</sup> Moreover, medical researchers and institutions have historically not behaved in ways that would support earning the trust of individuals from minoritized communities. This is partially related to many non-consensual research atrocities, such as the notorious Tuskegee syphilis study, but also to the more structurally and systemically complicit ways of conducting clinical research that has either harmed or excluded minoritized individuals.<sup>88-92</sup> Therefore, most, if not all, clinical research studies are primarily performed with well educated, non-Latinx White people. For some years, ADNI rationalized its lack of cohort diversity as being an issue common to all clinical studies and clinical trials. We have since recognized that this is a major problem for ADNI and perhaps the greatest problem in the AD clinical trial field and in other areas of medicine, requiring urgent attention and remediation. ADNI's attempts to deal with this issue are discussed briefly in the ADNI3 and ADNI4 sections above and in more detail in the publications by the Engagement Core (Rivera-Mindt et al., in this Special Issue).

## 4.2 | Complexity of ADNI data

ADNI's success can also be a limitation as the huge amount of data produced by ADNI and the different methods that were introduced in successive phases of ADNI add layers of complexity for data users. Some examples are (1) differences in MRI technology (1.5T vs. 3T MRI); (2) changes in MRI and PET scanners over the years; (3) different sequences for perfusion, diffusion, and functional MRI in different waves; (4) different versions of FreeSurfer<sup>93</sup> and other image processing techniques; (5) different methods used to analyze CSF in ADNI1, -2, and -3; and (6) introduction of different PET tracers. When we launched ADNI in 2004, we had no idea that the project would go on for > 20 years, and we could not plan for the problems that would arise due to evolving methods and technologies. This problem has been confounded by ADNI releasing samples to outside labs that provide their results in various formats with varying levels of documentation. In fact, all our data documentation has been prepared by the group generating the data, and we have never imposed any common standards. Those scientists who are experienced with large data sets and committed to fully understanding the structure of ADNI data have been able to conduct research studies and write many publications. Our concern is that inexperienced scientists, especially younger students, may be confused by the complexity of the data and may either misuse the data or give up and move on. In ADNI4, we are now undertaking major efforts to improve the situation (described elsewhere in this Special Issue in the papers by the Administrative Core, Biostatistics Core, and Informatics Core).

## 5 | ADNI AND THE CLINICAL TRIALS OF THE FUTURE

### 5.1 | ADNI and ongoing clinical trials

The demonstration that plaque-clearing monoclonal antibodies slow AD progression has initiated the treatment era in AD research.<sup>94,95</sup> Other clinical trials of antibodies and small molecules against amyloid will continue while major efforts are underway to find treatments for AD therapy that are mainly directed at tau and multiple other mechanisms.<sup>96</sup> Biogen's recent antisense oligonucleotide (ASO) therapy of a Phase 1b clinical report demonstrated a lowering of tau in patients with early-stage AD in a phase 1 study, which is remarkable and encouraging.<sup>97</sup> Significant efforts are underway to discover treatments for  $\alpha$ -synuclein in Parkinson's and Lewy body disease. Several prevention trials, including AHEAD (using lecanemab by Eisai),<sup>33</sup> the DIAN Trials Unit (DIAN-TU),<sup>98</sup> and TRAILBLAZER-ALZ 2 phase 3 study (using donanemab by Lilly), are in progress. Last, while the progress in pharmacological treatments for AD is groundbreaking and provides great hope, it is crucial to note the lack of inclusive participation of URPs in these clinical trials. This limitation underscores the need for greater efforts to increase inclusivity and highlights the necessity for AD clinical trials to address the significant gaps in progress achieved thus far.<sup>99</sup>

Beyond pharmacological approaches, there is a great interest in the value of non-pharmacological treatments, including diet, nutritional supplements, docosahexaenoic acid, exercise, and mental stimulation.<sup>100</sup> The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) study on preventing cognitive impairment and disability in the elderly has shown promising results.<sup>101</sup> Similarly, the World-Wide FINGER project<sup>102</sup> and the U.S. POINTER study (U.S. Study to Protect Brain Health through Lifestyle Intervention to Reduce Risk), supported by the Alzheimer's Association, are potentially very impactful.<sup>103</sup> Many of these investigations have leveraged longitudinal ADNI data, particularly from CU individuals with amyloid positivity who exhibit a higher rate of decline and conversion to MCI compared to amyloid-negative individuals.

### 5.2 | ADNI's role in improving future clinical trials

We believe that there will be a continuing need for ADNI in the coming years. What role should ADNI play in shaping the landscape of the future of AD clinical trials? The answer to this critical question is not completely clear, but firmly addressing the limitations of ADNI, reviewed above, is an excellent start. The long-term goal of our field is to prevent and eliminate cognitive decline and dementia due to AD and other causes. To do this, we need to have preventative measures that can be used by the entire population, not just well-educated White older adults. We need to make our studies resemble the census of the United States geographically, by ethnocultural status, and importantly, by socioeconomic status, education, income, access to health care, rural residence, and exposure to pollutants. We need to enroll elders with  $\leq 12$  years of education, people who are part of the working class, and those living on social security income. In other words, people with backgrounds that more accurately reflect American socioeconomic experiences. This is going to be difficult if we largely rely on the AD centers in major academic institutions and major cities, even as some of these centers seek to increase URP enrollment in their own cohorts. Instead, we must bring the study "to the participants." There are likely to be many elements to this, including community engagement strategies, public education initiatives, workforce diversity efforts, digital marketing and outreach, and measures to minimize travel challenges.

#### 5.2.1 | Inclusion and enrollment of participants

To help diversify the ADNI participant cohort and thereby improve the generalizability of ADNI data and results, ADNI's Engagement Core has implemented a CI-CER approach and established a Community Science Partnership Board to oversee all aspects of the activities of this core.<sup>75</sup> This approach, promoting sustained and cooperative partnerships with communities, should be a feature in future phases of ADNI and other projects and is built on the following: better education, improved enrollment strategies, better cultural competency and relevance of staff and assessments, and reduced participant burden.



The public in general, and some URPs in particular, often falsely believe that cognitive decline is a normal part of aging. We need further education to help the public understand that dementia and AD are not a normal or natural part of the advancing human age.

To improve the enrollment of people from URP backgrounds in clinical research, greater efforts must be made to communicate in ways that connect and resonate with those communities. Culturally informed digital marketing, guided by community stakeholders and greater use of social media, will also play an increasing role because mobile phone usage has greatly increased in all demographic groups.<sup>75</sup> Although a digital divide still exists, increasing numbers of older adults, including minoritized older adults, use the Internet for a wide variety of activities (Pew Research Center, *Mobile fact sheet*. Internet, science and tech, 2017).<sup>104-107</sup> Inclusive participation efforts via local “boots on the ground” staff called community research liaisons, who have established relationships within the community, will be essential. There will be partnerships with health-care organizations and private practice groups, including family physicians, who are the major health-care providers specializing in elderly care. Sustained partnerships with community-based organizations will help to earn the trust of URP communities. Considerable effort will be required to make our research studies more trustworthy.

To promote diversity in both our workplaces and research teams, it is essential to have leaders, scientific investigators, and staff at every level with cultural and linguistic competence. This not only enriches the inclusivity of our studies but also facilitates effective community-engaged research by empowering and engaging the communities in the research process. To this end, the ADNI4 HESP program, which is administered through the Engagement Core, provides a model for our large-scale studies such as how ADNI can contribute to AD workforce capacity development in this area. Including culturally relevant assessments for evaluating individuals from URPs will also play an important role in increasing URP participation.<sup>76</sup> Additionally, adjusting the study design by reducing exclusion criteria and offering flexibility in required invasive procedures like lumbar puncture and incorporating remote engagement will enhance participation from URPs.

Importantly, the study should also minimize the length of travel from the participant's home to clinics, scanners, phlebotomy centers, and so on, and offer alternatives to invasive procedures such as lumbar puncture. The recent advent of blood-based biomarkers makes this goal attainable without jeopardizing the acquisition of critical data such as AD biomarkers.

## 5.2.2 | Home-based data collection

Home-based data collection is becoming more feasible as mobile devices offer a convenient way to gather demographic and self-report information and for digital cognitive assessments.<sup>108</sup> The use of voice robots to provide instructions, ask questions, and record responses is also growing. Integrating AI into voice robots could further streamline data collection and questionnaire responses. However, it is crucial to maintain a 24/7 concierge service approach, with minimal wait times, using trained, culturally sensitive human support staff. Additionally, the

use of various devices such as smartwatches and activity and sleep trackers holds great potential for monitoring health parameters.<sup>109,110</sup> Blood samples can be collected at home using innovative methods like blood spot collection (on blotting paper) and small tubes of blood that can be filled using finger pricks.<sup>111</sup> Genetic analysis using saliva has been used for many years<sup>112-114</sup> and efforts are underway to explore saliva-based collection of biomarkers like amyloid or tau.<sup>115,116</sup> Moreover, for MRI and PET scanning, neighborhood facilities could be used through contracts, while mobile scanners could be stationed directly outside participants' homes to facilitate the assessment of AD.<sup>117,118</sup>

## 5.2.3 | New models for clinical trial design

A variety of approaches can address challenges in AD clinical trial design, with newly developed statistical methods playing a crucial role in accommodating the complexities of precision medicine.<sup>119-121</sup> These methods can facilitate the identification of patient subgroups with distinct treatment responses, optimize individualized treatment, and simplify the assessment of treatment efficacy in heterogeneous patient populations. Further consideration should be given to non-AD neuropathological changes, which account for up to 25% variance in cognitive decline in clinical trials.<sup>122</sup>

Integrating electronic health records (EHRs) as a cost-efficient digital platform in AD clinical trials can significantly enhance research efficiency and patient-centered care. EHRs can streamline various trial processes, from ordering and administering research drugs to scheduling study visits and enhancing overall clinical trial management. Therefore, EHRs provide a cost-efficient digital platform that aligns with patient-oriented clinical research, fostering collaboration between researchers and care providers.<sup>123</sup> Furthermore, the linkage of EHRs and clinical trial data can facilitate precision medicine approaches.

A rising proportion of studies using ADNI data report AI or machine learning (ML) methods, which have the potential to improve clinical trials significantly. ML algorithms can assist in patient recruitment by identifying suitable candidates based on the analysis of diverse datasets, ensuring the recruitment of a more focused and representative study population. Additionally, AI can efficiently process large datasets, which may expedite data analysis and enhance the overall efficiency of clinical trials.<sup>124</sup> However, AI/ML models can also be susceptible to biases, particularly when trained on data that lack diversity. This may limit the potential of AI/ML algorithms to perform predictions for a broader population and may exacerbate discrimination against underrepresented groups. The objective of ADNI4 is to incorporate more diverse data, which will likely enhance the suitability of the dataset for model development.

## 6 | ADNI LEADERSHIP

Considering the pivotal role of ADNI in advancing research on AD, it is noteworthy that since its inception in 2004, the same PI has led ADNI

and largely the same Core leaders are in place. This stability has contributed to ADNI's remarkable success and impact. However, as ADNI plays a leading role in the field, this is an opportune time to think and plan for future leadership to ensure ADNI's ongoing success and productivity. This crucial consideration will allow ADNI to continue its leading role in the field toward ultimately preventing and eliminating AD and other causes of cognitive decline.

## 7 | WHAT HAVE WE LEARNED FROM 20 YEARS OF ADNI?

While ADNI has achieved remarkable success in addressing the broader needs of the field and has encouraged innovative, outside-the-box thinking to develop new solutions for these challenges, ADNI's limitations, problems, and failures have provided key lessons. Our struggles with improving cohort diversity have taught us that the primary challenge of clinical research is the recruitment of the desired population. Most studies underfund recruitment, instead dedicating major efforts to science and data analysis, and underrecognize recruitment difficulties. More "recruitment science" is needed concerning how to engage with and recruit people from URPs, especially those with low socioeconomic status, low income, low education, and those living in economically deprived areas with poor air, water, and food quality, which are not optimal for brain health. Reliance on AD centers places limitations on the ability to reach certain individuals, especially URPs, so innovative approaches are required. The use of social media and digital advertising can supplement "boots on the ground" recruitment efforts by each clinical site. Bringing trials to people's homes, using at-home blood draws, and digital assessments may also help.

The unprecedented volume of publications arising from ADNI data clearly demonstrates the success of ADNI data sharing. However, we have learned that it is difficult to enforce adherence to ADNI's Data Use Agreement, and therefore ADNI is frequently not acknowledged correctly as a source of data. Furthermore, in the burgeoning field of ML and AI, ADNI data represent a convenient dataset with which to test algorithms for diagnosis and predicting future decline. This has led to a plethora of publications that describe these methodologies, sometimes differing only marginally from previous work and, therefore, contributing little to clinical advancements in AD. This issue is reflected in the large number of publications appearing in low-impact journals (Table 1).

The widespread availability of AI tools also introduces a new vulnerability for the ADNI dataset. The ADNI Data Use Agreement prohibits investigators from releasing ADNI data downloaded from the LONI website. Many AI tools, such as OpenAI's Chatbox GPT and Anthropic Claude, retain all provided data and may distribute it to other users. For a variety of reasons, especially to protect patient privacy, the new ADNI Data Use Agreement explicitly forbids the use of AI tools and requires users to affirm that they will not share the data with others. However, AI tools with restricted use within a university or company, which prevents external release, are allowed. The updated ADNI poli-

cies are fully explained in the revised Data Use Agreement posted on the LONI ADNI website.<sup>14</sup>

Finally, one of the most crucial lessons learned from ADNI's two-decade journey is the critical importance of selecting individuals who not only work well together as a team but also share a passion for achieving common goals of the project. These choices have certainly been fundamental to the many achievements of ADNI.

## ACKNOWLEDGMENTS

Data collection and sharing for the Alzheimer's Disease Neuroimaging Initiative (ADNI) is funded by the National Institute on Aging (National Institutes of Health Grant U19 AG024904). The grantee organization is the Northern California Institute for Research and Education. In the past, ADNI has also received funding from the National Institute of Biomedical Imaging and Bioengineering, the Canadian Institutes of Health Research, and private sector contributions through the Foundation for the National Institutes of Health (FNIH) including generous contributions from the following: AbbVie; Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC; Johnson & Johnson Pharmaceutical Research & Development LLC; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California. We gratefully acknowledge and thank the members of the following boards for their tremendous support and guidance toward advancing the culturally informed community-engaged research and brain health equity aims of ADNI3 and ADNI4, including the ADNI3 Diversity Task Force External Advisory Board (Drs. Lisa Barnes, Goldie Byrd, Dorothy Farrar-Edwards, Carl Hill, Gladys Maestre, and Donna Masterman) and the ADNI4 Community Science Partnership Board (CSPB). This work was supported by NIH grant U19 -AG 024904 funded by the National Institute on Aging to Dr. Michael Weiner.

## CONFLICT OF INTEREST STATEMENT

Dr. Weiner serves on editorial boards for *Alzheimer's & Dementia*, *MRI*, and *TMRI*. He has served on advisory boards for Acumen Pharmaceutical, ADNI, Alzheon, Inc., Biogen, Brain Health Registry, Cerecin, Dolby Family Ventures, Eli Lilly, Merck Sharp & Dohme Corp., National Institute on Aging (NIA), Nestle/Nestec, PCORI/PPRN, Roche, University of Southern California (USC), NervGen. He has provided consulting to Baird Equity Capital, BioClinica, Cerecin, Inc., Cytox, Dolby Family Ventures, Duke University, Eisai, FUJIFILM-Toyama Chemical (Japan), Garfield Weston, Genentech, Guidepoint Global, Indiana University, Japanese Organization for Medical Device Development,

Inc. (JOMDD), Medscape, Nestle/Nestec, NIH, Peerview Internal Medicine, Roche, T3D Therapeutics, University of Southern California (USC), and Vida Ventures. He has acted as a speaker/lecturer to The Buck Institute for Research on Aging, China Association for Alzheimer's Disease (CAAD), Japan Society for Dementia Research, and Korean Dementia Society. He holds stock options with Alzheon, Inc., Alzeca, and Anven. The following entities have provided funding for academic travel: University of Southern California (USC), NervGen, ASFNR, and CTAD Congress. Dr. Kanoria is employed by both NCIRE and Houston Methodist Academic Institute. However, only NCIRE provided financial support for the work presented in this manuscript. Dr. Beckett, Dr. Miller, Dr. Morris, Dr. Nho, Dr. Okonkwo, Dr. Perrin, Dr. Toga, Dr. Tosun, and Dr. Veitch have no conflicts to declare. Mr. Diaz, Mr. Flenniken, and Ms. Conti also have no conflicts to report. Dr. Aisen has research grants from NIH, Lilly, and Eisai, and consults with Merck, Roche, BMS, Genentech, Abbvie, Biogen, ImmunoBrain Checkpoint, and Arrowhead. Dr. Green has received compensation for advising the following companies: Allelica, Atria, Fabric, Genome Web, Genomic Life, Grail, Verily, and VinBigData and is co-founder of Genome Medical and Nurture Genomics. Dr. Harvey serves as a statistical advisor for PLOS ONE. Dr. Nosheny receives support in the form of grants to UCSF from NIH, The Alzheimer's Association, and Genentech, Inc. Dr. Petersen has consulted for Roche, Inc., Merck, Inc., Biogen, Inc., Eisai, Inc., Nestle, Inc., and Genentech, Inc. Dr. Rivera Mindt receives support in the form of grants to Fordham University or the Icahn School of Medicine at Mount Sinai from NIH/NIA, The Alzheimer's Association, and Genentech Inc. Charitable Foundation. Dr. Okonkwo is supported by NIH grants to the University of Wisconsin-Madison. Dr. Saykin has received support from Avid Radiopharmaceuticals, a subsidiary of Eli Lilly (in kind contribution of PET tracer precursor) and consulting fees from Bayer Oncology (Scientific Advisory Board), Eisai (Scientific Advisory Board), Siemens Medical Solutions USA, Inc. (Dementia Advisory Board), Springer-Nature Publishing (editorial office support as editor-in-chief, *Brain Imaging and Behavior*). Dr. Shaw receives support from Roche (IIS and in-kind reagents and instrumentation support for CSF AD biomarkers). He has also received honoraria from Roche, Biogen, and Fujirebio for participation in teaching programs and served on advisory boards for Roche and Biogen. Dr. Jack is employed by the Mayo Clinic. He receives no personal compensation from any commercial entity. He receives research support from NIH and the Alexander Family Alzheimer's Disease Research Professorship of the Mayo Clinic. Dr. Jagust has consulted for Lilly, Biogen, Clario, and Eisai and holds equity in Molecular Medicine and Optoceutics. Dr. Green has received compensation for advising the following companies: Allelica, Atria, Fabric, Genomic Life, and Juniper Genomics; and is co-founder of Genome Medical and Nurture Genomics. J.C. Morris is funded by NIH grants # P30 AG066444; P01AG003991; P01AG026276; neither Dr. Morris nor his family owns stock or has equity interest (outside of mutual funds or other externally directed accounts) in any pharmaceutical or biotechnology company. ADNI is funded by NIH grant, U19 AG024904. Author disclosures are available in the [supporting information](#).

## CONSENT STATEMENT

All human subjects provided informed consent.

## ORCID

Michael W. Weiner  <https://orcid.org/0000-0002-0144-1954>

## REFERENCES

- Jagust WJ, Landau SM, Koeppe RA, et al. The Alzheimer's Disease Neuroimaging Initiative 2 PET Core: 2015. *Alzheimers Dement*. 2015;11:757-771. doi:10.1016/j.jalz.2015.05.001
- Weiner MW, Veitch DP, Aisen PS, et al. The Alzheimer's Disease Neuroimaging Initiative: a review of papers published since its inception. *Alzheimers Dement*. 2012;8:S1-68. doi:10.1016/j.jalz.2011.09.172
- Shaw LM, Vanderstichele H, Knapiak-Czajka M, et al. Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. *Ann Neurol*. 2009;65:403-413. doi:10.1002/ana.21610
- Budd Haeberlein S, O'Gorman J, Chiao P, et al. Clinical development of aducanumab, an anti- $\alpha\beta$  human monoclonal antibody being investigated for the treatment of early Alzheimer's disease. *J Prev Alzheimers Dis*. 2017;4:255-263. doi:10.14283/jpad.2017.39
- van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in early Alzheimer's disease. *N Engl J Med*. 2023;388:9-21. doi:10.1056/NEJMoa2212948
- Hao W, Lenhart S, Petrella JR, et al. Optimal anti-amyloid-beta therapy for Alzheimer's disease via a personalized mathematical model. *PLoS Comput Biol*. 2022;18:e1010481. doi:10.1371/journal.pcbi.1010481
- Sperling RA, Donohue MC, Raman R, et al. Trial of solanezumab in preclinical Alzheimer's disease. *N Engl J Med*. 2023;389:1096-1107. doi:10.1056/NEJMoa2305032
- Egan MF, Kost J, Voss T, et al. Randomized trial of verubecestat for prodromal Alzheimer's disease. *N Engl J Med*. 2019;380:1408-1420. doi:10.1056/NEJMoa1812840
- Ostrowitzki S, Bittner T, Sink KM, et al. Evaluating the safety and efficacy of crenezumab vs placebo in adults with early Alzheimer disease: two phase 3 randomized placebo-controlled trials. *JAMA Neurol*. 2022;79:1113-1121. doi:10.1001/jamaneurol.2022.2909
- Bateman RJ, Smith J, Donohue MC, et al. Two phase 3 trials of gantenerumab in early Alzheimer's disease. *N Engl J Med*. 2023;389:1862-1876. doi:10.1056/NEJMoa2304430
- Frisoni GB, Weiner MW. Alzheimer's Disease Neuroimaging Initiative special issue. *Neurobiol Aging*. 2010;31:1259-1262. doi:10.1016/j.neurobiolaging.2010.05.006
- Khachaturian ZS. Perspective on the Alzheimer's disease neuroimaging initiative: progress report and future plans. *Alzheimers Dement*. 2010;6:199-201. doi:10.1016/j.jalz.2010.04.002
- Thies WH. Alzheimer's Disease Neuroimaging Initiative: a decade of progress in Alzheimer's disease. *Alzheimers Dement*. 2015;11:727-729. doi:10.1016/j.jalz.2015.06.1883
- Laboratory of Neuro Imaging (LONI). Available at, <https://adni.loni.usc.edu/data-samples/access-data/>
- Toga AW, Neu S, Sheehan ST, Crawford K. Alzheimer's Disease Neuroimaging Initiative. The informatics of ADNI. *Alzheimers Dement*. Published online August 14, 2024. doi:10.1002/alz.14099
- Neu SC, Crawford KL, Toga AW. The image and data archive at the laboratory of neuro imaging. *Front Neuroinform*. 2023;17:1173623. doi:10.3389/fninf.2023.1173623
- Schwarz CG, Kremers WK, Wiste HJ, et al. Changing the face of neuroimaging research: comparing a new MRI de-facing technique with popular alternatives. *Neuroimage*. 2021;231:117845. doi:10.1016/j.neuroimage.2021.117845

18. Forman MS, Trojanowski JQ, Lee VM. Neurodegenerative diseases: a decade of discoveries paves the way for therapeutic breakthroughs. *Nat Med*. 2004;10:1055-1063. doi:10.1038/nm1113
19. Forman MS, Farmer J, Johnson JK, et al. Frontotemporal dementia: clinicopathological correlations. *Ann Neurol*. 2006;59:952-962. doi:10.1002/ana.20873
20. Selkoe DJ. Cell biology of protein misfolding: the examples of Alzheimer's and Parkinson's diseases. *Nat Cell Biol*. 2004;6:1054-1061. doi:10.1038/ncb1104-1054
21. Skovronsky DM, Lee VM, Trojanowski JQ. Neurodegenerative diseases: new concepts of pathogenesis and their therapeutic implications. *Annu Rev Pathol*. 2006;1:151-170. doi:10.1146/annurev.pathol.1.110304.100113
22. Jagust WJ, Bandy D, Chen K, et al. The Alzheimer's Disease Neuroimaging Initiative positron emission tomography core. *Alzheimers Dement*. 2010;6:221-229. doi:10.1016/j.jalz.2010.03.003
23. Beckett LA, Harvey DJ, Gamst A, et al. The Alzheimer's Disease Neuroimaging Initiative: annual change in biomarkers and clinical outcomes. *Alzheimers Dement*. 2010;6:257-264. doi:10.1016/j.jalz.2010.03.002
24. Weiner MW, Aisen PS. The Alzheimer's disease neuroimaging initiative: progress report and future plans. *Alzheimers Dement*. 2010;6:202-211.e207. doi:10.1016/j.jalz.2010.03.007
25. Hansson O, Seibyl J, Stomrud E, et al. CSF biomarkers of Alzheimer's disease concord with amyloid- $\beta$  PET and predict clinical progression: a study of fully automated immunoassays in BioFINDER and ADNI cohorts. *Alzheimers Dement*. 2018;14:1470-1481. doi:10.1016/j.jalz.2018.01.010
26. Bittner T, Zetterberg H, Teunissen CE, et al. Technical performance of a novel, fully automated electrochemiluminescence immunoassay for the quantitation of  $\beta$ -amyloid (1-42) in human cerebrospinal fluid. *Alzheimers Dement*. 2016;12:517-526. doi:10.1016/j.jalz.2015.09.009
27. Lifke V, Kollmorgen G, Manuilova E, et al. Elecsys® Total-Tau and Phospho-Tau (181P) CSF assays: analytical performance of the novel, fully automated immunoassays for quantification of tau proteins in human cerebrospinal fluid. *Clin Biochem*. 2019;72:30-38. doi:10.1016/j.clinbiochem.2019.05.005
28. Shaw LM, Hansson O, Manuilova E, et al. Method comparison study of the Elecsys®  $\beta$ -Amyloid (1-42) CSF assay versus comparator assays and LC-MS/MS. *Clin Biochem*. 2019;72:7-14. doi:10.1016/j.clinbiochem.2019.05.006
29. Esquivel RN, Benina N, Hawkins DM, et al. Clinical validation of the Lumipulse G  $\beta$ -amyloid ratio (1-42/1-40) in a subset of ADNI CSF samples. *Alzheimers Dement*. 2021;17:e055657. doi:10.1002/alz.055657
30. Esquivel RN, De Simone F, Benina N, et al. Reducing misdiagnosis of Alzheimer's Disease pathology utilizing CSF and amyloid PET. *Alzheimers Dement*. 2022;18:e066569. doi:10.1002/alz.066569
31. Veitch DP, Weiner MW, Aisen PS, et al. Using the Alzheimer's Disease Neuroimaging Initiative to improve early detection, diagnosis, and treatment of Alzheimer's disease. *Alzheimers Dement*. 2022;18:824-857. doi:10.1002/alz.12422
32. Mintun MA, Lo AC, Duggan Evans C, et al. Donanemab in early Alzheimer's disease. *N Engl J Med*. 2021;384:1691-1704. doi:10.1056/NEJMoa2100708
33. Raffi MS, Sperling RA, Donohue MC, et al. The AHEAD 3-45 Study: design of a prevention trial for Alzheimer's disease. *Alzheimers Dement*. 2023;19:1227-1233. doi:10.1002/alz.12748
34. Marek K, Chowdhury S, Siderowf A, et al. The Parkinson's progression markers initiative (PPMI)—establishing a PD biomarker cohort. *Ann Clin Transl Neurol*. 2018;5:1460-1477. doi:10.1002/acn3.644
35. Iwatsubo T, Iwata A, Suzuki K, et al. Japanese and North American Alzheimer's Disease Neuroimaging Initiative studies: harmonization for international trials. *Alzheimers Dement*. 2018;14:1077-1087. doi:10.1016/j.jalz.2018.03.009
36. Frisoni GB, Henneman WJ, Weiner MW, et al. The pilot European Alzheimer's disease neuroimaging initiative of the European Alzheimer's Disease Consortium. *Alzheimers Dement*. 2008;4:255-264. doi:10.1016/j.jalz.2008.04.009
37. Byun MS, Yi D, Lee JH, et al. Korean brain aging study for the early diagnosis and prediction of Alzheimer's disease: methodology and baseline sample characteristics. *Psychiatry Investig*. 2017;14:851-863. doi:10.4306/pi.2017.14.6.851
38. Hirschfeld LR, Deardorff R, Chumin EJ, et al. White matter integrity is associated with cognition and amyloid burden in older adult Koreans along the Alzheimer's disease continuum. *Alzheimer's Research & Therapy*. 2023;15:218. doi:10.1186/s13195-023-01369-5
39. China-Alzheimer's Disease Neuroimaging Initiative (China-ADNI). Available at, [https://www.alz.org/research/for\\_researchers/partnerships/wwadni/china\\_adni](https://www.alz.org/research/for_researchers/partnerships/wwadni/china_adni)
40. Méndez PC, Calandri I, Nahas F, et al. Argentina-Alzheimer's disease neuroimaging initiative (Arg-ADNI): neuropsychological evolution profile after one-year follow up. *Arq Neuropsiquiatr*. 2018;76:231-240. doi:10.1590/0004-282x20180025
41. Hendrix JA, Finger B, Weiner MW, et al. The Worldwide Alzheimer's Disease Neuroimaging Initiative: an update. *Alzheimers Dement*. 2015;11:850-859. doi:10.1016/j.jalz.2015.05.008
42. Weber CJ, Carrillo MC, Jagust W, et al. The Worldwide Alzheimer's Disease Neuroimaging Initiative: aDNI-3 updates and global perspectives. *Alzheimers Dement (N Y)*. 2021;7:e12226. doi:10.1002/trc2.12226
43. Morris JC, Aisen PS, Bateman RJ, et al. Developing an international network for Alzheimer research: the dominantly inherited alzheimer network. *Clin Invest (Lond)*. 2012;2:975-984. doi:10.4155/cli.12.93
44. ADRC Consortium for Clarity in ADRC Research Through Imaging (CLARITI). <https://naccdata.org/nacc-collaborations/clariti>
45. Apostolova LG, Aisen P, Eloyan A, et al. The Longitudinal Early-onset Alzheimer's Disease Study (LEADS): framework and methodology. *Alzheimers Dement*. 2021;17:2043-2055. doi:10.1002/alz.12350
46. Shishegar R, Cox T, Rolls D, et al. Using imputation to provide harmonized longitudinal measures of cognition across AIBL and ADNI. *Scientific Reports*. 2021;11:23788. doi:10.1038/s41598-021-02827-6
47. ARTFL LEFFTDS Longitudinal Frontotemporal Lobar Degeneration (ALLFTD). Available at, <https://www.allftd.org/mission>
48. Diverse Vascular Contributions to Cognitive Impairment and Dementia (VCID). Available at, <https://diversevcid.ucdavis.edu>
49. MarkVCID. Available at, <https://markvcid.partners.org>
50. Whitwell JL, Wiste HJ, Weigand SD, et al. Comparison of imaging biomarkers in the Alzheimer disease neuroimaging initiative and the mayo clinic study of aging. *Arch Neurol*. 2012;69:614-622. doi:10.1001/archneurol.2011.3029
51. Alzheimer's Disease Metabolomics Consortium. Available at, <https://sites.duke.edu/adnimetab/adni/>
52. Centrally-linked longitudinal peripheral biomarkers of AD (CLEAR-AD). Available at, <https://clear-ad.org>
53. Alzheimer's Disease Sequencing Project. Available at, <https://adsp.niagads.org/about/>
54. Artificial Intelligence For Alzheimer's Disease (AI4AD) Machine Learning Initiative. Available at, <http://ai4ad.org/>
55. Jo T, Nho K, Risacher SL, Saykin AJ. Deep learning detection of informative features in tau PET for Alzheimer's disease classification. *BMC Bioinformatics*. 2020;21:496. doi:10.1186/s12859-020-03848-0
56. Jo T, Nho K, Bice P, Saykin AJ, Initiative, F.T.A.s.D.N. Deep learning-based identification of genetic variants: application to Alzheimer's disease classification. *Briefings in Bioinformatics*. 2022;23:bbac022. doi:10.1093/bib/bbac022

57. The Accelerating Medicines Partnership® Program for Alzheimer's Disease (AMP® AD). Available at, <https://www.nia.nih.gov/research/amp-ad>
58. Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol.* 1991;82:239-259. doi:10.1007/bf00308809
59. Grundke-Iqbal I, Iqbal K, Tung YC, Quinlan M, Wisniewski HM, Binder LI. Abnormal phosphorylation of the microtubule-associated protein tau (tau) in Alzheimer cytoskeletal pathology. *Proc Natl Acad Sci U S A.* 1986;83:4913-4917. doi:10.1073/pnas.83.13.4913
60. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of department of health and human services task force on Alzheimer's disease. *Neurology.* 1984;34:939-944. doi:10.1212/wnl.34.7.939
61. Khachaturian ZS. Diagnosis of Alzheimer's disease. *Arch Neurol.* 1985;42:1097-1105. doi:10.1001/archneur.1985.04060100083029
62. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science.* 2002;297:353-356. doi:10.1126/science.1072994
63. Schenk D, Barbour R, Dunn W, et al. Immunization with amyloid-beta attenuates Alzheimer-disease-like pathology in the PDAPP mouse. *Nature.* 1999;400:173-177. doi:10.1038/22124
64. Albala B, Appelmans E, Burrell R, et al. The Alzheimer's Disease Neuroimaging Initiative and the role and contributions of the Private Partners Scientific Board (PPSB). *Alzheimers Dement.* 2024;20:695-708. doi:10.1002/alz.13483
65. Mueller SG, Weiner MW, Thal LJ, et al. Ways toward an early diagnosis in Alzheimer's disease: the Alzheimer's Disease Neuroimaging Initiative (ADNI). *Alzheimers Dement.* 2005;1:55-66. doi:10.1016/j.jalz.2005.06.003
66. Jack CR Jr, Barnes J, Bernstein MA, et al. Magnetic resonance imaging in Alzheimer's Disease Neuroimaging Initiative 2. *Alzheimers Dement.* 2015;11:740-756. doi:10.1016/j.jalz.2015.05.002
67. Klunk WE, Engler H, Nordberg A, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Ann Neurol.* 2004;55:306-319. doi:10.1002/ana.20009
68. Winblad B, Palmer K, Kivipelto M, et al. Mild cognitive impairment—beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *J Intern Med.* 2004;256:240-246. doi:10.1111/j.1365-2796.2004.01380.x
69. Clark CM, Schneider JA, Bedell BJ, et al. Use of florbetapir-PET for imaging beta-amyloid pathology. *Jama.* 2011;305:275-283. doi:10.1001/jama.2010.2008
70. Jack CR Jr, Bernstein MA, Borowski BJ, et al. Update on the magnetic resonance imaging core of the Alzheimer's disease neuroimaging initiative. *Alzheimers Dement.* 2010;6:212-220. doi:10.1016/j.jalz.2010.03.004
71. Aisen PS, Petersen RC, Donohue M, Weiner MW. Alzheimer's disease neuroimaging initiative 2 clinical core: progress and plans. *Alzheimers Dement.* 2015;11:734-739. doi:10.1016/j.jalz.2015.05.005
72. Weiner MW, Veitch DP, Aisen PS, et al. Impact of the Alzheimer's Disease Neuroimaging Initiative, 2004 to 2014. *Alzheimer's & Dementia.* 2015;11:865-884. doi:10.1016/j.jalz.2015.04.005
73. Baker SL, Lockhart SN, Price JC, et al. Reference tissue-based kinetic evaluation of 18F-AV-1451 for tau imaging. *J Nucl Med.* 2017;58:332-338. doi:10.2967/jnumed.116.175273
74. Weiner MW, Veitch DP, Aisen PS, et al. The Alzheimer's Disease Neuroimaging Initiative 3: continued innovation for clinical trial improvement. *Alzheimers Dement.* 2017;13:561-571. doi:10.1016/j.jalz.2016.10.006
75. Weiner MW, Veitch DP, Miller MJ, et al. Increasing participant diversity in AD research: plans for digital screening, blood testing, and a community-engaged approach in the Alzheimer's Disease Neuroimaging Initiative 4. *Alzheimers Dement.* 2023;19:307-317. doi:10.1002/alz.12797
76. Mindt MR, Okonkwo O, Weiner MW, et al. Improving generalizability and study design of Alzheimer's disease cohort studies in the United States by including under-represented populations. *Alzheimers Dement.* 2023;19:1549-1557. doi:10.1002/alz.12823
77. Ashford MT, Raman R, Miller G, et al. Screening and enrollment of underrepresented ethnocultural and educational populations in the Alzheimer's Disease Neuroimaging Initiative (ADNI). *Alzheimers Dement.* 2022;18:2603-2613. doi:10.1002/alz.12640
78. Zahnd WE, Del Vecchio N, Askelson N, et al. Definition and categorization of rural and assessment of realized access to care. *Health Serv Res.* 2022;57:693-702. doi:10.1111/1475-6773.13951
79. Skirrow C, Meszaros M, Meepegama U, et al. Validation of a remote and fully automated story recall task to assess for early cognitive impairment in older adults: longitudinal case-control observational study. *JMIR Aging.* 2022;5:e37090. doi:10.2196/37090
80. Miller MJ, Diaz A, Conti C, et al. The ADNI4 Digital Study: A novel approach to recruitment, screening, and assessment of participants for AD clinical research. *Alzheimers Dement.* Published online September 1, 2024. doi:10.1002/alz.14234
81. Erickson CM, Karlawish J, Grill JD, et al. A pragmatic, investigator-driven process for disclosure of amyloid PET scan results to ADNI-4 research participants. *J Prev Alzheimers Dis.* 2024;11:294-302. doi:10.14283/jpad.2024.33
82. Veitch DP, Weiner MW, Miller M, et al. The Alzheimer's Disease Neuroimaging Initiative in the era of Alzheimer's disease treatment: a review of ADNI studies from 2021 to 2022. *Alzheimers Dement.* 2024;20:652-694. doi:10.1002/alz.13449
83. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. *The Lancet.* 2017;390:2673-2734. doi:10.1016/S0140-6736(17)31363-6
84. Mackin RS, Insel PS, Landau S, et al. Late-life depression is associated with reduced cortical amyloid burden: findings from the Alzheimer's disease neuroimaging initiative depression project. *Biol Psychiatry.* 2021;89:757-765. doi:10.1016/j.biopsych.2020.06.017
85. Weiner MW, Veitch DP, Hayes J, et al. Effects of traumatic brain injury and posttraumatic stress disorder on Alzheimer's disease in veterans, using the Alzheimer's Disease Neuroimaging Initiative. *Alzheimers Dement.* 2014;10:S226-235. doi:10.1016/j.jalz.2014.04.005
86. Weiner MW, Harvey D, Hayes J, et al. Effects of traumatic brain injury and posttraumatic stress disorder on development of Alzheimer's disease in Vietnam Veterans using the Alzheimer's Disease Neuroimaging Initiative: preliminary Report. *Alzheimers Dement (N Y).* 2017;3:177-188. doi:10.1016/j.trci.2017.02.005
87. Weiner MW, Harvey D, Landau SM, et al. Traumatic brain injury and post-traumatic stress disorder are not associated with Alzheimer's disease pathology measured with biomarkers. *Alzheimers Dement.* 2023;19:884-895. doi:10.1002/alz.12712
88. Gamble VN. Under the shadow of Tuskegee: african Americans and health care. *Am J Public Health.* 1997;87:1773-1778. doi:10.2105/ajph.87.11.1773
89. Washington HA. Medical Apartheid: the Dark History of Medical Experimentation on Black Americans from Colonial Times to the Present. *Journal Of The National Medical Association.* Doubleday Books; 2007:1074-1075.
90. Scharff DP, Mathews KJ, Jackson P, Hoffsuemmer J, Martin E, Edwards D. More than Tuskegee: understanding mistrust about research participation. *J Health Care Poor Underserved.* 2010;21:879-897. doi:10.1353/hpu.0.0323
91. Gilmore-Bykovskiy A, Croff R, Glover CM, et al. Traversing the aging research and health equity divide: toward intersectional frameworks of research justice and participation. *Gerontologist.* 2022;62:711-720. doi:10.1093/geront/gnab107

92. Byrd DA, Rivera Mindt MM, Clark US, et al. Creating an antiracist psychology by addressing professional complicity in psychological assessment. *Psychol Assess*. 2021;33:279-285. doi:10.1037/pas0000993
93. Fischl B. FreeSurfer. *Neuroimage*. 2012;62:774-781. doi:10.1016/j.neuroimage.2012.01.021
94. DeMattos RB, Lu J, Tang Y, et al. A plaque-specific antibody clears existing  $\beta$ -amyloid plaques in Alzheimer's disease mice. *Neuron*. 2012;76:908-920. doi:10.1016/j.neuron.2012.10.029
95. Sevigny J, Chiao P, Bussière T, et al. The antibody aducanumab reduces A $\beta$  plaques in Alzheimer's disease. *Nature*. 2016;537:50-56. doi:10.1038/nature19323
96. Cummings J, Zhou Y, Lee G, Zhong K, Fonseca J, Cheng F. Alzheimer's disease drug development pipeline: 2023. *Alzheimers Dement (N Y)*. 2023;9:e12385. doi:10.1002/trc2.12385
97. Biogen: antisense oligonucleotide (ASO) therapy early-stage AD in a phase 1 study. 2023. Accessed 03/29/2024. Available at <https://investors.biogen.com/news-releases/news-release-details/new-data-biogens-investigational-antisense-oligonucleotide-aso>
98. Bateman RJ, Benzinger TL, Berry S, et al. The DIAN-TU Next Generation Alzheimer's prevention trial: adaptive design and disease progression model. *Alzheimers Dement*. 2017;13:8-19. doi:10.1016/j.jalz.2016.07.005
99. Manly JJ, Glymour MM. What the aducanumab approval reveals about Alzheimer's disease research. *JAMA Neurol*. 2021;78:1305-1306. doi:10.1001/jamaneurol.2021.3404
100. Li X, Ji M, Zhang H, et al. Non-drug therapies for Alzheimer's disease: a review. *Neurology and Therapy*. 2023;12:39-72. doi:10.1007/s40120-022-00416-x
101. Ngandu T, Lehtisalo J, Solomon A, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. *Lancet*. 2015;385:2255-2263. doi:10.1016/s0140-6736(15)60461-5
102. Kivipelto M, Mangialasche F, Snyder HM, et al. World-Wide FINGERS Network: a global approach to risk reduction and prevention of dementia. *Alzheimers Dement*. 2020;16:1078-1094. doi:10.1002/alz.12123
103. Baker LD, Snyder HM, Espeland MA, et al. Study design and methods: u.S. study to protect brain health through lifestyle intervention to reduce risk (U.S. POINTER). *Alzheimers Dement*. 2024;20:769-782. doi:10.1002/alz.13365
104. Perrin, A.a.D., M.. Americans' Internet Access: 2000-2015. 2015.
105. Smith A. African Americans and Technology Use: A Demographic Portrait. 2014.
106. Brown A, López G, Lopez MH. Digital divide narrows for Latinos as more Spanish speakers and immigrants go online. 2016.
107. Pew Research Center, Mobile fact sheet. Internet, science and tech, 2017. 2017. Accessed 03/29/2024. Available at <https://www.pewresearch.org/short-reads/2017/01/12/evolution-of-technology/>
108. Nosheny RL, Yen D, Howell T, et al. Evaluation of the electronic clinical dementia rating for dementia screening. *JAMA Netw Open*. 2023;6:e2333786. doi:10.1001/jamanetworkopen.2023.33786
109. Kaye J. Making pervasive computing technology pervasive for health & Wellness in Aging. *Public Policy & Aging Report*. 2017;27:53-61. doi:10.1093/ppar/prx005
110. Beattie Z, Miller LM, Almirola C, et al. The Collaborative Aging Research Using Technology Initiative: an Open, Sharable, Technology-Agnostic Platform for the Research Community. *Digit Biomark*. 2020;4:100-118. doi:10.1159/000512208
111. Simrén J, Ashton NJ, Blennow K, Zetterberg H. Blood neurofilament light in remote settings: alternative protocols to support sample collection in challenging pre-analytical conditions. *Alzheimers Dement (Amst)*. 2021;13:e12145. doi:10.1002/dad2.12145
112. Eriksson N, Macpherson JM, Tung JY, et al. Web-based, participant-driven studies yield novel genetic associations for common traits. *PLoS Genet*. 2010;6:e1000993. doi:10.1371/journal.pgen.1000993
113. Tung JY, Do CB, Hinds DA, et al. Efficient replication of over 180 genetic associations with self-reported medical data. *PLoS One*. 2011;6:e23473. doi:10.1371/journal.pone.0023473
114. Han E, Carbonetto P, Curtis RE, et al. Clustering of 770,000 genomes reveals post-colonial population structure of North America. *Nat Commun*. 2017;8:14238. doi:10.1038/ncomms14238
115. Sabbagh MN, Shi J, Lee M, et al. Salivary beta amyloid protein levels are detectable and differentiate patients with Alzheimer's disease dementia from normal controls: preliminary findings. *BMC Neurol*. 2018;18:155. doi:10.1186/s12883-018-1160-y
116. Pekeles H, Qureshi HY, Paudel HK, Schipper HM, Gornistky M, Chertkow H. Development and validation of a salivary tau biomarker in Alzheimer's disease. *Alzheimers Dement (Amst)*. 2019;11:53-60. doi:10.1016/j.dadm.2018.03.003
117. Bodily TA, Ramanathan A, Wei S, et al. In pursuit of degenerative brain disease diagnosis: dementia biomarkers detected by DNA aptamer-attached portable graphene biosensor. *Proc Natl Acad Sci U S A*. 2023;120:e2311565120. doi:10.1073/pnas.2311565120
118. Liu Y, Liu X, Li M, Liu Q, Xu T. Portable vertical Graphene@Au-based electrochemical aptasensing platform for point-of-care testing of tau protein in the blood. *Biosensors (Basel)*. 2022;12(8):564. doi:10.3390/bios12080564
119. van Oudenhoven FM, Swinkels SHN, Hartmann T, Rizopoulos D. Modeling the underlying biological processes in Alzheimer's disease using a multivariate competing risk joint model. *Statistics in Medicine*. 2022;41:3421-3433. doi:10.1002/sim.9425
120. Raket LL. Progression models for repeated measures: estimating novel treatment effects in progressive diseases. *Statistics in Medicine*. 2022;41:5537-5557. doi:10.1002/sim.9581
121. Donohue MC, Langford O, Insel PS, et al. Natural cubic splines for the analysis of Alzheimer's clinical trials. *Pharmaceutical Statistics*. 2023;22:508-519. doi:10.1002/pst.2285
122. Tosun D, Yardibi O, Benzinger TLS, et al. Identifying individuals with non-Alzheimer's disease co-pathologies: a precision medicine approach to clinical trials in sporadic Alzheimer's disease. *Alzheimers Dement*. 2024;20:421-436. doi:10.1002/alz.13447
123. Gale SA, Heidebrink J, Grill J, et al. Preclinical Alzheimer disease and the electronic health record: balancing confidentiality and care. *Neurology*. 2022;99:987-994. doi:10.1212/wnl.0000000000201347
124. Mirkin S, Albeni BC. Should artificial intelligence be used in conjunction with Neuroimaging in the diagnosis of Alzheimer's disease?. *Front Aging Neurosci*. 2023;15:1094233. doi:10.3389/fnagi.2023.1094233

## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Weiner MW, Kanoria S, Miller MJ, et al. Overview of Alzheimer's Disease Neuroimaging Initiative and future clinical trials. *Alzheimer's Dement*. 2024;1-15. <https://doi.org/10.1002/alz.14321>

**APPENDIX 1****Collaborators**

Michael W. Weiner, Shaveta Kanoria, Melanie J. Miller, Paul S. Aisen, Laurel A. Beckett, Catherine Conti, Adam Diaz, Derek Flenniken, Robert C. Green, Danielle J Harvey, Clifford R. Jack Jr., William Jagust,

Edward B. Lee, John C. Morris, Kwangsik Nho, Rachel Nosheny, Ozioma C. Okonkwo, Richard J. Perrin, Ronald C. Petersen, Monica Rivera-Mindt, Andrew J. Saykin, Leslie M. Shaw, Arthur W. Toga, Duygu Tosun, and Dallas P. Veitch