

Review Article

The Alzheimer's Disease Neuroimaging Initiative 3: Continued innovation for clinical trial improvement

Michael W. Weiner^{a,b,c,d,e,*}, Dallas P. Veitch^a, Paul S. Aisen^f, Laurel A. Beckett^g, Nigel J. Cairns^{h,i}, Robert C. Green^j, Danielle Harvey^g, Clifford R. Jack, Jr.^k, William Jagust^l, John C. Morris^f, Ronald C. Petersen^m, Jennifer Salazar^f, Andrew J. Saykin^{n,o}, Leslie M. Shaw^p, Arthur W. Toga^q, John Q. Trojanowski^{r,s,t,u}, Alzheimer's Disease Neuroimaging Initiative

^aDepartment of Veterans Affairs Medical Center, Center for Imaging of Neurodegenerative Diseases, San Francisco, CA, USA

^bDepartment of Radiology, University of California, San Francisco, CA, USA

^cDepartment of Medicine, University of California, San Francisco, CA, USA

^dDepartment of Psychiatry, University of California, San Francisco, CA, USA

^eDepartment of Neurology, University of California, San Francisco, CA, USA

^fAlzheimer's Therapeutic Research Institute, University of Southern California, San Diego, CA, USA

^gDivision of Biostatistics, Department of Public Health Sciences, University of California, Davis, CA, USA

^hKnight Alzheimer's Disease Research Center, Washington University School of Medicine, Saint Louis, MO, USA

ⁱDepartment of Neurology, Washington University School of Medicine, Saint Louis, MO, USA

^jDivision of Genetics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

^kDepartment of Radiology, Mayo Clinic, Rochester, MN, USA

^lHelen Wills Neuroscience Institute, University of California Berkeley, Berkeley, CA, USA

^mDepartment of Neurology, Mayo Clinic, Rochester, MN, USA

ⁿDepartment of Radiology and Imaging Sciences, Indiana University School of Medicine, Indianapolis, IN, USA

^oDepartment of Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, IN, USA

^pTailored Therapeutics, Eli Lilly and Company, Indianapolis, IN, USA

^qLaboratory of Neuroimaging, Institute of Neuroimaging and Informatics, Keck School of Medicine of University of Southern California, Los Angeles, CA, USA

^rInstitute on Aging, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

^sAlzheimer's Disease Core Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

^tUdall Parkinson's Research Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

^uDepartment of Pathology and Laboratory Medicine, Center for Neurodegenerative Research, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Abstract

Introduction: The overall goal of the Alzheimer's Disease Neuroimaging Initiative (ADNI) is to validate biomarkers for Alzheimer's disease (AD) clinical trials. ADNI-3, which began on August 1, 2016, is a 5-year renewal of the current ADNI-2 study.

Methods: ADNI-3 will follow current and additional subjects with normal cognition, mild cognitive impairment, and AD using innovative technologies such as tau imaging, magnetic resonance imaging sequences for connectivity analyses, and a highly automated immunoassay platform and mass spectroscopy approach for cerebrospinal fluid biomarker analysis. A Systems Biology/pathway approach will be used to identify genetic factors for subject selection/enrichment. Amyloid positron emission tomography scanning will be standardized using the Centiloid method. The Brain Health Registry will help recruit subjects and monitor subject cognition.

Results: Multimodal analyses will provide insight into AD pathophysiology and disease progression.

Discussion: ADNI-3 will aim to inform AD treatment trials and facilitate development of AD disease-modifying treatments.

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*Corresponding author. Tel.: +1-415-221-4810x3642; Fax: +1-415-668-2864.

E-mail address: michael.weiner@ucsf.edu

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1. Introduction

The number of Americans with Alzheimer's disease (AD) is projected to increase from 5.2 million in 2016 to 13.8 million in 2050 [1]. On the current trajectory, the total cost for AD and other dementias during this time is predicted to rise from \$236 billion in 2015 to more than \$1 trillion in 2050 [1]. The Alzheimer's Association estimates that a treatment that delays the onset of AD by 5 years would save an estimated \$935 billion in just the first 10 years. Indeed, the ~30% reductions in AD incidence in people older than 60 years with a high school education reported from the Framingham study [2] are estimated to have resulted in more than \$300 million in health care cost savings. The Alzheimer's Disease Neuroimaging Initiative (ADNI) was launched in 2004 with overarching aims of validating biomarkers for, and informing the design of, therapeutic trials in AD [3]. Funded by a unique public-private partnership, ADNI has now been running for 12 years, studying subjects with AD, and amnesic mild cognitive impairment (MCI) and cognitively normal (CN) elders. ADNI began with an initial 5-year study termed ADNI-1 [4], and was followed by a 2-year extension, which enrolled early MCI subjects, termed ADNI-GO, and then by a further 5-year competitive renewal termed ADNI-2 [5]. Over this time, ADNI has made a profound impact on nearly all aspects of AD pathobiology and patient-oriented research [6]. A 5-year competitive renewal of ADNI-2, termed ADNI-3, began on August 1, 2016. ADNI has been the subject of several journal Special Issues [7–9], has generated more than 1000 publications, and has been the subject of many iterative reviews of its progress and major milestones [3,10,11].

ADNI has played and continues to play a central role in improving treatment trials. The development of AD therapeutics has stalled in efforts to move beyond modestly effective symptomatic drugs, which are likely to have an impact at the dementia stage, to disease-modifiers, requiring treatment at earlier prodementia or even presymptomatic stages of disease. There are many reasons for this failure, including issues of target selection, off-target toxicity, subject selection, and insufficient pharmacokinetic and pharmacodynamics data to support trial design. In the past, AD and MCI were diagnosed clinically. Unfortunately, the clinical diagnosis lacked specificity (some patients diagnosed with MCI or dementia because of AD did not have AD pathology) and sensitivity (it is not possible to identify CN subjects who have amyloid pathology using clinical measurements). One of the major accomplishments of ADNI has been to validate amyloid phenotyping, which detects the presence of amyloid β ($A\beta$) pathology in living subjects with amyloid positron emission tomography (PET) [12–14] and cerebrospinal fluid (CSF) measures of $A\beta$ [15–17]. In the past, subjects with

clinical AD but without AD pathology have likely been enrolled in trials because of lack of amyloid phenotyping [18–20]. This has now changed, in part, because of the contributions of ADNI. ADNI investigators have advanced the design of prodementia trials in the statistical [21–24], methodological [25–34], cognitive [35], and clinical [31,32,36,37] literature, and with regulators [25] in the US and abroad facilitating the design of major completed and ongoing trials (avagacestat, gantenerumab, aducanumab, solanezumab, Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) study, and A5 study). These advances have included the move from time-to-end point designs to continuous outcome measures as primaries [21,25], the use of biomarker-based subject selection [22], single primary outcomes in prodromal trials [25], and cognitive end points in prodementia clinical trials [38–41].

Current clinical trials use measures of memory, cognition, and/or function as outcomes. These are imperfect measures as they are subject to high test-retest variability and are influenced by factors other than changes due to AD. A "biological marker" that represents progression of AD pathology, correlates with symptomatology (especially memory and cognitive decline), and is not affected by non-AD pathology could be used as a surrogate outcome measure, overcoming the problems associated with the current clinical measures. Despite some early hopes, brain $A\beta$ burden, measured with amyloid PET or in CSF, does not correlate well with disease severity and has not yet been proven an effective surrogate outcome [42,43]. Several counterintuitive results in which increased brain atrophy was reported in response to anti- $A\beta$ therapy [44–49] have also ruled out volumetric magnetic resonance imaging (MRI) measures as satisfactory surrogate markers for therapeutic $A\beta$ reduction. However, MR measures may still be a highly useful outcome measure for neuroprotective interventions. What therefore might be the ideal surrogate outcome measure? Pathologic studies have indicated that AD symptomatology is more closely associated with tau tangles than $A\beta$ deposits [43,50,51] and that brain tau correlates with cognition [43,50,51], suggesting a cause-effect relationship between tau tangles, synaptic dysfunction/synapse loss/neurodegeneration, and cognitive function. Recently, [^{18}F]-T807 (also known as AV-1451) and other tau PET ligands have been developed to detect tau in humans [52], raising the possibility that tau PET could ultimately be used as a surrogate marker for AD clinical trials. However, synaptic loss correlates most closely with cognitive impairment in AD, so it is likely that CSF synaptic protein biomarkers such as neurogranin could play a significant role as a surrogate marker in concert with biomarkers of AD pathology [53].

ADNI-3 aims to directly improve clinical trials in four major ways. First, it will study the use of tau PET for subject selection, as a baseline covariate and as a potential surrogate outcome measure. Second, it will investigate other signals such as change in CSF biomarkers, and functional imaging techniques ($[^{18}\text{F}]$ -fluorodeoxyglucose-PET (FDG-PET), arterial spin labeling (ASL) perfusion MRI, and task-free functional MRI (TF-fMRI) that may detect treatment effects in phase 2 trials [54]). Third, it will directly address the lack of reliability of A β and tau phenotyping through the standardization of different amyloid PET tracers in the “Centiloid project,” and the development of new immunoassay platforms and mass spectroscopy techniques to improve the reliability of CSF analysis of A β and tau as well as assess the utility of CSF synaptic protein biomarkers such as neurogranin [55]. Finally, in conjunction with the Brain Health Registry (BHR; www.brainhealthregistry.org; R.S. Mackin et al, 2016, submitted), it will implement web-based methods for recruitment and characterization of subjects to overcome the problems of slow recruitment and high trial costs because of high “screen fails.”

A secondary goal of ADNI-3 is to deepen our understanding of the progression and pathophysiology of AD. Continuation of the longitudinal phenotyping of AD from preclinical to prodromal to dementia stages will provide further insight into the disease process. Tau PET studies will investigate the relationship between A β and tau across the spectrum of cognition. The provision of biofluid samples to outside “omics” projects such as lipidomics and metabolomics [56,57] will facilitate a Systems Biology/pathway analysis approach to characterize AD. Improvement in methods for measuring functional and structural connectivity using MRI “Connectome-like” sequences will provide insight into the role of connectivity in this disease. Finally, ADNI-3 will continue to serve three Department of Defense ADNI grants investigating the relationship between traumatic brain injury and post-traumatic stress disorder in development of AD in Vietnam Veterans [58].

Given that ADNI has had a myriad of impacts on diverse aspects of AD [6] and in fields beyond the mandate of the study, and that these impacts continue to multiply with the growing pool of shared data, is expected that ADNI-3 will make even greater inroads into enabling successful clinical trials of AD therapies, and that its multimodal, longitudinal approach will provide important insights into disease progression.

2. Methods

2.1. Study design

ADNI-3 will be a continuation of ADNI-2 and is projected to retain 697 subjects from ADNI-2 (295 CN, 274 amnesic MCI, and 128 AD). To provide sufficient power and compensate for loss of dropouts, ADNI-3 will enroll an additional 133 CN (with and without the subjective memory concerns),

151 amnesic MCI (both early and late MCI), and 87 AD subjects (371 total new subjects), which will result in a cohort with 40% CN, 40% MCI, and 20% AD subjects (Table 1). The BHR, an innovative internet-based registry for recruitment, assessment, and longitudinal monitoring for neuroscience studies will be used for the identification and screening of eligible ADNI-3 participants and for subsequent cognitive longitudinal monitoring using online neuropsychological tests. Enrollment is expected to be completed in 2017. There will be 3 to 4 years of follow-up for all newly enrolled subjects. MCI and AD subjects will be seen every year for a clinical visit and MRI. Most CN subjects will be seen in alternating years for clinical visits and phone checks, although some CN subjects selected to receive a tau PET will have annual clinical visits. All MCI and CN subjects will receive a tau PET scan at baseline and in Year 5. Amyloid positive subjects may be randomly selected to receive two additional tau PET scans on the basis that A β level correlates with the level of brain tau tangles. AD subjects will receive a tau PET scan every year. All subjects receive amyloid PET and lumbar punctures every other year. MCI and AD subjects will receive an FDG-PET scan at baseline. CN and MCI subjects will be followed through the entire project, whereas AD subjects will be followed up for 24 months.

2.2. Clinical Core

The Clinical Core/Coordinating Center, led by Paul Aisen and Ronald Petersen, will continue to be responsible for managing the day-to-day clinical operations of ADNI, including the retention and follow-up of ADNI-2 subjects, and the enrollment of new subjects. Most clinical assessments from ADNI-2 will be continued in ADNI-3 to preserve the value of the longitudinal data set. The proprietary Boston Naming Test will be replaced with the license-free Multilingual Naming Test [59]. The Core will also incorporate a performance-based functional assessment, the Financial Capacity Instrument–Short Form [60].

The BHR will be used to assist recruitment of new enrollees and for at home longitudinal monitoring. Like the BHR, ADNI-3 will use the web-based computerized cognitive assessment, CogState, which may be more sensitive early in the disease course, is simple to perform, culture free, and exhibits minimal learning effects [61,62]. BHR currently has more than 40,000 participants, 37% of whom

Table 1
Enrollment plan

	Rollover (enrolled YR01)	New (enrolled YR01)	New (enrolled YR02)	Total
Normal cognition	295	65	68	428
Amnesic mild cognitive impairment	274	65	86	425
Alzheimer's disease	128	17	70	215
Total	697	147	224	1068

are older than 55 years and report memory concerns, and 29% of whom endorse a first-degree relative with dementia.

2.3. PET Core

The PET Core, led by William Jagust, will establish harmonized protocols for the collection of tau PET and amyloid PET data, quality control of all acquired data, and data analysis. Florbetaben (Neuraceq) [63] will be incorporated as a second amyloid tracer in addition to florbetapir. Those subjects from ADNI-2 will continue to be evaluated with [18F]florbetapir, whereas new subjects enrolled in ADNI-3 will be evaluated with longitudinal [18F]florbetaben. Tau PET data acquired using the tau ligand [18F]T807 will be examined using region of interest (ROI)-based approaches that recapitulate Braak staging to define tracer uptake. The Banner Alzheimer Institute will examine whole-brain voxelwise approaches to tau PET data and will calculate a cerebral tau index (CTI) to define extent and magnitude of brain tau deposition. The PET Core will continue FDG-PET imaging at the baseline examination on all subjects. Multimodal analysis including all PET and MRI data will form the basis for testing a proposed set of hypotheses that examine the ability of different PET biomarkers to predict outcomes at different stages of the AD pathophysiological process, how the biomarkers relate to one another, and how changes in biomarkers are related to clinical change.

2.3.1. Centiloid scale for the comparison of amyloid PET tracers

To allow direct comparison of amyloid tracers ([18F]florbetapir, [18F]florbetaben, and [11C]Pittsburgh compound B [PiB]), regional brain standardized uptake value outcomes will be converted into Centiloids, a process that reports amyloid tracer retention on a 0 to 100 scale using [11C]PiB as a reference. We hypothesize that different amyloid imaging agents will have similar effect sizes for prediction of decline and detection of longitudinal change when placed on the Centiloid scale. Combining different amyloid imaging agents on this scale will increase statistical power.

2.3.2. Tau imaging

A major feature of ADNI-3 is the incorporation of multi-site, longitudinal tau PET imaging, which in conjunction with clinical/cognitive assessments amyloid PET, MRI, CSF analysis, genetics, and widespread data sharing is expected to make a substantial contribution to our understanding of the role of tau in AD pathophysiology. Previous exploratory work using both ROI and voxel-based approaches has suggested a correlation between tau and cognition. In the ROI approach, patients were classified according to Braak staging determined by T1 MRI scan. Higher PiB retention and smaller hippocampal volumes were significantly associated with higher Braak stages even excluding those subjects with manifest clinical AD. There was a strong correlation ($\beta = -3.191$, $P = .008$) between performance on

a standard laboratory episodic memory factor score and retention of [18F]T807 in Braak stage 1/2 ROIs and between global cognition and [18F]T807 retention in Braak stage 3/4 and 5/6 ROIs (Fig. 1) [64]. Voxelwise analysis using a CTI differentiated between patient groups and young control subjects. In these data, CTI also correlated with the Mini-Mental State Examination ($r = 0.558$, $P = .016$ in elderly control subjects, MCI, AD).

2.4. MRI Core

The MRI Core, led by Clifford Jack, will continue to improve clinical trials by developing and standardizing protocols, operationalizing definitions of clinical subgroups to accommodate biological heterogeneity, and optimizing inclusion/stratification and outcome metrics. ADNI-2 acquisition protocols will be expanded in ADNI-3 to include seven sequences (structural MRI, fluid attenuation inversion recovery [FLAIR], T2*gradient echo [GRE], diffusion MRI (dMRI), TF-fMRI, ASL perfusion MRI, and a high-resolution coronal T2 fast spin echo) in all subjects (Table 2). In addition, the dMRI and TF-fMRI protocols will be implemented using both standard and advanced protocols. The advanced dMRI and TF-fMRI acquisitions will be implemented in systems that are capable and will resemble those performed in the Human Connectome Project (HCP). ADNI-3 will be the largest multisite, multivendor study to leverage several advanced MRI methods. HCP-like dMRI will offer more precise region-based fractional anisotropy and mean diffusivity measures as well as higher-fidelity characterization of white matter tract geometry. HCP-like TF-fMRI acquisitions will offer many advantages over standard TF-fMRI, including greater temporal and spatial resolution, less noisy connectivity measures, and time-varying connectivity. ASL perfusion MRI in ADNI-3 will be acquired, using the three-dimensional Pseudocontinuous ASL protocol recommended by the International Society for Magnetic Resonance in Medicine perfusion work group, in systems where this is possible. High-resolution medial temporal lobe (MTL) subregion imaging offers quantification of changes in hippocampal subfields and parahippocampal gyrus subregions, which are the location of the earliest stages of tau pathology [66–69]. All ADNI-3 scans will be acquired at 3 T.

2.5. Biomarker Core

The Biomarker Core, led by Leslie Shaw and John Trojanowski, will continue the ADNI Biofluid Biobank and distribution of samples to investigators, provide highly standardized $A\beta_{1-42}$, t-tau, and p-tau₁₈₁ measurements on CSF samples, and collaborate in the development of new tests for blood biomarkers (e.g., apoE4 protein in plasma; t-tau in plasma; exosomal fraction) and CSF biomarkers that detect copathologies such as Lewy bodies and -TAR

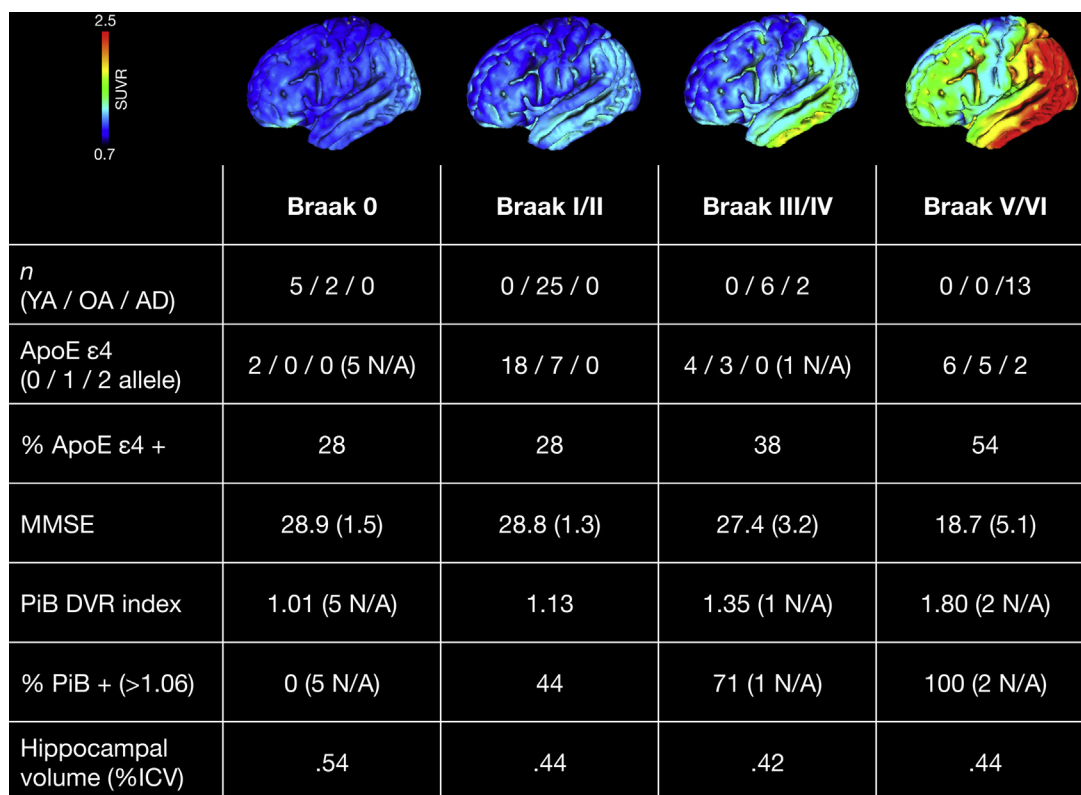


Fig. 1. In vivo Braak staging. Braak staging of healthy young adults (YA, $n = 5$), healthy older adults (OA, $n = 15$), and AD patients ($n = 15$) based on AV-1451 Braak region of interest uptake, with participant characterization by in vivo assigned Braak stage. ICV, intracranial volume. Values for Mini-Mental State Examination (MMSE), Pittsburgh compound B distribution volume ratio (PiB DVR) index, and hippocampal volume are mean (standard deviation). Reproduced with permission from [64].

DNA-binding protein 43 proteinopathy in addition to other informative CSF proteins such as neurogranin.

Previously, the Core found close agreement in the measurement of CSF $A\beta_{1-42}$ with a codeveloped reference method that uses the same sample preparation steps but different high performance liquid chromatography (HPLC) and mass spectrometry instrumentation (Fig. 2). An effort involving four laboratories in the Alzheimer's Association Global Biomarker Standardization Consortium showed very good concordance across 12 CSF pool samples ($R^2 = 0.98$; average intralaboratory %CV of 4.7%; interlaboratory %coefficient of variation (CV) of 12.2%) that improved further when adjusted using a common calibrator [72]. Validation efforts for the fully automated accuracy- and precision-based Roche Elecsys immunoassay platform for the measurement of $A\beta_{1-42}$, t-tau, and p-tau₁₈₁ in all ADNI CSF samples are ongoing. One study has been completed in multiple centers and suggests that this method shows the best interlaboratory performance reported for any method to date: the total measurement error across four participating laboratories and three different reagent lots and across 5 days of runs ranged from 2.2% to 5.1% in more than five different CSF pools used for this study [73]. This system will be fully implemented in ADNI-3. In addition, a newly validated mass spectrometry assay for

$A\beta_{1-42}$, $A\beta_{1-40}$, and $A\beta_{1-38}$ using a 2D-ultra performance liquid chromatography tandem mass spectrometry (UPLC/MS-MS) platform [55,70], calibrated with a surrogate calibrator matrix prepared from artificial CSF plus 4 mg/mL bovine serum albumin, will be implemented in all ADNI-3 CSF samples. A mass spectrometry-based measurement of t-tau using a high sensitivity multiple reaction monitoring (MRM) mass spectrometry system will be validated and implemented for t-tau measurement in CSF of all ADNI-2 and ADNI-3 study subjects.

Using these improved methods of measurement, we predict that the CSF biomarkers alone and in combination for subject selection will reduce sample sizes thus improving efficiency for treatment trials, and that pathologic concentrations of $A\beta_{1-42}$ will predict decline in measures of memory, cognition, and function. Furthermore, we hypothesize that rates of change in CSF $A\beta_{1-42}$ will be predictive of decline in memory, cognition, and function and ADNI-3 subjects.

2.6. Genetics Core

The Genetics Core, led by Andrew Saykin, will continue to provide genomic biosample banking and genotyping, identify and validate genetic markers to enhance clinical trial design and drug discovery, and provide an

Table 2
MRI sequences in ADNI-3

Modality	System	Measures	Notes
3D T1 volume	MPRAGE—Siemens/Philips; IRFSPGR—GE	Structural changes	Approximate 1 mm ³ resolution
3D-FLAIR	All	Cerebral microbleeds	As in ADNI-2
Diffusion MRI	Advanced if available or basic	White matter tract geometry	Similar to Human Connectome Project
Task-free fMRI	Advanced if available or basic	Functional connectivity	Similar to Human Connectome Project
ASL	Capable systems	Whole brain cerebral blood flow	Follows recommendations of ISMRM Perfusion Study Group and the European consortium for ASL in dementia [65]
Coronal high-resolution T2	All	MTL subregion analysis	

Abbreviations: ASL, arterial spin labeling; ADNI, Alzheimer's Disease Neuroimaging Initiative; fMRI, functional magnetic resonance imaging; IRFSPGR, inversion recovery fast spoiled gradient echo; MPRAGE, magnetization prepared rapid gradient echo; MRI, magnetic resonance imaging; MTL, medial temporal lobe.

organizational framework to foster collaboration on genomic studies within ADNI-3. In addition to protocols used in ADNI-2, peripheral blood mononuclear cells will be banked for use in the development of induced pluripotent stem cells, functional drug development-related assays, and other purposes. Systems Biology modeling approaches yielding polygenic risk scores and gene pathway- and network-based metrics will be used to predict disease progression and outcomes. Associations between variation in the *MAPT* gene, encoding tau protein, and other pathways, and tau PET will be investigated and the influence of genetic variation on proteomics and metabolomics biomarker assays will be assessed.

We anticipate that ADNI data will demonstrate that the efficiency of clinical trials can be improved by enrichment with genetic markers beyond *APOE*, thereby reducing sample size, time required to complete trials, and lowering costs. Beginning with AD candidate genes nominated by large genome-wide association studies [74], sequencing studies (e.g., *TREM2* [56–58], *PLD3* [59]), prior studies of AD endophenotypes in ADNI [75,76], and other studies, followed by genome-wide association (e.g., [77,78]), we expect to identify variants that improve prediction of disease

trajectory (i.e., onset, course, and outcome). We also predict that variants associated with biomarkers may yield clues to biological mechanisms and serve as potential targets for enrichment or therapeutic development. Examples of candidate trial enrichment markers that will be further studied in ADNI-3 include *BCHE* [77] and *IL1RAP* [79]. Additional data generated by ADNI-3 will enhance power by increasing participants with complete longitudinal data (and the range of phenotypes).

We envision that the innovative Systems Biology modeling approaches yielding polygenic risk scores and gene pathway- and network-based metrics will prove more powerful than single variants in predicting disease progression and outcomes, and that variation in the *MAPT* gene and other pathways will be associated with tau PET. Finally, we predict that controlling for the influence of genetic variation on proteomics (from studies of ADNI plasma and CSF samples) and metabolomics (through collaboration with the AD Metabolomics Consortium), biomarker assays will improve the performance of 'omics' biomarkers in predicting disease progression and outcomes.

2.7. Neuropathology Core

The Neuropathology Core, led by John Morris and Nigel Cairns, will continue to foster and facilitate a voluntary brain autopsy for each ADNI participant at each site to maintain a repository of frozen and fixed brain tissue from ADNI participants and to validate the clinical, CSF biomarker, and neuroimaging data of participants collected during the period of the grant. Additionally in ADNI-3, the contribution of common comorbidities (Lewy bodies, TDP-43 proteinopathy, vascular disease, hippocampal sclerosis, and tau astroglialopathy) to the variance in clinical, CSF biomarker, and neuroimaging data will be investigated, and the relationships between neuropathology and genomic data in multimodal studies of ADNI participants will be characterized. In participants who have undergone tau PET imaging, the spatial organization of tau burden in the postmortem brain will be correlated with tau PET data in collaboration with the PET Core.

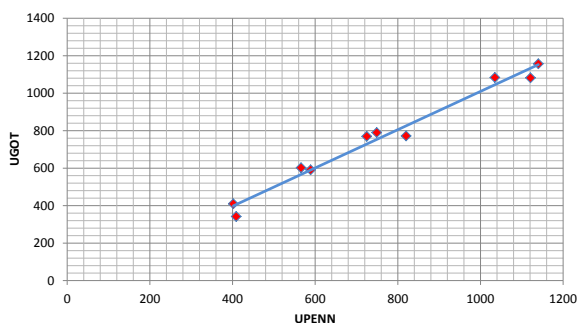


Fig. 2. Comparison of A β _{1–42} results (picograms per milliliter) for 10 patient cerebrospinal fluid samples. UGOT, University of Gothenburg; UPENN, University of Pennsylvania. Each laboratory used their multiple reaction monitoring/tandem mass spectrometry method [70,71], each approved by the Joint Committee for Traceability in Laboratory Medicine as reference methods.

From the inception of the ADNI Neuropathology Core, the overall autopsy rate (number of autopsies/number of deaths) is 62%, with tissue received from 49 of the 52 patients who have come to autopsy at one of the ADNI sites. Currently, 42 of 57 ADNI-2 sites are fully operational to obtain autopsy consent and brain donation and we anticipate that during ADNI-3, a number of additional sites will become operational. Thus far, nearly half (18/41) of autopsied patients diagnosed with documented plaque and tangle AD pathology also had some form of comorbidity, most commonly Lewy bodies (synucleinopathy) and TDP-43 proteinopathy in the MTL as well as argyrophilic grain disease and hippocampal sclerosis. We hypothesize that these comorbidities contribute to the variance in clinical, CSF biomarker, and neuroimaging data. By obtaining at least 100 total brains by the end of the next grant cycle, we calculate we will have 80% power to detect a correlation coefficient accounting for 8% of variation ($r = \pm 0.28$). We expect to gain insight into the relationship between these comorbidities and genetics using comprehensive integrative genomics and bioinformatics analyses with ADNI genome sequencing data in collaboration with the Genetics Core. We hypothesize that tau PET will be a better predictor of cognitive decline than other imaging and CSF biomarkers.

2.8. Biostatistics Core

The Biostatistics Core, led by Laurel Beckett, will carry out analyses of ADNI-3 data separately and in combination with data from previous phases with the aim of validating the potential of key clinical, functional, MRI, PET, CSF, and genetic biomarkers. Baseline biomarker distribution and performance, and longitudinal biomarker change will both be characterized as predictors of cognitive, functional, and biological change of progression from CN to MCI and MCI to AD, and for use as inclusion/exclusion criteria, screening and stratification. New biostatistical methodologies will be developed to support ADNI-3 goals including those that account for missing and/or skipped data. A model for disease progression [24] will be extended to include tau PET data and to capture heterogeneity among subpopulations in the order of marker progression. Generalized Mallows models will be extended to estimate the most likely sequence of progression events and its variation within and between subpopulations.

By combining results from PET tracers for amyloid, tau, and metabolism (FDG), and other measures, we predict that metabolism and tau, but not amyloid, will be correlated with cognition, and that metabolism will be negatively correlated with tau but not with amyloid. Moreover, we hypothesize that longitudinal changes in tau will be most strongly related to cognitive decline in all subject groups, whereas amyloid and metabolism will be very weakly related, and moderately related, respectively, to longitudinal cognitive decline. We hypothesize that future cognitive decline will be predicted by baseline PET, with amyloid and tau having stronger predictive power in control subjects than metabolism, and that

all three PET imaging agents will be predictive in MCI, with tau the most predictive. Finally, we predict that in all groups except AD, individuals with more brain amyloid will have more tau in the neocortex and that longitudinally, those with amyloid will show increases in neocortical tau over time.

2.8.1. Assessment of the contribution of non-AD pathology

We predict that hypoperfusion, altered diffusion, and atrophy on structural MRI will predict concurrent tau PET ligand uptake, and that the severity of cerebrovascular disease and cerebral microbleeds will modify the ability of MRI and other modalities to predict future cognitive decline. In combination with PET, biofluids, and clinical measures, we will operationalize the definitions of subgroups within the ADNI population. Formal definitions of groups like suspected non-Alzheimer's pathophysiology [80,81] and cerebrovascular phenotypes are needed to accommodate the biological heterogeneity within clinical trial populations. We anticipate that the development of new/optimized analysis methods and the creation of "AD-signature" summary numeric measures for each MR modality, and the optimization of inclusion/stratification, outcome metrics, and trial design will lower sample sizes and increase power of clinical trials.

2.9. Informatics Core

The Informatics Core, led by Arthur Toga, will continue to provide an information infrastructure to support the operational and research aims of each of the ADNI Cores and to provide data access and information resources for the wider research community. All new data acquired and produced as part of ADNI-3 will be stored in the Informatics Core ADNI repository at the Laboratory of Neuroimaging at the University of Southern California. Data across all ADNI phases and data sources will be harmonized to enable coherent search functionality for interested investigators and visualization on an interactive data platform. ADNI-3 data along with previous ADNI data will be provided in an "analysis-ready" form for searching and downloads. They will also be provided for data aggregation efforts such as the Global Alzheimer's Association Interactive Network.

3. Conclusions

ADNI-3 is poised to make substantial contributions to the improvement of clinical trials for AD therapies through the use of a variety of innovative approaches that build on the basis of knowledge accumulated in the study for more than the last 12 years. Recent results with tau PET suggest that increased misfolded or aggregated tau levels and brain (which occurs in concert with reduced levels of soluble brain tau [82]) correlate with cognition, correlate with CSF tau levels, correlate with the presence of amyloidosis, and show longitudinal progression. Thus, tau PET is a promising

biomarker to track change and treatment effects. Tau PET may also demonstrate the features required to serve as a surrogate marker in AD treatment trials, greatly reducing the number of subjects and length of trials. The development of the Centiloid approach for comparing amyloid tracers will facilitate use of multiple amyloid PET tracers for diagnosis and clinical trial enrollment. Use of the new automated Roche immunoassay platform by the Biomarker Core may reduce the previous variance problems with CSF measurements of A β ₁₋₄₂ and tau/p-tau₁₈₁. The BHR will facilitate recruitment of characterized participants for ADNI-3 and provide at home assessments. ADNI-3 will be augmented by the addition of MRI techniques that target structural and functional connectivity in the brain and allow sub-regional examination of the MTL. A Systems Biology approach promises to uncover novel genetic contributions to AD that may be used for subject selection or enrichment. Continuation of the longitudinal phenotyping across all stages of the disease process and with the inclusion of tau imaging and connectivity analyses will provide further insights into AD pathophysiology. Therefore, the innovative approach of ADNI-3 will facilitate the validation of biomarkers for AD trials, enabling development of effective preventive or disease-modifying treatments for AD. Ultimately, we hope to build models that enable the implementation of precision medicine approaches to stratifying patients for clinical trials and therapy including combination therapy [83,84].

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Conflicts of Interest: M.W.W. has served on the scientific advisory boards for Lilly, Araclon and Institut Catala de Neurociències Aplicades, Gulf War Veterans Illnesses Advisory Committee, VACO, Biogen Idec, and Pfizer; has served as a consultant for Astra Zeneca, Araclon, Medivation/Pfizer, Ipsen, TauRx Therapeutics Ltd, Bayer Healthcare, Biogen Idec, Exonhit Therapeutics, SA, Servier, Synarc, Pfizer, and Janssen; has received funding for travel from NeuroVigil, Inc, CHRU-Hopital Roger Salengro, Siemens, AstraZeneca, Geneva University Hospitals, Lilly, University of California, San Diego—ADNI, Paris University, Institut Catala de Neurociències Aplicades, University of New Mexico School of Medicine, Ipsen, CTAD (Clinical Trials on Alzheimer's Disease), Pfizer, AD PD meeting, Paul Sabatier University, Novartis, Tohoku University; has served on the editorial advisory boards for Alzheimer's and Dementia and MRI; has received honoraria from NeuroVigil, Inc, Institut Catala de Neurociències Aplicades, PMDA/Japanese Ministry of Health, Labour, and Welfare, and Tohoku University; has received commercial research support from Merck and Avid; has received government research support from DOD and VA; has stock options in Synarc and Elan;

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RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the literature pertaining to the achievements of Alzheimer's Disease Neuroimaging Initiative (ADNI) and the development of future methodologies for the ADNI-3 study using traditional sources such as PubMed. Extensive literature supports the widespread impact of the ADNI study in multiple areas and particularly in the improvement of clinical trials such as the ongoing A4 and A5 studies.
2. Interpretation: Results from analysis of ADNI-1 and ADNI-2 data combined with latest advances in technology have informed the structure and approach of the upcoming ADNI-3 study.
3. Future directions: Innovative technologies such as longitudinal tau imaging, magnetic resonance imaging connectivity analyses, and a mass spectroscopy approach to biomarker analysis, in addition to the standardization of amyloid positron emission tomography scanning using the Centiloid method, and continued multimodal analysis will be used to further understand Alzheimer's disease pathophysiology and disease progression. The Brain Health Registry will help recruit subjects and monitor their cognition.

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