Component Summary

Components	Component Project Title	Organization Name	Contact PD/PI Name or Project Lead Name
Overall	Alzheimer's Disease Neuroimaging Initiative	NORTHERN CALIFORNIA INSTITUTE FOR RESEARCH AND EDUCATION	WEINER, MICHAEL W
Admin-Core-001 (145)	Administrative Core	NORTHERN CALIFORNIA INSTITUTE FOR RESEARCH AND EDUCATION	WEINER, MICHAEL W
Core-001 (681)	Clinical Core	NORTHERN CALIFORNIA INSTITUTE FOR RESEARCH AND EDUCATION	WEINER, MICHAEL W
Core-002 (922)	PET Core	NORTHERN CALIFORNIA INSTITUTE FOR RESEARCH AND EDUCATION	WEINER, MICHAEL W
Core-003 (302)	MRI Core	NORTHERN CALIFORNIA INSTITUTE FOR RESEARCH AND EDUCATION	WEINER, MICHAEL W
Core-004 (168)	Biomarker Core	NORTHERN CALIFORNIA INSTITUTE FOR RESEARCH AND EDUCATION	WEINER, MICHAEL W
Core-005 (981)	Genetics Core	NORTHERN CALIFORNIA INSTITUTE FOR RESEARCH AND EDUCATION	WEINER, MICHAEL W
Core-006 (800)	Neuropathology Core	NORTHERN CALIFORNIA INSTITUTE FOR RESEARCH AND EDUCATION	WEINER, MICHAEL W
Core-007 (115)	Biostatistics Core	NORTHERN CALIFORNIA INSTITUTE FOR RESEARCH AND EDUCATION	WEINER, MICHAEL W
Core-008 (329)	Informatics Core	NORTHERN CALIFORNIA INSTITUTE FOR RESEARCH AND EDUCATION	WEINER, MICHAEL W

OMB Number: 4040-0010
Expiration Date: 06/30/2016

Project/Performance Site Location(s)

Project/Performance Site Primary Location

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:	NORTHERN CALIFORNIA INSTITUTE FOR RESEARCH AND EDUCATION
Duns Number:	6133387890000
Street1*:	4150 CLEMENT STREET (151-NC)
Street2:	
City*:	SAN FRANCISCO
County:	
State*:	CA: California
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	941211545
Project/Performance Site Congressional District*:	CA-012

File Name

Additional Location(s)

Overall: Project Summary/Abstract The overall goal of the Alzheimer's Disease (AD) Neuroimaging Initiative (ADNI) is to discover, standardize, and validate biomarkers for AD treatment trials. Validation is accomplished by comparing and correlating clinical/cognitive with biomarker data. Impact of ADNI has been to optimize, standardize and validate biomarkers, especially brain amyloid by PET and CSF measurements of Aβ peptides, termed "Aβ amyloid- phenotyping." There are 907 papers published using ADNI data. We will follow-up with annual visits, 697 subjects previously enrolled in ADNI2 (cognitively normal controls, subjects currently enrolled subjects with MCI, and patients with dementia diagnosed as AD) and will enroll 371 new subjects, while collecting clinical, cognitive, MRI (structural, diffusion, perfusion, resting state), amyloid PET, FDG PET, cerebrospinal fluid (for a Aβ, tau, phosphotau, and other proteins), genetic and autopsy data. In addition longitudinal measurements of brain tau PET will be performed on all subjects. All data is available without embargo to from USC/LONI/ADNI. **Specific Aims:**

1. Longitudinal changes in cognition and associated biomarkers: To determine those measures of cognition and function, including composite measures, and those biomarker measures which best capture longitudinal change with highest statistical power to detect treatment effects in clinical trials. Longitudinal change of brain tau tangles measured with tau PET will be correlated/compared with other measures.

2. Prediction of cognitive decline: To determine the clinical, cognitive, and biomarker measures which best predict decline of cognition in cognitively normal controls, subjects with MCI, and patients with dementia. In addition, to determine those biomarkers, especially tau PET, which correlate with cognitive decline.

3. Validation: To validate biomarker measures obtained at baseline and longitudinally by correlating results with "gold standard" clinical measurements and pathology.

4. Clinical trial design: To determine the optimum outcome measures (especially rate of cognitive decline and tau PET), predictors of cognitive decline, and inclusion/exclusion criteria for clinical trials of cognitively normal subjects (for secondary preclinical AD trials) and MCI patients (for prodromal AD trials).

5. Discovery: To determine the effects of other known disease proteins found in AD brains (e.g. alpha-synuclein, TDP 43,progranulin) and genes, and newly discovered proteins (from proteinomics), genes,and other analytes (from metabolomics) which provide useful information concerning the pathogenesis/diagnosis of AD. Discovery is conducted through the add-on studies led/driven by ADNI investigators with oversight by the NIA and the ADNI Resource Allocation Review Committee (RARC). ADNI methods and data are used in study design by government and industry funded clinical trials. Continuation of ADNI will help lead to development of effective treatments which slow progression and prevent AD.

Overall: Project Narrative

Alzheimer's disease (AD) causes cognitive impairment and dementia in millions of Americans and costs more than $100 billion/year in the USA. The Alzheimer’s Disease Neuroimaging Initiative (ADNI) is a large multisite public private partnership that will validate brain imaging, blood tests, and other diagnostics. This initiative will greatly facilitate design of clinical treatment trials and will help develop new diagnostic techniques, which identify AD at an early stage, ultimately leading to effective treatment and prevention of AD.

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: First Name*: MICHAEL Middle Name W Last Name*: WEINER Suffix:

Position/Title*: Professor in Residence
Organization Name*: NORTHERN CALIFORNIA INSTITUTE FOR RESEARCH AND EDUCATION
Department: Radiology
Division:
Street1*: 4150 Clement St (114M)
Street2:
City*: San Francisco
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 941210000

Phone Number*: 415-221-4810 x3642 Fax Number: 415-668-2864 E-Mail*: michael.weiner@ucsf.edu

Credential, e.g., agency login: MICHAELW

Project Role*: PD/PI Other Project Role Category:

Degree Type: Degree Year:

	File Name
Attach Biographical Sketch*:	Weiner_Biosketch_9.25.15.pdf
Attach Current & Pending Support:	

Overall: Specific Aims

The overall goal of the Alzheimer's Disease (AD) Neuroimaging Initiative (ADNI) is to discover, standardize, and validate biomarkers for AD clinical treatment trials. Validation is accomplished by comparing and correlating clinical measurements of cognition and function with all ADNI biomarkers including PET scans of both Aβ and tau amyloid deposits, cerebrospinal fluid (CSF) measurements of Aβ and tau, and other direct and indirect measures of these peptides/proteins, as well as, other associated changes in the brain including quantification of brain structure, perfusion, and activity.

AD is an amyloid-β facilitated tauopathy resulting in synapse loss and neurodegeneration. In order to develop effective treatments that slow the progression of AD, large multi-site treatment trials must be performed to meet regulatory standards. Prior to the initiation of ADNI in 2004, AD dementia and MCI were diagnosed by clinical and cognitive criteria. Furthermore, the rate of progression was determined using conversion to dementia, or cognitive and functional measures. Although very important, clinical and cognitive assessments lack both sensitivity (i.e. they detect disease pathology in the brain at a relatively late stage) and specificity (i.e. they fail to accurately distinguish cognitive impairments due to AD from problems resulting from other pathologies). Additionally, clinical/cognitive measures have considerable within-subject variability due to the many additional factors (other illnesses, family support, sleep, emotions, etc.) which influence cognition and function. In other words, clinical/cognitive measurements reflect both AD progression and other factors. The increased within-subject variability greatly diminishes the statistical power of any clinical trial to detect treatment effects that slow the progression of AD pathology, and limits diagnostic accuracy in enrolling subjects into therapeutic trials. The impact of ADNI has been to optimize, standardize and validate biomarkers, especially amyloid deposits formed by fibrillar Aβ amyloid by Positron Emission Tomography (PET) and CSF measurements of Aβ peptides, which reflect brain Aβ amyloid load, termed "Aβ amyloid-phenotyping." This has revolutionized AD clinical trials. Recently, tau amyloid PET scans have emerged, which may be a sensitive tool to detect tau tangle progression, a sensitive/specific "outcome measure."

Our goal will thus be accomplished by continuing to follow-up with annual visits of approximately 697 subjects previously enrolled in ADNI (cognitively normal controls, subjects currently enrolled with MCI, and patients with dementia diagnosed as AD). Furthermore, we will enroll approximately 371 new subjects, while collecting clinical, cognitive, MRI (structural, diffusion, perfusion, resting state), amyloid PET, FDG PET, cerebrospinal fluid (for amyloid B, tau, phosphotau, and other proteins), genetic and autopsy data. In addition, longitudinal measurements of brain tau PET will be performed on all subjects. All data will be made available without embargo to the scientific community from USC/LONI/ADNI. **Specific Aims:**

1. Longitudinal changes in cognition and associated biomarkers: To determine those measures of cognition and function, including composite measures, and those biomarker measures which best capture longitudinal change with the highest statistical power to detect treatment effects in clinical trials of controls, MCI and AD subjects. In addition, the longitudinal change of brain tau tangles measured with tau PET will be determined and correlated/compared with other measures.

2. Prediction of cognitive decline: To determine the clinical, cognitive, and biomarker measures which best predict decline of cognition in cognitively normal controls, subjects with MCI, and patients with dementia. In addition, to determine those biomarkers, especially tau PET, which correlate with cognitive decline.

3. Validation: To validate biomarker measures obtained at baseline and longitudinally by correlating results with "gold standard" clinical measurements and pathology.

4. Clinical trial design: To determine the optimum outcome measures (especially rate of cognitive decline and tau PET), predictors of cognitive decline, and inclusion/exclusion criteria for clinical trials of cognitively normal subjects (for secondary preclinical AD trials) and MCI patients (for prodromal AD trials).

5. Discovery: To determine the effects of other known disease proteins found in AD brains (e.g. alpha-synuclein, TDP 43, progranulin) and genes, and newly discovered proteins (from proteinomics), genes, and other analytes (from metabolomics) which provide useful information concerning the pathogenesis/diagnosis of AD, and are able to predict longitudinal decline, informing development of new treatments and clinical trial design. Biomarker discovery is conducted through the add-on studies led/driven by ADNI investigators with oversight by the NIA and the ADNI Resource Allocation Review Committee (RARC).

All data is public at USC/LONI/ADNI, without embargo; 5,892 investigators have access leading to over 900 publications (2/3 not directly funded by ADNI); ADNI methods and data are used in study design by government and industry funded clinical trials. This demonstrates the feasibility/value of widespread data sharing without embargo, and by the establishment of similar ADNI-like projects worldwide (World-wide ADNI). ADNI is supported by the pharmaceutical industry and major AD foundations. Continuation of ADNI will help lead to development of effective treatments which slow progression and prevent AD.

Overall: Research Strategy

SIGNIFICANCE

Prevalence and costs of Alzheimer's Disease (AD): The number of Americans with AD is projected to increase from 5.1 million in 2015 to 13.5 million in 2050. Of these, 3.1 million will be in the mild stage, 3.8 million in the moderate stage, and 6.5 million in the severe stage! In 2015, the costs to all payers for the care of people living with AD and other dementias will total an estimated $226 billion, with Medicare and Medicaid paying 68% of the costs. Based on the current trajectory, costs are projected to increase to over $1.1 trillion in 2050, with Medicare and Medicaid costs increasing to nearly 70% of the total. 18% of the Medicare budget will be spent on people living with AD and other dementias in 2015. The following costs are projected to triple by 2050: Medicaid, costs to other payers, out-of-pocket costs for families affected by AD and other dementias. Thus cumulative costs to all payers for AD and other dementias from 2015 to 2050 will be $20.8 trillion! It is estimated that a treatment that delays the onset of AD by five years would save an estimated $935 billion in just the first 10 years (all data from Report on Alzheimer's Association website). ADNI plays a central role in improving treatment trials.

Pathophysiology of AD: AD is characterized by brain pathology with extracellular amyloidβ ((Aβ) plaques), and phosphorylated tau protein aggregated inside neurons as paired helical filaments (PHF-tau), synapse loss, and neuronal loss, leading to dementia. AD is also frequently associated with other pathologies including amyloid angiopathy, cerebrovascular disease, Lewy body disease (α-synuclein), TDP 43, and neurogranin. Clinical signs and symptoms of AD include cognitive impairments, especially memory, as well as emotional disturbances. Age and family history are the major risk factors for the development of AD. Several factors including occupation, education, and intellectual/social activity affect cognitive decline and incidence of AD, leading to the concept of "cognitive reserve" [1].

AD clinical trials, past failures, current and future trials: The development of AD therapeutics has stalled in the efforts to move past modestly effective symptomatic drugs to disease-modifiers, with no drugs reaching the clinic since memantine in 2003. There are many reasons for this failure, including issues of target selection, off-target toxicity, and insufficient pharmacokinetic and pharmacodynamics data to support trial design. In the past many subjects with clinical AD but without AD pathology have likely been enrolled in trials due to lack of amyloid phenotyping [2-4]. Timing of intervention is also critically important; while symptomatic drugs are likely to be most effective at the dementia stage, disease-modifiers may require treatment at earlier stages of disease, prior to dementia or even prior to symptoms. From its launch in 2004, the overarching aim of ADNI has been to inform the design of therapeutic trials in AD; ADNI investigators have advanced the design of pre-dementia trials in the statistical [5-8], methodological [9-18], cognitive [19, 20] and clinical [15, 16, 21, 22] literature, and with regulators [9] in the US and abroad facilitating the design of major completed and ongoing trials (avagacestat, gantanerumab, aducanumab, solanezumab, A4 and, A5). These advances have included the move from time-to-endpoint designs to continuous outcome measures as primaries [5, 9], the use of biomarker-based selection [6], single primary outcomes in prodromal trials [9], and cognitive endpoints in predementia clinical trials [19, 20, 23-25]. The aducanumab Phase 1b trial (which used ADNI data for design and ADNI methods), while limited and preliminary, is perhaps the most exciting data from any anti-amyloid study, showing a substantial, dose-related treatment effect on both brain amyloid load and clinical outcome [26]. In ADNI3 we will continue to study the optimization of subject selection criteria and composite outcome measures across the spectrum of AD, new analytical approaches for demonstration of disease modification, and the use of tau PET for subject selection, as a baseline covariate and as a potential surrogate outcome measure. AD clinical trials also suffer from adverse effects, and ADNI has standardized MRI imaging to detect brain edema and microbleeds (ARIA) [27]. Another current limitation is the lack of signals which can detect treatment effects in Phase 2 trials. Change in CSF biomarkers, tau PET, and the functional imaging techniques (FDG PET, ASL perfusion MRI, and resting state fMRI) in ADNI may be helpful in Phase 2 trials.

A major problem in the field of AD trials is the lack of reliability and standardization of amyloid and tau phenotyping. This issue will be directly addressed by: first, the standardization of two different amyloid positron emission tomography (PET) tracers in a "Centiloid project," and second, improvement of the reliability of cerebrospinal fluid (CSF) analysis of Aβ and tau through the use of new immunoassay platforms and mass spectroscopy (which does not depend on antibody variability).

Other problems in the field of AD trials include delayed performance of clinical trials due to slow recruitment, high costs due to high "screen fails," and low statistical power of clinical/cognitive/functional instruments to detect rate of change. ADNI is implementing on-line recruitment and screening to address this problem.

Impact of this renewal of ADNI: Pathological studies have indicated that AD symptomatology is most closely associated with tau tangles [28-30], suggesting a cause-effect relationship between tau tangles, synaptic

dysfunction/synapse loss/neurodegeneration, and cognitive function. Recently, [^{18}F]-T807 and other tau PET ligands have been developed to detect tau in humans [31]. Therefore, the first major significant aspect of this proposed research is that it will provide important new information concerning the pathophysiology of AD including the relationship between Aβ (assessed using amyloid PET [^{18}F]florbetapir and [^{18}F]florbetaben, as well as CSF Aβ) and tau in humans across the spectrum of cognition. The second, and equally important, significance concerns the possible practical use of tau PET as a treatment outcome measure, even a validated "surrogate marker" (that is, one which directly correlates with disease pathology, and is beneficially affected by effective treatment) for AD clinical trials. It is generally accepted that there have been difficulties identifying effective treatments for AD, and the high cost of clinical trials hinders this search. Current clinical trials require use of 'clinical outcomes" such as measures of memory, cognition, and or function. But all these measures are subject to variability of several types: high test-retest variability and factors other than AD changes in the brain influence performance on cognitive tests. These include depression, sleep quality, other diseases, and events in the subject's life that affect attention or other cognitive functions. What is needed is a "biological marker" which (1) represents progression of AD pathology; (2) correlates with symptomatology (especially memory and cognitive decline); and (3) is not affected by non-AD pathology (e.g. depression, sleep, daily events, other diseases) which also affects cognitive and functional tests. Despite some early hopes, brain Aβ burden, measured with Aβ PET or CSF cannot be a surrogate marker because brain Aβ does not correlate very well with disease severity [29, 32]. For example, with the same level of brain Aβ burden, some elders can be cognitively normal while others have dementia. Volumetric magnetic resonance imaging (MRI) measures have also been disappointing as a surrogate marker because, although some treatments have been associated with slowing of brain atrophy [33-37], there have been several counter-intuitive results where there was more rapid brain shrinkage in response to anti-Aβ therapy [38-43]. Thus neither amyloid imaging nor MRI are good biomarker outcomes for trials.

The pathological findings that brain tau correlates with cognition [28-30], and preliminary results showing high correlation between tau PET agents, including [^{18}F]-T807 [44-46] and cognition, suggest that tau PET may be a useful outcome measure and raise the possibility that tau PET could ultimately be used as a surrogate marker (that is a marker which might replace clinical or cognitive measures) for AD clinical trials. Thus the significance/impact of ADNI3 is: longitudinal tau PET with many other clinical/biomarker measurements!

In addition to multisite tau PET, ADNI will continue to significantly impact the field through: (1) implementation of web-based methods for recruitment and characterization of subjects for AD trials, including online neuropsychological testing as described in the Clinical Core; (2) standardization of amyloid PET by the "Centiloid project," (PET Core); (3) improvement and standardization of CSF analysis using a new automated platform and mass spectroscopy (Biomarker Core); (4) improvement of methods to measure functional brain connectivity using the MRI "Connectome" sequences (MRI Core); (5) provision of biofluid samples to outside investigators for "omics" analysis and facilitating a Systems Biology approach to characterizing clinical AD (Genetics Core); (6) the ADNI network spawned and serves three Department of Defense ADNI grants investigating relationship of traumatic brain injury and post traumatic stress disorder on development of AD in Vietnam Veterans [47]; and (7) potentially providing the last opportunity to longitudinally phenotype the natural history AD from CN to MCI to dementia with AD, using all the currently available state of the art methods employed by this project. This is because some recent treatment trials have had encouraging results, and it is hoped that within the next five years at least one disease modifying treatment for AD will be approved, at least for some of the subject groups studied by ADNI. Once that happens, it will not be possible to investigate large numbers of untreated subjects.

Autopsy validation, data and sample sharing: The significance of ADNI is underscored by autopsy validation of data obtained from deceased ADNI subjects by the Neuropathology Core [48, 49]. All ADNI data is publicly available without embargo on the http://adni.loni.usc.edu/ website, and the results of this proposed study will be similarly available, together with *all* of the other longitudinal clinical/cognitive/imaging/biomarker data, and neuropathology data from autopsy, generated on the ADNI subjects. Furthermore, the CSF, serum, plasma, and DNA/RNA samples of ADNI subjects are banked and available to all investigators upon request (all such requests are reviewed by a NIA appointed committee independent of the ADNI leadership team, described in Resource Sharing Plan). The final significance of this proposal pertains to ADNI being funded by a public-private partnership, between the pharmaceutical industry and the NIA, discussed below. In conclusion, ADNI will obtain longitudinal tau PET in a multisite setting, on a large well characterized population with many other biomarkers. Therefore, this study will be a landmark event in the development of tau PET as a surrogate outcome measure for AD clinical trials, as well as providing invaluable information to the community concerning the role of brain tau in the pathophysiology of AD.

Significance of the public private partnership: The significance and impact of the community of international investigators from academe and industry (more than 25 companies are represented in the PPSB) cannot be overemphasized. The various ADNI meetings, workgroups, and teleconferences provide a "precompetitive" space allowing free-flow of information and idea generation concerning the optimum methods to employ biomarkers for AD clinical trials.

Institutional Changes: During 2010-2016, there have been two major institutional changes. First, in 2013, Dr. Arthur Toga moved the Informatics Core of ADNI from UCLA to USC. Despite some legal issues between UCLA and USC, the Informatics Core function of Dr. Toga's lab was not adversely affected and the flow and release of ADNI data was not interrupted. Second, recently in 2015, Dr. Paul Aisen moved the ADNI Clinical Core from UCSD to USC. This has resulted in legal and administrative difficulties, which have been widely reported in the press. The Clinical Core subcontract from NCIRE was transferred from UCSD to Dr. Aisen's Alzheimer's Disease Treatment Research Institute (ATRI) in early August 2015 and all Clinical Core functions of ADNI have been successfully performed in an uninterrupted fashion during this transition period. For both, the moves of the Informatics Core and the Clinical Core, patient safety, the rate of data collection, and the scientific integrity of ADNI have not been adversely affected. In fact, the transfers of the Informatics and Clinical Cores have both resulted in ADNI having substantially greater resources (due to greater availability of funds recovered by indirect costs, and new infrastructure provided as part of the recruitment) and much greater flexibility to use their resources (due to the moves to a private university from a public university). Therefore, the ADNI project has been strengthened by these events.

INNOVATION

Although it is not required in U19 applications to present "innovation," from its outset, ADNI has been innovative: (1) ADNI was developed as an innovative public (NIH)/private (pharmaceutical and biotech industry, and AD non-profits) partnership [50, 51] aimed at validating biomarkers for AD clinical trials; (2) ADNI developed an MRI phantom to standardize multisite MRI acquisitions; (3) ADNI implemented the Hoffman PET phantom [52, 53], together with preprocessing methods, to standardize multisite PET acquisitions; (4) in the midst of the first ADNI, we added on the first multisite C-11 PIB study to evaluate the value of amyloid PET [52]; (5) ADNI has led CSF-analysis standardization methods; (6) ADNI facilitated the first large whole genome sequencing project of AD subjects, together with clinical/cognitive and biomarker data; (7) ADNI samples have been used for proteomics and metabolomics, facilitating a "systems biology" analysis; and (8) ADNI's public sharing of all data without embargo has been innovative.

The current competitive renewal application has several innovative aspects: (1) the combination of multisite longitudinal tau PET with clinical/cognitive assessments, amyloid PET, MRI, CSF collections and analysis, and genetics, with widespread data sharing; (2) standardization of amyloid PET scanning by the "Centiloid project"; (3) the improvement of CSF analysis standardization via implementation of a new highly-automated platform for immunoassay of CSF analytes, together with mass spectroscopy; (4) multisite implementation of the MRI sequences developed by the NIH-funded Human Connectome Project [54]. These MRI protocols may be useful to detect early effects of disease modifying treatments on brain functional connectivity, thus improving the statistical power of Phase 2 studies; (5) use of ADNI samples to facilitate a Systems Biology/Pathway analysis; (6) development of improved AD clinical trial design, especially prevention trials;(7) the growth of many "World Wide ADNI" projects, aided by support from the Alzheimer's Association, leading to a world-wide network of AD clinical sites for international trials;(8) use of the BrainHealthRegistry.org, an innovative internet-based registry for recruitment, assessment, and longitudinal monitoring for neuroscience studies. We conclude that ADNI has been extremely innovative in developing state of the art methods for AD clinical trials, leading in the development of effective disease-modifying treatments which slow the progression of, and prevent, AD.

APPROACH

Overall Strategy: Our strategy is based on the concept that AD is a process characterized by the accumulation of Aβ and tau tangles, synapse loss and neurodegeneration, leading to cognitive decline. Clinical and cognitive measures alone lack both sensitivity and specificity to detect AD pathology. Therefore, as is true for so many other diseases, biomarkers must be used for identification of subjects at risk for cognitive decline and dementia, and to measure disease progression. We will continue to optimize and validate biomarkers for AD clinical trials by correlating biomarkers with the clinical outcomes of diagnostic category (CN, MCI, AD) and rates of change of cognition and function (statistical methods for such correlations in the Biostatistics Core). We will accomplish our goals through our public private partnership, which brings together investigators from academe with our pharmaceutical industry and non-profit foundation partners, including collaborators in the World Wide ADNI project (WW-ADNI). Widespread public sharing of data and ADNI samples multiplies the impact of ADNI.

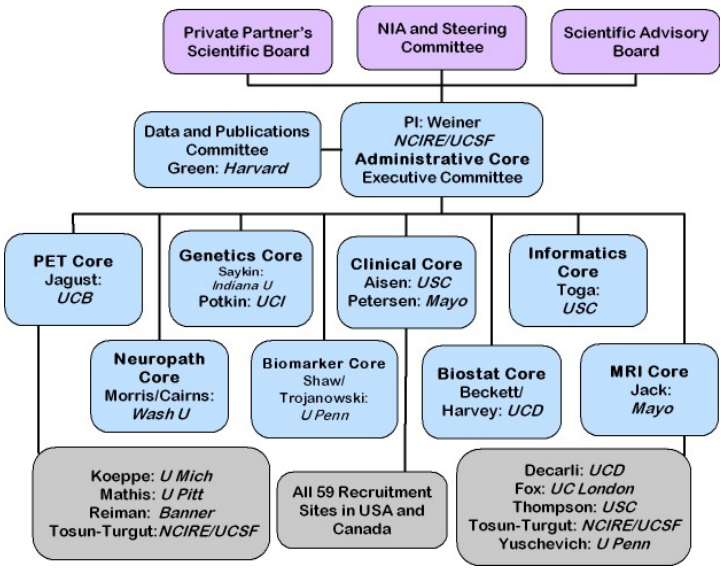
Study Design: The study design will be a continuation of the current study and will retain as many subjects as possible. We believe that recruiting new subjects will be critical to provide sufficient power and to compensate for loss of subjects due to drop outs. If we didn't propose enrolling new subjects, and if the dropout rate for follow-ups were higher than we projected, we would have difficulty using the funds for new subject enrollments because this would be considered out of scope. Finally we believe that by enrolling subjects in year 1 and 2 of the grant we will have 3-4 years of follow-up for all newly enrolled subjects. Virtually all clinical trials performed at the present time are 1-4 years in length. Therefore the length of follow-up of the newly enrolled subjects fits that model. Based on a projection of the active subjects with a rollover dropout rate (estimated at double the prior annual dropout rate) the estimated number of subjects to rollover into ADNI3 is: 295 Normal, 274 MCI and 128 AD subjects (697 total rollover subjects). ADNI3 will also enroll new subjects to provide sufficient power and compensate for loss of drop outs: 133 Normal, 151 MCI and 87 AD subjects (371 total new subjects). The number of new subjects recruited was determined using the following distribution of subjects: 40% NL, 40% MCI and 20% AD. All rollover subjects will be seen in year 1 and new subjects will be enrolled in Years 1 and 2. There will be 3-4 years of follow-up for all newly enrolled subjects. (All AD trials at the present time are 1-4 years in length.) MCI and AD subjects will be seen every year for a clinical visit and MRI. Normal (NL) subjects will be seen on alternating years for clinical visits and phone checks, although some NL subjects will have annual clinical visits, depending if they receive a tau PET. Table 1 summarizes the enrollment plan. Due to the fact that amyloid negative subjects have few brain tau tangles, the frequency of tau PET scans depends on amyloid status (explained in PET Core). MCI and NL subjects will receive two or four tau scans. All MCI and NL subjects receive a tau scan at baseline and YR05. They can receive two additional tau scans if they are randomly selected based on their amyloid positivity. AD subjects receive a tau scan every year. All subjects receive amyloid PET and lumbar punctures every other year. MCI and AD subjects receive FDG at baseline.

Table1: Enrollment Plan

	Rollover (enrolled YR01)	New (enrolled YR01)	New (enrolled YR02)	Total
Normal (NL)	295	65	68	428
MCI	274	65	86	425
AD	128	17	70	215
Total	**697**	**147**	**224**	**1,068**

There will be exceptions to this schedule depending on which procedures rollover subjects received in the last year of ADNI2 or which year new subjects were enrolled. NL and MCI subjects are followed through the entire project while AD subjects are only followed for 24 months. A much more detailed description of the enrollment schedule and schedule of events of all procedures is provided in Clinical Core: Budget Justification.

Figure 1: ADNI Governance Diagram



Administrative Core (PI, Michael Weiner, MD): The Administrative Core consists of the Principal Investigator of ADNI (Dr. Michael Weiner, at the VA Medical Center in San Francisco, CA, and UCSF), his administrative staff, statistical support, and the Data and Publications Committee administered by Dr. Robert Green at Harvard University. Dr. Weiner has responsibility for all administrative, financial, and scientific aspects of ADNI. ADNI is a U19 cooperative agreement grant, and the NIA requires that this project be governed by a Steering Committee which consists of: the PI and all funded core leaders, all site PI's, representatives from NIH and FDA, representatives from each of the contributing companies as observers only, and guests from foreign countries and other related multisite projects (see Figure 1).

More than 150 people have been attending the Annual Steering Committee Meetings. The Scientific Advisory Board (SAB) attends the Steering Committee and then meets with the Executive Committee. The SAB consists of: Zaven Khachaturian, PhD, Chair (Khachaturian & Associates), Maria Carillo, PhD (Alzheimer's Association), Peter Davies, PhD (Albert Einstein College of Medicine), Franz Hefti, PhD (Acumen Pharmaceuticals), Howard Fillit, MD (Alzheimer's Drug Discovery Foundation), David Holtzman, MD

(Washington University), Lewis Kuller, MD, DrPH (University of Pittsburgh), Marek-Marsel Mesulam, MD (Northwestern University), William Potter, MD, PhD (NIMH/FNIH), Marc Raichle, MD (Washington University), and Gregory Sorensen, MD (Siemens Healthcare North America).
The Administrative Core also houses the Brain Health Registry (BHR), an on line registry for recruitment, assessment and longitudinal monitoring for ADNI subjects. BHR will also facilitate minority enrollment through targeted public relations and advertising. Finally, some scientists working with Dr. Weiner who are analyzing ADNI clinical, biofluid, and multimodality imaging data (described in other Cores) are funded through the Administrative Core to reduce indirect costs. In the event that Dr. Weiner is unable to perform his duties as PI, Dr. William Jagust at U.C. Berkeley will become the Director of ADNI (and will be given an appointment at NCIRE, the prime recipient of ADNI funds).
Clinical Core (PI's, Paul Aisen, MD and Ronald Petersen, PhD, MD): The Clinical Core/Coordinating Center for ADNI3 will continue to be responsible for managing the day-to-day clinical operations of ADNI. The ADNI2 Clinical Core has been operating all the ADNI sites, based at the Alzheimer's Therapeutic Research Institute (ATRI) at USC since early August 2015. The Clinical Core will be responsible for oversight of ADNI3 clinical activities, contracting with all sites, data management (including creating of an ADNI portal in the data capture system for digital upload of all data from the clinical sites), tracking and quality control, recruitment and retention of participants, regulatory oversight (IRB tracking), financial management of site costs, safety monitoring including DSMB reporting, and creation of a final "locked document" of all data at the close of the study (this was done for ADNI1, ADNI-GO, and is being completed for ADNI2). The study design is described above in **Study Design**. As detailed on the ADNI/LONI website (http://adni.loni.usc.edu/about/centers-cores/clinical/subject-tables/) we fully enrolled and managed all cohorts during the current grant cycle. The Clinical Core will focus on retention and continued follow-up of the cognitively normal participants (with and without subjective memory concerns) and those with mild cognitive impairment (MCI) due to Alzheimer's disease (AD) (both early and late MCI). Careful follow-up of these individuals, some of whom have been participating in ADNI for eight years or longer, will allow study of the conversion from normal aging to preclinical AD, as well as the detailed characterization of preclinical AD as it progresses to MCI and dementia due to AD. This will powerfully address major gaps in current understanding and facilitate the continuing refinement of early trial designs. New ADNI3 enrollees will fall primarily into two categories: cognitively normal individuals with and without subjective concerns (ages 65 and older, global CDR=0), and early/late amnestic mild cognitive impairment (global CDR=0.5, MMSE 24-30 and education appropriate memory impairment). Individuals with MCI who convert to AD dementia will continue to be followed for two additional years. Almost all ADNI2 assessments will be continued in ADNI3 to preserve the value of the rich longitudinal dataset. Because of concern about proprietary instruments in trials, the Boston Naming test will be dropped; the MINT test [55], which is license-free, will replace it. The major additions will be web-based computerized cognitive assessments and a performance-based functional assessment. Clinical core aims include characterization of the cross-sectional features and longitudinal trajectories of participants who are cognitively normal and those with mild cognitive impairment, including those who progress to dementia, study of the relationships among clinical/demographic, cognitive, genetic, biochemical and neuroimaging features (including tau PET imaging) of AD from the preclinical through dementia stages, assessment of genetic, biomarker, cognitive and clinical predictors of AD-related decline, refinement of clinical trial designs, including in particular secondary prevention and slowing of progression in symptomatic disease, and evaluation/optimization of cognitive and functional outcome measures for prodromal and preclinical stage trials. The core will also explore a new functional performance instrument, will evaluate the relationship of longitudinal web-based cognitive assessment to in-person assessments, biomarkers and risk of decline, and will assess the utility of the Brain Health Registry for recruitment.
PET CORE (PI, William Jagust, MD): Contributions to date: The ADNI PET core has a major impact on the project and on the entire field. Most recently, ADNI-GO/ADNI2 saw the initiation of [^{18}F]florbetapir-PET amyloid imaging, and the PET Core was key to establishing and harmonizing data acquisition protocols, PET QC procedures, and most importantly data analysis. The PET Core established methods for analysis of cross sectional data [53], as well as, defining new procedures for maximizing sensitivity to longitudinal change in β-amyloid deposition [56, 57]. Work in ADNI also showed the potential for interconversion of quantitative, numerical measures of amyloid PET tracer uptake across different tracers [58, 59], which has led to the concept of "centiloids" – the use of a standard 0-100 scale for reporting all amyloid imaging results [60]. ADNI amyloid PET imaging methods have been employed in clinical trials around the world, including the recent Biogen/Aducanumab trial which generated considerable enthusiasm in showing reductions of brain Aβ and clinical improvement. In addition to these methodological advances, ADNI PET data has contributed broadly to

the field of AD clinical trials by helping to establish the frequency of brain Aβ deposition in different stages of AD, examining the relationships between amyloid PET and other biomarkers including APOE genotype, and defining cognitive decline in relation to brain Aβ. This work was accomplished by ADNI Core labs and in multiple labs worldwide that have used ADNI PET data.

Tau imaging: A major development in the AD biomarker field has been the recent availability of PET ligands that bind to tau which is deposited as paired helical filaments (PHF). Initial reports used the [^{11}C] labeled tracer PBB3 [61] but this is problematic for many reasons not the least of which is the too short half-life of the radioisotope to allow multisite delivery. The subsequent compound to be reported was [^{18}F]T807, now also known as AV1451; this compound shows high *in vitro* affinity and specificity for PHF tau, and good *in vivo* discrimination of AD patients and controls [46]. This tracer suffers to some extent from slow pharmacokinetics and considerable off-target binding. These problems are discussed in more detail in the PET Core section, but in brief, the pharmacokinetics are not likely to be a problem since short acquisitions (at 80-100 min post injection) are highly correlated with 2.5 hour long DVR measures (see preliminary data in PET Core). Thus we have a clear plan for implementation of data collection for quantitation. Off target binding has been suggested to be related to MAO-A [62] but this does not seem a likely explanation for the PET signal given the low abundance of the enzyme in brain and its distribution [63]. In any case this binding does not appear to affect cortical measurements. There is extensive preliminary data available from the lab of the PET Core PI, as well as from Avid Radiopharmaceuticals and the Harvard Aging Brain Study indicating that tau-PET correlates with clinical symptoms more strongly than does amyloid-PET [30]. In addition, an ongoing pilot project in ADNI will provide us with considerable AV1451 data by the time ADNI3 begins. However, we recognize that multiple laboratories in academia and industry are developing tau PET ligands, some of which may be equal or superior to AV1451 in their properties. In the PET Core, we review the current state of the tau imaging field and outline a plan for review and inclusion of other tau PET ligands in the project.

Other PET ligands: We plan to continue amyloid imaging as part of ADNI3 because of the continued importance of measures of brain Aβ as a biomarker and therapeutic target. In addition, a key goal is to understand how Aβ and tau differ as biomarkers, and how they are related to one another. A distinctive feature of ADNI3 is the incorporation of florbetaben (Neuraceq) [64] as a second amyloid imaging agent. This will allow us to establish the generalizability of ADNI findings to multiple amyloid PET tracers, and to examine comparison across tracers using the centiloid approach. In addition to amyloid imaging, we will continue FDG-PET imaging at the baseline examination on all participants. Measurement of glucose metabolism is of considerable interest in its association with tau PET imaging. We anticipate that changes in glucose metabolism will be more closely related to tau deposition than to Aβ.

Summary of ADNI3 PET activities: The work of the ADNI3 PET core will entail establishment of harmonized protocols for the collection of tau PET data and all amyloid PET ligand data, selection of additional tau PET ligands, quality control of all acquired data, and data analysis. Plans for analysis of amyloid PET data will essentially follow those already deployed in ADNI2, with the addition of conversion of all values to centiloids by the University of Pittsburgh laboratory, and comparison between amyloid tracers. Tau PET data will be examined using region-of-interest based approaches (in Berkeley) that recapitulate Braak staging in order to define tracer uptake by topography. The Banner Alzheimer Institute will examine whole-brain voxelwise approaches to tau PET data and will calculate a cerebral tau index to define extent and magnitude of brain tau deposition. The UCSF group will perform a multimodal analysis including all PET and MRI data. These data will be 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, to examine how the biomarkers relate to one another, and to examine how changes in biomarkers are related to clinical change

MRI Core (PI, Clifford Jack, MD): The overall goal of the MRI Core is to facilitate clinical trials in all clinical stages of Alzheimer's disease (AD). During the previous funding period the MRI Core has been highly influential in shaping industry standards for acquisition and post-processing of brain MRI in AD clinical trials. *The MRI Core developed and characterized standardized acquisition protocols compatible with a variety of hardware/software configurations within each of the three major MRI vendors' product lines* [65]. The protocols became the leading industry standard that was adopted by a wide range of industry and academic entities outside of ADNI for their trials. MRI Core comparisons of competing techniques have shaped study design choices beyond ADNI itself. Example findings include a lack of major advantage of 3T over 1.5T field strength for sMRI acquisition [66, 67] and a lack of data quality downside to accelerated (vs. unaccelerated) structural (sMRI) acquisition [68-70]. Numerous publications have used ADNI MR data to justify newly developed MRI analytic methods, many of which have enhanced the validity, repeatability, or depth of MRI-based biomarker readouts. Methods that measure rates of change in anatomic MRI data [71-85] provided smaller sample size

estimates compared to biofluid and cognitive indices [79, 81, 86-92]. In addition, ADNI contributed MRI data to the large-scale EADC hippocampus tracing harmonization effort, which resulted in the new industry standard for delineating this structure that is a crucial imaging readout in AD [93-95]. A number of studies using ADNI data have found that MRI is as effective as any biomarker (or more so) in predicting short-term future clinical decline [96-100]. These studies contributed to the European Medical Agency's decision to approve the use of hippocampal volume to enrich clinical trial populations in prodromal AD/MCI [101, 102]. ADNI played a key role in characterizing the biological heterogeneity that has reduced power in AD treatment trials. ADNI studies determined that[103] the extent of baseline and change in WMH volume were associated with cognitive decline, and that three separate subtypes within the cognitively normal cohort of ADNI[104-106] were evident, including a cerbro-vascular disease subtype.

Primary objectives of the MRI Core in ADNI 1 and 2 included optimizing and standardizing methods for AD clinical trials. The ADNI 2 acquisition protocol included seven different imaging sequences. Structural MRI, FLAIR and T2*GRE were acquired for all subjects. In addition, diffusion MRI (dMRI), task-free functional MRI (TF-fMRI), perfusion MRI (ASL), and a high resolution coronal T2 fast spin echo (to measure medial temporal lobe (MTL) subregion volumes,) were acquired, but each was limited to a single vendor to optimize uniformity of acquisition. In ADNI 3, we will continue to acquire all seven of these sequences, but with several important changes from ADNI 2. First, to the maximum extent possible all modalities will be acquired in every subject, greatly increasing the sample size for these sequences. The dMRI and TF-fMRI protocols will be implemented with both standard and advanced protocols. The advanced dMRI and TF-fMRI acquisitions will resemble those performed in the Human Connectome Project (HCP) and will be performed only on systems that can support multi-band acquisition. The advanced dMRI and TF-fMRI protocols will be designed so that a (second) series that is equivalent to the basic acquisition can be derived by post hoc data subsampling. ASL in ADNI 3 will be acquired using the 3D pCASL protocol recommended by the ISMRM perfusion work group. All ADNI 3 scans will be acquired at 3T. Our specific aims are:

1) **Data acquisition and QC:** Create and distribute protocols to each site that are applicable for clinical trials. Qualify each scanner and requalify after every upgrade. Quality control every exam.
2) **Quantitative MR measurements applicable for clinical trials:** Develop or employ new/optimized analysis methods for each modality. Create "AD-signature" summary numeric measures, both continuous and binary (positive/negative), for each MR modality and make these measures available to the scientific community for every exam.
3) **Operationalize definitions of subgroups for clinical trials**: In combination with PET, biofluids, and clinical measures, we will operationalize the definitions of subgroups within the ADNI population. Formal definitions of groups like SNAP (suspected non-Alzheimers pathophysiology) and cerebrovascular phenotypes are needed to accommodate the biological heterogeneity within clinical trials populations.
4) **Predict tau:** Test the hypothesis that atrophy on sMRI, hypo perfusion, and altered diffusion will predict the concurrent presence of tau PET ligand uptake.
5) **Optimum inclusion/stratification metrics and covariates for clinical trials:** Clinical/cognitive outcomes are the ultimate source of biomarker validation in living persons. Therefore, we will determine variables that best predict change on functional/psychometric measures and progression from normal to MCI, and MCI to dementia;
    a. Compare basic vs. advanced dMRI and TF-fMRI methods
    b. Comparison among the MRI-based AD biomarker methods (sMRI, dMRI, TF-fMRI, ASL, and MTL subregions)
    c. Compare MRI with non-MRI measures (PET (amyloid, FDG and tau)) and CSF
    d. Test the hypothesis that degree to which sMRI, dMRI, TF-fMRI, ASL, and MTL subregions predict future change is modified by the severity of cerebrovascular disease and CMB
6) **Optimum outcome metrics for clinical trials:** determine variables with the best longitudinal power and that best correlate with change on functional/psychometric measures over time: sample sizes,
    a. Compare basic vs. advanced dMRI and TF-fMRI methods
    b. Comparison among the MRI-based AD biomarker methods (sMRI, dMRI, TF-fMRI, ASL, and MTL subregions)
    c. Compare MRI with non-MRI measures (PET (amyloid, FDG and tau)) and CSF
    d. Test the hypothesis that degree to which sMRI, dMRI, TF-fMRI, ASL, and MTL subregions correlate with change on functional/psychometric measures over time is modified by the severity of cerebrovascular disease and CMB.

Biomarker Core (Co-PI's, Leslie M. Shaw, PhD and John Q. Trojanowski, MD, PhD): The overall goals of the ADNI3 Biomarker Core will be to: continue the ADNI Biofluid Biobank and distribution of samples to investigators approved by the NIA and ADNI Resource Allocation Review Committee (RARC), provide highly standardized $A\beta_{1-42}$, t-tau and p-tau_{181} measurements on aCSF samples, collaborate in the development of new tests for blood biomarkers (eg, ApoE4 protein in plasma; t-tau in plasma; exosomal fraction) and CSF biomarkers that detect co-pathologies such as Lewy Body and TDP43 pathologies.
Major accomplishments since 2010. Biofluid biobank: 9,461 biofluid samples were received processed and 164,120 aliquots prepared, resulting in a total of 19,171 and 295,209 biofluids stored in the ADNI Biofluid Biobank. The 20 RARC-approved requests for ADNI biofluids are summarized in the latest edition of the annual Biofluids reports on the LONI ADNI website [107]. Using either multiplex immunoassays, mrmMass spectrometry or single-plex ELISAs, there is now biomarker data on more than 7,000 biofluid aliquot samples [108-110]. **Standardization progress.** We validated and optimized the performance of methods for measurement and use of CSF-based quality control samples of CSF biomarkers using the flow cytometry-based xMAP technology and bead-based immunoassay reagents (Fujirebio, Ghent, Belgium). We conducted an interlaboratory study that showed good within-laboratory assay precision (5.3% for $A\beta_{1-42}$, 6.7% for t-tau and 10.8% for p-tau_{181}) but reduced interlaboratory precision (17.9%, 13.1% and 14.6%, respectively) [111]. We developed an alternative assay to measure $A\beta_{1-42}$ and in a multiplex version, $A\beta_{1-40}$ and $A\beta_{1-38}$, using two-dimensional ultra-performance liquid chromatography tandem mass spectrometry, showing at least equivalent clinical utility compared to the validated xMAP immunoassay using receiver operator characteristic and correlation curve analyses [112]. The ADNI Biomarker Core actively collaborates under the auspices of the Alzheimer's Association and the International Federation of Clinical Chemistry and Institute for Reference Materials and Methods towards the goal of greatly improved agreement, across the various immunoassay platforms [113, 114]. **Clinical utility of CSF AD biomarkers.** Shaw et al. [115] defined cut-points for CSF $A\beta_{1-42}$, t-tau and p-tau_{181} based on an ADNI-independent cohort of autopsy-confirmed AD patients and age-matched living normal controls successfully applied these cut-points to the ADNI1 cohort and subsequent ADNI subjects. Follow-up studies have successfully used these cut-points [116], confirmed in an ADNI-independent autopsy-based study cohort [117] and others [118]. **Neuropathologic heterogeneity of AD in the ADNI study.** There is a high incidence of co-pathologies in brains of subjects with a clinical diagnosis of probable AD/MCI including Lewy Body pathology (rich in α-synuclein [α -SYN] inclusions) and TDP43 inclusions that accompanied plaque and tangle pathology [119]. This confirms prior results, and emphasizes the importance of developing methods for measurement of new biomarkers such as α-SYN, phosphorylated α-SYN and TDP43 [120]. **Major Impact on AD clinical trials:** Assessment of the NIA-AA criteria in the ADNI cohort supported their utility and suggested improvements to these criteria to improve stratification of patients across the AD spectrum [121], and showing feasibility of using CSF data prospectively in a phase III treatment trial.
AIMS: ***ADNI biofluid biobank at U. Penn.*** Continue biofluid biobanking, including receipt, aliquoting, labeling, storage in secure -80 ^{0}C ADNI freezers with 24/7 tracking of all biofluids collected, and data management for subjects in ADNI1, ADNI-GO, ADNI2 and ADNI3, and continue regular reconciliation of subjects' biofluid information with sites and ADNI Clinical Core. Continue to support biomarker discovery by providing ADNI blinded biofluid samples to investigators with oversight by the NIA and ADNI RARC. ***Automated immunoassay platform for CSF $A\beta_{1-42}$ and tau proteins.*** Following an extensive validation study during current year of ADNI2, we plan to implement the accuracy- and precision-based Roche Elecsys immunoassay platform for fully automated analysis of $A\beta_{1-42}$, t-tau and p-tau_{181} in ADNI3. ***Mass spectrometry-based assay for $A\beta_{1-42}$, $A\beta_{1-40}$ and $A\beta_{1-38}$.*** Implement our newly validated mass spectrometry assay for $A\beta_{1-42}$, $A\beta_{1-40}$ and $A\beta_{1-38}$ in all ADNI CSFs. This candidate reference methodology will be used in collaboration with Dr. Kaj Blennow and others to assign accurate $A\beta_{1-42}$ concentration values to candidate CSF pool-based certified reference material. ***Validation of a mass spectrometry method for t-tau.*** Pending the outcome of ongoing feasibility studies done in collaboration with Waters, we plan to fully validate mass spectrometry-based measurement of t-tau using an advanced Time of Flight MRM mass spectrometry system and, if successful, implement for t-tau measurement in CSF of all ADNI2 and ADNI3 study subjects. ***New biomarkers in CSF or plasma.*** Continue to closely follow the progress being made in validation of measurements of new biomarker tests in plasma (ApoE4 protein; t-tau; as well as biomarkers in the neurally-derived exosomal fraction of plasma) to determine the likelihood of incorporating these new analytes into ADNI3. Neurogranin, α-SYN, PS129-α-SYN, TDP43, measured in CSF, are among biomarkers we believe have shown promise to reflect different aspects of the heterogeneity of AD (eg, neurogranin-***synaptic loss***; α-SYN and PS129-α-SYN-***Lewy Body pathology***; TDP43-TDP43 deposits).

Genetics Core (PI, Dr. A. Saykin): Overall goals: The overarching goals of the core are to provide genomic biosample banking and genotyping, to identify and validate genetic markers to enhance clinical trial design and drug discovery, and to provide an organizational framework to foster collaboration on genomic studies within ADNI. **Accomplishments (2010-2015):** The core banked and analyzed DNA, RNA and lymphoblastoid cell lines, and provided genome-wide data sets, downloaded 1000's of times, enabling ADNI to support several large and important GWAS studies, e.g. [122-124]. Data were also made available through other consortia [107, 125] and the core enabled rapid scientific progress as groups worldwide analyzed these data. Results from genetic studies using ADNI data through 2012 were comprehensively reviewed in [127]. An update through 2014 [128] also included a discussion implications for clinical trial design and therapeutic development as well as systems biology approaches to study key pathways implicated in MCI and AD. Impact is demonstrated by over 300 publications using ADNI genetic data since 2010 [128]. Many of the first applications of quantitative endophenotype association analyses of MRI, PET, CSF and cognitive markers were performed using these data as reviewed in [127-129]. Whole exome and whole genome sequencing (WES, WGS) and gene expression data have were generated and provided to the scientific community [107, 125, 130]. Other contributions include among the first copy number variation (CNV) [131-134], WES/WGS data sets and reports [135-137], and systems biology pathway-based analyses in controls, MCI, and AD [138-143]. The ***Innovation*** and ***Progress Report*** sections of the Genetics Core provide a brief summary of key results through mid-2015 and discussion of future directions to maximally leverage this important and growing data set. **Specific Aims: 1) Continue sample collection, processing, banking, curation and dissemination.** This includes longitudinal DNA and RNA collection, processing, quality control (QC), and banking at the National Cell Repository for AD (NCRAD), as well as dissemination of samples when approved by the *Resource Allocation Review Committee (RARC)*. We will begin banking PBMCs, based on strong interest from academic and pharma investigators, for use in development of induced pluripotent stem cells (iPSCs), functional drug development-related assays and other purposes. **2) Continue to provide genome-wide genotyping data, including *APOE*, to the scientific community.** GWAS with imputation to the 1000G reference set will be run after full enrollment. **3) Continue to perform and facilitate bioinformatics analyses of ADNI genetics and quantitative phenotype data and test scientific hypotheses related to the goals of ADNI-3.** The major hypotheses are: H1: 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; H2: 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; H3: Variation in the *MAPT* gene and other pathways will be associated with [^{18}F]AV-1451 tau PET; and H4: Genetic variation influences proteomics and metabolomics biomarker assays and controlling for genetic effects will improve the performance of *–omics* biomarkers in predicting disease progression and outcomes. **4) Continue to provide organization, collaboration, and support for further development of genomic studies of quantitative biomarker phenotypes and outcomes in ADNI.** The core will collaborate with the other ADNI cores, industry and academic partners and with other national/international consortia to fully leverage ADNI resources. The core will continue to facilitate progress through organized working groups (WGS, RNA Analysis, Epigenomics, Systems Biology, and Functional Genomics) with regular conference calls. Several future directions have been identified that will require additional support before they can be fully realized, but within available resources, work will continue to develop these important areas: A) Work with other parties to find resources for WGS, transcriptome and epigenetic profiling of ADNI's longitudinal DNA and RNA samples; B) Provide a forum to work on issues of return of research results to participants; C) Work with the Clinical Core to develop new call back and family studies of ADNI participants; D) Facilitate replication studies with other cohorts/data sets; E) Collaborate with academic and industry partners on *molecular and functional validation* follow-up studies; and F) Collaborate with the Neuropathology Core to relate differential pathological features to genetic variation.

Neuropathology Core (PI's, J. Morris, MD and N. Cairns, PhD): The overall goal of the Neuropathology Core is to validate the clinical, CSF biomarker and neuroimaging data of participants collected during the period of the grant. This core's infrastructure has been successful in promoting brain donation at participating sites, shipping of tissues to the ADNI Neuropathology Core at Washington University School of Medicine in St. Louis, and undertaking standardized neuropathologic assessments in 50 participants (as of August 1, 2015). The diagnostic accuracy for AD is 48/50 (number of cases with neuropathologic AD/number of cases with DAT = 96%; two cases had argyrophilic grain disease only). A noteworthy finding is that age-related comorbidities (Lewy bodies, hippocampal sclerosis, tau astrogliopathy, argyrophilic grain disease, vascular disease and infarcts) are found in more than half of cases indicating that cognitive impairment may not be due solely to AD.

In collaboration with the Biomarker and MRI Cores, we have undertaken a preliminary multimodal study which revealed that comorbid Lewy bodies impact CSF biomarkers and MRI imaging. These are important observations because they indicate that the presence of comorbidity in a trial will impact CSF biomarker, MRI imaging, and clinical outcome measures. We will expand these studies to include multimodal analyses in a larger cohort and to include the recently available genomic data in collaboration with the Genetics Core.
Aims: Specifically, the Neuropathology Core will: 1) Foster and facilitate a voluntary brain autopsy for each ADNI participant at each site, 2) Provide a uniform neuropathologic assessment of all cases that are autopsied, 3) Maintain a repository of frozen and fixed brain tissue from ADNI participants in order to facilitate ADNI and non-ADNI investigator-led research, 4) Test the hypothesis that comorbidities (Lewy bodies, TDP-43 proteinopathy, vascular disease, hippocampal sclerosis, and tau astrogliopathy) contribute to the variance in clinical, CSF biomarker, and neuroimaging data, and 5) Characterize the relationships between neuropathology and genomic data in multimodal studies of ADNI participants.
Biostatistics Core (PI, Laurel Beckett): During this five-year review period, the Biostatistics Core has led analyses that utilize data across all ADNI Cores, collaborated with other Cores on influential projects in the field of Alzheimer's disease and clinical trials, and assisted outside users with the complexity of ADNI data. Extensions of work done during the 1st phase of ADNI led to identification of a subgroup of ADNI normal controls with atrophy and cognitive decline associated with vascular damage [144] similar work within ADNI MCI, identified subgroups including a couple that were non-AD like: one with characteristics very similar to normal controls and the other with severe atrophy but barely abnormal tau levels [145]. We developed methods for modeling long-term disease dynamics from preclinical to dementia [8] and showed the relative efficiency of time-to-threshold change and rate of change in longitudinal data [5]. In collaboration with the Clinical Core, we developed outcome measures [23] and study design for preclinical AD clinical trials [22]. With the MRI Core, we established best practices for analyzing and reporting results from ADNI MRI data [146]. In 2011, Drs. Beckett and Harvey participated as faculty at the Advanced Psychometrics Workshop in Friday Harbor which focused on ADNI; small groups worked on projects that were later published, including the development of composite memory [147] and executive function [148] scores and modeling the sequence of biomarkers for Alzheimer's disease [149]. We were co-authors on an additional 16 manuscripts with investigators analyzing ADNI data. We also contributed to the qualification of hippocampal volume, using ADNI data as one of the supporting datasets, as a biomarker for the European Medicines Agency[150].Finally, we serve as a major resource for outside users trying to work with ADNI data. In 2013, we held a web-conference that provided an overview of the data, commonly used tables, tips about working with the data, cross-validation, and an overview of the image data archive; slides from this workshop are posted on the ADNI-website [151]. We also developed R, SAS, SPSS, and Stata packages that merge commonly used data tables into a single file of longitudinal data, all of which are available for download on the LONI website. We also created a Google group (https://groups.google.com/d/forum/adni-data) for members to share information, ask questions of other members about the ADNI data; currently, there are 70 members and the group usage is increasing with an average of about 10 postings per month over the last year.
Informatics Core (PI, Arthur Toga, Ph.D.): The primary objective of the ADNI Informatics Core is 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. **MRI and PET data de-identification, storage and dissemination**: Each of the ADNI sites uploads raw MRI and PET scans to the **Informatics Core** (**IC**) repository where they remain quarantined until quality assessments (QA) are received to release scans from quarantine. The upload process incorporates de-identifications customized for specific scanners and file formats. Pre- and post-processed MRI and PET images are also uploaded by the MRI and PET cores and image analysts. Image processing provenance and links between raw and processed scans are automatically captured and maintained. More than 200,000 ADNI raw and processed MRI and PET scans are stored in the repository and made available to authorized investigators. Over 5 million MRI and PET images have been downloaded to date. **Clinical, Biomarker and Analysis Results data integration**: Data entered into the clinical core electronic data capture system are transferred into the IC repository on a daily basis. A subset of the clinical data is extracted and mapped into the IC common database to support queries.
Data use application and data dissemination: The IC repository provides automated systems to manage data use applications, approval/disapproval, renewal and manuscript submission activities. To date, more than 6,000 investigators have applied for access to use ADNI data and have submitted more than 900 manuscripts for review. The IC repository provides several search and data exploration interfaces allowing investigators to browse, search, select and download data. The aims of ADNI will greatly enhance the functionality of these systems and address the needs for improved data access and data exploration, increased flexibility in data

aggregation, more sophisticated download options, and accommodating the big data needs of whole genome data.

Specific Aims:

1) Provide a robust data repository and information infrastructure ensuring reliable, timely and secure data storage and sharing for all existing ADNI data and new data acquired and produced as part of ADNI 3.
2) Harmonize data across ADNI phases and data sources to enable coherent search and visualization.
3) Provide “analysis-ready” searching and downloads.
4) Map data from all ADNI phases into our interactive data visualization platform.
5) Support and provide ADNI data for data aggregation efforts such as GAAIN (the Global Alzheimer’s Association Interactive Network) national data-thons, hack-a-thons, and other organized investigations.
6) Build flexible tools to easily transform and map ADNI data.

Resource Allocation Review Committee (RARC): A goal of ADNI is the collection of biospecimens, including blood, urine, and cerebrospinal fluid (CSF) from participants. An accounting of the biospecimens (stored at UPenn and at NCRAD) available through ADNI is maintained on the ADNI website. Interested investigators, whether associated with ADNI or not, are encouraged to apply for use of ADNI biosamples. Application procedures are described on the ADNI website. Applications are reviewed by the Resource Allocation Review Committee (RARC), composed of scientists directly appointed by NIA staff and who are not funded by ADNI. No ADNI investigator serves on the RARC. The RARC makes recommendations concerning sample distribution which are finally approved/denied by NIA. Use of ADNI samples for technology development or comparisons among different technologies is not recommended for well-established analytes unless there is preliminary data showing clearly superior performance. In order to prevent manipulation of data, ADNI policy is that samples are provided with a code number that blinds to subject codes. Once labs obtain their results, the data is sent to the Clinical Core for unblinding and upload to the ADNI database at USC/LONI/ADNI. Any scientist with access to this public database may then download the results, analyze the data and relate the results to diagnosis and other subject data. Neither ADNI investigators nor the lab that performs the assay has any advance access to the data. All policies, procedures and functions of the RARC are determined by NIA.

Private Partner Scientific Board (PPSB): The PPSB serves as an independent, open, and pre-competitive forum for all private-sector partners in ADNI to collaborate, share information, and offer scientific and private-sector perspectives and expertise on issues relating to the project. The PPSB is convened by the Foundation for the NIH (FNIH). The members of the ADNI Private Partner Scientific Board (PPSB) that help fund ADNI include: AbbVie, Alzheimer's Association, Alzheimer's Drug Discovery Foundation (ADDF), Araclon Biotech, BioClinica, Biogen, Bristol-Myers Squibb (BMS), Canadian Institutes of Health Research, CereSpir, Cogstate, Eisai, Elan Pharmaceuticals, Eli Lilly and Company, EUROIMMUN, F. Hoffman-La Roche Ltd., Fujirebio, GE Healthcare, Genentech, IXICO Ltd., Janssen Alzheimer Immunotherapy, J&J, Lumosity, Lundbeck, Merck, Meso Scale Diagnotics, NeuroRx Research, Neurotrack Technologies, Novartis, Pharmaceuticals, Pfizer, Piramal Imaging, Servier, and Takeda. The PPSB elects a chair each year (current Chair is Dr. Susan DeSanti, Piramal Pharma, Inc.). The PPSB meets monthly by teleconference and has in-person meetings twice/year. The PPSB also has the following work groups: PET End Points, Biofluid Biomarker, and Clinical End Points. More detailed information concerning the activities of the PPSB is provided [152].

Data and Publications Committee (DPC) (PI, R.C. Green, MD, MPH): The DPC performs three primary tasks: (1) to develop and propose policy to the Executive and Steering Committees with regard to data access and publication; (2) to screen all applications for access to ADNI data; and (3) to review all publications for adherence to ADNI publication policy guidelines. The DPC helps develop policies for open data access such that all legitimate requests for data access are granted. Persons requesting access to the data fill out a brief online application form in which they indicate their academic affiliation, reason for requesting access, or statement about the project area in which they are interested. The DPC Chair and DPC Administrator individually review each application. A table of individuals with access to the data and the projects they are pursuing is publicly available so that data users can be aware of the interests of others and reach out to other data users to form collaborations if they wish. Additionally, the DPC Administrator reviews manuscript submissions and requires all scientists who are developing manuscripts using ADNI data to adhere to ADNI publication guidelines. ADNI publication guidelines are as follows: (1) Recognition of organizations providing funding in the support acknowledgment section; (2) Recognition of data collection by ADNI staff in the Methods section; and (3) A standard phrase of acknowledgement of ADNI in the author line. Accordingly, ADNI leadership and ADNI personnel obtain modest academic acknowledgement for the work they have done on behalf of all ADNI publications. Prior to manuscript submission, a member of the DPC reviews each manuscript using ADNI data for overall quality; but, importantly, does not attempt to review manuscripts for scientific

quality or for duplication. Scientific review occurs at the level of publication review to avoid practices that inhibit or slow the utilization of ADNI data by the worldwide scientific community. Since 2004 there are 907 papers published using ADNI data, 852 of these have been published during the current funding period, about 1/3 of the papers are published with ADNI funded investigators as authors and 2/3 from scientists not funded by ADNI. **Other ADNI-Related Projects:** ADNI has inspired several associated projects. First, three separate ADNI-related grants have been funded by the Department of Defense: Effects of Traumatic Brain Injury (TBI) and Post Traumatic Stress Disorder (PTSD) on AD in Vietnam Veterans using ADNI. All three fund establishment of a cohort of 400 Vietnam Veterans over age 65 at 20 ADNI sites. The subjects include cognitively normal and MCI subjects with documented history of TBI or PTSD acquired in Vietnam, and control subjects without TBI/PTSD. The subjects have the full ADNI protocol including longitudinal tau PET scans. Second, the Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing (AIBL) is a study to discover which biomarkers, cognitive characteristics, and health and lifestyle factors determine subsequent development of symptomatic AD. Launched on November 14, 2006, the Australian Imaging Biomarkers and Lifestyle (AIBL) Flagship Study of Ageing, the largest study of its kind in Australia, is 4.5+ year prospective longitudinal study of cognition with a large cohort of over 1000 participants. Third, other ADNI-like projects which participate in World Wide ADNI projects [153] including Japan ADNI [154], European ADNI [155], Korean ADNI [153], and Chinese ADNI [153]. Fourth, the Parkinson's Progressive Biomarkers Initiative (PPMI, PI, Dr. Kenneth Marek) is modeled on ADNI [156]. ADNI is also collaborating with the Dominantly Inherited Alzheimer's Disease Network (DIAN, PI, Dr. Randall Bateman) to compare data obtained on subjects with autosomal dominant familial AD with subjects from ADNI. ADNI data has also been used for the SAGE DREAM Challenge [157] and has been provided to the Genetics Consortium.

PROGRESS REPORT: The major impacts of ADNI have been: 1) Establishment of **standardized methods** for imaging/biomarker collection and analysis which are widely used in clinical trials. ADNI1 utilized a standardized neuropsychological battery, which has been subsequently used by industry and ADCS trials. The MRI Core developed a structural MRI protocol, identical across vendors, with an MRI phantom for calibration. This protocol has been used in numerous phase 2 and 3 treatment trials since. The PET Core established methods for multisite FDG PET and amyloid PET. The biomarker core established standardized methods for measurements of CSF Aβ amyloid and species of tau. The importance of these standardization efforts should not be underemphasized since the ADNI methods have now been adopted for other ADNI-like studies outside of the U.S. and this will facilitate comparisons of results among countries, cultures, and ethnicities, and provide an infrastructure for world-wide clinical trials by the pharmaceutical industry. 2) Provision of a **large data base of images, genetic, fluid biomarker, and clinical data** which is being used by many investigators and industry. Detailed tables of ADNI recruitment, visits and schedule of biomarker collections are provided: http://adni.loni.usc.edu/about/centers-cores/clinical/subject-tables/ 3) Since 2004 there are 907 papers published using ADNI data, 852 of these have been published during the current funding period, about 1/3of the papers are published with ADNI funded investigators as authors and 2/3 from scientists not funded by ADNI. 4) New results concerning the neuroscience of AD; evidence of AD pathology in normal subjects associated with greater rates of change of brain structure and brain glucose metabolism; demonstration of outcome measures with high power to detect treatment effects; evidence that abnormal CSF biomarkers predict future rates of brain atrophy, brain glucose metabolism, and cognition in MCI; evidence that amyloid imaging and CSF Aβ provide similar information. 5) ADNI investigators advanced the design of pre-dementia trials [5-18], facilitating the design of many trials (avagacestat [158], gantanerumab [159], solanezumab [3], A4 [22], A5, aducanumab [26]. 6) An important long term goal of our field is to identify and validate imaging/biomarkers for AD progression which can be used as "surrogate markers" in place of clinical/cognitive tests in clinical trials. A pilot longitudinal ADNI tau PET study is now underway.

This competitive renewal proposes multisite longitudinal tau PET, which may provide a biomarker to measure AD progression and could become a surrogate marker for clinical trials. Taking all of the above together, we conclude that the previously stated goals of ADNI have been accomplished and surpassed, evidenced by the large number of publications resulting from this project (Progress Report) of 852 publications since our last competitive renewal, 286 of these (one third) were from ADNI-funded investigators (Publication List). Additional impacts are the other ADNI projects around the world. ADNI is the only multisite study that obtains comprehensive longitudinal clinical, imaging, and biomarker information across the continuum from normal aging to dementia, and it is expected that a continuation of this project through the successful competitive renewal of ADNI will substantially contribute to development of effective treatments and preventative approaches to AD.

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OMB Number: 4040-0001
Expiration Date: 06/30/2016

APPLICATION FOR FEDERAL ASSISTANCE

SF 424 (R&R)

5. APPLICANT INFORMATION **Organizational DUNS*:** 6133387890000

Legal Name*: NORTHERN CALIFORNIA INSTITUTE FOR RESEARCH AND EDUCATION
Department:
Division:
Street1*: 4150 CLEMENT STREET (151-NC)
Street2:
City*: SAN FRANCISCO
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 941211545

Person to be contacted on matters involving this application

Prefix:	First Name*:	Middle Name:	Last Name*:	Suffix:
	Azarah	Sr. Grant Specialist	Wong	

Position/Title:
Street1*: 4150 CLEMENT STREET (151-NC)
Street2:
City*: SAN FRANCISCO
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 941211545
Phone Number*: 415-750-6954 x 23891 Fax Number: 415-750-9358 Email: cgawards@ncire.org

7. TYPE OF APPLICANT* M: Nonprofit with 501C3 IRS Status (Other than Institution of Higher Education)

Other (Specify):
Small Business Organization Type ❍ Women Owned ❍ Socially and Economically Disadvantaged

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
Administrative Core

12. PROPOSED PROJECT

Start Date*	Ending Date*
08/01/2016	07/31/2021

Tracking Number:

OMB Number: 4040-0010
Expiration Date: 06/30/2016

Project/Performance Site Location(s)

Project/Performance Site Primary Location

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:	NORTHERN CALIFORNIA INSTITUTE FOR RESEARCH AND EDUCATION
Duns Number:	6133387890000
Street1*:	4150 CLEMENT STREET (151-NC)
Street2:	
City*:	SAN FRANCISCO
County:	
State*:	CA: California
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	941211545
Project/Performance Site Congressional District*:	CA-012

Project/Performance Site Location 1

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:	Brigham and Women's Hospital
DUNS Number:	0308112690000
Street1*:	75 Francis Street
Street2:	
City*:	Boston
County:	Suffolk
State*:	MA: Massachusetts
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	02115-6110
Project/Performance Site Congressional District*:	MA-007

File Name

Additional Location(s)

Administrative Core: Project Summary/Abstract

The overall goal of the ADNI Administrative Core is to provide overall leadership, continue the long term strategic plan, facilitate financial support, and to monitor scientific, administrative, regulatory, and financial activities. This consists of the PI, collaborating scientists, and administrative staff who manage financial and regulatory issues, organize teleconferences and meetings of ADNI committees, and prepare manuscripts. This core operates both the Brain Health Registry (BHR) for on-line recruitment, assessment, and longitudinal monitoring of ADNI subjects and the Data and Publications Committee (DPC) which reviews applications for data access and reviews all publications for adherence to ADNI publication policy guidelines**.** The Administrative Core is responsible for the scientific, administrative and financial coordination of the entire project including annual progress reports, non-competitive and competitive renewals, and NIA supplements. Additional responsibilities include soliciting funding from industry and foundations; contacting NIA officials concerning all issues; interacting with NIH, FNIH, PPSB, SAB, and ADNI projects in other countries; interacting with and facilitating other ADNI-like projects around the world in order to build a world-wide network of AD sites (World-Wide ADNI sponsored by Alzheimer's Association); participating in conference calls with the ADNI Excom (bi-weekly), ADNI Clinical Core (bi-weekly), all other ADNI Cores (monthly) and PPSB (as needed); organizing meetings with the Scientific Advisory Board (SAB); organizing the annual "ADNI weekend" which consists of meetings of the Steering Committee, Department of Defense ADNI, PPSB, Scientific Advisory Board, Excom, and other meeting; collaborating with ADNI related projects; planning, execution, and preparation for publication of ADNI data analyses; organizing and preparing review articles and special journal issues; presenting at invited talks about ADNI. The Administrative core is also responsible for all budgets and subcontracts including administering subcontracts, reconciling budgets, tracking expenses and carryovers, maintaining an updated financial accounting and projections which must closely match reconciliation data with financial status reports (FSR). The core also tracks of all scientific activity of ADNI including publications, abstracts, and posters and tracks the activities of the Resource Allocation Research Committee (RARC). In regards to the Brain Health Registry, the Administrative Core designs and executes queries in the BHR in order to contact eligible participants for ADNI enrollment and will also be responsible for the collection, and transfer of the BHR longitudinal questionnaire and cognitive test data to the Clinical Core. Therefore, the Administrative Core plays a central and vital role in the success and impact of ADNI.

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: First Name*: MICHAEL Middle Name W Last Name*: WEINER Suffix:

Position/Title*: Professor in Residence
Organization Name*: Northern California Institute for Research and Education
Department: Radiology
Division:
Street1*: 4150 Clement St (114M)
Street2:
City*: San Francisco
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 941210000

Phone Number*: 415-221-4810 x3642 Fax Number: 415-668-2864 E-Mail*: michael.weiner@ucsf.edu

Credential, e.g., agency login: MICHAELW

Project Role*: Other (Specify) Other Project Role Category: Project Lead

Degree Type: Degree Year:

File Name

Attach Biographical Sketch*:

Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: Robert Middle Name C. Last Name*: Green Suffix:

Position/Title*: Associate Professor of Medicine
Organization Name*: BRIGHAM AND WOMEN'S HOS
Department: Medicine
Division: Genetics
Street1*: 41 Avenue Louis Pasteur
Street2: Suite 301
City*: BOSTON
County: Sulfolk
State*: MA: Massachusetts
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 021150000

Phone Number*: (617) 264-5838 Fax Number: (617) 264-8795 E-Mail*: rcgreen@genetics.med.harvard.edu

Credential, e.g., agency login: rcgreen

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: MD,MPH Degree Year:

File Name
Attach Biographical Sketch*: Green_NewNIH_Biosketch_9-21-15.pdf
Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: NORBERT Middle Name Last Name*: SCHUFF Suffix:

Position/Title*: Professor
Organization Name*: Northern California Institute for Research and Education
Department: DEPARTMENT OF RADIOLOGY
Division:
Street1*: 4150 Clement St (114M)
Street2:
City*: SAN FRANCISCO
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 941210000

Phone Number*: (415) 221-4810 Fax Number: (415) 668-2864 E-Mail*: norbert.schuff@ucsf.edu

Credential, e.g., agency login: nschuff

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: DSC Degree Year:

File Name
Attach Biographical Sketch*: Schuff_Biosketch.pdf
Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: Duygu Middle Name Last Name*: Tosun-Turgut Suffix:

Position/Title*: Assistant Adjunct Professor
Organization Name*: Northern California Institute for Research and Education
Department: Radiology
Division:
Street1*: 4150 Clement St. VAMC, Bldg 13
Street2:
City*: San Francisco
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 941210000

Phone Number*: 4152214810 ext 4800 Fax Number: E-Mail*: duygu.tosun@ucsf.edu

Credential, e.g., agency login: dtosun

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: Degree Year:

File Name
Attach Biographical Sketch*: Tosun_Biosketch_9.28.15.pdf
Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: Susanne Middle Name G. Last Name*: Mueller Suffix:

Position/Title*: Assistant Adjunct Professor
Organization Name*: Northern California Institute for Research and Education
Department:
Division:
Street1*: 4150 Clement St (114M)
Street2: VAMCSF
City*: San Francisco
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 941210000

Phone Number*: 415 221 4810 ext 2538 Fax Number: E-Mail*: susanne.mueller@ucsf.edu

Credential, e.g., agency login: susmue

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: MD Degree Year:

File Name
Attach Biographical Sketch*: cv_ADNI3_Mueller.pdf
Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: Ashish Middle Name Last Name*: Raj Suffix:

Position/Title*: Associate Professor
Organization Name*: WEILL MEDICAL COLLEGE OF CORNELL UNIVERSITY
Department:
Division:
Street1*: 1300 YORK AVENUE
Street2:
City*: NEW YORK
County:
State*: NY: New York
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 100650000

Phone Number*: 212 746 1280 Fax Number: E-Mail*: asr2004@med.cornell.edu

Credential, e.g., agency login: ashish

Project Role*: Consultant Other Project Role Category:

Degree Type: PHD Degree Year:

File Name
Attach Biographical Sketch*: Raj_Biosketch_ADNI3.pdf
Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: Keith Middle Name A. Last Name*: Johnson Suffix:

Position/Title*: Associate Radiologist, Neurolo
Organization Name*: Harvard Medical School
Department:
Division:
Street1*: 55 Fruit Street
Street2:
City*: Boston
County:
State*: MA: Massachusetts
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 021140000

Phone Number*: 617-724-7066 Fax Number: 617-726-6165 E-Mail*: kajohnson@pet.mgh.harvard.edu

Credential, e.g., agency login: keijohnson

Project Role*: Consultant Other Project Role Category:

Degree Type: MD,BA Degree Year:

File Name
Attach Biographical Sketch*: KJohnson_Bio_09_17_2015.pdf
Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: Niklas Middle Name Last Name*: Mattsson Suffix:

Position/Title*: Consultant and Senior Researcher
Organization Name*: Lund University
Department: Clinical Memory Research Unit
Division:
Street1*: Simrisbanvägen 14
Street2:
City*: Malmö
County:
State*:
Province:
Country*: SWE: SWEDEN
Zip / Postal Code*: 212240000

Phone Number*: +46 72 575 9329 Fax Number: E-Mail*: Niklas.mattsson@med.lu.se

Credential, e.g., agency login:

Project Role*: Consultant Other Project Role Category:

Degree Type: Degree Year:

File Name
Attach Biographical Sketch*: Biosketch_NM.pdf
Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: NORMAN Middle Name L Last Name*: FOSTER Suffix:

Position/Title*: Professor and Director
Organization Name*: University of Utah
Department: Neurology
Division:
Street1*: 650 Komas Drive, #106A
Street2:
City*: Salt Lake City
County:
State*: UT: Utah
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 841080000

Phone Number*: 801-587-7236 Fax Number: E-Mail*: norman.foster@hsc.utah.edu

Credential, e.g., agency login: nlfoster

Project Role*: Consultant Other Project Role Category:

Degree Type: MD Degree Year:

File Name
Attach Biographical Sketch*: ADNI3_Foster_biosketch.pdf
Attach Current & Pending Support:

Administrative Core: Specific Aims

The overall goal of the ADNI Administrative Core is to ensure the success and impact of the project. This goal will be achieved by providing overall leadership, continuing to develop the long term strategic plan, ensuring and facilitating financial support from both NIH and private partners (industry and foundations), and by carefully monitoring all aspects of the project including administrative, regulatory, financial, scientific, and day-to-day operations of all clinical sites and cores.

ADNI receives funding from two sources in the NIA: internal funds from NIA and external funds from private partners which are passed through FNIH to NIA. These funds are awarded to the prime recipient, Northern California Institute for Research and Education (NCIRE) at the San Francisco VA Medical Center, affiliated with UCSF, with Dr. Weiner as the PI. A substantial portion of the funding is subcontracted to the Clinical Core (PI, Dr. P. Aisen) at USC, who subcontracts to all the clinical sites. Furthermore, NCIRE directly subcontracts to all the other cores and analysis sites. Strategic decisions about ADNI are made by the Steering Committee (all Clinic Site PIs, all Core PIs, NIA staff). Operational decisions are made by the Executive Committee (Excom, all Core leaders, industry/foundation representatives, NIA staff).

The Administrative Core consists of: (1) PI's administrative staff, who manage financial and regulatory issues, organize teleconferences and meetings of ADNI committees, and prepare manuscripts; (2) scientists who analyze ADNI data resulting in 50 publications, including imaging, biomarker, genetics, and clinical/neuropsychological data (these individuals are also listed in their respective Cores (e.g. MRI, PET) but for administrative simplicity are funded on the Administrative Core budget); (3) online recruitment and assessment staff, who manage participant recruitment, data collection and organization using the Brain Health Registry (BHR). **Specific Aims**:

1) Scientific, administrative and financial coordination of the entire project including annual progress reports, non-competitive and competitive renewals, and NIA supplements.
2) Soliciting funding from industry and foundations.
3) Responsibility for all budgets and subcontracts: administering all subcontracts, reconciling budgets, tracking expenses and carryovers, maintaining an updated financial accounting and projections which must closely match reconciliation data with financial status reports (FSR).
4) Responsibility for interactions with NIH, FNIH, PPSB, SAB, and ADNI projects in other countries.
5) Contact with NIA officials concerning all issues.
6) Conference calls with the ADNI Excom (bi-weekly), ADNI Clinical Core (bi-weekly), all other ADNI Cores (monthly) and PPSB (as needed).
7) Organizing meetings with the Scientific Advisory Board (SAB).
8) Organizing the annual “ADNI weekend” which consists of meetings of the Steering Committee, Department of Defense ADNI, PPSB, Scientific Advisory Board, Excom, and other meetings.
9) Tracking of all scientific activity of ADNI including publications, abstracts, and posters.
10) Tracking activities of the Resource Allocation Research Committee (RARC).
11) Designing and executing queries in the BHR in order to contact eligible participants for ADNI enrollment.
12) Collection, management, storage, and transfer of BHR longitudinal questionnaire and cognitive test data for ADNI participants within the BHR.
13) Planning, execution, and preparation for publication of ADNI data analyses.
14) Interacting with all companies involved with or with interest in ADNI (e.g. amyloid imaging, tau imaging, and blood/CSF biomarker companies, MRI manufacturers, Alzheimer’s Association).
15) Interacting with and facilitating other ADNI-like projects around the world in order to build a world-wide network of AD sites: World-Wide ADNI sponsored by Alzheimer’s Association.
16) Collaborating with ADNI related projects (Department of Defense ADNI), DIAN, Sage Challenge, and PPMI. Presenting invited talks about ADNI
17) Organizing and preparing review articles about ADNI [2], reviews of all ADNI papers [4, 5, 44], special issues of journals about ADNI [6-8].

The Data and Publications Committee (DPC) (PI, Dr. R.C. Green) is also a part of the Administrative Core. The DPC has three primary mandates: (1) to develop and propose policy to the Executive and Steering Committees with regard to data access and publication; (2) to screen all applications for access to ADNI data; and (3) to review all publications for adherence to ADNI publication policy guidelines. Since 2004 there are 907 papers published using ADNI data, 852 of these have been published during the current funding period, about 1/3 of the papers are published with ADNI funded investigators as authors and 2/3 from scientists not funded by ADNI. In summary, the ADNI Administrative Core plays a central role in the success and impact of ADNI, leading to the development of treatments which slow the progression of AD.

Administrative Core: Research Strategy

SIGNIFICANCE

Overall Significance of the Administrative Core: From the very outset of ADNI, the PI and the Administrative Core have provided leadership and coordination, with the overall goal of maximizing the impact of ADNI on the use of biomarkers for AD treatment trials. Elsewhere in this grant, we review the overall significance of AD, including its prevalence and costs to society, and failures to demonstrate the effects of treatments that slow the progression of AD. The Administrative Core focuses on the "big picture" to advance the use of various biomarkers for diagnosis and inclusion/exclusion criteria in clinical trials as predictors of cognitive decline and dementia, and to measure rates of change which can be used as outcome measures in clinical treatment trials. The ADNI leadership believes that the overall impact of ADNI on clinical trials, diagnostic methods, and in providing a greater understanding of the pathophysiology of AD has been huge. The use of CSF biomarkers and amyloid PET for amyloid phenotyping, and the recent introduction of tau PET at the end of ADNI2 are a few of the most obvious examples of this impact. The Administrative Core is led by the PI of ADNI, Dr. Michael Weiner. NIA awards the prime ADNI grant to the Northern California Institute for Research and Education (NCIRE), which is the VA non-profit foundation of the San Francisco VA Medical Center, and the University of California, San Francisco (UCSF) where Dr. Weiner is located.

History of ADNI: Since the original description by Alzheimer, AD has been defined by clinical criteria (memory loss and progressive cognitive decline leading to dementia) and pathological criteria at autopsy (amyloid plaques and tau tangles). Over the past 25 years, various biomarkers, including PET, MRI, and CSF measurements, were used in research studies to investigate AD. In the late 1990's, the availability of transgenic mice which overexpressed brain amyloid and the first demonstrations of immunotherapy in animals led to development of treatments (immunotherapy, secretase inhibitors etc.) aimed at slowing the progression of AD. This led those in the AD field to recognize the importance of using biomarkers for both diagnosis and to monitor change and the effects of treatment. In 2001, the PI proposed a multisite study which would be supported by NIA, the pharmaceutical industry, and non-profit foundations, with the overall goal of validating biomarkers for AD. Industry supported this concept and the NIA convened workgroups leading to a Request for Proposal in 2003. The PI organized a team of Core leaders who, together, were awarded the ADNI grant in 2004 (called ADNI1, total funds: $60 million). From the outset, an important feature of ADNI was consensus leadership and the sharing of all materials, including protocols, biological samples, and all raw and processed data without embargo (on ADNI-info.org and USC/LONI/ADNI). Subsequent support from GE and the Alzheimer's Association funded a small "add on" study of C-11 PIB PET at 12 ADNI sites. In 2009, ADNI competed for and was awarded a $24 million "Grand Opportunities" grant (called ADNI-GO) from the NIA using funds from the American Recovery and Reinvestment Act (ARRA). In 2010, ADNI was awarded a competitive renewal of ADNI1 (called ADNI2) funded by the NIA for $60 million. Both ADNI-GO and ADNI2 performed "amyloid phenotyping" on a large multisite scale, at baseline and longitudinally, using amyloid PET imaging (with florbetapir) together with CSF measurements and many other clinical/cognitive and imaging/genetics measurements. ADNI2 ends on July 31, 2016, and the current application requests $75 million for an additional 5 years of funding to follow currently enrolled subjects and to enroll new subjects, continuing previous measurements, with the addition of longitudinal tau PET.

It should be mentioned that during ADNI2 (2010-2016) there have been two major administrative changes. First, in 2013, Dr. Arthur Toga moved the Informatics Core of ADNI from UCLA to USC. Despite some legal issues between UCLA and USC, the Informatics Core function of Dr. Toga's lab was not adversely affected and the flow and release of ADNI data was not interrupted. Second, recently in 2015, Dr. Paul Aisen moved the ADNI Clinical Core from UCSD to USC. This has resulted in legal and administrative difficulties, which have been widely reported in the press. The Clinical Core subcontract from NCIRE was transferred from UCSD to Dr. Aisen's Alzheimer's Disease Treatment Research Institute (ATRI) in early August 2015 and all Clinical Core functions of ADNI have been successfully performed in an uninterrupted fashion during this transition period. For both the moves of the Informatics Core and the Clinical Core, patient safety, the rate of data collection, and the scientific integrity of ADNI have not been adversely affected. In fact, the transfers of the Informatics and Clinical Cores have both resulted in ADNI having substantially greater resources (due to greater availability of funds recovered by indirect costs, and new infrastructure provided as part of the recruitment) and much greater flexibility to use their resources (due to the moves to a private university from a public university). Therefore, the ADNI project has been strengthened by these events.

ADNI is a Public/Private Partnership: The importance of the public/private partnership aspects of ADNI cannot be over-emphasized! From the very onset of this project, our goal has been to validate biomarkers for clinical trials, and the majority of AD clinical trials worldwide are performed by the pharmaceutical industry. Our

goal has been to enable and facilitate AD clinical trials by optimizing, standardizing, and validating the most promising biomarkers, which can be used in the AD clinical trial setting, and ultimately in the routine clinical setting when effective treatments, which slow the progression of AD, finally become available. The extent of communication, interaction, and sharing of data and opinions are extensive among: (1) the various industry representatives (who serve on the Private Partners Scientific Board; PPSB), (2) AD foundation representatives (who also serve on the PPSB), (3) the ADNI PI and Clinical Core leaders, and (4) NIA staff. Such communication occurs on the Executive Committee (Excom) call, the PPSB call, all the Core calls, the various in-person meetings (described below), and through voluminous emails and personal communications. It is difficult to adequately describe the multiplicity of opinions and agendas at play. The magnitude and complexity of these interactions has greatly increased in recent years for several reasons: First, promising results from several recent trials, especially aducanumab [1], have increased enthusiasm and hope that successful treatments, which slow the progression AD, can be developed and demonstrated to work in a practical clinical trial environment. Second, the development of several types of amyloid imaging ligands, several types of tau imaging ligands (all discussed in PET Core), and several assay platforms for measuring peptides/proteins and analytes in biofluids (all discussed in Biomarker Core) have led to increased competition between ADNI corporate sponsors and others. Despite the presence of tensions, which arise from these competitive concerns, the overwhelming consensus is that a successful ADNI benefits all. This has led to considerable discussions, which ultimately resulted in the study design presented in this application. A major function of the PI and the Administrative Core has been to track and oversee all this activity, leading to developments of consensus and a shared plan of action.

Significance of Data and Sample Sharing: From the outset, a bedrock principle of ADNI was sharing of data and samples. This did not grow out of pure altruism. The fact that ADNI was partially funded by the pharmaceutical industry necessitated that our industry partners were able to rapidly access ADNI data, so that they could use it for making decisions about clinical trials, and specifically for clinical trial design. Industry had no interest in providing millions of dollars for a project, which would provide data years later! Furthermore, it made no sense to provide data to industry while withholding it from the academic community. The same rationale applied to the various types of biofluid (serum, plasma, CSF, urine) and other materials (DNA, RNA, cell lines, neuropathological specimens from autopsy) obtained from ADNI subjects. All this led to our “ADNI model” of sharing data and samples without any embargo following QC procedures. Despite concerns by some that widespread data sharing would lead to many erroneous reports, duplication of results, and problems of scientific integrity, we believe that our approach has been extremely successful and has produced little controversy. In fact, ADNI is often cited as an example of the type of data sharing that most large federally or privately funded projects should be doing.

INNOVATION

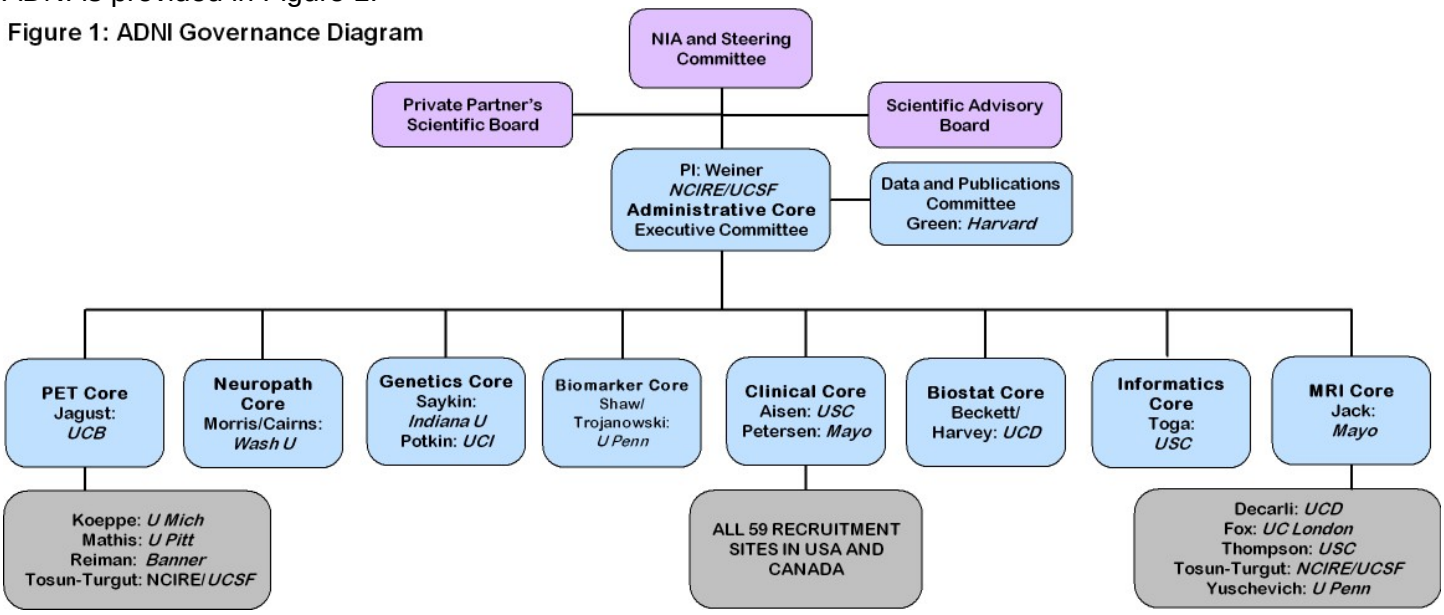
The innovative aspects of the Administrative Core are shared leadership including a genuine public/private partnership, sharing of samples, and sharing of data. We believe that our shared leadership model is innovative when contrasted with the usual “top down” leadership of most NIH-funded projects. This approach evolved from the public/private nature of the project (as described above). The academic core leaders necessarily collaborate with their industry counterparts, because the overall goal of the project is to validate biomarkers for clinical trials, and not to generate publications for the academic leadership. Furthermore, the various core leaders were all internationally recognized leaders in their field at the inception of ADNI. Therefore, the overall leadership style of the PI has been to repeatedly ask each core leader and industry partner to identify developments in the field, to propose specific plans of action, and to work with the Executive Committee to come to consensus on the best plans of action. This approach has been used on a day-to-day level to deal with problems that arise, and to plan this ADNI3 competitive renewal. Another innovation of the Administrative Core of ADNI has been widespread sharing of data without embargo (by use of Dr. Toga’s LONI site on which all data is provided), and sample sharing using the Resource Allocation Review Committee (RARC - described below). Finally, the Brain Health Registry (BHR, described further below), a website for recruitment, assessment, and longitudinal monitoring of ADNI subjects, represents an innovative approach to traditional recruitment methods (including recruitment of minorities) and longitudinal monitoring.

APPROACH

Overall Description of Organization and Governance: ADNI was initially a UO1 grant, but is now designated a U19 grant. NIA requires that this project be governed by a Steering Committee which consists of: the PI and all funded core leaders, all site PIs, representatives from NIH, FDA, and each of the contributing companies. Representatives from ADNI projects in foreign countries and from other similar multisite projects (e.g. Progressive Parkinson’s Biomarkers Initiative; PPMI) also attend. More than 150 people attended the

Steering Committee meeting in the spring of 2015.The ADNI project closely follows the study design and methodology laid out in the grant proposal but changes in scope are permitted. The organizational structure of ADNI is provided in Figure 1.

Figure 1: ADNI Governance Diagram



All final decisions concerning ADNI are made by a consensus of the Executive Committee, with approval from NIA. Strategic decisions (determined by NIA) require a vote of the entire Steering Committee. In the event that Dr. Weiner is unable to perform his duties as PI, Dr. William Jagust at U.C. Berkeley (currently PI of the PET Core) will become the PI of ADNI and will be given an appointment at NCIRE, the prime recipient of ADNI funds. Operational decisions are made by the ADNI Executive Committee (Excom) which comprises the PI, the core leaders, representatives of the NIA (Drs. Hsiao and Ryan), the current, past, and future Chairs of the Private Partner Scientific Board (PPSB), and Foundation for NIH (FNIH) representatives. The ADNI Excom holds two teleconferences/month and has in-person meetings at the annual meeting of the Steering Committee and at the International Conference on AD (ICAD). In addition, the Clinical Core has an ADNI conference call twice a month, and the MRI, PET, Genetics, and Biostatistics Cores have conference calls monthly. All requests for specimens (blood, plasma, CSF, DNA, immortalized cell lines) go directly to the RARC (designated by the NIA) chaired by Dr. Tom Montine, which is completely independent of all ADNI investigators. Following approval by the RARC, the NIA determines release of all specimens (described in more detail below). Following the initial award of funds by the NIA, any additional funds provided by industry to the FNIH are provided to ADNI by administrative supplements, which are approved by the NIA Council. All sites are managed by the ADNI Clinical Core at the Alzheimer's Treatment Research Institute, University of Southern California, located in San Diego (Paul Aisen, PI). The Publications Committee vets all publications using ADNI data (see description below). The PPSB is composed of all companies and private foundations that provide funds to ADNI (the funding structure is managed by the FNIH and is scaled according to the total value of the contributing company). The PPSB is chaired on a rotating basis (12 separate chairs since the outset of ADNI), and the current chair is Dr. Susan DeSanti (Piramal Pharma, Inc.).

Administrative Core: The Administrative Core, located at the VA Medical Center/University of California San Francisco/Northern California Institute for Research and Education (the nonprofit foundation to which all ADNI funds are awarded), consists of the Principal Investigator of ADNI (M.W. Weiner), his administrative staff, Brain Health Registry (BHR) staff, scientific collaborators, and the Data and Publications Committee administered by Dr. Robert Green, at Harvard University. Dr. Weiner has responsibility for overall leadership including all administrative, financial, and scientific aspects of ADNI. Specifically, this core is responsible for all activities of ADNI, including strategic direction.

The following lists specific functions:

1) Scientific, administrative and financial coordination of the entire project including annual progress reports, non-competitive and competitive renewals, and NIA supplements.
2) Soliciting funding from industry and foundations.
3) Responsibility for all budgets and subcontracts: administering all subcontracts, reconciling budgets, tracking expenses and carryovers, maintaining an updated financial accounting and projections which must closely match reconciliation data with financial status reports (FSR).
4) Responsibility for interactions with NIH, FNIH, PPSB, SAB, and ADNI projects in other countries.

5) Contact with NIA officials concerning all issues.
6) Conference calls with the ADNI Excom (bi-weekly), ADNI Clinical Core (bi-weekly), all other ADNI Cores (monthly) and PPSB (as needed).
7) Organizing meetings with the Scientific Advisory Board (SAB): Members include Drs. Zaven Khachaturian, Maria Carillo (Alzheimer's Association), Peter Snyder (University of Connecticut), Howard Fillit (Alzheimer's Drug Discovery Foundation), Gregory Sorenson (Harvard, MGH), Lewis Kuller (University of Pittsburgh), William Potter (NIMH), Franz Hefti (NeuroPhage), Greg Sorenson (Siemens), and David Holtzman (Washington University).
8) Organizing the annual "ADNI weekend" which consists of meetings of the Steering Committee, Department of Defense ADNI, PPSB, Scientific Advisory Board, Excom, and other meetings.
9) Tracking of all scientific activity of ADNI including publications, abstracts, and posters.
10) Tracking activities of the Resource Allocation Research Committee (RARC).
11) Designing and executing queries in the BHR in order to contact eligible participants for ADNI enrollment.
12) Collection, management, storage, and transfer of BHR longitudinal questionnaire and cognitive test data for ADNI participants within the BHR.
13) Planning, execution, and preparation for publication of ADNI data analyses.
14) Interacting with all companies involved with or with interest in ADNI (e.g. amyloid imaging, tau imaging, and blood/CSF biomarker companies, MRI manufacturers, Alzheimer's Association).
15) Interacting with other ADNI projects around the world and development of new ADNI projects in other countries like DIAN, Sage Challenge and PPMI in order to build a world-wide network of AD sites.
16) Collaborating with ADNI related projects (Department of Defense ADNI (3 funded projects), World-wide ADNI (WW-ADNI: sponsored by Alzheimer's Association), and PPMI).
17) Presenting invited talks about ADNI.
18) Organizing and preparing review articles about ADNI [2], reviews of all ADNI papers [3-5], special issues of journals about ADNI [6-8].

Dr. Weiner supervises Diana Truran-Sacrey and Juliet Fockler who are the grants administrators for ADNI. The financial tracking is highly complex and involves the awarding of many different subcontracts to the various core leaders and analysis sites, tracking work performed and unspent funds, etc. Scientists working in Dr. Weiner's group who are analyzing ADNI clinical, biofluid, and multimodality imaging data (described in other cores) are funded through the Administrative Core to reduce indirect costs. These scientists include Dr. Duygu Tosun (PET and MRI), Dr. Rachel Nosheny (BHR), Dr. Susanne Mueller (MRI), Philip Insel (statistics) and Dr. Niklas Mattsson (analysis/publications), and published 50 manuscripts in this funding period (Administrative Core: Progress Report Publication List).

Resource Allocation Review Committee (RARC): The RARC is a completely independent committee, appointed by the NIA (which determines its policies, rules, and functions), which receives no ADNI funds and is completely separate from ADNI. The current Chair is Dr. Tom Montine (University of Washington) and other committee members are Anne Fagan (Washington University), Kaj Blennow (University of Gothenburg), David Hawver (FDA), and Johan Luthman (Eisai - industry representative). The RARC is now being expanded by NIA to include experts in both genetics and systems biology. Members periodically rotate.

RARC oversees applications to use ADNI's collection of participant biospecimens, including blood, urine, cerebrospinal fluid (CSF), and neuropathology (from autopsy of ADNI subjects) samples. An accounting of the biospecimens available through ADNI is maintained on the ADNI website. Several analyses of general interest (homocysteine, species of isoprostanes, tau and Aβ) have been performed by the ADNI Biomarker Core, with completed results immediately made available on the ADNI website. Interested investigators, whether associated with ADNI or not, are encouraged to apply for use of these ADNI biosamples. However, use of ADNI samples for technology development or for comparisons of different technologies is not recommended unless there is preliminary data showing clearly superior performance. The ADNI-info.org website provides an application for ADNI samples. All applications are reviewed by the RARC and their recommendations are reviewed by the NIA which makes final decisions. ADNI sends all samples to applicants using a unique code number that is blinded to subject codes. Once labs obtain their results, the data is sent to the Clinical Core for unblinding and upload to the ADNI database at USC/LONI/ADNI. The lab performing the assay, and all scientists with access to this public database, may then download the results, analyze the data and relate the results to diagnosis and other subject data. Neither ADNI investigators nor the lab performing the assay has any advance, or unique, access to the data. Detailed tables of sample requests to the RARC can be found in the Administrative Core: Resource Sharing plan of this application.

Private Partner Scientific Board (PPSB): The PPSB serves as an independent, open, and pre-competitive

forum for all private-sector partners in ADNI to collaborate and share information, and to offer scientific and private-sector perspectives and expertise on issues relating to the project. The PPSB is convened by the FNIH. The corporate and foundation members of the ADNI Private Partner Scientific Board (PPSB) that help fund ADNI include: AbbVie, Alzheimer's Association, Alzheimer's Drug Discovery Foundation (ADDF), Araclon Biotech, BioClinica, Biogen, Bristol-Myers Squibb (BMS), Canadian Institutes of Health Research, CereSpir, Cogstate, Eisai, Elan Pharmaceuticals, Eli Lilly and Company, EUROIMMUN, F. Hoffman-La Roche Ltd., Fujirebio, GE Healthcare, Genentech, IXICO Ltd., Janssen Alzheimer Immunotherapy, J&J, Lumosity, Lundbeck, Merck, Meso Scale Diagnotics, NeuroRx Research, Neurotrack Technologies, Novartis, Pharmaceuticals, Pfizer, Piramal Imaging, Servier, and Takeda. The PPSB elects a chair each year (currently Susan DeSanti, Piramal Pharma, Inc.), who joins the ADNI Excom. The PPSB meets monthly by teleconference and has in-person meetings twice/year. The PPSB also has the following work groups: PET End Points, Biofluid Biomarker, and Clinical End Points. More detailed information concerning the activities of the PPSB is provided in the following publication [9].

Data and Publications Committee (DPC) (PI, Dr. R.C. Green): The DPC has three primary mandates: (1) to develop and propose policy to the Executive and Steering Committees with regard to data access and publication; (2) to screen all applications for access to ADNI data; and (3) to review all publications for adherence to ADNI publication policy guidelines. The DPC helps develop policies for open data access such that all legitimate requests for data access are granted. Persons requesting access to the data fill out a brief online application form in which they indicate their academic affiliation, reason for requesting access, or statement about the project area in which they are interested. The DPC Chair and DPC Administrator individually review each application. A table of individuals with access to the data and the projects they are pursuing is publically available so that data users can be aware of the interests of others and reach out to other data users to form collaborations if they wish. Additionally, the DPC Administrator reviews manuscript submissions and requires all scientists who are developing manuscripts using ADNI data to adhere to ADNI publication guidelines. ADNI publication guidelines are as follows: (1) recognition of organizations providing funding in the support acknowledgment section; (2) recognition of data collection by ADNI staff in the Methods section; and (3) a standard phrase of acknowledgement of ADNI in the author line. Accordingly, ADNI leadership and ADNI personnel obtain modest academic acknowledgement for the work they have done on behalf of all ADNI publications. Prior to manuscript submission, a member of the DPC reviews each manuscript using ADNI data for overall quality; however, importantly, does not attempt to review manuscripts for scientific quality or for duplication. Scientific review occurs at the level of publication to avoid practices that inhibit or slow the utilization of ADNI data by the worldwide scientific community. Since 2004 there are 907 papers published using ADNI data, 852 of these have been published during the current funding period, about 1/3 of the papers are published with ADNI funded investigators as authors and 2/3 from scientists not funded by ADNI.

Collaborations with Other Projects (WW-ADNI, DOD ADNI, PPMI, DIAN, Sage Challenge, and Genetics Consortium): ADNI has made an extensive and successful effort to impact science by collaborating with other projects and by facilitating development of ADNI-like projects in other fields. The WW-ADNI project is funded by the Alzheimer’s Association and has quarterly phone calls and an annual meeting of all ADNI-like projects in the AD field worldwide [10-18]. Three Department of Defense ADNI projects [19-34] are investigating the links between traumatic brain injury and the development of AD in 400 Vietnam Veterans who are cognitively normal or who have MCI. These projects include clinical/cognitive assessments, MRI, LP, and amyloid and tau PET. The Parkinson’s Progression Biomarkers Initiative (PPMI) was proposed by Dr. Ken Marek (PI) and is built on the ADNI model, using many of the ADNI cores including the USC/LONI site for data sharing [35]. The Dominantly Inherited Alzheimer’s Network (DIAN, PI, Dr. John Morris) was inspired by ADNI, uses many ADNI methods, and is engaged in collaboration with ADNI comparing early onset with late onset AD [21, 22, 36, 37]. The SAGE Bionetworks DREAM Challenge [38] was an open competition using ADNI data to find improved methods for identifying subjects at-risk for cognitive decline. Finally, ADNI has provided its genome-wide association studies (GWAS) data and whole genome sequencing data [39-41] to the NIA funded Genetics Consortium.

Recruitment and Assessment Using the Brain Health Registry: The Brain Health Registry (BHR, PI: M Weiner) is a UCSF-based, internet-based registry with the overall goal of accelerating the development of new treatments for brain diseases by facilitating subject recruitment, screening, and longitudinal assessment for neuroscience clinical trials. BHR, using IRB approved electronic informed consent, collects longitudinal health, cognitive, and lifestyle data through detailed self-report questionnaires and online neuropsychological tests (NPT).The BHR currently has over 30,000 participants. Sixty percent (60%) report memory concerns, 37% are

over age 55 with memory concerns, and 29% endorse a first degree relative with dementia. A mock screening process identified more than 6,400 participants over age 55, who may be eligible for preclinical or prodromal AD trials. Forty-nine percent (49%) of participants have returned for a 6-month follow-up, and 37% have returned for a 1-year follow-up. NPT, provided through partnerships with Cogstate, Ltd. and Lumosity, Inc., include measures of memory, learning, attention, and processing speed. A public relations campaign with the B. Smith (model, restaurateur, author, and television host) resulted in 32% minorities with 11% African American enrollment, which is more than double the usual enrollment for this population. This demonstrates the value of targeted internet advertising and public relations for minority recruitment, which will be used to increase minority enrollment in ADNI. The BHR is currently being used to recruit participants for six other clinical studies; an average of 20% of participants contacted with a request to take part in a study respond to the request. The BHR will be used to (1) recruit new ADNI participants; and (2) longitudinally monitor and assess all new participants, as well as previously-enrolled ADNI participants continuing in ADNI3. A new addition to the BHR will be an “informant portal” for informants/study partners to register and provide information on their study partners (similar to CDR and AD8), as well as on themselves, and to take neuropsychological tests, and measures of caregiver stress. For recruitment of new participants, the BHR database will be queried to identify current BHR participants who meet (or are likely to meet) ADNI3 eligibility requirements, including participants with and without subjective memory complaints, and with or without objective evidence of cognitive impairment based on NPT scores. Participants meeting eligibility criteria will be contacted by email, and asked to contact their local ADNI clinical site. Those ADNI3 participants registering with BHR will have longitudinal NPT and questionnaire data available in the ADNI database.

Organization of Review of ADNI Papers, Special Issues: The progress and achievements of ADNI have been described in a wide range of papers since its outset. Mueller, et al [42, 43] initially described its goals and structure. In 2010, ADNI was featured in special journal issues of Alzheimer’s and Dementia, and of Neurobiology of Aging. The first [8] contained a series of papers outlining the achievements and future goals of the individual ADNI Cores, in addition to, the roles and perspectives of the PPSB (described in detail in [44]). The second, introduced by Frisoni and Weiner [7], contained the first significant collection of scientific results to emerge from the data generated by ADNI and included a report on AD biomarker dynamics [45], an analysis of C11 PiB PET amyloid imaging [46], and methods for predicting future clinical decline [47], among others. More recently, a 2015 special edition of Alzheimer’s and Dementia [6] reported industry perspectives and progress from the ADNI cores and WW-ADNI in the intervening five years. Military risk factors for AD have been an area of increasing interest [20] and were the focus of a 2014 special issue of Alzheimer’s and Dementia [21, 22] highlighting the link between traumatic brain injury (TBI) and cognitive decline. These papers have contributed to the three current DOD-ADNI studies which focus on exploring this link [48]. The overall impact of ADNI, including the development of biomarkers, the standardization of methods, the establishment of WW-ADNI and other initiatives, and the publication of a substantial body of work based on ADNI data, was recently described by Weiner et al [49]. Successive reviews of ADNI publications [4, 5, 44] comprehensively detail this latter body of work.

PROGRESS REPORT

The progress of the Administrative Core is summarized in the Significance section of this core. In addition, please see Administrative Core: Progress Report Publication List for publications that have arisen from Dr. Weiner and the collaborators on his team.

OMB Number: 0925-0002

Cumulative Inclusion Enrollment Report

Study Title: Alzheimer Disease Neuroimaging Initiative ADNI3

Comments: ADNI2 total subject enrollment

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/Alaska Native	0	1	0	0	0	0	0	0	0	**1**
Asian	7	13	0	0	0	0	0	0	0	**20**
Native Hawaiian or Other Pacific Islander	2	0	0	0	0	0	0	0	0	**2**
Black or African American	31	13	0	0	1	0	0	0	0	**45**
White	462	582	0	24	13	0	3	1	0	**1085**
More than One Race	5	6	0	1	2	0	0	0	0	**14**
Unknown or Not Reported	0	0	0	3	0	0	0	14	0	**17**
Total	**507**	**615**	**0**	**28**	**16**	**0**	**3**	**15**	**0**	**1184**

Study 1 of 1

Funding Opportunity Number: RFA-AG-16-019. Received Date:

OMB Number: 0925-0002

Planned Enrollment Report

Study Title: Alzheimer Disease Neuroimaging Initiative ADNI3

Domestic/Foreign: Domestic

Comments: ADNI3 new subjects only

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/Alaska Native	2	1	0	0	**3**
Asian	6	5	0	0	**11**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	21	9	0	0	**30**
White	168	138	9	7	**322**
More than One Race	3	2	0	0	**5**
Total	**200**	**155**	**9**	**7**	**371**

Study 1 of 2

OMB Number: 0925-0002

Planned Enrollment Report

Study Title: Alzheimer Disease Neuroimaging Initiative ADNI3

Domestic/Foreign: Domestic

Comments: ADNI3 rollover and new subjects

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/Alaska Native	2	2	0	0	**4**
Asian	11	14	0	0	**25**
Native Hawaiian or Other Pacific Islander	2	0	0	0	**2**
Black or African American	40	17	0	1	**58**
White	441	482	25	16	**964**
More than One Race	6	6	1	2	**15**
Total	**502**	**521**	**26**	**19**	**1068**

Study 2 of 2

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OMB Number: 4040-0001
Expiration Date: 06/30/2016

APPLICATION FOR FEDERAL ASSISTANCE

SF 424 (R&R)

5. APPLICANT INFORMATION **Organizational DUNS*:** 6133387890000

Legal Name*: NORTHERN CALIFORNIA INSTITUTE FOR RESEARCH AND EDUCATION
Department:
Division:
Street1*: 4150 CLEMENT STREET (151-NC)
Street2:
City*: SAN FRANCISCO
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 941211545

Person to be contacted on matters involving this application

Prefix:	First Name*:	Middle Name:	Last Name*:	Suffix:
	Azarah	Sr. Grant Specialist	Wong	

Position/Title:
Street1*: 4150 CLEMENT STREET (151-NC)
Street2:
City*: SAN FRANCISCO
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 941211545
Phone Number*: 415-750-6954 x 23891 Fax Number: 415-750-9358 Email: cgawards@ncire.org

7. TYPE OF APPLICANT* M: Nonprofit with 501C3 IRS Status (Other than Institution of Higher Education)

Other (Specify):
Small Business Organization Type ❍ Women Owned ❍ Socially and Economically Disadvantaged

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
Clinical Core

12. PROPOSED PROJECT

Start Date*	Ending Date*
08/01/2016	07/31/2021

OMB Number: 4040-0010
Expiration Date: 06/30/2016

Project/Performance Site Location(s)

Project/Performance Site Primary Location

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: University of Southern California
Duns Number: 0729333930000
Street1*: 1540 Alcazar St., CHP 216
Street2:
City*: Los Angeles
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 900330000
Project/Performance Site Congressional District*: CA-034

Project/Performance Site Location 1

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Oregon Health and Science University
DUNS Number: 0969975150000
Street1*: Sponsored Projects Administration
Street2: 0690 SW Bancroft St. MC L106SPA
City*: Portland
County:
State*: OR: Oregon
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 97239-0000
Project/Performance Site Congressional District*: OR-002

Project/Performance Site Location 2

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: University of California, San Diego
DUNS Number: 8043557900000
Street1*: 9500 Gilman Dr. MC 0949
Street2:
City*: La Jolla
County: San Diego
State*: CA: California
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 92093-0949
Project/Performance Site Congressional District*: CA-053

Project/Performance Site Location 3

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: University of Michigan
DUNS Number: 0731335710000
Street1*: Neurology Dept.
Street2: 2301 Commonwealth Blvd.
City*: Ann Arbor
County:
State*: MI: Michigan
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 48105-2945
Project/Performance Site Congressional District*: MI-015

Project/Performance Site Location 4

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Mayo Clinic
DUNS Number: 0064717000000
Street1*: 200 First Street SW
Street2:
City*: Rochester
County:
State*: MN: Minnesota
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 55905-0000
Project/Performance Site Congressional District*: MN-001

Project/Performance Site Location 5

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Baylor College of Medicine
DUNS Number: 0511133300000
Street1*: Dept. of Neurology
Street2: 7200 Cambridge St., 9th Floor, MS BCM609
City*: Houston
County:
State*: TX: Texas
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 77030-0000
Project/Performance Site Congressional District*: TX-007

Project/Performance Site Location 6

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Columbia University
DUNS Number: 0491794010000
Street1*: 630 West 168th Street, Box 49
Street2:
City*: New York
County:
State*: NY: New York
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 10032-3702
Project/Performance Site Congressional District*: NY-015

Project/Performance Site Location 7

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Washington University
DUNS Number: 0685522070000
Street1*: Neurology Dept.
Street2: 4488 Forest Park Ave. Suite 101
City*: St. Louis
County:
State*: MO: Missouri
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 63108-0000
Project/Performance Site Congressional District*: MO-001

Project/Performance Site Location 8

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: University of Alabama at Birmingham
DUNS Number: 0636907050000
Street1*: Neurology, 350 Sparks Center
Street2: 1720 7th Ave. South
City*: Birmingham
County:
State*: AL: Alabama
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 35233-0000
Project/Performance Site Congressional District*: AL-007

Project/Performance Site Location 9

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Mount Sinai SOM
DUNS Number: 0460251440000
Street1*: Alzheimer's Disease Research Center
Street2: Box 1230

City*: New York
County:
State*: NY: New York
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 10029-0000
Project/Performance Site Congressional District*: NY-014

Project/Performance Site Location 10

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Rush University Medical Center
DUNS Number: 0686102450000
Street1*: 1735 W. Harrison
Street2: Suite 312
City*: Chicago
County:
State*: IL: Illinois
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 60612-0000
Project/Performance Site Congressional District*: IL-007

Project/Performance Site Location 11

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Wein Center for Clinical Research
DUNS Number: 0460251440000
Street1*: Mt. Sinai Med Center Pearlman Res Bldg.
Street2: 4300 Alton Rd.
City*: Miami Beach
County:
State*: FL: Florida
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 33140-0000
Project/Performance Site Congressional District*: FL-020

Project/Performance Site Location 12

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: John Hopkins University School of Medicine
DUNS Number: 0019107770000
Street1*: 1620 McElderry St.
Street2: Reed Hall 2E -Room 2226
City*: Baltimore
County:
State*: MD: Maryland

Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 21205-0000
Project/Performance Site Congressional District*: MD-007

Project/Performance Site Location 13

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: University of South Florida
DUNS Number:
Street1*: 3702 Spectrum Blvd. Suite 165
Street2:
City*: Tampa
County:
State*: FL: Florida
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 33612-9445
Project/Performance Site Congressional District*:

Project/Performance Site Location 14

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Center for Cognitive Neurology
DUNS Number:
Street1*: 145E 32nd St.
Street2: 5th Floor
City*: New York
County:
State*: NY: New York
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 10016-0000
Project/Performance Site Congressional District*:

Project/Performance Site Location 15

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Duke University Medical Center
DUNS Number: 0443877930000
Street1*: Department of Psychiatry
Street2: DUMC - 3018
City*: Durham
County:
State*: NC: North Carolina
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 27710-0000
Project/Performance Site Congressional District*: NC-004

Project/Performance Site Location 16

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: University of Pennsylvania
DUNS Number: 0422507120000
Street1*: Department of Research Services
Street2: 3451 Walnut St.
City*: Philadelphia
County:
State*: PA: Pennsylvania
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 19104-6205
Project/Performance Site Congressional District*: PA-002

Project/Performance Site Location 17

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: University of Kentucky
DUNS Number: 9390178770000
Street1*: Research Foundation
Street2: 500 South Limestone
City*: Lexington
County:
State*: KY: Kentucky
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 40526-0001
Project/Performance Site Congressional District*: KY-006

Project/Performance Site Location 18

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: University of Pittsburgh
DUNS Number: 0045143600000
Street1*: Department of Neurology
Street2: 200 Lothrop Street
City*: Pittsburgh
County:
State*: PA: Pennsylvania
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 15213-0000
Project/Performance Site Congressional District*: PA-014

Project/Performance Site Location 19

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: University of Rochester Medical Center
DUNS Number: 0412941090000
Street1*: Monroe Community Hosp., Psychiatry
Street2: 435 East Henrietta Rd.
City*: Rochester
County:
State*: NY: New York
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 14620-0000
Project/Performance Site Congressional District*: NY-028

Project/Performance Site Location 20

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: University of California, Irvine
DUNS Number: 0467058490000
Street1*: Contract and Grants Accounting
Street2: 111 Academy Way, Suite 210
City*: Irvine
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 92697-1050
Project/Performance Site Congressional District*: CA-040

Project/Performance Site Location 21

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: University of Texas, Southwestern Med Center at Dallas
DUNS Number: 8007715450000
Street1*: P.O. Box 841753
Street2:
City*: Dallas
County:
State*: TX: Texas
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 75284-1753
Project/Performance Site Congressional District*: TX-030

Project/Performance Site Location 22

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Emory University
DUNS Number: 0664699330000
Street1*: Office of Sponsored Programs

Street2: 1599 Clifton Rd. NE 5th Fl.
City*: Atlanta
County:
State*: GA: Georgia
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 30322-0000
Project/Performance Site Congressional District*: GA-005

Project/Performance Site Location 23

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: University of Kansas, Medical Center Research Institute
DUNS Number: 0160608600000
Street1*: 3910 Rainbow Blvd.
Street2: Mail-stop 1039
City*: Kansas City
County:
State*: KS: Kansas
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 66160-7702
Project/Performance Site Congressional District*: KS-003

Project/Performance Site Location 24

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: University of California, Los Angeles
DUNS Number: 0925303690000
Street1*: 710 Westwood Plaza, RNRC-4231
Street2:
City*: Los Angeles
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 90095-0000
Project/Performance Site Congressional District*: CA-030

Project/Performance Site Location 25

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Mayo Clinic, Jacksonville
DUNS Number: 1532231510000
Street1*: Neurology Dept.
Street2: 4500 San Pablo Road
City*: Jacksonville

County:
State*: FL: Florida
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 32224-0000
Project/Performance Site Congressional District*: FL-004

Project/Performance Site Location 26

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Indiana University
DUNS Number: 0060467000000
Street1*: Goodman Hall
Street2: 355 West 16th St., Suite 4700
City*: Indianapolis
County:
State*: IN: Indiana
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 46202-0000
Project/Performance Site Congressional District*: IN-007

Project/Performance Site Location 27

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Yale University
DUNS Number: 0432075620000
Street1*: Treasury Operations, I 100 SHM
Street2:
City*: New Haven
County:
State*: CT: Connecticut
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 06520-8087
Project/Performance Site Congressional District*: CT-003

Project/Performance Site Location 28

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Jewish General Hospital
DUNS Number:
Street1*: 3755 Cote Ste. Catherine Pav.E.:0012
Street2:
City*: Montreal
County:
State*:
Province: Quebec

Country*: CAN: CANADA
Zip / Postal Code*: H3T1E2
Project/Performance Site Congressional District*:

Project/Performance Site Location 29

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Sunnybrook Health Sciences
DUNS Number:
Street1*: S132
Street2: 2075 Bayview Avenue
City*: Toronto
County:
State*:
Province: Ontario
Country*: CAN: CANADA
Zip / Postal Code*: M4N3M5
Project/Performance Site Congressional District*:

Project/Performance Site Location 30

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: University of British Columbia
DUNS Number:
Street1*: The University-Industry Liaison Office
Street2: 103-6190 Agronomy Road
City*: Vancouver
County:
State*:
Province: BC
Country*: CAN: CANADA
Zip / Postal Code*: V6T 1Z3
Project/Performance Site Congressional District*:

Project/Performance Site Location 31

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: St. Joseph's Health Center - Cognitive Neurology
DUNS Number:
Street1*: 801 Commissioners Road East
Street2:
City*: London
County:
State*:
Province: Ontario
Country*: CAN: CANADA
Zip / Postal Code*: N6C 5J1
Project/Performance Site Congressional District*:

Project/Performance Site Location 32

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Northwestern University
DUNS Number: 0054368030000
Street1*: Cognitive Neurology & Alzheimer's Disease
Street2: 320 E. Superior St., Searle 11-508
City*: Chicago
County:
State*: IL: Illinois
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 60611-0000
Project/Performance Site Congressional District*: IL-007

Project/Performance Site Location 33

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Medical University of South Carolina
DUNS Number: 1837107480000
Street1*: Alzheimer's Research and Clinical Programs
Street2: 5900 Core Road, Suite 203
City*: Charleston
County:
State*: SC: South Carolina
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 29406-0000
Project/Performance Site Congressional District*: SC-001

Project/Performance Site Location 34

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Research Foundation for Mental Hygiene, Inc.
DUNS Number:
Street1*: Riverview Ctr.
Street2: 150 Broadway Ste. 301
City*: Menands
County:
State*: NY: New York
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 12204-0000
Project/Performance Site Congressional District*:

Project/Performance Site Location 35

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Premiere Research Institute
DUNS Number:
Street1*: Department of Research
Street2: 4631 N. Congress Ave., Suite 200
City*: Charleston
County:
State*: SC: South Carolina
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 29406-0000
Project/Performance Site Congressional District*:

Project/Performance Site Location 36

● I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: University of California, San Francisco
DUNS Number: 0948783370000
Street1*: Regents of the University of CA
Street2: 1294 9th Avenue, Room 3
City*: San Francisco
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 94143-0000
Project/Performance Site Congressional District*: CA-008

Project/Performance Site Location 37

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Georgetown University
DUNS Number: 0495158440000
Street1*: 3300 Wisconsin Avenue, NW
Street2: Harris Building, Suite 1100
City*: Washington DC
County:
State*: DC: District of Columbia
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 20007-0000
Project/Performance Site Congressional District*:

Project/Performance Site Location 38

● I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Birgham and Women's Hopistal
DUNS Number: 0308112690000

Street1*: 221 Longwood Ave., BL-104
Street2: Div of Cog Behavioral Neurology
City*: Boston
County:
State*: MA: Massachusetts
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 02115-0000
Project/Performance Site Congressional District*: MA-008

Project/Performance Site Location 39

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Stanford University
DUNS Number: 0092142140000
Street1*: Attn: Ref: SPO #34254
Street2: P.O. Box 44253
City*: San Francisco
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 94144-4253
Project/Performance Site Congressional District*: CA-014

Project/Performance Site Location 40

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Banner Sun Health Research Institute
DUNS Number: 9601810550000
Street1*: Dept. of Administration
Street2: 10515 West Santa Fe Dr.
City*: Sun City
County:
State*: AZ: Arizona
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 85351-0000
Project/Performance Site Congressional District*: AZ-002

Project/Performance Site Location 41

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Boston University
DUNS Number: 0494352660000
Street1*: Neurology/Alzheimer's Disease Center
Street2: 72 E. Concord Street, Robinson Suite 7800
City*: Boston

County:
State*: MA: Massachusetts
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 02118-0000
Project/Performance Site Congressional District*: MA-008

Project/Performance Site Location 42

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Howard University
DUNS Number: 0562822960000
Street1*: Research Administrative Services
Street2: 525 Bryant St. Suite 137
City*: Washington
DC
County:
State*: DC: District of Columbia
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 20059-0000
Project/Performance Site Congressional District*:

Project/Performance Site Location 43

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Case Western Reserve University
DUNS Number: 0777584070000
Street1*: Neurological Institute Clinical Trials
Street2: 11100 Euclid Ave.
City*: Cleveland
County:
State*: OH: Ohio
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 44106-0000
Project/Performance Site Congressional District*: OH-011

Project/Performance Site Location 44

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: University of California, Davis (EBIRE)
DUNS Number: 0471200840000
Street1*: 4860 Y St.
Street2: Suite 3900
City*: Sacramento
County:
State*: CA: California
Province:

Country*: USA: UNITED STATES
Zip / Postal Code*: 95817-0000
Project/Performance Site Congressional District*: CA-005

Project/Performance Site Location 45

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Dent Neurologic Institute
DUNS Number: 0204136190000
Street1*: Clinical Research
Street2: 3980 Sheridan Dr., Suite 500
City*: Amherst
County:
State*: NY: New York
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 14226-0000
Project/Performance Site Congressional District*: NY-027

Project/Performance Site Location 46

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Parkwood Hospital
DUNS Number:
Street1*: 801 Comissioners Road East
Street2:
City*: London
County:
State*:
Province: Ontario
Country*: CAN: CANADA
Zip / Postal Code*: N6C 5J1
Project/Performance Site Congressional District*:

Project/Performance Site Location 47

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: University of Wisconsin
DUNS Number: 1612021220000
Street1*: 21 N. Park Street, Room 6432
Street2:
City*: Madison
County:
State*: WI: Wisconsin
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 53715-0000
Project/Performance Site Congressional District*: WI-002

Project/Performance Site Location 48

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: University of California, Irvine-BIC
DUNS Number: 0467058490000
Street1*: 1400 Biological Sciences III
Street2:
City*: Irvine
County: Orange
State*: CA: California
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 92697-4540
Project/Performance Site Congressional District*: CA-047

Project/Performance Site Location 49

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Banner Alzheimer's Institute (BAI)
DUNS Number: 7882406740000
Street1*: PET Center - Research
Street2: 901 E. Willetta, Third FL
City*: Phoenix
County:
State*: AZ: Arizona
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 85006-0000
Project/Performance Site Congressional District*: AZ-004

Project/Performance Site Location 50

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Ohio State University
DUNS Number: 0716507090000
Street1*: OSURF
Street2: 1960 Kenny Road
City*: Columbus
County:
State*: OH: Ohio
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 43210-0000
Project/Performance Site Congressional District*: CA-015

Project/Performance Site Location 51

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Albany Medical College

DUNS Number: 0394869230000
Street1*: Dept. of Neurosciences MC 70
Street2: 47 New Scotland Ave.
City*: Albany
County:
State*: NY: New York
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 12208-0000
Project/Performance Site Congressional District*: NY-021

Project/Performance Site Location 52

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: University of Iowa
DUNS Number:
Street1*: B5 Jessup Hall
Street2:
City*: Iowa City
County:
State*: IA: Iowa
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 52242-0000
Project/Performance Site Congressional District*:

Project/Performance Site Location 53

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Dartmouth-Hithcock Medical Center
DUNS Number: 0410278220000
Street1*: One Medical Center Dr.
Street2:
City*: Lebanon
County:
State*: NH: New Hampshire
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 03756-0001
Project/Performance Site Congressional District*: NH-002

Project/Performance Site Location 54

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Wake Forest University SOM
DUNS Number: 9377279070000
Street1*: Controller's Office
Street2: Medical Center Blvd.

City*: Winston-Salem
County:
State*: NC: North Carolina
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 27157-0000
Project/Performance Site Congressional District*: CA-012

Project/Performance Site Location 55

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Rhode Island Hospital
DUNS Number: 0757109960000
Street1*: Office of Research Admin Coro Bldg.
Street2: One Hoppin Street, Suite 1.300
City*: Providence
County:
State*: RI: Rhode Island
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 02903-4923
Project/Performance Site Congressional District*: RI-002

Project/Performance Site Location 56

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: The Weill Cornell Memory Disorders Program
DUNS Number:
Street1*: 428 East 72nd Street, Suite 500
Street2:
City*: New York
County:
State*: NY: New York
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 10021-4635
Project/Performance Site Congressional District*:

Project/Performance Site Location 57

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Cleveland Clinic Lou Ruvo Center for Brain Health
DUNS Number:
Street1*: PO Box 931531
Street2:
City*: Cleveland
County:

State*: OH: Ohio
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 44193-0000
Project/Performance Site Congressional District*:

Project/Performance Site Location 58

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Roper St. Francis Healthcare
DUNS Number:
Street1*: Clinical Biotechnology Research Institute
Street2: Roper Hospital-316 Calhoun Street, 5th Floor
City*: Charleston
County:
State*: SC: South Carolina
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 29401-0000
Project/Performance Site Congressional District*:

Project/Performance Site Location 59

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Butler Hospital
DUNS Number:
Street1*: 345 Blackstone Blvd.
Street2:
City*: Providence
County:
State*: RI: Rhode Island
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 02906-0000
Project/Performance Site Congressional District*:

File Name

Additional Location(s)

Clinical Core Summary/Abstract
The Clinical Core/Coordinating Center for ADNI3 will continue to be responsible for managing the day-to-day clinical operations of ADNI. The ADNI Coordinating Center has been based at the Alzheimer's Therapeutic Research Institute (ATRI) at USC since early August 2015. The Clinical Core will be responsible for oversight of ADNI3 clinical activities, contracting with sites, data management, tracking and quality control, recruitment and retention of participants, regulatory oversight, financial management of site activities, and safety monitoring including DSMB reporting. In ADNI3, the Clinical Core will focus on retention and continued follow-up of the current cognitively normal participants (with and without subjective memory concerns) and those with mild cognitive impairment (MCI) due to Alzheimer's disease (AD) (both early and late MCI). Careful follow-up of these individuals, some of whom have been participating in ADNI for eight years or longer, will allow study of the conversion from normal aging to preclinical AD, as well as the detailed characterization of preclinical AD as it progresses to MCI and dementia due to AD. This will powerfully address major gaps in current understanding and facilitate the continuing refinement of early trial designs. New ADNI3 enrollees will fall primarily into two categories: cognitively normal individuals with and without subjective concerns (ages 65 and older, global CDR=0), and early/late amnestic mild cognitive impairment (global CDR=0.5, MMSE 24-30 and education appropriate memory impairment). Individuals with mild dementia due to AD will also be enrolled. Almost all ADNI2 assessments will be continued in ADNI3 to preserve the value of the rich longitudinal dataset. Because of concern about proprietary instruments in trials, the Boston Naming test will be dropped; the MINT test [55], which is license-free, will replace it. The major additions will be web-based computerized cognitive assessments and a performance-based functional assessment. Clinical core aims include characterization of the cross-sectional features and longitudinal trajectories of participants who are cognitively normal and those with mild cognitive impairment, including those who progress to dementia, study of the relationships among clinical/demographic, cognitive, genetic, biochemical and neuroimaging features (including tau PET imaging) of AD from the preclinical through dementia stages, assessment of genetic, biomarker, cognitive and clinical predictors of AD-related decline, refinement of clinical trial designs, including in particular secondary prevention and slowing of progression in symptomatic disease, and evaluation/optimization of cognitive and functional outcome measures for prodromal and preclinical stage trials. The core will also explore a new functional performance instrument, will evaluate the relationship of longitudinal web-based cognitive assessment to in-person assessments, biomarkers and risk of decline, and will assess the utility of the Brain Health Registry for recruitment.

PROFILE - Senior/Key Person

Prefix: Dr. First Name*: Rema Middle Name Last Name*: Raman Suffix:

Position/Title*: Professor
Organization Name*: University of Southern California
Department: Department of Neurology
Division: Keck School of Medicine
Street1*: Alzheimer's Therapeutic Research Institute (ATRI)
Street2: 10182 Telesis Court, 3rd Floor
City*: San Diego
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 921210000

Phone Number*: 858-964-0795 Fax Number: 858-452-4291 E-Mail*: rema.raman@usc.edu

Credential, e.g., agency login: reraman

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: PHD Degree Year:

File Name

Attach Biographical Sketch*: Core_B_Biosketch_Raman.pdf

Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: Michael Middle Name C Last Name*: Donohue Suffix:

Position/Title*: Associate Professor
Organization Name*: University of Southern California
Department: Department of Neurology
Division: Keck School of Medicine
Street1*: 10182 Telesis Court, 3rd Floor
Street2:
City*: San Diego
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 921280000

Phone Number*: 8587358469 Fax Number: E-Mail*: mdonohue@usc.edu

Credential, e.g., agency login: mdonohue

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: PHD,MA,BS Degree Year:

File Name

Attach Biographical Sketch*: Core_B_Biosketch_Donohue.pdf

Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: RONALD Middle Name C Last Name*: PETERSEN Suffix:

Position/Title*: ASSOCIATE PROFESSOR
Organization Name*: MAYO CLINIC ROCHESTER
Department: Neurology
Division:
Street1*: 200 First Street SW
Street2:
City*: ROCHESTER
County:
State*: MN: Minnesota
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 559050000

Phone Number*: 507-284-4006 Fax Number: E-Mail*: peter8@mayo.edu

Credential, e.g., agency login: peter8@mayo.edu

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: MD,PHD Degree Year:

File Name
Attach Biographical Sketch*: CoreB_Biosketch_Petersen.pdf
Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: Paul Middle Name S. Last Name*: Aisen Suffix:

Position/Title*: Professor
Organization Name*: University of Southern California
Department: Department of Neurology
Division: Keck School of Medicine
Street1*: Alzheimer Therapeutic Research Institute (ATRI)
Street2: 10182 Telesis Court
City*: San Diego
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 921280000

Phone Number*: 858-252-8555 Fax Number: 858-622-1904 E-Mail*: paisen@usc.edu

Credential, e.g., agency login: paisen

Project Role*: Other (Specify) Other Project Role Category: Clinical Core Lead

Degree Type: MD,BA Degree Year:

File Name
Attach Biographical Sketch*: Aisen_biosketch_ADNI3_v2.pdf
Attach Current & Pending Support:

Clinical Core: Specific Aims

The goal of the ADNI Clinical Core/Coordinating Center is to insure that the ADNI project will accomplish its central mission: to validate biomarkers for clinical trials. The Coordinating Center is based at the USC Alzheimer's Therapeutic Research Institute (ATRI); the Clinical Core will continue to be responsible for managing the day-to-day operations of ADNI in a manner similar to ATRI management of clinical trials. As detailed on the ADNI/LONI website (http://adni.loni.usc.edu/about/centers-cores/clinical/subject-tables/) and described below, we fully enrolled and managed all cohorts during the current grant cycle. The Clinical Core will focus on retention and continued follow-up of the cognitively normal (NL) participants (with and without subjective memory concerns, SMC) and those with amnestic mild cognitive impairment (MCI) due to Alzheimer's disease (AD) (both early and late MCI). Careful follow-up of these individuals, some of whom have been participating in ADNI for eight years or longer, will allow study of the conversion from normal aging to preclinical AD, as well as the detailed characterization of preclinical AD as it progresses to MCI and dementia due to AD. This will powerfully address gaps in current understanding and facilitate the refinement of early trial designs. New ADNI3 enrollees will fall mainly into two categories: NL individuals with and without subjective concerns (ages 65 and older, global CDR=0), and early/late amnestic MCI (global CDR=0.5, MMSE 24-30 and education appropriate memory impairment). To provide a reference group and to generate data in support of dementia-stage trials, the core will follow individuals who have progressed from MCI to AD dementia and new participants with mild AD dementia will be enrolled. Almost all ADNI2 assessments will be continued in ADNI3 to preserve the value of the rich longitudinal dataset. The proprietary Boston Naming Test will be replaced by the Multi-Lingual Naming Test (MINT) (1), which is license-free. The major additions will be web-based computerized cognitive assessments and a performance-based functional assessment.

The ***Specific Aims*** of the ADNI3 Clinical Core will include:

1. *Operational*: Oversight of ADNI3 clinical activities in a manner identical to AD clinical trials, including: data management, tracking and quality control, recruitment and retention of participants, regulatory oversight and financial management. ADNI3 will follow approximately 600 ADNI2 subjects, and recruit 300 new normal, MCI and mild AD dementia subjects. The Clinical Core will ensure that well-characterized participants are available for the assessments and analyses of the other cores.

b. *Clinical*: a. Characterization of the cross-sectional features and longitudinal trajectories of participants who are cognitively normal and those with MCI, including those who progress to dementia. b. Study of the relationships among clinical/demographic, cognitive, genetic, biochemical and neuroimaging features (including tau PET imaging) of AD from the preclinical through dementia stages. c. Assessment of genetic, biomarker, cognitive and clinical predictors of AD-related decline.

2. *Trial design*: Refinement of clinical trial designs, including in particular secondary prevention and slowing of progression in symptomatic disease. Evaluation/optimization of cognitive and functional outcome measures for prodromal and preclinical stage trials.

3. *Discovery*: Relationship of longitudinal web-based cognitive assessment to in-person assessments, biomarkers and risk of decline and to explore a new functional assessment instrument. Value of web-based registries such as the Brain Health Registry for recruitment. Assessment of "mixed" (cognitive and functional) composites as potential primary outcome measures.

Key hypotheses: 1. *Nearly all normal participants with brain amyloidosis will show cognitive decline compared to those without amyloidosis, and will progress to MCI (CDR-0.5).* Rate of progression will be influenced by baseline cognition, tau biomarkers and APOE genotype. Confirmation of this hypothesis is critical to early stage trial design and regulatory support.

2. *Early stage AD cognitive decline predicts later functional and clinical decline.* Trials in preclinical AD generally utilize composite cognitive measures as sole primary outcome measures, since functional and clinical decline at this stage is minimal. To establish clinical meaningfulness of cognitive change in preclinical AD requires evidence that such change is related to the functional decline at later stages of disease. Long-term follow-up is necessary to establish this link.

3. The course of cognitively normal and MCI participants will be influenced by APOE genotype, baseline cognitive and functional performance, cerebrospinal fluid amyloid and tau biomarkers, and amyloid and tau PET scan results. Continuing characterization of the predictors of long-term course of NL and MCI individuals is essential to the optimal design of prodromal AD trials. The inclusion of a functional performance assessment will provide a measure of early clinically meaningful change.

4. *AD-related cognitive decline can be captured by unsupervised web-based testing at the preclinical and prodromal stages*, and w*eb-based registries will facilitate recruitment for ADNI (and therapeutic trials).* Web-based methods are essential to support the selection of participants for early stage trials.

Clinical Core: Research Strategy

SIGNIFICANCE. The need for effective, disease-slowing therapy for AD remains enormous. ADNI data has facilitated the launch of many trials across the spectrum of disease, with recent studies moving to earlier phases (2). A continuing theme in this renewal application pertains to the longitudinal assessment of cognitive and functional measures combined with biomarkers to characterize the trajectory of participants in the early stages of the AD spectrum, to facilitate optimal trial designs. The refinement of trial designs, including the evaluation of the clinical meaningfulness of subtle cognitive change in the earliest stages (3), is essential for the acceleration of drug development.

INNOVATION. ADNI 3 will extend the follow up of preclinical and prodromal stage participants to as long as 13 years, while also enrolling new participants. The relationship among cognitive, functional (both interview-based and performance-based) and clinical trajectories to existing imaging and biochemical markers, and, in particular, tau PET imaging, will be studied. The value of web-based cognitive assessment for capturing early stage AD-related decline and to accelerate enrollment in studies will be assessed.

PROGRESS REPORT. The ADNI Clinical Core has now had over a decade of success in the enrollment and retention of carefully characterized participants who are cognitively normal or meet criteria for mild cognitive impairment (MCI) or mild AD dementia. This experience is described in our recent paper on the ADNI2 Clinical Core (4), and briefly summarized in Figures 1 and 2, and Table 1, below. (Current tables of ADNI participants and activities can be viewed on the LONI website http://adni.loni.usc.edu/about/centers-cores/clinical/subject-tables/). Enrollment goals were met, and drop-out rates in the normal and MCI groups were 5-8% per year. With the exception of the self-reported subjective complaints (required for entry), the SMC group was similar to the NL group cross-sectionally and longitudinally (Figures 1 and 2); SMC and NL will be combined in ADNI3.

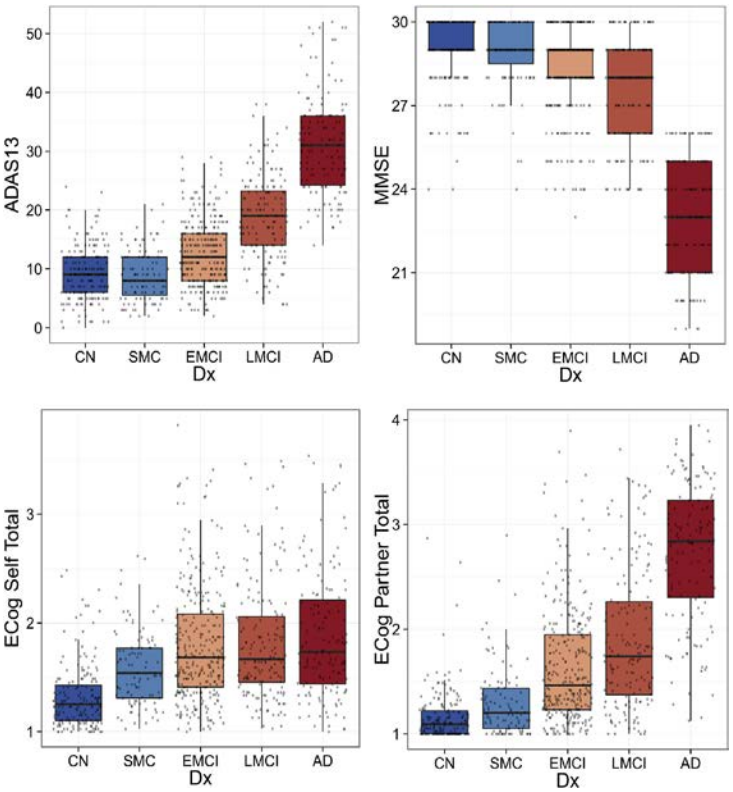

Figure 1. Baseline assessments by diagnosis. Abbreviations: CN, clinically normal; SMC, subjective memory concerns; EMCI, early mild cognitive impairment; LMCI, late mild cognitive impairment; AD, mild Alzheimer's disease dementia; ADAS13, 13 item version of the cognitive subscale of the Alzheimer's Disease Assessment Scale; MMSE, Mini-Mental .State Examination; ECog, everyday cognition.

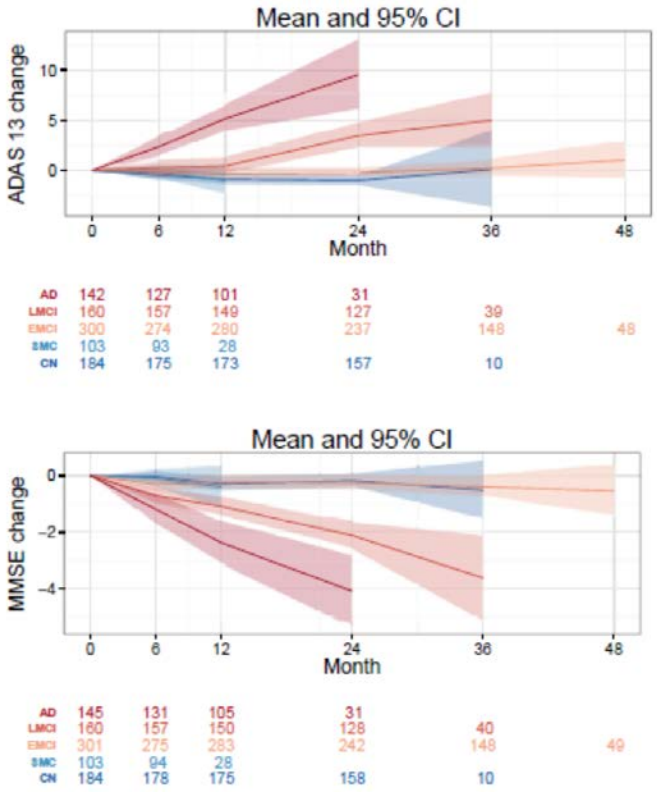

Figure 2. Mean change (observed scores) by baseline diagnosis. Shaded areas represent 95% confidence intervals. The number of observations for each cohort at each time point is shown below the graphs. Abbreviations: CN, clinically normal; SMC, subjective memory concerns; EMCI, early mild cognitive impairment; LMCI, late mild cognitive impairment; AD, mild Alzheimer's disease dementia; ADAS13, 13 item version of the Alzheimer's Disease Assessment Scale cognitive subscale; MMSE, Mini-Mental State Examination.

	CN n=184	SMC n=103	EMCI n=301	LMCI n=160	AD n=145	Combined n=893	P
Age (yrs)	73.4 (6.3)	72.2 (5.6)	71.3 (7.4)	72.2 (7.5)	74.6 (8.1)	72.5 (7.3)	<0.001
Female	94 (51%)	61 (59%)	132 (44%)	74 (46%)	59 (41%)	420 (47%)	0.027
Education	16.5 (2.5)	16.7 (2.6)	16.0 (2.7)	16.5 (2.6)	15.8 (2.7)	16.3 (2.6)	0.009
CDR-SB	0.0 (0.1)	0.01 (0.2)	1.3 (0.8)	1.7 (1.0)	4.5 (1.7)	1.5 (1.7)	<0.001
ADAS 13	9.2 (4.5)	8.9 (4.3)	12.7 (5.4)	18.7 (7.1)	31.0 (8.4)	15.5 (9.6)	<0.001
MMSE	29.0 (1.3)	29.0 (1.2)	28.3 (1.6)	27.6 (1.8)	23.1 (2.1)	27.6 (2.6)	<0.001
Part. ECog	1.3 (0.3)	1.6 (0.3)	1.8 (0.5)	1.8 (0.5)	1.9 (0.6)	1.7 (0.5)	<0.001
Study Part. Ecog	1.2 (0.3)	1.3 (0.3)	1.6 (0.5)	1.9 (0.7)	2.7 (0.7)	1.7 (0.7)	<0.001

Table 1. Baseline ADNI measures, ADNIGO and ADNI2

Interestingly, EMCI participants, despite a global CDR of 0.5 indicating mild clinical impairment, were similar to NL in longitudinal cognitive decline (Figure 2).

APPROACH. Work plan for the operational aims. The Clinical Core will continue to provide the operational infrastructure for ADNI in a fashion that reflects the Core's management of AD clinical trials (5-10).

As noted in the Overview section of this application, the ADNI Coordinating Center moved from UCSD to USC in the summer of 2015 coincident with the establishment of the USC Alzheimer's Therapeutic Research Institute (ATRI) in San Diego. The move of Paul Aisen with the key personnel and most of the staff from the ADCS Administrative, Clinical Operations, Informatics and Regulatory/Safety Cores to ATRI allowed a major strengthening of the administrative support for the program (particularly with regard to contracting, human resources and return on indirect funds). Despite an unfortunately contentious transition, ATRI has been successfully coordinating ADNI along with multiple multicenter therapeutic trials (including the A4 trial, LEARN, the Intranasal-Insulin Study, the FYN inhibitor study and the soon-to-begin transdermal nicotine study). Growing collaboration with other USC investigators, particularly Arthur Toga's group, has already produced an NIA R01 application for a new infrastructure initiative (GAP TRC-PAD).

The work of the ATRI Administrative, Clinical Operations, Medical and Informatics Cores to support the financial management, day-to-day operations, regulatory oversight, secure electronic data capture, tracking, site monitoring and safety of ADNI is described in the Budget Justification section.

Historically, ADNI has recruited cognitively normal (NL), amnestic MCI (aMCI) and AD-dementia subjects with criteria based on the Mini–Mental State Examination (MMSE), Clinical Dementia Rating (CDR) scale and one paragraph delayed recall from the Logical Memory subtest (LMII) of the Wechsler Memory Scale-Revised and clinical judgment (11). In ADNI GO, we introduced the construct of early MCI (EMCI) to capture a milder stage of MCI, adjusting the LMII criteria. In ADNI2, we incorporated an assessment of subjective memory concern (SMC) to the NL group using the Cognitive Change Index (CCI), a 20 item short form derived from a larger set of items used to quantify cognitive complaints in relation to neuroimaging measures in a series of studies (12). The 20 item self-administered version (CCI-S) included those items most sensitive to clinical progression or hippocampal neurodegeneration (12 episodic memory, 5 executive function and 3 language). In ADNI2, the CCI-S was used to help select significant memory concerns (SMC) but CDR 0 and normal performance. A score of >16 on the 12 episodic memory items was used for inclusion to the SMC group by consensus based on the pattern in the 2006 report. This score indicates endorsing at least minimal adverse changes on 25% of the memory items or more pronounced problems with fewer items.

While the NL and SMC groups look similar, there is a gradual progression in cognitive impairment from NL/SMC to MCI and to dementia (Figure 1C). There is likewise a gradual progression of positive AD biomarkers as we move across the clinical spectrum, confirming that the clinical groups represent a progression of the underlying AD pathophysiology. We will continue using similar criteria and the same clinical instruments in ADNI3 with a slight modification to simplify the groups: we now combine the EMCI and LMCI groups into a single aMCI designation, and NL and SMC into a single NL cohort. The enrollment criteria for ADNI3 are outlined in the Human Subjects section.

Based on our history with ADNI1 and ADNI GO rolling over to ADNI2, we project carrying forward the following numbers of subjects into ADNI3: NL/SMC, 295; aMCI, 274; AD, 128. In ADNI3, we will recruit new participants in the three categories as follows: NL/SMC 133, aMCI 151, mild AD dementia 87. The total number of participants in ADNI3 will thus be 1068, sufficient for the planned key analyses as described below and in the Biostatistics Core. The distribution of participants in ADNI3, with roughly 40% each in the NL/SMC and MCI groups and 20% mild AD dementia, corresponds to the focus of current disease-modification trials on the preclinical and prodromal, and to a lesser extent mild AD dementia, populations. Inclusion/exclusion criteria are included in the Human Subjects section.

Assessing early AD-related change: ECog, CogState and FCI. As mentioned, we will be instituting new clinical measures: the Financial Capacity Instrument (13) and a computerized battery, CogState (14). We will continue to administer the subjective cognitive concern instrument, Everyday Cognition (ECog)(15), to both the participants and the study partners.

ECog. With the emphasis on moving earlier in the clinical spectrum of AD, there has been intense interest in developing instruments designed to assess the subjective perception of progression or improvement (16). Toward this end, ADNI GO and ADNI2 adopted the ECog instrument to assess both the participants' and study partners' assessment of the participants' cognitive activity. Data from the ECog have demonstrated validity with objective measures of neuropsychological function and neurobiological markers as reflected by structural neuroimaging, e.g., MRI hippocampal volume measures and brain volume measures (15). Longitudinal changes in function have also been demonstrated to be correlated with ECog performance at baseline, indicating that the ECog can predict subsequent development of MCI (17). Using ADNI2 data, subscales of the ECog were demonstrated to correlate with cognitive functioning, structural brain atrophy, cerebrospinal fluid abnormalities and markers of amyloid deposition using PET. In the Mayo Clinic Study of Aging memory, planning, organization, divided attention and the ECog total score tended to predict progression to MCI after adjusting for age, education, baseline ECog domain or total score and cognitive function and longitudinal data of changes in ECog measures for the participants and study partners have indicated that the ECog assessment changes over time in NL participants have predicted progression to MCI (Petersen, unpublished data). These studies in aggregate suggest that subjective impression as an index of patients' response measures are informative and can be sensitive to subtle therapeutic change as used as performance measures in randomized controlled trials. Data from ADNI, when correlated with biomarker indices, will be useful in the design of future randomized control trials as measured of early change, perhaps even prior to cognitive and functional alterations.

CogState. It has recently become apparent that the potential value of a computerized cognitive instrument for assessing cognition has been recognized. A computerized battery may have several advantages over standard neuropsychological testing including a possibility of being more sensitive early in the disease course. In addition, conceivably, a computerized instrument could be used frequently by study participants even from home. The CogState instrument has an extensive history of use in a variety of clinical settings and has been proposed as an instrument that has sensitivity to early impairment while being relatively simple to perform, culture free and exhibiting minimal learning effects (14). As such, we have begun a pilot study in ADNI2 to assess the utilization of CogState at our participating sites. There is an extensive history of use of the CogState instrument, and recently, in the Mayo Clinic Study of Aging, CogState has been shown to be quite acceptable to participants when performed on a personal computer, and iPad or at home (18). This study demonstrates feasibility in remote settings. Another study demonstrated the correlation between CogState and standard neuropsychological instruments and some correlations with biomarkers including hippocampal volumes (19). Finally, the instrument has also been demonstrated to be applicable to individuals across the age range from 51 years and older, and to be sensitive to amyloid-related cognitive change (20). The administration of the CogState battery includes four playing card tasks as measures of psychomotor function: detection (DET), identification (IDN), visual episodic memory (one card learning) and visual working memory (one card back). The CogState battery provides a large number of equivalent alternative forms for serial assessment.

FCI-SF. We also include in ADNI3 a performance-based functional assessment, the Financial Capacity Instrument - Short Form (FCI-SF). The FCI-SF has been found to be sensitive to clinical changes across a continuum of early AD stages. It employs a range of simple and complex financial/monetary tasks combined in a way that allows for sensitivity beginning with very early stages of AD, when patients start to develop subtle deficits. It also maintains its sensitivity across a relatively wide spectrum of the disease, covering MCI/Prodromal AD and mild AD dementia. The FCI-SF assesses an activity of daily living that is very important to independent functioning. The FCI-SF has shown promising correlation to amyloid status (Marson, unpublished results) and clinical stage (13, 21-23). The FCI-SF represents a type of tool in which both US and EU regulatory authorities have expressed a great deal of interest when discussing clinical assessments of early AD populations.

Minority recruitment. The Clinical Core is committed to increasing minority enrollment in ADNI3. In addition to continuing the targeted efforts utilized in ADNI2, BHR (see Administrative Core), has successfully enrolled large numbers of African Americans and will be the registry for AD-PCORnet, which utilizes African-Americans Against AD and Latinos Against AD to engage and enroll participants from these groups.

ADNI 3 Schedule of Events. Complete schedules for all biomarker assessments including MRI and PET scans for all participants can be found in the Human Subjects, and Budget sections of this application.
Work plan and analyses for the Clinical, Trial Design and Discovery aims and hypotheses of the Clinical Core: Characterization of the cross-sectional features and longitudinal trajectories of cognitively normal older individuals and mild cognitive impairment, including those who progress to dementia. This key activity will continue on an ongoing basis, consistent with our recent publication on ADNI2 (4). To facilitate clinic-pathological correlations, pre-consent for autopsy is discussed with all participants.
Study of the relationships among clinical/demographic, cognitive, genetic, biochemical and neuroimaging features (including tau PET imaging) of AD from the preclinical through dementia stages. In addition to tabulation of associations among biomarkers within the three cohorts, we will continue our work on the generation of data-driven long-term trajectories from the observed longitudinal data from ADNI (24). In ADNI3 for the first time we will incorporate tau PET data into these analyses.
Assessment of genetic, biomarker, cognitive and clinical predictors of AD-related decline. Our particular focus will be the impact of baseline measures and longitudinal change in biomarkers cognitive performance on long-term cognitive change, an indicator of clinical progression across the disease span. Cognitive change will be studied using individual test scores as well as composite cognitive and cognitive/functional measures that are gaining increasing use in AD trials. To maximize future genetic analyses, we modify consent form language for ADNI3 to obtain permission to re-contact participants with potentially informative family history or genetic markers for future studies (e.g., genome/exome sequencing or deeper phenotype of family).
Refinement of clinical trial designs, including in particular secondary prevention and slowing of progression in symptomatic disease. The development of AD therapeutics has stalled in the efforts to move past modestly effective symptomatic drugs to disease-modifying agent, with no drugs reaching the clinic since memantine in 2003. There are many reasons for this failure, including issues of target selection, off-target toxicity, and insufficient pharmacokinetic and pharmacodynamics data to support trial design. But the consensus holds that the timing of intervention is also critically important; while symptomatic drugs are likely to be most effective at the dementia stage, disease-modifiers may require treatment at earlier stages of disease, prior to dementia or even prior to symptoms (2, 25). From its launch in 2004, the overarching aim of ADNI has been to inform the design of therapeutic trials in AD; ADNI investigators have advanced the design of pre-dementia trials in the statistical (24, 26-28) and methodological (2, 27, 29-35) literature, and with regulators in the US and abroad (27), facilitating the design of major completed and ongoing trials (avagacestat, gantanerumab, aducanumab, A4, A5 (EARLY)). These advances have included the move from time-to-endpoint designs to continuous outcome measures as primaries (27, 28), the use of biomarker-based selection (27, 28), single primary outcomes in prodromal trials (27), and cognitive composite endpoints in preclinical trials (36). The Phase 1b data on aducanumab, while limited and preliminary, are perhaps the most exciting data from any anti-amyloid study, showing a substantial, dose-related treatment effect on both brain amyloid load and clinical outcome. While the specific activity of the antibody, as well as careful management of amyloid-related imaging abnormalities (ARIA) in the study are obviously critical to the encouraging progress, the aducanumab study implemented most of the ADNI-based ideas listed above. In ADNI3 we will continue to study the optimization of subject selection criteria and composite outcome measures across the spectrum of AD, new analytical approaches for demonstration of disease modification, and the use of tau PET for subject selection, as a baseline covariate and as a potential surrogate outcome measure.
Relationship of longitudinal web-based cognitive assessment to in-person assessments, biomarkers and risk of decline. ADNI3 will build on the recent experience with web-based remote cognitive and patient-reported assessments pioneered in ongoing registries such as the Brian Health Registry and HealthyBrains.org (as well as the ongoing pilot study in ADNI2). Specifically we will use the CogState Brief Battery, which has been implemented for in-clinic and at-home use in ADNI 2 and is being use in the Brain Health Registry. Our focus will be on optimizing user interfaces to improve quality, the correlation and predictive value of cognitive and symptomatic change to in-person cognitive evaluations and biomarker trajectories (including tau PET).
Key hypotheses: 1. *Nearly all normal participants with brain amyloidosis will show cognitive decline compared to those without amyloidosis, and will progress to MCI (CDR-0.5).* Rate of progression will be influenced by baseline cognition, tau biomarkers and APOE genotype. Confirmation of this hypothesis is critical to early stage trial design and regulatory support. ADNI data support this hypothesis (Figure 3), but other data suggest more limited progression of normals with amyloidosis (37). The ADNI data are based on relatively few participants at the later time points. ADNI3 data will allow definitive conclusions on the relationship between brain amyloid as measured by amyloid PET and cerebrospinal fluid Aβ42 and cognitive and clinical (CDR-SB) trajectories, and allow assessment of the contribution of APOE genotype and biomarkers.

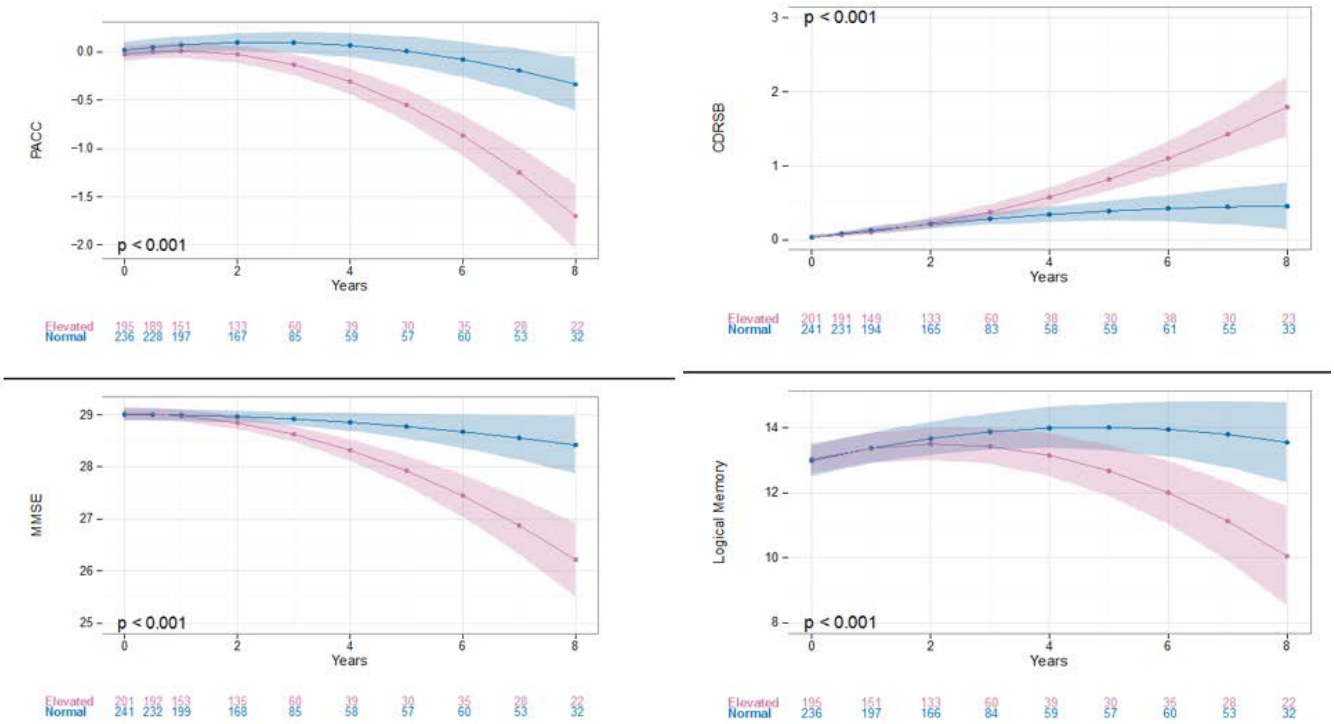

Figure 3. Cognitive profiles of participants in ADNI normal cohort by amyloid status. The profiles use linear mixed effect models controlling for age, plus other baseline covariates selected by Akaike Information Criterion (*APOE*ε4, education, and ventricular volume for the ADCS PACC and Logical Memory, education for the MMSE; and no additional covariates for CDRSB). All models treat time as continuous and include a quadratic term. P-values are from likelihood ratio tests comparing models with versus without Amyloid group. Shaded regions represent 95% confidence intervals.

2. *Early stage AD cognitive decline predicts later functional and clinical decline.* Clinical trials in preclinical AD rely on composite cognitive measures as primary outcomes. But such measures cannot demonstrate clinically meaningful treatment effects. For both scientific and regulatory concerns, it is essential to establish the relationship between cognitive decline in preclinical AD and later functional and clinical change indicative of clinically meaningful decline. As shown in Figure 3, amyloid elevation in preclinical AD is associated with eventual clinical change, as indicated by the CDR score (CDRSB). ADNI3 will provide the follow-up to confirm this finding, and extend it to other clinically meaningful measures including the Functional Activities Questionnaire (FAQ) and ECog, and demonstrate the association between cognitive change and progression to MCI.

3. *The course of cognitively normal and MCI participants is influenced by APOE genotype, baseline cognitive performance, cerebrospinal fluid amyloid and tau biomarkers, and amyloid and tau PET scan results.* Much effort in AD drug development now focuses on the prodromal stage, i.e. MCI with biomarker evidence of AD pathology. Continued characterization of this population is important for the design of such studies, informing subject selection, selection of outcome measures, duration of treatment and analysis plans. Tau PET imaging in particular holds great promise as an indicator of stage among individuals with prodromal AD, and as a potential indicator of disease-modifying effects of interventions.

4. *AD-related cognitive decline can be captured by unsupervised web-based testing at the preclinical and prodromal stages. Web-based registries will facilitate recruitment for ADNI (and therapeutic trials).* With the emphasis of moving earlier in the clinical spectrum in an attempt to capture the evolving disease process at its earliest stage, ADNI has begun exploring computer-assisted cognitive measures to “screen” participants more efficiently on a broad scale. CogState has an extensive history of use in multiple studies including AIBL, the Mayo Clinic Study of Aging (MCSA), A4, the Harvard Brain Aging Study, DIAN and others. Data from the MCSA demonstrate that CogState can be used effectively in the clinic using personal computers, iPad’s, and at home in an unsupervised setting (38). Based on experience with unsupervised cognitive testing in BHR that demonstrates close correlation between in-person and unsupervised testing, and external data establishing the utility of CogState scores in measuring amyloid-related cognitive change, we are optimistic regarding the utility of web-based testing. Having established the methods and feasibility in the current ADNI pilot, we will incorporate semiannual unsupervised CogState testing of participants in all ADNI3 cohorts. This will provide essential guidance for the use of web-based testing to evaluate candidates for trials, and as outcome

measures. This may facilitate large simple trial designs for testing the impact of low-risk interventions on AD-related decline. BHR has been studying the use of web methods to gather and retain older individuals interested in AD-related trials: characterizing them in terms of demographics, medical comorbidity, lifestyle factors and cognition, and following them longitudinally with periodic cognitive testing.

Analysis Plan. The approach to the analyses of the ADNI3 clinical data is described in the Biostatistics Core section. In brief, enrollment and retention, drop-outs, cross-sectional features and longitudinal progression will be described and reported (at ADNI meetings and in summary papers), as shown for ADNI2 in Figure 1, above. The analysis of Hypotheses 1 and 2 involves data spanning all phases of ADNI. Hypotheses 3 and 4 involve new measures only captured in ADNI3.

Hypothesis 1. *All or almost all normal participants with brain amyloidosis will show cognitive decline compared to those without amyloidosis, and will progress to MCI (CDR-0.5).* We extend the logistic mixed effects models represented in Figure 2 out to 10 years. These are standard models appropriate for longitudinal binary data. Assuming the rate of CDR 0.5 progression at 10 years is 90%, and we observe n=30 subjects with elevated amyloid, we should have good precision (95% confidence interval width at most 24%). Secondary analyses will include multiple imputation and causal model estimates of the amyloid effect(39).

Hypothesis 2. *Early stage AD cognitive decline predicts later functional and clinical decline.* We use a two-stage model in which we (1) obtain subject-level estimates of cognitive (PACC, Preclinical Alzheimer's Cognitive Composite [36], the primary outcome measure in the A4 trial) rate of change over the initial two years; and (2) use these cognitive change estimates as predictors in a second stage model of functional decline (FAQ) over 10 years. Both stages of this two-stage model can be fit simultaneously using Bayesian techniques (MCMC sampling). Assuming that we capture year 10 visits for N=100 NL subjects and pilot estimates based on existing FAQ data (random intercept sd=0.7, random slope sd= 0.5, residual sd=1.3), we will have 80% power to detect an effect as small as 0.20 FAQ units per PACC unit change per year.

Hypothesis 3. *The course of cognitively normal and MCI participants will be influenced by APOE genotype, baseline cognitive and functional performance, cerebrospinal fluid amyloid and tau biomarkers, and amyloid and tau PET scan results.* The analysis for Hypothesis 3 follows the approach described in Biostatistics Section C1.1, and power is described in Section C1.6. Sample sizes for hypotheses that involve NC subjects and newly added variables (e.g. tau PET imaging and CogState) will be most limited. For example, we anticipate collecting N=428 tau PET scans from NL subjects at baseline. If we split the sample into the 1/3 vs 2/3 most and least pathological tau PET scans (N=285 low vs N=143 high tau PET) and compare PACC trajectories over 4 years, we will have 80% power to detect group differences as small as 0.29 points (assuming two-side α=5% and ADNI pilot estimates of within-subject correlation ρ=0.68, 34% attrition, and residual σ=0.90 (40). As a comparison, we observe *amyloid* group differences in PACC as small as 0.26 points (SE=0.08, p=0.002) at 4 years. Similarly we have 80% power to detect group differences of 0.50 MMSE points and 0.019% ICV of hippocampal volume. For the MCI cohort (N=425), we project 80% power to detect group differences as small as 0.8 PACC points, 1.8 MMSE points, and 0.027% ICV of hippocampal volume. We anticipate collecting year 4 data from about N=282 NL (N=243 MCI) subjects. This will provide 80% power (two-sided α=5%) to detect *correlations of change* between any two measures as small as ρ=0.17 (0.18). For *cross-sectional correlations at baseline*, N=428 NL (N=425 MCI) will provide 80% power to detect correlations as small as ρ=0.13 (0.14).

Hypothesis 4. *AD-related cognitive decline can be captured by unsupervised web-based testing at the preclinical and prodromal stages*, and w*eb-based registries will facilitate recruitment for ADNI (and therapeutic trials).* We will build predictive random forest models (41) of in-person cognitive assessments and study eligibility based on BHR and CogState pilot data from ADNI2. We will use these models to prospectively predict eligibility of new ADNI3 participants. We will test the effectiveness of this approach by comparing the screen fail rate for BHR vs traditional recruitment. BHR will be targeting N=40,000 registrants in 10 cities and we anticipate that 23% (N=9,200) of the registrants will be eligible for screening for ADNI. The ADNI2 screen fail rate, using traditional recruitment, was 35%. If we invite N=135 registrants to undergo in-person screening, we will have 80% power (two-sided α=5%) to detect an improvement in the screen fail rate from 35% to 24%. As mentioned under Hypothesis 3, N=428 NCs will provide 80% power to detect cross-sectional correlations between CogState One-Card Learning and in-person measures (LMII and ADAS Delayed Word Recall) as small as ρ=0.13.

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OMB Number: 4040-0001
Expiration Date: 06/30/2016

APPLICATION FOR FEDERAL ASSISTANCE

SF 424 (R&R)

5. APPLICANT INFORMATION **Organizational DUNS*:** 6133387890000

Legal Name*: NORTHERN CALIFORNIA INSTITUTE FOR RESEARCH AND EDUCATION
Department:
Division:
Street1*: 4150 CLEMENT STREET (151-NC)
Street2:
City*: SAN FRANCISCO
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 941211545

Person to be contacted on matters involving this application

Prefix:	First Name*:	Middle Name:	Last Name*:	Suffix:
	Azarah	Sr. Grant Specialist	Wong	

Position/Title:
Street1*: 4150 CLEMENT STREET (151-NC)
Street2:
City*: SAN FRANCISCO
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 941211545
Phone Number*: 415-750-6954 x 23891 Fax Number: 415-750-9358 Email: cgawards@ncire.org

7. TYPE OF APPLICANT* M: Nonprofit with 501C3 IRS Status (Other than Institution of Higher Education)

Other (Specify):

Small Business Organization Type ❍ Women Owned ❍ Socially and Economically Disadvantaged

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
PET Core

12. PROPOSED PROJECT

Start Date*	Ending Date*
08/01/2016	07/31/2021

OMB Number: 4040-0010
Expiration Date: 06/30/2016

Project/Performance Site Location(s)

Project/Performance Site Primary Location

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: UC Berkeley
Duns Number: 1247267250000
Street1*: 132 Barker Hall
Street2: UC Berkeley
City*: Berkeley
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 94720-3197
Project/Performance Site Congressional District*: CA-009

Project/Performance Site Location 1

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: University of Pittsburgh
DUNS Number: 0045143600000
Street1*: PET Facility, 9th Floor B-Wing PUH
Street2: 200 Lothrop Street
City*: Pittsburgh
County: Allegheny
State*: PA: Pennsylvania
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 15213-3583
Project/Performance Site Congressional District*: PA-014

Project/Performance Site Location 2

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Banner Health dba Banner Alzheimer's Institute
DUNS Number: 7882406740000
Street1*: 901 East Willetta St.
Street2:
City*: Phoenix
County: Maricopa
State*: AZ: Arizona
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 85006-2727
Project/Performance Site Congressional District*: AZ-007

Project/Performance Site Location 3

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:	Northern California Institute for Research and Education
DUNS Number:	6133387890000
Street1*:	4150 Clement St.
Street2:	VAMC Building 13
City*:	San Francisco
County:	San Francisco
State*:	CA: California
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	94121-1545
Project/Performance Site Congressional District*:	CA-012

Project/Performance Site Location 4

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:	Regents of the University of Michigan
DUNS Number:	0731335710000
Street1*:	3003 S. State Street
Street2:	
City*:	Ann Arbor
County:	Washtenaw
State*:	MI: Michigan
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	48109-1274
Project/Performance Site Congressional District*:	MI-012

File Name

Additional Location(s)

PET Core: Project Summary/Abstract

The standardization of PET data acquisition, processing, and analysis developed through ADNI has been crucial for subject selection and treatment monitoring as clinical trials have moved to earlier stages of AD with mild or absent symptoms. This next phase of the ADNI PET core will continue these advances by incorporating two new developments in PET research: (1) the availability of multiple PET ligands for imaging brain β-amyloid and (2) the availability of PET ligands for imaging tau deposition. With regard to the former, it is increasingly important to understand how results from one amyloid imaging tracer will generalize to others. Therefore, we propose the use of 2 amyloid imaging agents – [^{18}F]florbetapir and [^{18}F]florbetaben – to assess participants from all subject groups. Carryforward subjects will be continued on florbetapir, while newly enrolled subjects will receive florbetaben. We will compare data by transforming all quantitative values to a 0-100 "centiloid" scale using published and validated methods. Tau imaging is a fast-moving field and there is now a tau PET ligand, [^{18}F]AV1451 (originally known as T807) that shows favorable *in vitro* and *in vivo* characteristics. Substantial preliminary data are available with this compound, which also has the advantage that it can be delivered to all ADNI sites. All ADNI participants will undergo tau PET imaging with AV1451; however, we realize that other tau PET ligands are in development and therefore we have a plan to review this field and add additional ligand(s) as available. All ADNI participants will continue to receive amyloid scans every 2 years, and all will receive tau scans at the beginning and conclusion of the study, with additional tau PET scans obtained based on diagnosis and amyloid status according to the following protocol: all AD patients will have 3 tau scans at yearly intervals, all control and MCI subjects will receive a tau PET scan at the beginning and end of the study, with 80% of amyloid positive and 20% of amyloid negative subjects receiving 2 additional scans for a total of 4 tau PET scans over the 5 year study. All subjects will have glucose metabolism measured with PET at the baseline exam. Data analysis will use existing ADNI approaches for glucose and amyloid imaging. Tau imaging data analysis will employ a region of interest method that defines brain areas that parallel Braak staging to characterize tracer retention in these Braak regions, as well as a voxelwise index of the amount and distribution of total tau tracer retention. These data will be used in multivariate models to validate tau imaging based on its association with cognitive function and change in cognition over time. Analytic approaches will also stress examination of how each biomarker, alone and in combination, predicts change over time in order to model subject selection for clinical trials. In addition, longitudinal change in tau PET will be examined in order to assess the sample sizes that would be necessary to detect clinically relevant therapeutic effects.

PROFILE - Senior/Key Person

Prefix: First Name*: SUSAN Middle Name M Last Name*: LANDAU Suffix:

Position/Title*:
Organization Name*: University of California Berkeley
Department: Neuroscience Institute
Division:
Street1*: 132 Barker Hall
Street2:
City*: BERKELEY
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 947203190

Phone Number*: (510) 642-2839 Fax Number: (510) 643-4966 E-Mail*: SLANDAU@SOCRATES.BERKELEY.EDU

Credential, e.g., agency login: slandau

Project Role*: Other (Specify) Other Project Role Category: Research Neuroscientist

Degree Type: PHD,MA,BA Degree Year:

File Name
Attach Biographical Sketch*: Landau_BioSketch_Sept2015.pdf
Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: Robert Middle Name A Last Name*: Koeppe Suffix:

Position/Title*: Professor
Organization Name*: UNIV OF MICHIGAN MED CTR
Department: RADIOLOGY- NUCLEAR MEDICINE DE
Division:
Street1*: 3003 S. State Street
Street2:
City*: ANN ARBOR
County:
State*: MI: Michigan
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 481091274

Phone Number*: (734) 763-9247 Fax Number: 734-764-0288 E-Mail*: KOEPPE@UMICH.EDU

Credential, e.g., agency login: koeppe

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: PHD,MS,BS Degree Year:

File Name
Attach Biographical Sketch*: Koeppe_Bio_DIANTU_ADNI3_0915.pdf
Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: CHESTER Middle Name A Last Name*: MATHIS Suffix: Ph.D

Position/Title*: Professor
Organization Name*: University of Pittsburgh
Department: Radiology
Division: PET Facility, B-938, PUH
Street1*: 200 Lothrop St
Street2:
City*: Pittsburgh
County: Allegheny
State*: PA: Pennsylvania
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 152130000

Phone Number*: 412-647-0736 Fax Number: E-Mail*: mathisca@upmc.edu

Credential, e.g., agency login: mathis

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: PHD Degree Year:

File Name
Attach Biographical Sketch*: Biosketch_Mathis.pdf
Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: Julie Middle Name C Last Name*: Price Suffix: Ph.D

Position/Title*: Professor
Organization Name*: University of Pittsburgh
Department: Radiology
Division:
Street1*: PET Facility, PUH B938
Street2: 200 Lothrop Street
City*: Pittsburgh
County:
State*: PA: Pennsylvania
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 152130000

Phone Number*: 412-647-0736 Fax Number: E-Mail*: pricejc@upmc.edu

Credential, e.g., agency login: pricejc

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: PHD,MS,BS Degree Year:

File Name
Attach Biographical Sketch*: Biosketch_Price.pdf
Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: Eric Middle Name Michael Last Name*: Reiman Suffix:

Position/Title*: Executive Director
Organization Name*: Banner Health
Department: Banner Research
Division: Banner Alzheimer's Institute
Street1*: 901 E. Wiletta Drive
Street2:
City*: Phoenix
County:
State*: AZ: Arizona
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 850060000

Phone Number*: 602-239-6999 Fax Number: E-Mail*: Eric.Reiman@bannerhealth.com

Credential, e.g., agency login: ereiman

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: MD,BS Degree Year:

File Name

Attach Biographical Sketch*: Biosketch_Reiman.pdf

Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: Kewei Middle Name Last Name*: Chen Suffix:

Position/Title*: Sr. Biomathematician, lab director
Organization Name*: Banner Health
Department: Image Processing & Analysis
Division: Banner Alzheimers Institute
Street1*: 901 East Willetta Street
Street2:
City*: Phoenix
County:
State*: AZ: Arizona
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 850060000

Phone Number*: 602-839-4851 Fax Number: E-Mail*: kewei.chen@bannerhealth.com

Credential, e.g., agency login: kewei-chen

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: PHD Degree Year:

File Name

Attach Biographical Sketch*: Biosketch_Chen.pdf

Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: Duygu Middle Name Last Name*: Tosun-Turgut Suffix:

Position/Title*:
Organization Name*: NORTHERN CALIFORNIA INSTITUTE FOR RESEARCH AND EDUCATION
Department:
Division:
Street1*: 4150 Clement St. VAMC, Bldg 13
Street2:
City*: San Francisco
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 941210000

Phone Number*: 4152214810 ext 4800 Fax Number: E-Mail*: duygu.tosun@ucsf.edu

Credential, e.g., agency login: dtosun

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: PHD,MA,MS,BS Degree Year:

File Name

Attach Biographical Sketch*:

Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: William Middle Name J. Last Name*: JAGUST Suffix:

Position/Title*: Professor
Organization Name*: University of California Berkeley
Department: Neuroscience Institute
Division:
Street1*: 132 Barker Hall
Street2:
City*: Berkeley
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 947208119

Phone Number*: (510) 486-5065 Fax Number: 510-486-4768 E-Mail*: WJJagust@lbl.gov

Credential, e.g., agency login: wjjagust

Project Role*: Other (Specify) Other Project Role Category: PET Core Lead

Degree Type: MD,BA Degree Year:

File Name

Attach Biographical Sketch*: Jagust_NIH_Biosketch.pdf

Attach Current & Pending Support:

PET CORE: SPECIFIC AIMS

The overall goal of the ADNI PET core is to validate PET in clinical trials by standardizing the acquisition, processing, and analysis of β-amyloid-, tau- and FDG-PET for all ADNI participants. The ADNI PET Core was focused on FDG-PET in a 50% subsample of participants at the start of the project. Subsequently, a small pilot multisite [^{11}C]PIB study was undertaken. Most recently imaging of β-amyloid with [^{18}F]florbetapir was performed in all participants every 2 years, along with continuation of FDG-PET. The first ADNI Florbetapir PET scan was acquired in May 2010; as of August 2015 60% of subjects have had a 2nd scan and about 10% have had a 3rd scan. ADNI open access policies have enabled extensive data analysis and helped in the design of worldwide clinical trials that use PET imaging. Based in large part on this work accomplished in ADNI, amyloid imaging has become a key component of subject selection and treatment evaluation in clinical trials.

Two new features resulting from changes in the PET dementia imaging landscape characterize our approach to ADNI3. The first is the maturation of the field of amyloid imaging, with multiple [^{18}F]-labeled agents available. A pragmatic scheme for merging PET data from different tracers uses a “centiloid” scale[1], based in part on previous ADNI work showing the ability to interconvert such measurements[2, 3]. In ADNI3 we will employ 2 amyloid imaging agents, [^{18}F]florbetapir and [^{18}F]florbetaben in order to develop a large database for use in clinical trials that is not limited to a single tracer.

A second advance is the availability of tau PET ligands. Because of its likely correlation with clinical symptoms tau may be a crucial “missing link” in explaining the effects of amyloid on brain atrophy and cognitive decline; ADNI, with a broad range of clinical severity and multiple biomarkers is an ideal setting to examine tau in relation to other outcomes. A number of programs for tau tracer development are underway; at present the compound [^{18}F]AV1451 (known in earlier developmental stages as [^{18}F]T807)[4] has the widest existing preclinical and clinical data supporting its use, and can be delivered to all ADNI PET sites. For these reasons, and in response to the RFA, we have incorporated tau imaging with [^{18}F]AV1451 in ADNI3. We also outline a plan to evaluate and incorporate different tau PET ligands as more data become available.

The operational/technical specific aims of the ADNI3 PET core are:

1. Develop and implement a standardized protocol for multisite acquisition of [^{18}F]AV1451 PET images.
2. Continue the protocol for multisite acquisition of [^{18}F]florbetapir images, and develop and implement a protocol for multisite acquisition of [^{18}F]florbetaben amyloid PET
3. Acquire amyloid PET data every 2 years in all participants, and longitudinal tau-PET data according to a stratified scheme based on amyloid positivity. Acquire FDG-PET at the baseline examination in all subjects.
4. Apply standardized quality control and processing to assure quality and comparability of all PET data.
5. Analyze data to provide standardized metrics of amyloid and tau deposition and glucose metabolism in each subject at each time point. Develop methods for tau PET data analysis that include both voxelwise and ROI-based approaches to maximize effect sizes for prediction of change and as an outcome.
6. Standardize measurement of amyloid deposition using a “centiloid” scale.
7. Maintain an administrative infrastructure for these operational tasks, interactions with other cores, site PIs, and the PPSB that will also include evaluation of new tau PET radiotracers as they become available.

These operational aims are intended to facilitate the following ***scientific specific aims***:

1. Compare baseline relationships between glucose metabolism, amyloid, tau PET measures and cognition.
2. For AD clinical trial subject selection: characterize and compare how baseline measures of amyloid, tau and glucose metabolism predict longitudinal cognitive decline.
3. Crucial to the use of tracers as possible outcomes in clinical trials: Track longitudinal changes in these measurements, estimate sample sizes needed to detect treatment effects
4. Characterize and compare the relationships between amyloid, tau, and cognition longitudinally to define how changes in amyloid and tau relate to each another, and how they relate to change in cognition.
5. Evaluate how combining different amyloid imaging agents into a single analysis affects the ability to predict subsequent clinical decline, select subjects for clinical trials and measure change in amyloid deposition.
6. Examine the relationship between baseline amyloid and longitudinal changes in tau, and the relationship between baseline tau and longitudinal changes in amyloid.
7. On a multi-modal level, examine relationships between these imaging variables, brain atrophy, CSF biomarkers, presence or absence of the Apolipoprotein E4 allele, and cognition both at baseline, in prediction models, and by examining relationships between longitudinal change.

The overall impact of this core will be to validate PET in clinical trials especially with regard to the potentially high impact of tau PET as a biomarker and its possible use as a surrogate marker in clinical trials.

PET Core: Research Strategy

SIGNIFICANCE

In large part due to the work done in ADNI, PET amyloid imaging is now a major component of clinical trials in AD, used for subject selection and for monitoring treatment effects. ADNI has shown the feasibility of large-scale multicenter trials using amyloid PET, and has developed widely adopted methods for acquiring, processing, and analyzing PET data. Now, because of the availability of PET imaging agents that bind to paired-helical filament (PHF) tau, we can examine the role of tau in AD development and pathogenesis and thereby have a specific biomarker that reflects neurodegeneration, where previously such biomarkers were nonspecific measures like brain atrophy and glucose hypometabolism. Data from both neuropathology and early tau PET imaging suggests that tau deposition will bear a stronger relationship to symptomatology than does Aβ[5, 6]. Tau imaging may be useful for subject selection and stratification for clinical trials, particularly enabling subject selection in a "sweet spot" for a clinical trial – progressed enough to evidence change over time, but not so advanced for treatment to be hopeless. Most importantly, tau may be a useful outcome measure either for tau-based therapeutics or for other approaches in phase 2 or 3 trials. Thus the addition of tau imaging to clinical trials is an important next step in clinical trial design paving the way for use as a potential surrogate biomarker and its comparison to other biomarkers of disease stage and severity.

This renewal of ADNI has one other major important feature in the PET core – the addition of a second amyloid imaging agent. The current availability of multiple amyloid imaging agents that are FDA approved ([^{18}F]-florbetapir, florbetaben and flutemetamol) has enhanced the ability to do clinical trials. However this also raises questions as to how data from multiple tracers can be combined in a single study. Standardization across amyloid imaging agents, a key feature of this phase of ADNI, will be accomplished through the conversion of raw PET data into standardized centiloid units, a process recently proposed in detail that reports amyloid tracer retention on a 0-100 scale using [^{11}C]PIB as a reference[1]. We plan to study approximately 700 continuing participants with florbetapir and ~300 new participants with florbetaben which is also an autopsy-validated tracer[7]. All data will be available for combined analysis after centiloid conversion, and also for comparison in native retention units.

INNOVATION

There are several major innovative aspects to this project:

- Tau imaging – a new approach to tracking the molecular pathology on the aging/AD continuum
- ADNI is unique in including a large scale, study of longitudinal tau PET, FDG and amyloid PET, CSF biomarkers, and open-access data sharing without embargo.
- Use of multiple amyloid imaging agents with plans for data harmonization using centiloids

APPROACH

Selection of the tau imaging agent: As noted, the tracer with the widest application to tau imaging as of October 2015 is [^{18}F]AV1451 (T807). This tracer has been shown in preclinical studies to bind to PHF-tau and clearly separate AD patients from controls[4]. A very recent paper using autoradiography including postmortem tissue shows high specificity for intra- and extraneuronal tangles and dystrophic neurites without binding to Aβ, α-synuclein or TDP-43[8]. Its uptake parallels clinical symptoms in AD, in contrast to the nearly absent relationship between Aβ and clinical presentation[6]. We recognize that this tracer has 2 major problems: slow pharmacokinetics and off-target binding. Neither of these problems appear to be crucial. Data from the PI's laboratory in Berkeley shows that dynamic PET data from 0-150 min, when analyzed as a distribution volume ratio (DVR), is highly correlated (slope = 1.02, R^2=.96) with early data obtained from 80-100 min (figure 1). This indicates that early frame image acquisition do not suffer appreciably because of the slow kinetics. Off target binding in brainstem and basal ganglia has been suggested to be related to MAO-A[9] but this does not seem a likely explanation for the PET signal given the low abundance of the enzyme in brain and its distribution, which does not parallel these regions[10]. In any case this binding does not appear to affect cortical measurements that are crucial in aging and dementia. Substantial data have been collected by Avid radiopharmaceuticals, the Harvard/MGH group, and the Berkeley group. These data have been presented at many international conferences and preliminary data are included in this application. A distribution network is available for delivery to all ADNI sites. We feel that the opportunity for novel insights gained by imaging tau

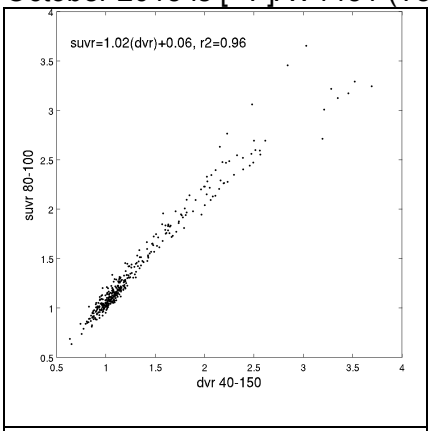


Figure 1: DVR (40-150 min) vs SUVR (80-100 min, cerebellar gray reference region) for 23 older controls and 16 AD patients. R^2=.96

greatly outweighs the limitations of the tracer. In addition, there are other ligands that are potentially available[11]. An in-depth review of the pros and cons of each compound is beyond the scope of this grant, but several groups have programs for the development of tau ligands. Based on requirements listed below, compounds indicated in figure 2 appear to be potential ligands for large scale human studies. Before the start of ADNI3 (when we receive word on the possible funding of the project), we will survey the field of tau imaging agents. A committee will be established for evaluation and possible selection of tau imaging agents. It will be chaired by Chester Mathis, PhD (University of Pittsburgh) and will include William Jagust MD, Eric Reiman MD, and 2 members selected by the Private Partners Scientific Board (PPSB). These members will represent companies that do not have tau imaging agent development programs. This committee will survey the field of available agents and will evaluate each according to the criteria below. These are ideal criteria, recognizing that all information may not be available for each tracer. The committee will report to the ADNI Executive Committee, which will make all final decisions on the recommendation of the committee.

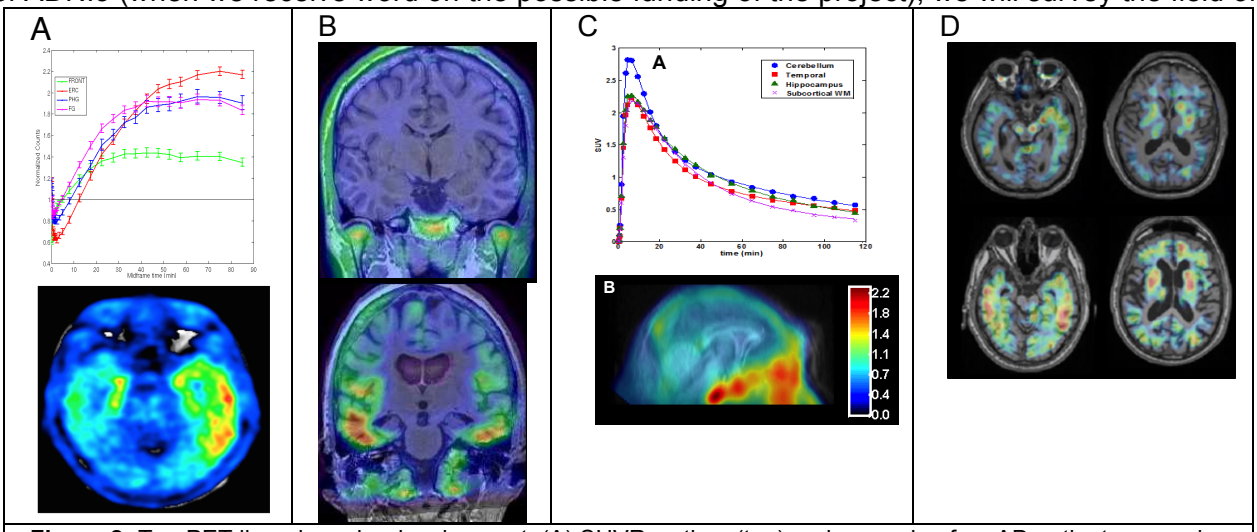


Figure 2: Tau PET ligands under development: (A) SUVR vs time (top) and example of an AD patient scan using [^{18}F]THK5351 (bottom) (B)Control (top) and AD Patient (bottom) scanned with [^{18}F]RO6958948 (C) time activity curve (top) and summed image 40-80 min of [^{18}F]MK-6240 in rhesus monkey (bottom) (D SUVR images, 69yr old control (MMSE 29, top) and 73 yr old AD Patient (MMSE 22, bottom) scanned with [^{18}F]PI-2014.

Preclinical criteria: High affinity for PHF-tau (Kd or Ki <10 nM), high selectivity for tau over Aβ (at least 10-fold and a Kd or Ki value for Aβ >30 nM), high brain extraction (whole brain SUV >2 at early times after injection), rapid clearance from normal brain (early to late time ratios >2), moderate lipophilicity (logD7.4 ~1-3), low background binding to white matter (SUV <0.5 at late times), no brain penetrating radiometabolites.

Clinical criteria: Available human imaging data in a reasonable number of subjects (~50-75) with different relevant diseases/stages (normal controls, MCI, AD), pharmacokinetic data sufficient for planning PET data acquisition protocols within 90 min or less following injection, information on metabolism in humans, a clear pathway to quantitative data analysis that is robust, data on tracer reliability, interpretable human data that can be linked to tau by face validity (consistent with known tau neuropathology). Ideally full kinetic modeling data will be available and late time ratios (SUV ratios relative to cerebellum) will be minimally biased (<20%) relative to BPND values. There must also be a plan for managing regulatory issues (i.e., an IND and IRB approvals at all sites), a commitment to cover the relevant costs, and delivery to a reasonable number of ADNI sites. Current tau imaging tracers that have already been studied in humans include THK5351 (GE), PI-2014 (Piramal), and R06958948 (Roche), while MK-6240 (Merck) has been studied *in vitro* and monkeys. Preclinical work for all of these compounds indicates that they meet the criteria listed above. For the compounds with human data, pharmacokinetics are favorable and initial studies indicate binding in a pattern that reflects tau accumulation in AD. By mid-2016 we expect that a number of compounds will be available for use in ADNI and the final compound(s) in addition to AV1451 will be chosen.

Administration/Management Plan: We will continue the successful management strategy used in ADNI to date. Dr. Jagust will participate in all executive committee conference calls and meetings and will thereby regularly interact with Dr. Weiner, other core leaders, NIA representatives, and industrial partners. He will also participate in meetings of the Steering Committee, Private Partners Scientific Board (PPSB), External Advisory Committee, and international ADNI meetings as necessary. Current management of the PET core relies on monthly conference calls involving all of the major PET laboratories as well as advisors and representatives from the PPSB. These calls are concerned with planning, operations, logistics, data analysis, and publications.

The PET group also meets in person in conjunction with the Steering Committee meetings. The PET core, under the leadership of the Core leader will also have the responsibility for working closely with the Clinical Core in drafting procedures and startup. This will entail updating protocols and technical manuals to include tau PET imaging and florbetaben imaging, as well as reviewing IRB documents and regulatory documents. We will interact with ATRI and radiopharmaceutical manufacturers in the preparation of IND materials for tau imaging.

Image Acquisition: Site qualification has been thoroughly developed through previous phases of ADNI. We anticipate that all current ADNI sites will participate in ADNI3 with no need for re-qualification. Requalification occurs with scanner changes or new sites, and entails scanning of an ^{18}F-filled Hoffman brain phantom with a standard protocol. A library of such phantom images is maintained at the University of Michigan QA/QC core for processing of PET data to a common resolution[12].

Amyloid data acquisition with florbetapir will continue on all currently enrolled subjects who are carried through from ADNI2 to ADNI3; we anticipate that there will be ~700 such individuals. This protocol entails the injection of 10 mCi of florbetapir followed by 4 x 5 min scans beginning 50 min post injection. For all image acquisitions, attenuation correction will use either CT or PET transmission data, and reconstruction will use site-specific iterative algorithms. Detailed metadata on the scans are collected at all imaging visits. Approximately 300 new subjects are expected to be recruited into ADNI3; these individuals will undergo florbetaben PET imaging. The image acquisition protocol for florbetaben will entail injection of approximately 8 mCi of tracer, followed by a 20 minute acquisition as 4 x 5 min frames of emission data from 90-110 min[7].

Tau Imaging subject selection/preliminary data: All ADNI3 participants will undergo longitudinal tau imaging according to the schedule outlined in the Overview section. All AD subjects will undergo a tau PET scan at each of the 3 time points at which they are evaluated (baseline, 12 months, 24 months; amyloid PET at baseline and 24 months). All control and MCI subjects will receive a tau PET scan at the baseline examination (which will occur in either year 1 or 2) and in the last year of the project. Cross-sectional neuropathological data suggest that brains with Aβ plaque pathology have more tau pathology and increased rates of tau deposition with age[13]. These data are supported by the preliminary cross-sectional data from Berkeley (see below) showing greater tau accumulation in those with more Aβ. Preliminary data from Avid have shown high test-retest reliability for AV1451, with mean change across ROIs of 1% and ICC values of >0.93[14]. For 33 cognitively impaired older subjects (Mean MMSE = 24), baseline tau SUVRs in temporal cortex averaged 1.446 (SD= 0.379) and change averaged 0.0505 SUVR units (SD=0.0800) over 10 months (statistically significant paired t-test at p=0.001). Similar values were seen in other regions. Based on the likelihood that amyloid negative subjects will show slower rates of tau deposition, 80% of amyloid positive subjects and 20% of amyloid negative subjects will receive 2 additional annual tau PET scans. Projected samples are therefore174 AD patients with 3 tau PETs, 128 controls and 173 MCI patients with 4 tau PETs, and 209 controls and 137 MCIs with 2 tau PETs. This collects extensive longitudinal data, use of resources to track the most likely tau accumulators, and avoids releasing amyloid status to participants.

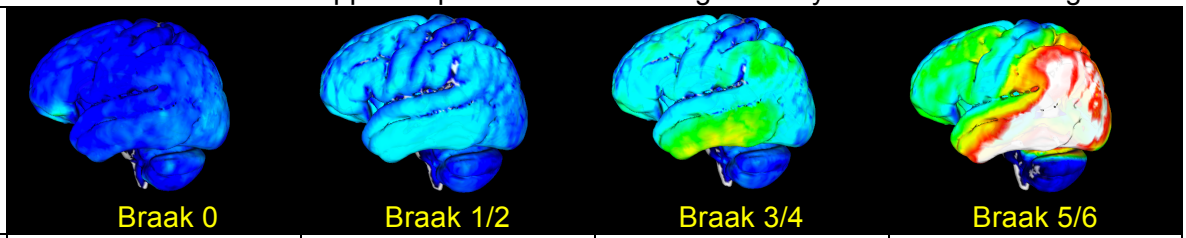
Tau data acquisition: The data acquisition protocol for AV1451 has already been implemented in the ADNI pilot project, and entails injection of ~10 mCi of tracer. Subjects are scanned beginning at 75 min post tracer injection, for 30 minutes as 6 x 5 min frames. The longer imaging frame than 80-100 min will allow us to adjust for incorrect timing, and also to examine different time frames as needed; data analysis will use 80-100 min. FDG-PET will be performed at the baseline examination (i.e., the first ADNI3 visit) using the standard ADNI protocol of a 5 mCi injection with 30 min of imaging from 30-60 min post injection.

Data flow, QC, and preprocessing: All PET scans will be run through the same stringent quality control (QC) procedures as currently performed in ADNI-2. QC includes a statistical noise check, motion assessment across temporal frames, checking for full coverage of the brain, visual checks to look for common PET artifacts (such as normalization issues or motion between attenuation and emission scans), as well as visual and image header checks to assure that the ADNI protocol has been followed. Routines read and convert original raw PET image sets to a standard file format. The sequence of temporal frames are co-registered to the first frame of each scan, and both a dynamic image set, as well as a single averaged-frame image set are produced in the original patient orientation and with the original pixel grid and intrinsic plane spacing for that scanner. In addition, the baseline FDG image for each subject is re-oriented to a common standard spatial orientation and interpolated onto a uniform image grid of 1.5 mm^3 voxels. Scans at baseline and all subsequent time points for amyloid and tau tracers will be registered to the standardized FDG scan and intensity normalized. Thus, all PET images for a given subject will have an orientation and image grid suitable for applying a single set of VOIs to each scan. In the final processing step, images are smoothed with a scanner-specific 3D-Gaussian filter derived from Hoffman phantom scans acquired for each scanner model used in ADNI. This filtering step

provides a common isotropic resolution of 8 mm FWHM across all PET scans. Using an image mask obtained from FDG normalization, the global correlation and RMSE are calculated between longitudinal scans (separately for amyloid and tau tracers). Global correlation and RMSE measures have proven to be sensitive for flagging problematic scans. Following completion of the QC process and the passing of a PET scan, four sets of "pre-processed" PET images sets in DICOM format will be uploaded to LONI; the co-registered (i) dynamic and (ii) averaged image sets in the original scan orientation and matrix, and the intensity scaled image sets in the common orientation and voxel-size, both (iii) unsmoothed and (iv) smoothed to 8mm FWHM.

Data analysis: Plans for data analysis of FDG and amyloid images will use existing approaches, which have been extensively published[15, 16]. Berkeley, Banner Alzheimer Institute, and Dr. Tosun at UCSF will analyze tau PET data and Pittsburgh will be responsible for centiloid conversion of all amyloid imaging data.

Berkeley data analysis: For quantification of Aβ with florbetapir, we will continue to use a ROI approach for both target and reference regions with FreeSurfer-defined whole cerebellum as the reference ROI and a suite of cortical ROIs in which Aβ deposition is common as the target ROI[2]. For tau imaging, in which topography appears to be more crucial than for Aβ, we will begin by exploring region-of-interest (ROI) based approaches, grouping ROIs according to Braak staging. We will continue to use contemporary T1 MRIs segmented and parcellated with Freesurfer 5.1 to define grouped ROIs in Braak stages according to the following scheme: Braak 1/2: entorhinal cortex, hippocampus, Braak 3/4: parahippocampal gyrus, lingual gyrus, amygdala, inferior and middle temporal cortex, temporal pole, thalamus, caudal/rostral/posterior cingulate, insula; Braak 5/6: frontal, parietal, occipital, transverse/superior temporal cortex, precuneus, banks of superior temporal sulcus, nucleus accumbens, caudate, putamen, pre- and post-central gyri, paracentral gyrus, cuneus, pericalcarine ctx. All data will be examined as both "raw SUVRs" and also will be atrophy corrected using the Rousset method[17, 18]. We have preliminary data based on work in Berkeley using [^{18}F]AV1451 and 80-100 min SUVR data (normalized to cerebellar gray). We used a conditional inference tree (R package "party/ctree") to sequentially define thresholds in each set of Braak ROIs. All subjects were initially included, and as the highest threshold was defined, those subjects were removed from subsequent analyses. In this way, individuals above the threshold in the Braak 5/6 aggregate ROI (SUVR = 2.66) were classified as Braak 5/6, those above the 3/4 threshold in that group of ROIs (SUVR = 1.7) were classified as Braak 3/4, and those above the threshold in the 1/2 aggregate ROIs (SUVR = 1.39) were classified as Braak 1/2, with the remainder classified as Braak 0. Figure 3 shows the results of this classification approach. All young controls were classified as Braak 0, and most old controls were either stage 1/2 or 3/4; most AD patients were Braak 5/6 (figure 3). Higher PIB retention and smaller hippocampal volumes were significantly associated with higher



	Braak 0	Braak 1/2	Braak 3/4	Braak 5/6
Subjects	5 YC/2OC	20 OC	6 OC/2AD	13 AD
PIB DVR	1.01	1.13	1.27	1.81
Hipp volume	.54	.44	.41	.44

Figure 3: Results of Braak staging. Top row of images shows average images of all subjects in each Braak stage group. Subjects indicate classification by group, YC=young controls (N=5), OC=old controls (N=28). Hippocampal volume trend by Braak stage and PIB DVR were significant even excluding AD patients. ROIs selected using FreeSurfer, atrophy corrected with Rousset algorithm.

Braak stage even excluding AD (AD patients comprised a particularly young and hippocampal sparing phenotype recruited from UCSF). We also found a strong correlation (β=-3.191, p = .008) between performance on a standard laboratory episodic memory factor score and AV1451 retention in Braak 1/2 ROIs in the old controls, and strong correlation between global cogntion and AV1451 retention in Braak 3/4 and 5/6 ROIs. Thus, we plan to use a similar approach initially with ADNI data. We will generate exploratory thresholds using this approach in Berkeley data (we expect 50 controls and 50 AD patients to be scanned by the time ADNI 3 begins) and then examine them in ADNI data. Each subject will then be categorized into a Braak stage. For data analyses, a first approximation will simply use subjects' Braak stage, which could be a useful way of predicting change or examining other associations. We recognize that this variable may be overly summarized and therefore we will also examine SUVR within each individual's highest Braak ROI. Finally, recognizing that Braak ROIs may also not capture the full extent of tau pathology we will experiment with summary ROIs (for example, an ROI including medial temporal lobe and another ROI containing lateral temporal/parietal cortex) to

categorize total tau burden in each subject and change over time. In addition to this ROI-based approach, the BAI investigators will use voxel-based methods that can help iteratively refine how ROIs are defined.
BAI data analysis: As in ADNI-1 and ADNI-2, Banner Alzheimer's Institute will be responsible for voxel-based analyses of PET images using the SPM platform. In ADNI-3, Banner will develop statistical brain maps to characterize AV1451 tracer retention. It will also generate brain maps to provide information about the magnitude and spatial extent of SUVR increases over time in each of the groups. Figure 4 shows BAI analyses which demonstrate whole brain maps and a voxel-wise calculation of a "cerebral tau index" (CTI)

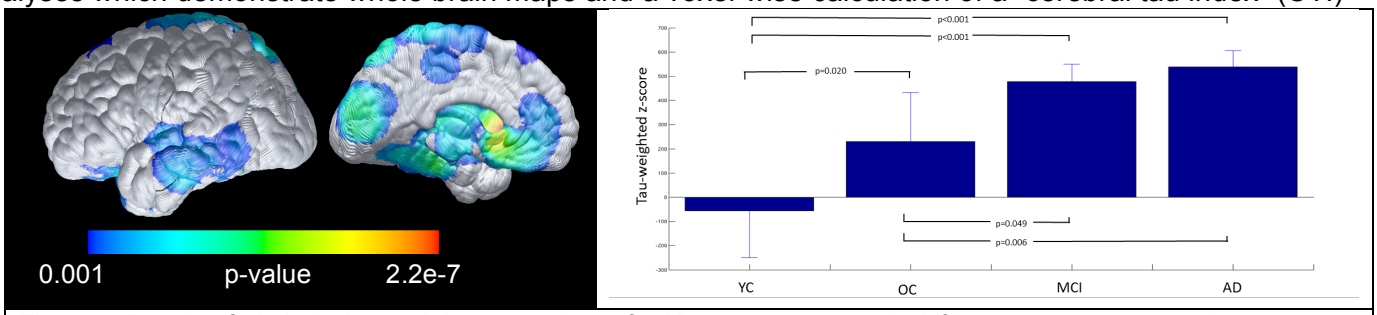


Figure 4: Results of whole-brain voxelwise comparison of 7 AD vs 5 young controls (left) are shown next to cerebral tau indices for young controls (YC), old controls (OC), MCI and AD patients (right).CTI is the z-sum from the entire image.

comparing groups of subjects. These are preliminary data from 7 AD patients, 5 MCI, 6 old controls and 5 young controls collected by Avid Radiopharmaceuticals. The CTI is calculated as the image-wide sum of z-scores relative to young controls. In these data, CTI also correlated with MMSE (r=.558 p=.016 in old controls, MCI, AD). BAI will compute individual CTIs from the sum of voxel-wise converted z-scores in each person's spatially standardized SUVR image compared to that in a young adult control group obtained from Avid and Berkeley investigators[19]. Similar to HCI, an alternative tau convergence index (CTI-AD) will be computed with proper weights to voxels inside and outside the cluster of cerebral voxels associated with significantly higher SUVRs in severe AD dementia patients (*e.g.*, patients who are Braak stages V-VI) to account for the high inter-individual location variability. The CTI and CTI-AD will be confirmed with careful cross-validations. Banner will also develop a "longitudinal tau change index" (e.g., the sum of all SUVR increases as an alternative and potentially more powerful way to track changes over time. These data will be used to compute sample sizes as described below.
UCSF Data analysis: Network diffusion models have great currency in accounting for the neuron-to-neuron spread of disease pathology in AD[20, 21]; these approaches may be useful in predicting change and measuring disease stage for translation to clinical trials. At UCSF, Duygu Tosun will perform analyses using this approach in order to validate predictions of future patterns of amyloid and tau deposition.
Pittsburgh data analysis: Standardization of PET data results across amyloid imaging agents will permit all ADNI data to be expressed on a single scale regardless of the specific ligand. The centiloid (CL)[1] process will be used to convert regional brain [^{18}F]florbetapir and [^{18}F]florbetaben SUVR outcomes to CL units through linear scaling of the SUVR data to an average value of zero in "high-certainty" Aβ-negative subjects and to an average value of 100 in "typical" Aβ-positive early to mid-stage AD subjects, using [^{11}C]PiB as reference. This project will build upon initial experience gained by the ADNI PET Core in the approximate CL conversion of ADNI [^{18}F]Florbetapir SUVR data collected within 2 years of the PiB[16]. A true CL conversion requires dual radiotracer reference data collected within a short interval, across a range of Aβ deposition. Dual radiotracer reference PiB/Florbetapir and PiB/Florbetaben datasets will be provided by Lilly (Avid) and Piramal, respectively. The dual tracer reference data were collected within the same subjects (within ~1 month interval) and consist of at least 25 subjects that are Aβ-negative and Aβ-positive (i.e., cognitively normal, MCI and AD)[1]. The CL processing will require linear conversion between: [1] the PIB and florbetapir (or florbetaben) SUVR values determined from the raw late frame dynamic (LFD) reference dataset and [2] the florbetapir (or florbetaben) SUVR determined from the raw LFD reference dataset and the ADNI-standardized reference dataset. The equations from these steps will be used to convert the individual florbetapir (or florbetaben) ADNI-standardized SUVR values to PiB-equivalent SUVR values. The final step[22] will convert these PiB-equivalent SUVR values to CL units (Eq. 1.3.a[1]). A quality control procedure will be applied to each scan to evaluate image quality, anatomical truncation (poor positioning) and motion. The PET data will be averaged over 50-70 min (PiB and florbetapir) or 90-110 min (florbetaben) post-injection. Cortical SUVR values will be computed using the CL global cortical region and whole cerebellar (WC) reference region. Statistical Parametric Mapping will be used for image registration and spatial normalization, [1, 16, 22].

Hypothesis testing: Preimary outcomes include a single metric to describe tracer retention: SUVR in the "Landau" meta-ROIs (FDG), cortical summary SUVR on the centiloid scale (amyloid), and a summary metric of SUVR in Braak ROIs (tau). Hypotheses related to each of the scientific specific aims are listed below followed by a brief description of the analytic approach; more details on analytic strategies may be found in the Biostatistics Core.

a) FDG and tau are correlated with cognition, but amyloid is not. Voxelwise FDG and tau are negatively correlated, but amyloid is not correlated with FDG.
b) Baseline PET predicts cognitive decline. Amyloid and tau will have stronger predictive power in controls than FDG, which will not be predictive in controls. In MCI all 3 PET imaging agents will predict outcomes, tau will be most predictive. This will also be tested in a multivariate model.
c) Longitudinal changes in tau will be most strongly related to cognitive decline in all subject groups. Amyloid will be very weakly related to longitudinal cognitive decline. FDG intermediate
d) 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.
e) Individuals with more brain amyloid will have more tau in neocortex. Longitudinally, those with amyloid will show increases in neocortical tau over time. This will be true in all groups except AD (ceiling effects).

Analyses will be performed in each diagnostic group separately. Linear regression will be used to assess the association between baseline FDG, tau, amyloid and cognition (Hypotheses a and e) and will have 80% power (α=0.05, two-sided test) to detect any association accounting for as little as 2% (NL, MCI) or 3.6% (AD) of the variation in the outcome. Mixed effects models will be used to assess associations between baseline PET metrics and cognitive decline (Hypotheses b and d). We will have 80% power to detect group differences (for example, amyloid positive/negative) in rates of change in ADAS as small as 0.43 (0.96, 2.28) pts/yr in NL (MCI, AD) if groups are equal in size; for a 25/75 split, the detectable difference increases. An extension of mixed effects regression models, called simultaneous random effects models[23, 24] will assess correlations between change in a PET metric and cognitive decline (Hypothesis c) and changes in amyloid and tau (Hypothesis e). We will have >80% power to detect correlations as small as 0.15 (NL, MCI) and 0.20 (AD) with change in amyloid and 0.16 (NL, MCI) and 0.21 (AD) with change in tau. Finally, estimates of mean rate of change and within- and between-person variation obtained from the mixed effects models will be used to compute sample size requirements for a 2-arm clinical trial, powered to detect a 25% reduction in rate of change. Estimates from each of the above analyses (such as correlations or sample size requirements), will be the basis for the comparisons across markers, including amyloid SUVR converted to the centiloid scale and the native retention units (Hypotheses b, c, d). A standardized framework for comparing different PET biomarkers on a set of criteria, including precision to measure change (related to sample size calculations) as well as clinical validity (correlation with cognitive decline), will be used [25]. This framework identifies participant level contributions to the relevant estimate, which are then analyzed using Friedman's rank test to detect an overall difference between measures. Post-hoc pairwise comparisons, adjusted for multiple comparisons are then used to identify specific differences between measures.

Progress Report: The PET core has had a major impact on the design and conduct of clinical trials; overall accomplishments in this regard have been summarized in publications in 2010 and 2015[15, 16]. Briefly, the PET core has pioneered in the development of approaches to multisite amyloid imaging that has both provided an infrastructure for clinical trials in North America, and provided methods for data acquisition and processing across sites, scanner models, and diagnoses. Use of a brain phantom for resolution standardization has been a widely adopted advance in PET imaging. Most importantly, ADNI has developed standardized methods for data analysis that include recent innovations in longitudinal data analysis related to the use of different reference regions for intensity normalization [26, 27]. Methods for PET acquisition, quality control, archiving, and data analysis have been directly applied to numerous clinical trials including the recent Biogen aducanumab trial – a clear example of how ADNI tools might help in detecting a therapeutic signal in Phase 2 trials. In addition to providing direct, concrete methods for clinical trials, the ADNI PET core's wealth of cross-sectional and longitudinal data have contributed to models of AD progression and pathophysiology that have broadly influenced the field. Biomarker-based approaches to AD diagnosis and staging, leading to models of "preclinical AD" have largely developed from ADNI data[28-30]. ADNI data have also been instrumental in demonstrating the relationships between Aβ and cognitive decline[31], ApoE genotype and Aβ[16, 32], amyloid PET and CSF [33, 34] and Aβ and neurodegeneration[35].

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OMB Number: 4040-0001
Expiration Date: 06/30/2016

APPLICATION FOR FEDERAL ASSISTANCE

SF 424 (R&R)

5. APPLICANT INFORMATION **Organizational DUNS*:** 6133387890000

Legal Name*: NORTHERN CALIFORNIA INSTITUTE FOR RESEARCH AND EDUCATION
Department:
Division:
Street1*: 4150 CLEMENT STREET (151-NC)
Street2:
City*: SAN FRANCISCO
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 941211545

Person to be contacted on matters involving this application

Prefix:	First Name*:	Middle Name:	Last Name*:	Suffix:
	Azarah	Sr. Grant Specialist	Wong	

Position/Title:
Street1*: 4150 CLEMENT STREET (151-NC)
Street2:
City*: SAN FRANCISCO
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 941211545
Phone Number*: 415-750-6954 x 23891 Fax Number: 415-750-9358 Email: cgawards@ncire.org

7. TYPE OF APPLICANT* M: Nonprofit with 501C3 IRS Status (Other than Institution of Higher Education)

Other (Specify):

Small Business Organization Type ❍ Women Owned ❍ Socially and Economically Disadvantaged

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
MRI Core

12. PROPOSED PROJECT

Start Date*	Ending Date*
08/01/2016	07/31/2021

OMB Number: 4040-0010
Expiration Date: 06/30/2016

Project/Performance Site Location(s)

Project/Performance Site Primary Location

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:	Mayo Clinic
Duns Number:	0064717000000
Street1*:	200 First St. SW
Street2:	
City*:	Rochester
County:	
State*:	MN: Minnesota
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	55905-0001
Project/Performance Site Congressional District*:	MN-001

Project/Performance Site Location 1

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:	The Regents of the University of California, Davis
DUNS Number:	0471200840000
Street1*:	1544 Newton Court
Street2:	Idea Lab
City*:	Davis
County:	
State*:	CA: California
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	95618-0000
Project/Performance Site Congressional District*:	CA-003

Project/Performance Site Location 2

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:	Dementia Research Centre, UCL Institute of Neurology
DUNS Number:	2254109190000
Street1*:	Sir Charles Symonds House
Street2:	8-11 Queen Square
City*:	London
County:	
State*:	
Province:	
Country*:	GBR: UNITED KINGDOM
Zip / Postal Code*:	WC1 3BG

Project/Performance Site Congressional District*:

Project/Performance Site Location 3

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: University of Southern California
DUNS Number: 0729333930000
Street1*: 2001 N. Soto St. Suite 102
Street2:
City*: Los Angeles
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 90032-3600
Project/Performance Site Congressional District*: CA-034

Project/Performance Site Location 4

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Northern California Institute for Research and Education
DUNS Number: 6133387890000
Street1*: 4150 Clement St. (151NC)
Street2:
City*: San Francisco
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 94121-1545
Project/Performance Site Congressional District*: CA-012

Project/Performance Site Location 5

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: The Trustees of the University of Pennsylvania
DUNS Number: 0422507120000
Street1*: Richards Building, Suite D601
Street2: 3700 Hamilton Walk
City*: Philadelphia
County: Philadelphia
State*: PA: Pennsylvania
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 19104-0000
Project/Performance Site Congressional District*: PA-002

File Name

Additional Location(s)

MRI Core: Project Summary/Abstract

The overall goal of the MRI Core is to facilitate clinical trials in all clinical stages of Alzheimer's disease (AD). Steps to achieving this goal, as related to MRI, include developing and disseminating standardized multi-modality MR acquisition protocols and providing an evidence base and data sets to assess the utility of MRI for clinical trials. Areas of emphasis include use of MRI for inclusion/exclusion, for safety monitoring, and as an outcome measure for Phase 1-3 trials. The MRI protocol in ADNI 3 will include structural MRI (sMRI) to measure brain mophometry; FLAIR to ascertain cerebro vascular disease and vasogenic edema; and T2*GRE to ascertain cerebral micro bleeds (CMBs). The protocol will also include diffusion MRI (dMRI), task-free functional MRI (TF-fMRI), and perfusion MRI (ASL), as potential measures with high sensitivity to very early/subtle disease-related changes. A high resolution coronal T2 fast spin echo (to measure medial temporal lobe (MTL) subregion volumes) will be acquired in order to assess the area of the brain (the MTL) where tau first appears in the AD disease process. The dMRI and TF-fMRI protocols will be implemented with both standard and advanced protocols. The advanced dMRI and TF-fMRI acquisitions will resemble those performed in the Human Connectome Project (HCP) in order to assess the value of advanced MR technologies for AD clinical trials in a realistic multi-site, multi-vendor environment. The MRI Core has two components; the central lab at the Mayo Clinic, and the seven funded image analysis investigators. The seven funded image analysis co-investigators are Drs. Paul Thompson, Duygu Tosun, Nick Fox, Clifford Jack, Charles DeCarli, David Jones, and Paul Yushkevich. The MRI Core approach falls into two broad categories. The first concerns service aims of the central MRI Core lab at Mayo Clinic needed to generate high quality data in all subjects at each time point. These data will be made available to the scientific community in real time and will be used by the seven funded ADNI MRI Core analysis labs to generate numeric summary MRI data – which in turn will also be made available to the scientific community. Analyses will include rates of change on sMRI images, which are used as outcome measures in clinical trials; measures of cerebrovascular disease; and ascertainment of CMBs. More sensitive methods to detect subtle/early treatment signals are needed as trials move into the preclinical phase of AD. DMRI, TF-fMRI and ASL will be evaluated as potential measures to provide this information. The potential of detailed anatomic measures of MTL subregions to detect atrophy due to the earliest appearance of tau will be evaluated.

PROFILE - Senior/Key Person

Prefix: First Name*: MATTHEW Middle Name A. Last Name*: BERNSTEIN Suffix:

Position/Title*: Professor of Medical Physics
Organization Name*: Mayo Clinic Rochester
Department:
Division:
Street1*: 200 First Street, SW
Street2:
City*: ROCHESTER
County:
State*: MN: Minnesota
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 559050000

Phone Number*: 507-266-1207 Fax Number: 507-266-1657 E-Mail*: mbernstein@mayo.edu

Credential, e.g., agency login: bernstein1

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: PHD Degree Year:

File Name
Attach Biographical Sketch*: Core_C_Biosketch_Bernstein.pdf
Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: David Middle Name T Last Name*: Jones Suffix: M.D.

Position/Title*: Assistant Professor
Organization Name*: Mayo Clinic
Department: Radiology
Division:
Street1*: 1002 1st St. SE
Street2:
City*: Rochester
County:
State*: MN: Minnesota
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 559040000

Phone Number*: 202-213-7381 Fax Number: E-Mail*: Jones..David@mayo.edu

Credential, e.g., agency login: jones12

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: MD,BA,BS Degree Year:

File Name
Attach Biographical Sketch*: Core_C_Biosketch_Jones.pdf
Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: Nicholas Middle Name Charles Last Name*: Fox Suffix: M.D.

Position/Title*: Professor of Neurology
Organization Name*: UCL Institute of Neurology
Department: Dementia Research Centre
Division:
Street1*: Box 16
Street2: National Hospital for Neurology & Neurosurgery
City*: London
County:
State*:
Province:
Country*: GBR: UNITED KINGDOM
Zip / Postal Code*: WC1N 3BG

Phone Number*: +44-203-448-3807 Fax Number: +44-203-448-3104 E-Mail*: n.fox@ucl.ac.uk

Credential, e.g., agency login:

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: Degree Year:

File Name
Attach Biographical Sketch*: Biosketch_Fox_updated.pdf
Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: Charles Middle Name Last Name*: DeCarli Suffix:

Position/Title*: Professor
Organization Name*: The Regents of University of California
Department: Neurology
Division: Alzheimers Disease Center
Street1*: 4860 Y Street
Street2: Suite 3700
City*: Sacramento
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 958170000

Phone Number*: 916-734-8413 Fax Number: E-Mail*: cdecarli@ucdavis.edu

Credential, e.g., agency login: cdecarli

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: MD Degree Year:

File Name
Attach Biographical Sketch*: biosketch_DeCarli_v2.pdf
Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: PAUL Middle Name M Last Name*: THOMPSON Suffix:

Position/Title*: Professor
Organization Name*: University of Southern California
Department: Ophthalmology
Division:
Street1*: Institute of Neuroimaging and Informatics
Street2: 2001 N. Soto Street, SSB1-102
City*: Los Angeles
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 900323600

Phone Number*: (323) 442-7246 Fax Number: E-Mail*: pthomp@usc.edu

Credential, e.g., agency login: thompsonp2

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: PHD,MA,BA Degree Year:

File Name
Attach Biographical Sketch*: 1_Biosketch_Thompson.pdf
Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: Paul Middle Name A. Last Name*: Yushkevich Suffix:

Position/Title*: Associate Professor
Organization Name*: University of Pennsylvania
Department: Radiology
Division: Perelman School of Medicine
Street1*: Richards Building, Room D605
Street2: 3700 Hamilton Walk
City*: Philadelphia
County:
State*: PA: Pennsylvania
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 191040000

Phone Number*: 215-349-8020 Fax Number: E-Mail*: pauly2@upenn.edu

Credential, e.g., agency login: YUSHKEVICH

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: PHD Degree Year:

File Name
Attach Biographical Sketch*: Biosketch_Yushkevich.pdf
Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: Sandhitsu Middle Name Last Name*: Das Suffix:

Position/Title*: Research Investigator Sr.
Organization Name*: University of Pennsylvania
Department: Neurology
Division: Perelman School of Medicine
Street1*: Richards Building, Room D606
Street2: 3700 Hamilton Walk
City*: Philadelphia
County:
State*: PA: Pennsylvania
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 191040000

Phone Number*: 2157467224 Fax Number: E-Mail*: sudas@seas.upenn.edu

Credential, e.g., agency login: sandydas

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: PHD,BTECH,MTECH Degree Year:

File Name

Attach Biographical Sketch*: Biosketch_Das_v2.pdf

Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: Duygu Middle Name Last Name*: Tosun-Turgut Suffix:

Position/Title*:
Organization Name*: NORTHERN CALIFORNIA INSTITUTE FOR RESEARCH AND EDUCATION
Department:
Division:
Street1*: 4150 Clement St. VAMC, Bldg 13
Street2:
City*: San Francisco
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 941210000

Phone Number*: 4152214810 ext 4800 Fax Number: E-Mail*: duygu.tosun@ucsf.edu

Credential, e.g., agency login: dtosun

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: Degree Year:

File Name

Attach Biographical Sketch*:

Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: Susanne Middle Name G. Last Name*: Mueller Suffix:

Position/Title*: Assistant Adjunct Professor
Organization Name*: Northern California Institute for Research and Education
Department:
Division:
Street1*: 4150 Clement St (114M)
Street2: VAMCSF
City*: San Francisco
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 941210000

Phone Number*: 415 221 4810 ext 2538 Fax Number: E-Mail*: susanne.mueller@ucsf.edu

Credential, e.g., agency login: susmue

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: Degree Year:

File Name

Attach Biographical Sketch*:

Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: Clifford Middle Name Robert Last Name*: Jack Suffix:

Position/Title*: Professor of Diagnostic Radiology
Organization Name*: Mayo Clinic Rochester
Department: Radiology
Division:
Street1*: 200 First Street SW
Street2:
City*: Rochester
County:
State*: MN: Minnesota
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 559050000

Phone Number*: 507.293.3793 Fax Number: E-Mail*: jack.clifford@mayo.edu

Credential, e.g., agency login: jack12

Project Role*: Other (Specify) Other Project Role Category: MRI Core Lead

Degree Type: MD Degree Year:

File Name

Attach Biographical Sketch*: Core_C_Biosketch_Jack.pdf

Attach Current & Pending Support:

MRI Core: Specific Aims

MRI is employed in all AD clinical trials for one or more of the following purposes: inclusion/exclusion, safety monitoring, to detect early signals of efficacy in Phase 2 trials and as a secondary outcome measure in Phase 3 registration trials. Primary objectives of the MRI Core in ADNI 1 and 2 included optimizing and standardizing methods for AD clinical trials. ADNI also seeks to validate MRI measures for clinical trials by demonstrating correlations with clinical outcomes, PET and biofluid measures. The objectives in ADNI 3 will continue this focus, but with new aims that incorporate technical advances in MRI. The ADNI 2 acquisition protocol included seven different imaging sequences. Structural MRI (sMRI), FLAIR and T2*GRE were acquired for all subjects. In addition, diffusion MRI (dMRI), task-free functional MRI (TF-fMRI), perfusion MRI (ASL), and a high resolution coronal T2 fast spin echo (to measure medial temporal lobe (MTL) subregion volumes,) were acquired, but each was limited to a single vendor to optimize uniformity of acquisition. In ADNI 3, we will continue to acquire all seven of these sequences, but with several important changes from ADNI 2. First, to the maximum extent possible all modalities will be acquired in every subject, greatly increasing the sample size for these sequences. Second, the dMRI and TF-fMRI protocols will be implemented with both standard and advanced protocols. The advanced dMRI and TF-fMRI acquisitions will resemble those performed in the Human Connectome Project (HCP) and will be performed only on systems that can support multi-band acquisition. The advanced dMRI and TF-fMRI protocols will be designed so that a (second) series that is equivalent to the basic acquisition can be derived by post hoc data subsampling. Thus, despite the 2-tiered acquisition approach, a common basic protocol will be produced for every subject/time point. This approach will also accommodate HCP-compatible system upgrades without a break in continuity which is important because we expect that an increasing number of ADNI MRI scanners will become capable of the advanced dMRI and/or TF-fMRI acquisition protocol over the course of the grant. Third, ASL in ADNI 3 will be acquired using the 3D pCASL protocol recommended by the ISMRM perfusion work group. All ADNI 3 scans will be acquired at 3T. Our specific aims are:

1) **Data acquisition and QC:** Create and distribute protocols to each site that are applicable for clinical trials. Qualify each scanner and requalify after every upgrade. Quality control every exam.
2) **Quantitative MR measurements applicable for clinical trials:** Develop or employ new/optimized analysis methods for each modality. Create “AD-signature” summary numeric measures, both continuous and binary (positive/negative), for each MR modality and make these measures available to the scientific community for every exam.
3) **Operationalize definitions of subgroups for clinical trials**: In combination with PET, biofluids, and clinical measures, we will operationalize the definitions of subgroups within the ADNI population. Formal definitions of groups like SNAP (suspected non-Alzheimers pathophysiology) and cerebrovascular phenotypes are needed to accommodate the biological heterogeneity within clinical trials populations.
4) **Predict tau:** Test the hypothesis that atrophy on sMRI, hypo perfusion, and altered diffusion will predict the concurrent presence of tau PET ligand uptake.
5) **Optimum inclusion/stratification metrics and covariates for clinical trials:** clinical/cognitive outcomes are the ultimate source of biomarker validation in living persons. Therefore, we will determine variables that best predict change on functional/psychometric measures and progression from normal to MCI, and MCI to dementia;
    a. Compare basic vs. advanced dMRI and TF-fMRI methods
    b. Comparison among the MRI-based AD biomarker methods (sMRI, dMRI, TF-fMRI, ASL, and MTL subregions)
    c. Compare MRI with non-MRI measures (PET (amyloid, FDG and tau)) and CSF
    d. Test the hypothesis that degree to which sMRI, dMRI, TF-fMRI, ASL, and MTL subregions predict future change is modified by the severity of cerebrovascular disease and CMB
6) **Optimum outcome metrics for clinical trials:** determine variables with the best longitudinal power and that best correlate with change on functional/psychometric measures over time: sample sizes,
    a. Compare basic vs. advanced dMRI and TF-fMRI methods
    b. Comparison among the MRI-based AD biomarker methods (sMRI, dMRI, TF-fMRI, ASL, and MTL subregions)
    c. Compare MRI with non-MRI measures (PET (amyloid, FDG and tau)) and CSF
    d. Test the hypothesis that degree to which sMRI, dMRI, TF-fMRI, ASL, and MTL subregions correlate with change on functional/psychometric measures over time is modified by the severity of cerebrovascular disease and CMB.

MRI Core: Research Strategy

SIGNIFICANCE

Overview: the importance of MRI for clinical trials: MRI is employed in all AD clinical trials for inclusion/exclusion and for safety monitoring. Subjects with non-AD causes of impairment (e.g., excessive cerebrovascular disease), or with excessive numbers of micro bleeds (CMBs) are excluded at screening on the basis of MRI findings. Serial MRI is also employed for safety monitoring to identify complications of therapy – e.g., incident CMBs (ARIA-H) or vasogenic edema (ARIA-E)[1]. Rate of change on structural MRI (sMRI) has been employed as a secondary outcome measure in many trials. However, new or improved biomarkers are needed. Interest continues in the potential of diffusion MRI (dMRI), task free functional MRI (TF-fMRI), and arterial spin labeling (ASL) perfusion MRI to provide early treatment signals. A major focus of ADNI 3 will also be to assess correlations between various MRI measures and tau PET.

Continued need to develop MR standards for clinical trials: In ADNI 1 and 2, the MRI Core was successful in developing and disseminating standardized MR acquisition protocols and providing an evidence base and data sets to guide future trial designs[2]. This work has influenced the planning and execution of essentially all current large-scale AD treatment trials. There is clearly a need for the MRI Core in ADNI 3 to continue this focus, while adding aims that build on experience gained in ADNI 2 and incorporate recent technical advances in MRI. Structural MRI continues to provide the smallest sample size estimates to power such trials, and knowledge of cerebrovascular disease (CVD) and cerebral micro bleeds (CMB) provided by FLAIR and T2*GRE is now considered an essential component of all AD clinical trials. Thus, we will continue to acquire these in ADNI 3. As methods for acquisition, image processing, and analysis of this data advance, yielding continuously improving results, it is vital that the MRI Core serve as a vehicle to standardize, evaluate, and validate these methods and thus improve clinical trial state-of-the-art and real-world applicability.

Need to evaluate utility of novel MRI sequences: ADNI 2 included dMRI, TF-fMRI, and ASL since these methods were increasingly being requested in trial protocols in an attempt to assess more fully the effects of therapy[3]. The core was successful in disseminating standardized protocols for these sequences, and although preliminary analyses have not shown clear-cut benefit over sMRI for basic questions of diagnostic discrimination and sample size[2], many other aspects of the data are still under study. Because we and the broader scientific community - notably projects such as the Human Connectome Project – recognize the potential added scientific value and complementarity of these sequences, we believe it is essential to evaluate current state-of-the-art versions of them using the head-to-head rigor of ADNI to determine their optimal use and relative value within clinical trials. Because not all ADNI systems will be capable of connectome-like acquisitions (at least when ADNI 3 begins), we will take a 2-tiered approach whereby more basic dMRI and TF-fMRI sequences are acquired on lower performance systems while more advanced acquisition protocols are used on high performance systems. This replaces the ADNI 2 approach of implementing more basic sequences in a vendor-specific manner, which benefitted homogeneity across systems but took a step back from the acquisition state-of-the-art available on high-end systems. Our focus on advanced sequences now reflects the fact that current “cutting-edge” sequences will likely be widely available later in the ADNI 3 grant cycle and thus appropriate for incorporation into trials at that time. Our objective is to anticipate this cycle of continual technical advance and have data to address the utility of these methods as they progressively become available for multi-center trials. Our goal is to be positioned at that time to answer substantive questions about not only the predictive power and longitudinal change characteristics of these sequences but also their relationships to AD pathophysiologically specific markers and established MR measures that help delimit how they can be interpreted.

Our emphasis on both standard and novel MR techniques is driven by the evolving state-of-the-art in AD clinical trials. Future trials will move earlier in the disease process when it will be even more important (esp. for Phase 2) to have imaging/biomarker read outs - as clinical measures will likely be uninformative within a reasonable time frame. Furthermore, it is increasingly recognized that the disease process has multiple pathological pathways occurring in parallel and a range of different therapeutic approaches will be tried and potentially combined. We therefore need the broadest range of measures of therapeutic effect and thus continual refinement of our understanding of relationships between MR measures and molecular and clinical markers. And, we need to continue to optimize image analysis approaches for all sequences - all of which are an ADNI 3 focus.

Emerging need to operationalize subgroups for clinical trials: Despite efforts to recruit patients who fit an AD-like phenotype profile, the biological heterogeneity inherent in aging populations continues to confound clinical trials. For example, recent clinical trials have found that over 30% of APOE 4 non-carriers who met clinical criteria for mild to moderate AD dementia are amyloid PET negative[4]. ADNI 3 will play an important role in helping future clinical trials meet this major challenge by evaluating formal criteria they can use to define rel-

evant AD subgroups based on MRI, PET, biofluid, and clinical measurements. Two specific subgroups we will target are SNAP[5] ((suspected non-Alzheimer's pathophysiology), defined by the presence of neurodegenerative biomarkers in subjects who are Aβ negative[5]) and cerebrovascular disease (CVD) phenotypes. The MRI Core will play a critical role in evaluating these subgroups by providing formal sMRI-based "AD-signature" summary measures[6] that contribute to "neurodegeneration positivity" in SNAP as well as the WMH volume and infarction measurements that contribute to CVD positivity.

INNOVATION

ADNI 3 will be the largest multi-site, multi-vendor study to leverage several advanced MRI methods. High-frame rate Human Connectome Project (HCP)-like dMRI will offer more precise region-based FA and MD 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 resolution, less noisy connectivity measures, and the ability to directly measure physiological parameters and time-varying connectivity. 3D pCASL will allow more robust whole-brain cerebral blood flow measurement and may be comparable to FDG PET. 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[7-10]. With the potential for eventual inclusion of more than one tau PET tracer in ADNI 3, evaluations of MTL subregional analysis as a potential surrogate (or predictive) biomarker for tau PET will be particularly informative, and may substantially add to the ability to interpret findings obtained with different tau PET tracers. Importantly, the higher end dMRI, TF-fMRI, and pCASL sequences can be down-sampled to give consistency across ALL ADNI 3 acquisitions. This approach provides an innovative solution to the competing objectives of: 1) creating within-subject data sets that are pool-able across time, 2) incorporating modern MR advances, and 3) allowing system upgrades – all in a multi-site, multi-vendor environment.

APPROACH

Organization and overview: The MRI Core of ADNI has two components; the central lab at the Mayo Clinic, and the seven funded image analysis PIs. Key personnel at the central lab at Mayo Clinic include Drs. Jack, Bernstein, and Jones in addition to support staff such as Bret Borowski, RTR and Kaely Thostenson, RTR. The seven funded image analysis co-investigators are Drs. Paul Thompson, Duygu Tosun, Nick Fox, Clifford Jack, Charles DeCarli, David Jones and Paul Yushkevich. Dr. Jack will be responsible for overall day-to-day MR-related operations for ADNI throughout the study. The MRI Core will communicate by teleconference monthly and email as needed to review progress, identify problem areas, and arrive at appropriate solutions. This approach has been proven extremely successful since the initiation of ADNI 1.

The MRI Core approach falls into two broad categories. The first concerns service aims of the central MRI Core lab at Mayo Clinic needed to generate high quality data in all subjects at each time point. These data will be made available to the scientific community in real time and will be used by the seven funded ADNI MRI Core analysis labs to generate numeric summary MRI data – which in turn will also be made available to the scientific community.

MRI protocol: All scanning will be at 3T with a protocol consisting of seven sequences (Table 1) each will be performed annually in every subject/time point - total exam duration is targeted to under one hour.

Considerations for multi-site implementation of MR protocol: System upgrades are inevitable over a 5-year grant period. The issue of acquisition stability and managing upgrades is a challenge for current clinical trials and will be more so for trials of longer duration needed to target earlier disease. Based on our survey of MR systems at ADNI sites, roughly half of the systems will be able to execute the advanced dMRI and TF-fMRI acquisitions when ADNI 3 begins in the fall of 2016; however, over the 5-year course of the study, many basic systems will be upgraded. Each advanced MRI and TF-fMRI acquisition will be down-sampled to form a "basic" series; thus, analyses of a basic dMRI and TF-fMRI will be available for every subject at every time point in the study. This approach enables us to incorporate advanced dMRI and TF-fMRI methods while also allowing upgrades while maintaining a consistent dataset over the course of the study.

Table 1. ADNI 3 MRI Protocol

1. 3D T1 volume: MPRAGE for Siemens and Philips and the equivalent (IRFSPGR) on GE systems, approximately 1 mm^3 resolution

2. FLAIR: 3D FLAIR on all systems

3. T2*GRE: 2D, long T2*GRE on all systems

4. dMRI: 2-tiered, use capability of advanced systems when present

a. Advanced: 2 b-shells; 48 encoding directions at b=1000 and 64 at b=2000
b. Basic: single shell b=1000

5. TF-fMRI: 2-tiered, use capability of advanced systems when present

a. Advanced: HCP-like, 10 minute duration, multi-band, subsecond TR
b. Basic: 10 minute duration, 3 sec TR

6. ASL: 3D pCASL with background suppression, following recommendations of the ISMRM Perfusion Study Group and the European Consortium for ASL in Dementia[11]. Acquired on capable systems.

7. Coronal high resolution T2: for MTL subregion analysis, on all systems

The advanced dMRI sequence will employ a multi-shell acquisition enabling diffusion kurtosis measures, HARDI tractography, and analyses such as NODDI[12, 13] that quantify the presence of different tissue components. The lower performance scanners will employ a more standard single shell acquisition suited to basic regional FA or MD measures. Voxel size will be kept constant and the gradient sets will overlap (i.e., scans with fewer gradients and b values will be a subset of the gradients and the b values in the more advanced scan). The b=1000 shell of the advanced acquisition will be extracted to create the equivalent of a "basic" acquisition, thus creating 2 dMRI data sets per exam on advanced systems.

The advanced TF-fMRI sequence will employ multi-band acceleration to achieve frame rates (i.e., TR) near 0.5 sec, while the basic TF-fMRI sequence will use the frame rate possible on more standard MRI systems ~ 3 sec. Voxel size will be kept constant between the two acquisition types. Each high temporal resolution HCP-like TF-fMRI time series will be down sampled to the equivalent of a standard 3.0 sec frame rate time series. The interpolant will include information from about same "receiver on" time as fully sampled data. Consequently, the SNR of fully sampled TR=3 sec data will be equivalent to down sampled data. Thus, we will create 2 TF-fMRI data sets per exam on advanced systems.

A possible confound which will be monitored and corrected for, if needed, is that advanced acquisition sites could be correlated with aspects of the cohort (e.g., different enrollment profile at advanced vs. basic sites).

Service aims of central MRI Core lab at Mayo Clinic: An overarching goal of the MRI Core lab is optimization of MR imaging across all scanners with an emphasis on methods that are applicable to clinical trials. An overview of the functions provided by the central core lab at Mayo Clinic for ADNI is below.

MRI Protocol Creation, Distribution, Site Certification: We perform a detailed equipment survey at each site – determine technical specifications for each potential scanner, select optimum 3T scanner at each site, and monitor upgrades throughout the study. We anticipate 55 clinical enrollment sites. The steps entailed are:

1. Create a generic, non-platform-specific MRI protocol.
2. With the aid of the existing MRI vendor support network (GE, Siemens and Philips), create a platform-specific protocol for each scanner and pilot the protocol on every platform prior to site distribution.
3. Distribute protocols to each scanner electronically.
4. Certify each scanner at baseline using both the ADNI phantom and human volunteer scans, and re-certify scanners after upgrades.

Quality Control (QC): Image QC is labor intensive but critical to ensure protocol adherence and data quality. The following QC operations will be performed.

1. Images are inspected manually for artifacts (e.g., patient motion), to evaluate overall image quality, to ensure all slices were transmitted, and the entire head was imaged.
2. Adherence to all sequence protocols is checked with an automated search of the DICOM header fields of each incoming data set for relevant pulse sequence parameters, e.g., TR, TE, matrix, etc.
3. If an image quality problem or a deviation of MR protocol is identified, the site will be contacted immediately. If the deviations are significant, the site will be asked to re-scan the patient.
4. Although sites are asked to inform the Mayo Clinic central lab of imminent upgrades, this does not always happen. Therefore, hardware and software versions of every data set will be verified.
5. The results of the MR QC inspection are cross-logged with the Informatics Core at LONI and the Clinical Coordinating Center.

Accommodating MRI Upgrades: We expect each MR system in the study to be upgraded one or more times per year. A significant effect which must be accounted for is the possibility that when the sequences in the protocol are recompiled under an updated version of the scanner's operating system, changes in some of the sequence parameters occur, an undesirable result in a longitudinal study that hinges on consistency over time. For example, changes in TE or bandwidth, etc., may be an unintended consequence of pulse sequence conversion for the new software revision. Our approach to software and hardware upgrades will be to anticipate effects of an impending upgrade at every participating site. We will test the pulse sequences in the ADNI protocol on every new hardware/software platform revision prior to installation at an ADNI site. This may require parameters to be adjusted for the recompiled sequence to be executed in a manner identical to the pre-upgrade sequence. This will allow us to effect appropriate corrective action before the fact.

Image analysis by the funded analysis PIs: In addition to the central lab at Mayo Clinic, the MRI Core of ADNI consists of seven funded image analysis PIs who have established significant publication track records in MRI of AD. Funded analysis PIs and their responsibilities for analyzing the core protocol sequences are:

Morphometry - 3D T1 Images: Rates of change on sMRI images are used as outcome measures in clinical trials. Also, all images in ADNI (MRI and PET) are registered to sMRI for image analysis purposes.

Paul Thompson: tensor-based morphometry. As detailed in Hua et. al. (2013, 2015)[14, 15], the Thompson lab will use a validated unbiased method to compute rates of brain atrophy at each time point in (1) atlas ROIs, and (2) ROIs that are statistically-defined based on using LDA on prior ADNI AD and MCI data[16]. Each subject's rate of atrophy is computed with a mutual information-based elastic registration method that shows competitively low sample size requirements to power clinical trials[14]. This method is also robust to MRI scan acceleration[17].

Duygu Tosun: FreeSurfer (FS) analytic analysis. The CIND will use automated probabilistic-based FS framework for regional estimates of subcortical gray matter (GM) tissue volume and cortical GM morphometrics including volume, thickness, surface area, and curvature measures[18]. Joint processing of 3D T1 and FLAIR, an advanced feature in FS, will be used to improve accuracy in cortical morphometrics. Within FS processing framework, high-res T2 images will be processed jointly with 3D T1 data for automated segmentation of hippocampal subfields based on a statistical atlas built upon ultra-high resolution (~0.1 mm isotropic) *ex vivo* MRI data[19]. To extract reliable GM morphometry estimates, serial images will be processed with the longitudinal stream in FS[20,Reuter, 2011 #213]. A thorough visual QC will be performed and regional recommendations will be reported.

Nick Fox: brain, ventricle and hippocampal boundary shift integral (BSI) and template-based regional measures. The Fox lab will use automated template-based methods for region delineation[21-23], these will include brain, ventricle and hippocampal regions with QC. The regions provide a volume estimate for each scan and, for serial imaging, the input into symmetric Kmeans normalized BSI measurement of volume change[24, 25] giving a rate of atrophy or change which has been shown to be robust to contrast differences and artifacts and to produce consistently amongst the lowest unbiased sample size estimates[26, 27] in ADNI and in other data sets. Furthermore, the BSI measures have been shown in real-world clinical trial settings to reproduce the level of reliability, precision and robustness seen in ADNI[4, 28].

Clifford Jack: TBM-SyN measurements. Within-subject change is captured by computing the log of the Jacobian determinants from a non-linear deformation estimated using SyN[29] to align longitudinal images. The deformation is computed in both directions explicitly, and the log of the Jacobian determinants formed in each direction. These log Jacobian maps are then annualized and integrated over ROIs, and the values from the forward and reverse directions averaged together within each ROI. Thus, the measure is forward/backward symmetric. Atrophy rates are computed over an AD-signature meta-ROI[30],[31].

Additional morphometry analyses: Duygu Tosun, in collaboration with Dr. Ashish Raj of Cornell University, will perform analyses using a network-diffusion model based on the concept that AD pathology travels along network connections via trans-neuronal transmission[32],[33] in order to validate predictions of future patterns of atrophy, metabolism, amyloid and tau deposition (described further in Administrative Core). Charles DeCarli will also perform hippocampal volume measurements using an automated multi-atlas segmentation framework based on the European Alzheimer's Disease Centers – ADNI harmonized protocol.[34]

Cerebrovascular Disease - Charles DeCarli: Cerebrovascular disease is extremely common in elderly persons and can confound relationships between AD pathology and clinical symptoms. Thus, knowledge of CVD is essential in trials. The DeCarli lab will use automated template-based methods to remove non-brain tissue from the high resolution T1 image. This image will then be processed via denoising, bias correction, alignment to a minimum deformation template and subsequent gray/white/CSF segmentation using Bayesian inference and maximal likelihood iterative convergence[35, 36]. FLAIR images will be similarly noise corrected and segmented via a Bayesian inference approach[37]. The presence, number, size and location of subcortical infarctions will also be determined.

GRE Imaging of Micro Hemorrhages - Clifford Jack: Ascertainment of CMBs is required for baseline inclusion/exclusion screening and for longitudinal safety monitoring. The Jack lab will visually grade T2*GRE scans for abnormal tissue iron deposits. The number and location of CMB and siderosis will be quantified by visual review of each scan and entered into a data form as described in Kantarci et. al.[38]. The x,y,z coordinates of each abnormality in subject space will be entered into a database along with anatomic location from the AAL atlas.

Diffusion Tensor Imaging - Paul Thompson: More sensitive methods to detect subtle/early treatment signals are needed as trials move into the preclinical phase of AD. DMRI may provide this information. As in their 20+ ADNI DTI publications[39-46], this group will use FSL software to correct for geometric distortions due to motion, eddy current, and susceptibility artifacts. DTI scans, denoised with Riemannian methods, are then registered to a geometrically-centered mean tensor image. The parcellated Mori DTI81 atlas is overlaid to compute average values of all DTI indices in ROIs. *Group Statistics*: We will perform voxel-by-voxel and ROI analysis of the following DTI measures known to distinguish MCI from controls[43]: fractional anisotropy (FA), geodesic

anisotropy (GA), mean diffusivity (MD), and parallel and transverse diffusivity (diffusion tensor eigenvalues), and some novel “beyond-tensor” metrics[42-45], all corrected for fiber crossing/mixing using our HARDI deconvolution methods. *Connectomics*: We will also compute standard “network” measures most sensitive to AD-related change and that predict decline (e.g., nodal degree, clustering, small-world coefficient[39-46]), that we have shown are robust to scan spatial and angular resolution.

TF-fMRI - Functional Connectivity - David Jones: More sensitive methods to detect subtle/early treatment signals are needed as trials move into the preclinical phase of AD. TF-fMRI may provide this information. HCP-inspired preprocessing will be used, including: despiking using AFNI’s 3dDespike program[47], slice-timing correction, two-pass realignment to mean EPI, 3D T1 co-registration to the mean EPI image, transforming a template space atlas (Mayo Clinic Study of Aging (MCSA) Functional Connectivity Atlas (MCSA-FCA))[48] into the subject space, intensity bias corrections, highpass filtering, re-sampling of the data onto the cortical mesh (surface analyses), denoising of the data using ICA-fix,[49] and spatial smoothing. Subject space spatial-temporal dual regression (STR)[50] is performed on preprocessed data within a multi-variate framework incorporating all four DMN subsystems of interest with scaling of the parameter estimates of functional connectivity to z-scores. Summary metrics for each of the network elements is then extracted from this result for each subject. Within network connectivity is estimated by extracting the median value from the scaled spatial maps within template ROIs. The connectivity between networks is estimated as the correlation between the time courses produced during the STR procedure.

Arterial Spin Labeling - Duygu Tosun: More sensitive methods to detect subtle/early treatment signals are needed as trials move into the preclinical phase of AD. ASL may provide this information. The CIND will use the basic model recommended by the ISMRM Perfusion Study Group[11] for quantification of cerebral blood flow (CBF) from 3D pCASL images in mL/min/100 mL units. Probabilistic tissue segmentation from the 3D T1 image will be used to correct for brain atrophy and gray/white matter partial volume effects. Summary CBF metrics for each subcortical and cortical FS parcellation will be reported.

MTL Subregions - Paul Yushkevich: Tau first appears in the medial temporal lobe. Detailed anatomic measures of MTL subregions may enable detection of atrophy due to the earliest appearance of tau. This will be ascertained by correlation with tau PET imaging. Will visually check the quality of the coronal T2-weighted scans for motion artifact, coverage of the MTL and other MRI artifacts and assign each scan a quality score using a scale developed in ADNI 2. Will generate segmentations of multiple MTL subregions: subfields CA1, CA2, CA3, dentate gyrus, and subiculum of the hippocampus; entorhinal cortex; parahippocampal cortex; and perirhinal cortex (split into Brodmann areas 35 and 36, the former also known as the transentorhinal region and shown to be the earliest site of tau pathology[51]). Subregions will be further parcellated along the anterior-posterior axis. The volume and average thickness of each subregion will be reported. Segmentations will be generated using ASHS, a multi-atlas technique optimized for MTL subregion segmentation that achieves best reported accuracy for MTL subregion segmentation[10]. An unbiased longitudinal pipeline optimized for high-resolution coronal T2 MRI will be used to report subregion-specific measures of change in volume over time.[52]

Statistical analysis methods: While Aims 1-3 are designed to produce high quality imaging exams and numeric summary data that are relevant to clinical trials, Aims 4-6 involve hypothesis testing designed to assess the value of various MRI modalities for clinical trials. Aims 4-6 and the approach to hypothesis testing is briefly outlined below with more detail in the Biostatistics Core.

Aim 4.Predict tau: Test the hypothesis that atrophy on sMRI, hypo perfusion, and altered diffusion will predict the concurrent presence of tau PET ligand uptake.

Aim 5. Optimum inclusion/stratification metrics and covariates for clinical trials: determine variables that best predict change on functional/psychometric measures and progression from normal to MCI, and MCI to dementia: a) Compare basic vs. advanced dMRI and TF-fMRI methods; b) Comparison among MRI-based AD biomarker methods (sMRI, dMRI, TF-fMRI, ASL, MTL subregions); c) Compare MRI with non-MRI measures (PET (amyloid, FDG and tau)) and CSF; d) Test the hypothesis that the degree to which sMRI, dMRI, TF-fMRI, ASL and MTL subregions predict future change is modified by the severity of CVD and CMB

Aim 6. Optimum outcome metrics for clinical trials: determine variables with i) greatest longitudinal power and ii) greatest correlation with change on functional/psychometric measures over time (same comparisons as Aim 5)

Key outcomes include tau PET ligand uptake (Aim 4), change in functional/psychometric measures (Aims 5 and 6), clinical progression (Aim 5), and change in MRI-based measures (Aim 6). Linear regression will be used to assess the correlation between baseline MRI measures and baseline co-localized tau PET ligand uptake (80% power (α=0.05, two-sided test) to detect a correlation as small as 0.14 (NL or MCI) or 0.19 (AD)).

Repeated measures, random effects models will be used to assess associations between a baseline MRI marker and change in co-localized tau PET ligand uptake or functional/psychometric measures. An extension of mixed effects regression models, called simultaneous random effects models[53, 54], which allows for multiple types of longitudinal outcomes, will assess correlations between change in an MRI measure and change in tau PET ligand uptake or functional/psychometric measures (80% power to detect a correlation as small as 0.16 (NL, MCI) or 0.21 (AD)). Survival models, such as accelerated failure time models, that account for interval censoring will be used to assess associations with clinical progression. In MCI, we would be able to detect a difference between annual progression rates of 17.7% (worst 50% of participants on a marker) and 10.5%/yr (6.1%/yr (worst 50%) and 2.2% (best 50%) for progression in NL). Detectable differences would be greater as we move to 25%-75% or 10%-90% splits based on biomarkers. Finally, estimates of mean rate of change and within- and between-person variation obtained from the repeated measures, random effects models will be used to compute sample size requirements for a 2-arm clinical trial, powered to detect a 25% reduction in rate of change. Estimates from each of the above analyses (such as correlations, hazard ratios or sample size requirements), will be the basis for the comparisons across markers (Aims 5 and 6). A standardized framework for comparing different fluid and imaging biomarkers on a set of criteria, including precision to measure change (related to sample size calculations) as well as clinical validity (correlation with cognitive decline or clinical progression), will be used[55]. This framework identifies participant level contributions to the relevant estimate, which are then analyzed using randomized block analysis of variance or Friedman's rank test to detect an overall difference between measures. Post-hoc pairwise comparisons, adjusted for multiple comparisons are then used to identify specific differences between measures. Comparison of MRI markers will have 80% power (α=0.01 to account for multiple comparisons) to detect differences in correlation between baseline level or change in MRI markers with cognitive and functional decline between, for example, 0.8 and 0.69 or 0.6 and 0.42 (NL, MCI) and 0.8 and 0.62 or 0.6 and 0.34 (AD) assuming the correlation between two markers is 0.2; the detectable difference in correlation decreases as the correlation between biomarkers increases.

PROGRESS REPORT

The MRI Core has been highly influential in shaping industry standards for acquisition and post-processing of brain MRI in AD clinical trials. Some specific successes are described briefly below.

Broad adoption of technical standards: The MRI Core developed and characterized standardized acquisition protocols compatible with a variety of hardware/software configurations within each of the three major MRI vendors' product lines[56]. The protocols also became the leading industry standard that was adopted by a wide range of industry and academic entities outside of ADNI for their trials.

Best acquisition practices: MRI core comparisons of competing techniques have shaped study design choices far beyond ADNI itself. Example findings include a lack of major advantage of 3T over 1.5T field strength for sMRI acquisition[57, 58] and a lack of data quality downside to accelerated (vs. unaccelerated) sMRI acquisition[17, 59],[60].

Improved image analysis methods: Numerous publications have used ADNI MR data to justify a newly developed MRI analytic method, many of which have enhanced the validity, repeatability, or depth of MRI-based biomarker readouts. For example, developed methods that measure rates of change in anatomic MRI data [14, 23, 25, 61-72] provided smaller sample size estimates compared to biofluid and cognitive indices[15, 16, 24, 68, 69, 73-76]. In addition, ADNI contributed MRI data to the large-scale EADC hippocampus tracing harmonization effort, which resulted in the new industry standard for delineating this structure that is a crucial imaging readout in AD[34, 77, 78].

MRI-based clinical trial enrichment: Selecting subjects for inclusion in clinical trials who are likely to decline cognitively over the typically short duration of a clinical trial can reduce costs considerably[66, 68, 79-81]. A number of studies using ADNI data have found that MRI is as effective as any biomarker (or more so) in predicting short-term future clinical decline[82-86]. These studies contributed to the European Medical Agency's decision to approve the use of hippocampal volume to enrich clinical trial populations in prodromal AD/MCI[87, 88].

New diagnostic criteria for AD: Two major working groups have published diagnostic criteria for AD[89-93] which define inclusion criteria for modern clinical trials. Several groups have used the ADNI data to assess validity and utility of these new diagnostic criteria[5, 94-103].

Impact of subgroups: CVD, SNAP, and microbleeds: ADNI played a key role in characterizing the biological heterogeneity that has reduced power in AD treatment trials. ADNI studies determined that[104] the extent of baseline and change in WMH volume were associated with cognitive decline[105-107] were evident. ADNI studies showed baseline prevalence of superficial siderosis to be 1% and 25% for CMB[38]. CMB prevalence increased with age, β-amyloid load and APOE 4 carriage.

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OMB Number: 4040-0001
Expiration Date: 06/30/2016

APPLICATION FOR FEDERAL ASSISTANCE

SF 424 (R&R)

5. APPLICANT INFORMATION **Organizational DUNS*:** 6133387890000

Legal Name*: NORTHERN CALIFORNIA INSTITUTE FOR RESEARCH AND EDUCATION
Department:
Division:
Street1*: 4150 CLEMENT STREET (151-NC)
Street2:
City*: SAN FRANCISCO
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 941211545

Person to be contacted on matters involving this application

Prefix:	First Name*:	Middle Name:	Last Name*:	Suffix:
	Azarah	Sr. Grant Specialist	Wong	

Position/Title:
Street1*: 4150 CLEMENT STREET (151-NC)
Street2:
City*: SAN FRANCISCO
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 941211545
Phone Number*: 415-750-6954 x 23891 Fax Number: 415-750-9358 Email: cgawards@ncire.org

7. TYPE OF APPLICANT* M: Nonprofit with 501C3 IRS Status (Other than Institution of Higher Education)

Other (Specify):

Small Business Organization Type ❍ Women Owned ❍ Socially and Economically Disadvantaged

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
Biomarker Core

12. PROPOSED PROJECT

Start Date*	Ending Date*
08/01/2016	07/31/2021

OMB Number: 4040-0010
Expiration Date: 06/30/2016

Project/Performance Site Location(s)

Project/Performance Site Primary Location

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:	The Trustees of the University of Pennsylvania
Duns Number:	0422507120000
Street1*:	3400 Spruce Street
Street2:	7 Maloney South
City*:	Philadelphia
County:	
State*:	PA: Pennsylvania
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	194010000
Project/Performance Site Congressional District*:	PA-002

File Name

Additional Location(s)

Biomarker Core: Summary/Abstract

The AD pathologies-Aβ plaques and neurofibrillary tangles-formed by abnormal tau proteins are reflected in cerebrospinal fluid (CSF) by lowered concentrations of $A\beta_{1-42}$ followed by elevated tau proteins. These changes in CSF proteins occur together with increased detection of Aβ and tau deposits by PET scanning, brain (especially hippocampal) atrophy, and cognitive decline. The role of CSF proteins for diagnosis, prediction of cognitive decline, and detection of treatment response is of great interest to the AD field. The ADNI Biomarker Core has contributed to an international consensus for CSF sample collection, preparation and storage best practices and established standardized measurement of $A\beta_{1-42}$, total tau(t-tau) and tau phosphorylated at threonine 181 (p-tau_{181}). The Biomarker Core defined concentration cutpoints for CSF $A\beta_{1-42}$ and tau that are recognized as major milestones contributing to use of these CSF biomarkers in research and especially in clinical trials. An ongoing problem in the field is variability in Aβ and tau measurements due to lack of an international reference material against which to standardize calibrators to aid in stabilizing variable lot-to-lot reagent performance and a second problem concerns so-called “matrix effects”. To overcome these problems we will perform immunoassays of CSF Aβ and tau using the Roche automated platform and mass spectrometry (which also identifies multiple species of Aβ) and establish cutpoints using CSF concentrations obtained with the validated new assays. The Biomarker Core will help standardize AD biomarkers by continuing to receive, aliquot, store and curate all ADNI CSF, plasma and serum samples, use them in studies conducted in this Core, and transfer aliquots to investigators following approval of their studies by the RARC and NIA. AD pathology is complex, often includes Lewy Bodies (LB’s) composed of alpha-synuclein (α-SYN) aggregates, TDP-43 inclusions and cerebrovascular disease (CVD pathology) and involves other pathologic processes such as neuron/synapse loss. We plan to collaborate with biomarker investigators to measure other promising biomarkers purported to reflect these additional pathological processes such as: total and phospho-α-SYN, neurogranin, NFL, Vilip1 and mass spectrometry-based analytes identified in metabolomic/lipidomic add-on studies. All study data generated in the Biomarker Core and in studies using ADNI biofluid samples through RARC-approval will be uploaded to the USC/LONI/ADNI website. The Biomarker Core will collaborate with the Biostatistics Core and other ADNI cores to test hypotheses on: predictive performance of CSF biomarkers for clinical decline; impact of CSF biomarkers for reducing sample size to improve treatment trial efficiency; relationships between rates of CSF $A\beta_{1-42}$ change and decline in memory, cognition and function; prediction by AD CSF biomarkers(e.g. amyloid pathology, $A\beta_{1-42}$ levels< cutpoint, precede tau pathology) of tau pathology based on tau ligand uptake; concordance between florbetapir(+/-) and CSF $A\beta_{1-42}$ concentration(-/+).

PROFILE - Senior/Key Person

Prefix: First Name*: JOHN Middle Name Q. Last Name*: TROJANOWSKI Suffix:

Position/Title*: Professor, Director, UPenn ADCC; UPenn IOA; N
Organization Name*: UNIVERSITY OF PENNSYLVANIA
Department: Pathology and Laboratory Medic
Division:
Street1*: 3400 Spruce Street
Street2:
City*: PHILADELPHIA
County:
State*: PA: Pennsylvania
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 191044283

Phone Number*: (215) 662-6399 Fax Number: (215) 349-5909 E-Mail*: TROJANOW@MAIL.MED.UPENN.EDU

Credential, e.g., agency login: trojanowski

Project Role*: Other (Specify) Other Project Role Category: Biomarker Core Co-Lead

Degree Type: MD,PHD,BA Degree Year:

File Name
Attach Biographical Sketch*: Biomarker_Core_Biosketch_Trojanowski_v2_10.14.pdf
Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: Leslie Middle Name Michael Last Name*: Shaw Suffix:

Position/Title*: Professor, Director, Biomarker Research Labor
Organization Name*: University of Pennsylvania
Department: Pathology and Laboratory Medic
Division:
Street1*: 3400 Spruce St
Street2:
City*: PHILADELPHIA
County:
State*: PA: Pennsylvania
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 191040000

Phone Number*: 2158987293 Fax Number: 2158989708 E-Mail*: shawlmj@mail.med.upenn.edu

Credential, e.g., agency login: shawlmj

Project Role*: Other (Specify) Other Project Role Category: Biomarker Core Co-Lead

Degree Type: PHD,BS Degree Year:

File Name
Attach Biographical Sketch*: Core_I_Biosketch_Shaw_10.14.pdf
Attach Current & Pending Support:

Biomarker Core: Specific Aims

The overall goal of the Biomarker Core is to validate CSF and blood biomarkers for AD clinical trials. AD, the most common form of dementia, is a complex progressive neurodegenerative disease that leads to loss of memory, cognitive function and daily living skills [1-3]. Hallmark pathologic characteristics in the brain of AD patients examined at autopsy include Aβ SP's and NFT's that are composed mainly of fibrillar forms of Aβ and hyperphosphorylated tau (p-tau), respectively [4-7]. Our understanding of the molecular characteristics and progression of AD neuropathology has accelerated over the past two decades based on a growing number of molecular and clinical studies [8-13] and it is clear that the underlying pathology in AD is not just SP's and NFT's, but also LB's formed of α-SYN aggregates, and TDP-43 inclusions, as well as CVD pathology [2,4-8,14-27]. The Aβ and tau aggregates as well as degenerative changes are reflected in CSF, respectively, by lowered concentrations of $A\beta_{1-42}$ followed by elevated tau proteins in addition to demonstration of Aβ and tau deposits on PIB PET and measures of CNS atrophy especially hippocampal atrophy as recently reviewed [28-32]. Achievement of standardization of measurements of these CSF biomarkers requires close attention to, and control of, sources of variation in (a) the pre-analytical steps involved in biofluid sample collection, preparation and storage and (b) the analytical method itself. Since the inception of ADNI the Biomarker Core Co-Leaders (Co-CL) participated in studies and discussions with industry (members of the ADNI PPSB) and academic biomarker researchers of pre-analytical sources of variability and continued in ADNI2. This contributed to an international consensus describing the best practices for CSF sample collection, preparation and storage [33,34]. To establish standardized measurement of $A\beta_{1-42}$, t-tau and p-tau_{181}, the ADNI Biomarker Core extensively validated the xMAP bead-based multiplex Research Use Only (RUO) AlzBio3 immunoassay including an interlaboratory "round-robin" study [35]. Using ADNI SOP's and this validated immunoassay, the Biomarker Core defined concentration cutpoints for CSF tau and $A\beta_{1-42}$ that have proven to be a major milestone and we successfully applied these cutpoints to the ADNI1 cohort, a Belgian autopsy cohort of AD patients and subsequently to ADNI (GO and 2) subjects [35-43]. Limitations of the immunoassay are the presence of matrix interference effects that result from the propensity of $A\beta_{1-42}$ to self-aggregate and to form aggregates with other protein and the lack of a certified reference material to permit the manufacturer a standard against which to reproducibly prepare calibration standards that has led to challenges to achieve acceptable lot to lot reagent performance [44-46]. These limitations will be addressed in this application. The growing awareness of the neuropathologic heterogeneity in AD is highlighted by the finding of a significant incidence of co-pathologies such as LB pathology and TDP43 deposits in the first series of ADNI autopsy cases reviewed by the Biomarker Core in collaboration with the Neuropathology core [14]. Thus, to support ADNI3, the Biomarker Core will build on this growing experience in the standardization of AD biomarker analyses by continuing to receive, aliquot, store and curate CSF, plasma and serum samples collected at all clinical sites according to ADNI SOP's, transfer these to investigators approved to study promising new biomarkers in ADNI3 and perform highly standardized assays for new and established CSF from all ADNI study subjects as well as upload all data to the USC/LONI/ADNI website.

Specific Aims:

1) **Receive, aliquot, store and curate biofluid samples following established ADNI SOP's and transfer samples to investigators approved by the Resource Allocation Review Committee (RARC) (described in the Administrative Core).**
2) **Provide highly standardized $A\beta_{1-42}$, t-tau and p-tau_{181} measurements in all ADNI subject CSF samples using the Roche fully automated platform (Cobas e601) and immunoassay reagents. In addition provide immunoassay-independent measurements Aβ species ($A\beta_{1-42}$, $A\beta_{1-40}$ and $A\beta_{1-38}$) using a validated candidate reference UPLC/tandem mass spectrometry method in baseline and longitudinal CSF samples. Collaboration with other investigators to achieve harmonization of these measurements across centers and different platforms in support of their use in clinical trials.**
3) **Collaboration with other investigators in the use of new tests for CSF (total and phosphor-a-SYN; neurogranin; neurofilament light (NFL); Vilip1 and TDP43) and possibly blood biomarkers (metabolic and lipidomic assays; $A\beta_{1-42}$ and tau proteins in neurally derived exosomes).**
4) **Collaborate in studies (a) of individual and combinations of CSF biomarkers for prediction of memory, cognitive and functional decline, (b) the effect of using individual and combinations of CSF biomarkers and associated cutpoints for reducing sample size thus improving efficiency of treatment trials, (c) study rates of change of CSF biomarkers over time to determine relationships to future cognitive decline, (d) determine the prediction of uptake of tau ligand by CSF $A\beta_{1-42}$ below cutpoint, and (e) determine the concordance between $A\beta_{1-42}$ and amyloid-β plaque ligand uptake with the Biostatistics Core and across all ADNI 3 Cores as well as with other outside investigators.**

Biomarker Core:Research Strategy

SIGNIFICANCE

Provide biofluid samples to RARC-approved investigators.

The Biomarker Core is responsible for, and provides highly annotated biofluid aliquot samples, collected, processed, stored and curated 24/7 under standardized conditions, to investigators who study new candidate biomarkers approved by the NIA ADNI RARC (see Administrative Core for a description of the RARC and a summary of biofluids shipped to approved investigators in Table 1, Biomarker Core Resource Sharing Plans).

Standardize $A\beta_{1-42}$, t-tau and p-tau_{181} measurements in ADNI CSF samples.

xMAP AlzBio3 immunoassay. The Biomarker Core has responsibility for providing the most highly standardized $A\beta_{1-42}$, t-tau and p-tau_{181} measurements possible on all ADNI CSF samples and has done this on the Luminex platform using the RUO xMAP micro-bead based AlzBio3 immunoassay (manufactured by Fujirebio Europe) in ADNI1, ADNIGO and ADNI2. A major effort in standardization of the AlzBio3 immunoassay resulted in a very high level of within-laboratory precision performance [48]. Limitations of the xMAP AlzBio3 immunoassay are (a) matrix effects that make it challenging to achieve linear measurements across the analyte concentrations [44,45], (b) the high complexity of the method requiring a number of manual steps, (c) the lack of a Certified Reference Material (CRM) for standardization of calibrators [46] and (d) the difficulty to achieve acceptable center-to-center precision performance [48-50]. Lack of a CRM is an important reason why the Biomarker Core has had to use extra aliquots of ADNI1 BASELINE CSF samples for each subsequent batch analysis over the course of ADNI1, ADNIGO and ADNI2 in order to anchor the CSF biomarker concentration data to a common reference (full details of this procedure are described in the analytical reports for each ADNI GO/2 batch analysis on the ADNI/LONI website). For these reasons and other considerations the AlzBio3 immunoassay manufacturer (for the Luminex platform), while successfully used in single centralized laboratories in two treatment trials for determination of eligibility based on $A\beta_{1-42}$ below cutpoint level [51,52] and/or above tau/$A\beta_{1-42}$ ratio level [53], this assay system is not likely to become an In Vitro Diagnostic Device(IVD), approvable by the US Federal Drug Administration(FDA). Thus, this is an important limitation for its further use in drug registration trials and ADNI3. For all of these reasons the Biomarker Core is working to replace the AlzBio3 immunoassay with a new highly automated immunoassay as described below. Further, this is why the Core has developed a candidate mass-spectrometry based method for $A\beta_{1-42}$ measurement, using a reference preparation of $A\beta_{1-42}$(described in Aim 2, Progress Report) to support having a definitive accuracy-based reference for the ADNI study and in an international effort to develop a CRM for this analyte. Accomplishment of this will promote harmonization across centers and platforms, a development that supports the need for consistent measurements in clinical and drug trials.

Roche elecsys (Cobas e601) automated immunoassay. Given the above limitations of the AlzBio3 immunoassay, the Biomarker Core has undertaken a validation study, described below, of the fully automated, random access(can run 1 or a few samples at a time at any time, not limited to running in 96 well plate batches) accuracy and precision-based Roche elecsys immunoassay platform. This is one of 9 new immunoassay platforms in various stages of development [24]. Importantly, selection of this new immunoassay platform was undertaken in consultation with the ADNI Executive Committee and the ADNI PPSB Due Diligence Working Group (DDWG)/Biofluid Biomarker Working Group (BBWG), led by Johan Luthman (Eisai). The PPSB DDWG members have considerable AD biomarker experience and undertook a detailed review of these new immunoassay systems. None of these participants had a stake in the competing immunoassay vendors, to assure an unbiased review of vendors interested in supporting the ADNI CSF biomarker effort.

Development and validation of an accuracy-based 2 Dimensional-Ultra Performance Liquid Chromatography/tandem mass spectrometry (2D-UPLC/MSMS) candidate reference method.

To provide the most highly standardized measurements for $A\beta_{1-42}$, t-tau and p-tau_{181} in all ADNI CSF samples, the Biomarker Core developed an accuracy- and precision-based 2D-UPLC/MSMS candidate reference methodology [54] to determine CSF $A\beta_{1-42}$, $A\beta_{1-40}$ and $A\beta_{1-38}$ concentrations in ADNI CSF samples. This provides for the first time an accuracy based measurement of $A\beta_{1-42}$ and related peptides and the ultimate anchor for the calibration is highly purified reference $A\beta_{1-42}$ standard prepared by the Institute for Reference Materials and Measurements (IRMM). Final mass value assignment is dependent on replicate amino acid analyses of purified $A\beta_{1-42}$ by IRMM. This is done in collaboration with Kaj Blennow and other investigators under the auspices of the Alzheimer's Association (AA) Global Biomarker Standardization Consortium (GBSC) and International Federation of Clinical Chemistry (IFCC) who participate in assignment of $A\beta_{1-42}$ concentration values to a CSF-based CRM by the IRMM[55,56]. These efforts strongly support improving across-laboratory and across-analytical platform harmonization of CSF $A\beta_{1-42}$--important to clinical trials since the CRM will be made available to all immunoassay vendors for standardizing their calibrators for this key CSF biomarker. The

significance of this and other studies conducted in this Core on AD biomarkers go beyond laboratory practice, analogous to the development of highly standardized tests for cholesterol for cardiovascular risk assessment in clinical trials and clinical practice [57]. The importance of this harmonization effort is as important as achieving standardized cholesterol measurement for cardiovascular disease clinical trials and routine patient care.

APPROACH

In ADNI3 the Biomarker Core will continue to receive, aliquot, store and curate biofluid samples and closely monitor and record important details associated with them. The Biomarker Core regularly communicates with the Clinical Core and Clinical Sites to assure completeness and accuracy of this sample-specific information. The Biomarker Core will respond to requests for biofluid samples, fully de-identified, by shipping them to investigators whose study protocol for new biomarker studies was approved by the RARC and NIA. In ADNI3 the Biomarker Core will implement highly standardized assays for $A\beta_{1-42}$, t-tau and p-tau_{181} in all CSF samples. We will collaborate with other investigators outside ADNI in the development and validation of new biomarkers and interact regularly with the Biostatistical Core and other Cores on the planning and implementation of statistical analyses that will test the hypotheses described in AIM4 below.

INNOVATION

In addition to its responsibilities for biofluid management the ADNI3 Biomarker Core innovates through its efforts to advance standardization of immunoassays and mass spectrometry-based candidate reference methodology for CSF biomarkers. These developments will improve CSF biomarker measurement quality in ADNI3 and support their use in clinical and drug registration trials. The Biomarker Core innovates by challenging clinical paradigms and research across the spectrum of AD by unique integration of clinical, genetic and biomarker data with neuropathology data to understand the pathobiology of AD accomplished through ongoing close collaboration between the Biomarker Core team especially Magda Korecka, Michal Figurski, Nirali Shah and visiting scholar Ju Hee Kang and colleagues in the UPenn CNDR such as Jon Toledo, David Irwin and Corey McMillan. We expect to continue in ADNI3 this activity that is helping to develop the next generation of AD biomarker scientists.

Approach to Specific Aims 1-4 in the Biomarker Core Renewal Period

Aim 1: Receive, aliquot, store and curate biofluid samples following established ADNI SOP's and transfer samples to investigators approved by the RARC as described in the Administrative Core.

A key function of the ADNI3 Biomarker Core at Penn is to continue to receive, aliquot, store, curate, and track all samples collected from subjects enrolled in ADNI3, including all who "carry over" from ADNI GO and 2. This is essential to enable studies of ADNI biofluid samples by investigators in this Core, as described in the subsequent Aims here, and by other investigators who are approved by the RARC for "add-on" studies.

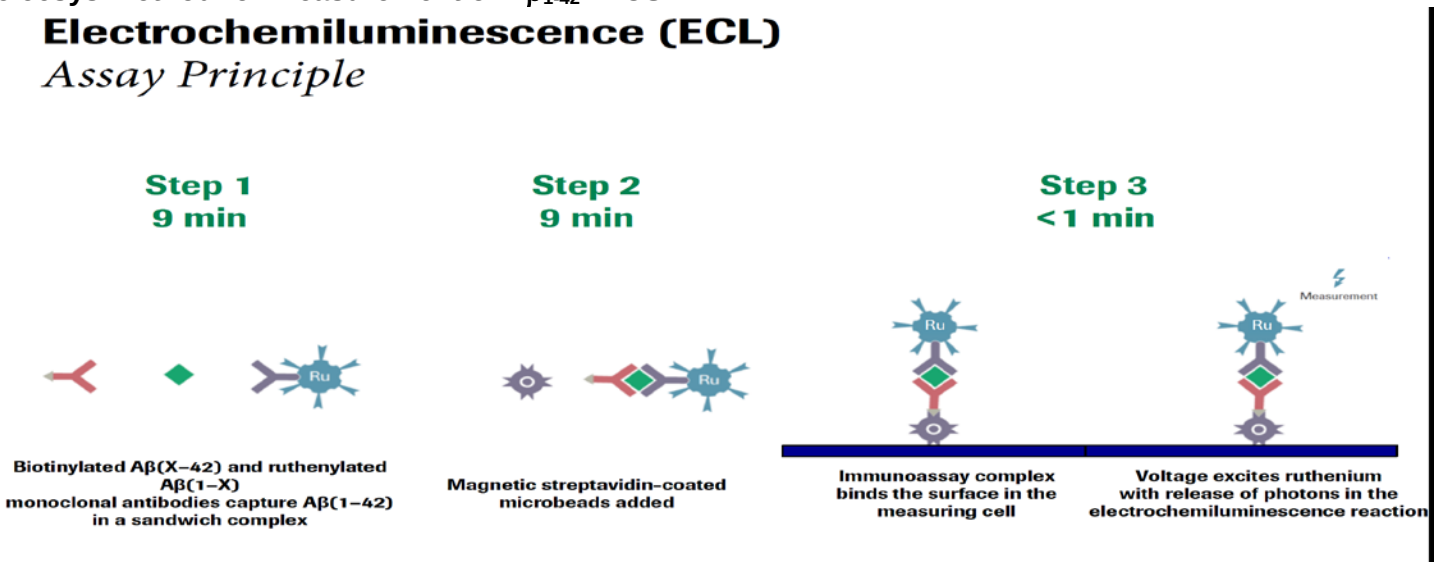
The same methods and SOP's implemented in ADNI1 that have been proven to be reliable and effective over the past 11 years will be used in ADNI3. These methods and procedures are summarized below in the PROGRESS REPORT, and they have been disseminated to all ADNI investigators and site personnel who have used them effectively. They also have been distributed to WW-ADNI investigators to assist them with their SOP's, and to promote harmonization of biomarker SOP's. To maximize broadest dissemination of these SOP's, they also are available to download on the ADNI website by any investigator around the globe. Thus, the SOP's required to implement this Aim in ADNI3 are up and running in the Biomarker Core as well as across all ADNI sites and they are being adopted by collaborators in WW-ADNI.

Aim 2: Provide highly standardized $A\beta_{1-42}$, t-tau and p-tau_{181} measurements on all ADNI subject CSF samples using the Roche automated immunoassay platform(Cobas e601) and immunoassay reagents. In addition provide immunoassay-independent measurements of Aβ species ($A\beta_{1-42}$, $A\beta_{1-40}$ and $A\beta_{1-38}$) using a validated candidate reference 2D-UPLC/tandem mass spectrometry method in baseline and longitudinal CSF samples. Continue collaboration with other investigators to achieve harmonization of these measurements across centers and different platforms in support of their use in clinical trials.

We will measure, as described in the PROGRESS REPORT, $A\beta_{1-42}$, t-tau and p-tau_{181} in all ADNI CSF samples using a new accuracy and precision-based random-access automated immunoassay platform that is undergoing comprehensive validation in the final year of ADNI2. The principles underlying this automated sandwich, single-plex electrochemiluminescence-detection immunoassay are presented in the drawing below for $A\beta_{1-42}$ (Figure 1). There are two incubation steps each of 9 minutes' duration: in the first step 35 μL of CSF sample is incubated with two monoclonal antibodies specific to Aβ(X-42)(biotinylated) and Aβ(1-X)(ruthenium-labelled), respectively, to form a sandwich complex specific for detection of $A\beta_{1-42}$; in the second incubation step, following addition of streptavidin-coated magnetic microbeads, the sandwich complex binds to the solid phase (Figure 1). A multicenter study has been completed showing the best intercenter performance reported

for any method to date: the total measurement error across 4 participating laboratories and 3 different reagent lots and across 5 days of runs ranged from 2.2 to 5.1% over the 5 different CSF pools used for this study [58].

Figure 1. The sandwich immunoassay principle and electrochemiluminescence detection in the Roche elecsys method for measurement of $A\beta_{1-42}$ in CSF.



A complete QC program based on the Biomarker Core-developed prospective QC, recently described [52], will be implemented as part of the SOP for this new system using AD-like and normal CSF pools. As part of the overall quality control program for this new immunoassay platform we will participate in the AA-sponsored CSF proficiency testing program that provides every 4 months three CSF samples for measurements of $A\beta_{1-42}$, t-tau and p-tau_{181} and continuing discussion of results and interpretation [59]. All of these analyses in the ADNI Biomarker Core will provide the benefit of invaluable long-term experience with this new analytical platform for future clinical trials. Analyses of all ADNI CSF samples using the newly validated 2D-UPLC/tandem mass spectrometry method for $A\beta_{1-42}$, $A\beta_{1-40}$ and $A\beta_{1-38}$ have been initiated and will be ongoing throughout ADNI3. We have initiated studies for high sensitivity mass spectrometry analysis of t-tau, using a Waters Xevo G2-X5 time of flight (TOF) MRM mass spectrometry system in collaboration with Waters and if successful propose to use this for analysis of CSF samples for ADNI3 subjects. We continue to work with Kaj Blennow and colleagues on the finalization, under the leadership of the IRMM and IFCC, of reference standard $A\beta_{1-42}$ as discussed below in Aim 2 of Progress Report. This continued collaboration has been fostered by the emphasis in the ADNI study on improved standardization of all biomarker methods, by the continuing collaboration with PPSB colleagues, the BBWG, the AA GBSC, and the efforts of the Coalition Against Major Diseases (CAMD) to support biomarker qualification for use in treatment trials [60].

Aim 3: Collaboration with other investigators in the use of new tests for CSF (total and phospho-α-SYN; neurogranin; NFL; Vilip1 and TDP-43) and possibly blood biomarkers (metabolomic and lipidomic assays; $A\beta_{1-42}$ and tau proteins in neurally derived exosomes).

This Specific Aim is designed to incorporate novel CSF and blood biomarker assays that emerged from ADNI1, GO and 2 add-on studies of potential AD biomarkers that have been published or for which the data on these add-on studies are in the process of being analyzed. The following new biomarkers will be analyzed by recently established immunoassays by outside investigators: CSF total and phospho-α-SYN, neurogranin, NFL, and Vilip1 (see letters of support). A new test for CSF TDP-43 is in development; selected analytes identified by mass spectrometry analyses in recent metabolomic/lipidomic add-on studies are at an initial stage of statistical analyses; and $A\beta_{1-42}$ and tau contained within neurally derived (ND) exosomes prepared from plasma[61-69] are promising biomarkers at earlier stages of development. For CSF total and phospho-α-SYN, neurogranin, NFL, Vilip1, and the mass spectrometry-based analytes identified in metabolomics/lipidomic studies, the lead investigators involved have each indicated their willingness to perform these tests in their laboratory on ADNI3 biofluid samples, pending approval by the RARC and NIA. To that end, we have letters of collaboration from the investigators who conducted the corresponding add-on studies to ensure the timeliness of this process as well as the validation of these assays which is a genuine expression of the desire of investigators to collaborate with the Biomarker Core. For new biomarkers in development such as the TDP-43 assay, we collaborate with Hugo Vanderstichele at ADx to develop this assay using a new panel of monoclonal antibodies we have developed that we have provided to ADx[68] and we adopt a similar approach to the

development of exosome based assays. The latter is of special interest as a possible index of $A\beta_{1-42}$ and tau proteins measurable in plasma but of neural origin since the soluble fraction of plasma is a very heterogeneous mixture of proteins from many tissue sources not just those of brain origin. The investigators suggested that concentrations of phospho-tau and $A\beta_{1-42}$ in extracts of ND-exosomes predict development of AD up to 10 years before onset of clinical symptoms.[69] These are promising findings but require confirmation in additional cohorts and further standardization studies are needed. In summary, we are well positioned to collaborate in adding novel assays in the ADNI3 renewal period and to collaborate on earlier stage developments.

Statistical Analysis Methods. Aims 1 and 2 are devoted to providing high quality CSF biomarker data in all ADNI3 CSF samples using highly standardized methods for biofluid collection and management, and highly standardized automated immunoassay measurement of CSF $A\beta_{1-42}$, t-tau and p-tau_{181} and mass spectrometry measurement of CSF $A\beta_{1-42}$ and related peptides. In Aim 3 we collaborate to design and implement analyses, with highest achievable standardization, of new CSF biomarkers in ADNI3. In AIM 4 we briefly describe below hypotheses that we will test that are more completely described in the Biostatistics Core.

Aim 4: Collaborate in studies (a) of individual and combinations of CSF biomarkers for prediction of memory, cognitive and functional decline, (b) the effect of using individual and combinations of CSF biomarkers and associated cutpoints for reducing sample size thus improving efficiency of treatment trials, (c) study rates of change of CSF biomarkers over time to determine relationships between rates of change and future cognitive decline, (d) determine the prediction of uptake of tau ligand by CSF $A\beta_{1-42}$ below cutpoint, and (e) determine the concordance between $A\beta_{1-42}$ and amyloid-β plaque ligand uptake with the Biostatistics Core and other ADNI3 Cores as well as with other outside investigators.

AIM4 (a): test the hypothesis that $A\beta_{1-42}$ alone, at pathologic concentrations (below cutpoint) predicts decline in measures of memory, cognition and function as compared to ADNI3 subjects with normal concentrations (above cutpoint concentrations) by including an indicator for abnormal $A\beta_{1-42}$ and its interaction with time in longitudinal models of memory, cognitive, and functional measures, separately for each baseline diagnostic category and by including this indicator in models of time to progression (see Biostatistics Core); we will also and will assess combinations of $A\beta_{1-42}$ and t-tau or p-tau_{181}. We will have 80% power (2-sided α=0.05) to detect group differences in rates of change in ADAS-COG as small as 0.43 (0.96, 2.28) pts/yr in NL, MCI and AD if groups are equal in size; for smaller biomarker subgroups, the detectable separation increases.

AIM4(b) test for the impact of CSF biomarkers and combinations on reducing sample size to improve efficiency of treatment trials. We will calculate required sample size and number needed to screen, for varying standard trial designs, assuming screening for high-risk levels of biomarkers and combinations, with 80% power to detect clinically relevant improvement in signal-to-noise ratio).

AIM4(c) test the hypothesis that rates of change of CSF $A\beta_{1-42}$ are predictive of decline in memory, cognition and function in ADNI3 subjects. We will use simultaneous longitudinal models of change in CSF $A\beta_{1-42}$ and decline in memory, cognition, or function to assess the correlation between biomarker change and decline.

AIM4(d) test the hypothesis that AD biomarker signature, eg. $A\beta_{1-42}$ below cutpoint, predicts tau ligand uptake. We will include $A\beta_{1-42}$ as continuous measure or indicator of below cutpoint as predictor of tau ligand uptake (cross-sectional, or with time-interaction in models of tau ligand uptake change). For power see PET Core.

AIM4(e) test the hypothesis that there is very good concordance between florbetapir(+/-) and CSF $A\beta_{1-42}$(-/+). Cross-sectional association will be tested in standard regression models (for continuous measures) and contingency tables (for categorical summaries); longitudinal using simultaneous models as in Aim 4c.

AIM4(f) test the hypotheses above for measures of the new biomarkers used in ADNI3. (Analyses as in 4a-e.)

PROGRESS REPORT

Biofluid Biobank. From the beginning of ADNI2 in 2010 through August 31, 2015, the ADNI biofluid repository in the Biomarker Core at Penn continuously received biofluids (CSF, plasma and serum) shipped from all ADNI sites followed by receipt, aliquoting and monitoring 24/7 in dedicated -80 ^{0}C freezers. Collection and shipment of biofluid samples are done in accordance with ADNI biomarker SOP's established, after consultation with industrial and academic biomarker researchers [33] in ADNI1, continued in ADNI GO and 2 as recently reviewed.[24] Biomarker Core staff continue to work closely with the Clinical Core and clinical sites on recording essential details for each collected sample from the jointly developed biofluid tracking form as described.[24] These SOP's are essential to ensure the integrity, quality and accurate identification of the samples received and the aliquots prepared from them. The following information is recorded for each biofluid sample in the database at Penn: biofluid type (CSF, plasma, serum, urine [only ADNI1]), coded subject and visit ID, six digit license plate number, visit date and time, date and time of receipt, condition of the samples as received, biofluid sample volume and number of aliquots, details of sample preparation such as time from collection to time of transfer, and to time of freezing are recorded for each sample from each study site and a

summary of (1) biofluid tracking time-the time from sample collection to freezing for ADNI2 CSF and plasma samples and (2) ADNI2 number of biofluids collected and number of aliquots in the Penn ADNI Biobank and the total of ADNI1/2/GO biofluids collected and banked through August 31, 2015 is available in the latest edition of Biofluid Reports on the LONI ADNI website [70].

Transfer of biofluid samples to investigators approved by the RARC. During the time span of the ADNI2 funding period, the Biomarker Core transferred to RARC-approved investigators 16 sets of de-identified biofluid samples totaling 3,276, 1,881 and 933 CSF, plasma or serum aliquot samples respectively [24] (see Table 1 in Resource Sharing Plans for details of RARC-approved studies including the PI, the types and numbers of biofluid samples, the number of blind replicate samples, and dates of study data upload/unblinding. As part of its responsibility, the Biomarker Core sends the unblinding code to the Clinical Core at USC for the unblinding process once an investigator has uploaded their blinded study data. This is another example of cooperation between ADNI Cores that is essential for the continuing success of ADNI. Investigators have applied state of the art analytical methods and platforms including xMAP multiplex immunoassay, mrm/mass spectrometry, Electrochemiluminescence Quickplex, Singulex and Simoa high sensitivity immunoassays, in the search for new AD biomarkers [71-76]. Detailed discussions of the major findings for these studies of new AD biomarkers are in a recent review [24] and won't be repeated here due to space limitations. Amongst the highlights of these studies are: (1) the promising findings from the Rules Based Medicine xMAP targeted multiplex immunoassay analysis of plasma proteins that supports the potential utility of a plasma proteome signature as a screening tool for AD [71,72]; and ongoing data analyses of studies completed in CSF; (2) application of an α-SYN assay for studies of CSF showing the tight correlation of this biomarker with t-tau and p-tau in normal, MCI and AD patients and in patients with Parkinson's disease, and a potentially significant deviation of this ratio in AD patients with accompanying LB pathology [74,77]; (3) As the third part (RBM studies were first, and BACE activity in CSF second) of a multiphase effort of the Foundation for the NIH(FNIH) Biomarkers Consortium (BC) to identify CSF-based biomarkers in AD, a targeted mass spectrometry proteomic study was performed by several members of the ADNI PPSB in collaboration with FNIHBC.[78] Several potential diagnostic or predictive biomarkers were identified as described[24,78] including neuronal pentraxin-2(NPTX2), neurosecretory protein VGF and secretogranin-2 (SCG2) predict the progression of MCI to AD [78]; (4) studies of neurogranin, a biomarker for synaptic pathology in AD in CSF, using an investigator-developed immunoassay which showed that CSF neurogranin was increased in predementia stages of AD and that higher concentrations correlated with a higher rate of cognitive deterioration, decreased glucose metabolism and higher hippocampal atrophy rates [79,80] supports earlier findings of the possible utility of these biomarkers to add to the predictive performance of CSF $A\beta_{1-42}$ and tau proteins for rates of progression to dementia in MCI patients [62].

Standardization of measurements of $A\beta_{1-42}$, t-tau and p-tau_{181} in CSF.

xMAP AlzBio3 RUO immunoassay. A total of 815 Baseline and 294 year 2 CSF samples from ADNI2 subjects and a total of 317 longitudinal CSF samples collected out to a maximum of 7 years in ADNI1 "carryover" subjects were analyzed during ADNI 2 using the highly standardized RUO AlzBio3 xMAP micro-bead based immunoassay and prospective quality control according to ADNI Biomarker Core SOP's providing a total of 4,278 results for CSF $A\beta_{1-42}$, t-tau and p-tau_{181}. The precision performance (%CV) results for all batch analyses was 4.5% to 6.4%, 5.4% to 8.6% and 7.5% to 13.8% for $A\beta_{1-42}$, t-tau and p-tau_{181}, respectively, based on test re-test performance across ADNI CSF samples as described in the ADNI2 analytical reports accessible on the ADNI LONI website under Biospecimen reports and further can be found in the recent ADNI Biomarker Core review [24]. Our experience to date is that within-laboratory performance has been very good for this RUO test, although p-tau_{181} performance in our hands has been less precise as noted above. The ongoing performance confirms earlier experience in the Biomarker Core including the demonstration across 7 participating laboratories [3 academic and 4 industrial laboratories] within-center precision from 5.3% to 10.8%CV, although center-to-center performance was less precise(13.1 to 17.9%), which is an important limitation considering that international drug registrations trials need multiple laboratories to perform this testing, and the strong need for tight lab-to-lab precision and accuracy performance [35]. The clinical utility value of this methodology had been demonstrated in many settings [36-39,41-43,54] as summarized in a recent review of the Biomarker Core [24]. Limitations of this RUO test include the limited center-to-center precision performance [35,59], matrix interference effects, the lack of a certified reference material for accuracy-based calibration, the high complexity involving many manual procedural steps and for the AlzBio3 test on the Luminex platform it is unlikely to be developed by the manufacturer Fujirebio Europe as an IVD test. Hence, the change to the Roche Cobas e601platform.

Mass spectrometry based assay for $A\beta_{1-42}$, $A\beta_{1-40}$ and $A\beta_{1-38}$.

The ADNI Biomarker Core continues to assess CSF assays and other methodological issues related to the chemical biomarker studies conducted in the ADNI Biomarker Core at Penn. In line with this is the development of a 2D-UPLC/MS-MS platform [24,54] using a Waters high sensitivity Xevo TQS tandem mass spectrometer acquired by the Biomarker Core. Described in Korecka et al[54] and in our recent review[24] the major features of this candidate reference method are: (a) extraction, and denaturation of intact Aβ peptides, internally standardized with ^{15}N-labelled Aβ peptides from 100 μL CSF samples, with high concentration guanidine hydrochloride(5M), followed by mixed bed ion exchange extraction, based on the work of Lame[81], and subsequent quantification by multireactant monitoring(MRM)tandem mass spectrometry(4+ charged precursor and fragment ion pairs: *m/z* 1129.5 → 1079.1 for $A\beta_{1-42}$ and m/z 1142.5 →1091.5 for ^{15}N-$A\beta_{1-42}$); (b) calibration using a surrogate calibrator matrix prepared from artificial CSF plus 4 mg/mL bovine serum albumin, validated for this method and successfully used in the Biomarker Core for 3½ years; (c) lower limit of quantification of 100 pg/mL; throughput 120 samples per week in batches of 30 CSF samples; (d) close agreement with a co-developed candidate reference method that uses the same sample preparation steps but different HPLC and mass spectrometry instrumentation[47](Figure 2 below). This work was undertaken as part of a joint effort under the auspices of the AA GBSC involving 4 laboratories, showing very good concordance across 12 CSF pool samples (R^2=0.98; avg intra-laboratory %CV of 4.7%; inter-laboratory %CV of 12.2%) that improved to 8.3% when adjusted using a common calibrator[56]. A follow-up intercenter study has been conducted and analysis of results is in progress. Using the common calibrant an acceptable uncertainty value of 3.7% was achieved demonstrating the reproducibility across the 5 centers using this common reference material. A key remaining task for IRMM is finalization of absolute mass value assignment for the reference standard that requires reproducible amino acid analyses with sufficient precision of replicate analyses, work that is ongoing and expected to be complete in the near future. In addition to providing $A\beta_{1-42}$, the reference method will also, in the same sample, provide with no extra sample preparation steps $A\beta_{1-40}$ and $A\beta_{1-38}$ concentrations with comparable analytical performance[82]. The inclusion of analysis of these two Aβ peptides in the same sample aliquot provides metabolite data that may improve on the interpretation of $A\beta_{1-42}$ results particularly detection of the presence of vascular Aβ deposits or congophilic angiopathy co-pathology[83].

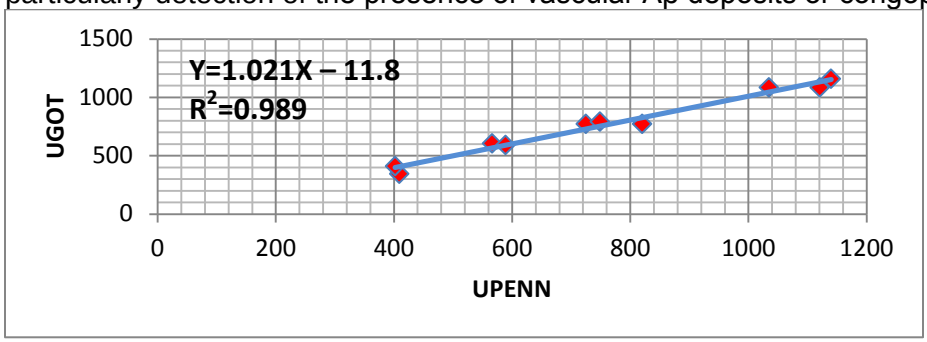


Figure 2. Comparison of $A\beta_{1-42}$ results (pg/mL) for 10 patient CSF samples. UGOT, University of Gothenburg; UPENN, University of Pennsylvania. Each laboratory used their Candidate mrm/tandem mass spectrometry method [47, 54]

Validation of a fully automated immunoassay platform for CSF $A\beta_{1-42}$, t-tau and p-tau_{181}.

Manufacturers are in various stages of developing "second generation" immunoassays for CSF $A\beta_{1-42}$, t-tau and p-tau_{181} [24]. The ADNI Biomarker Core reviewed all available data for the new and existing immunoassays platforms for measurement of $A\beta_{1-42}$, t-tau and p-tau_{181} in CSF for the past year. Included in evaluation criteria were short- and long-term precision performance, within- and between-laboratories, concordance for the $A\beta_{1-42}$ test with reference mass spectrometry method, lot-to-lot consistency, documentation of key analytical parameters [Limit of Detection(LOD), Limit of Blank (LOB), and Lower Limit of Quantification (LLOQ)], linearity, degree of automation, cutpoint, commitment to IVD status (US FDA). The Biomarker Core is conducting a validation study of the Roche automated Cobas e601 analyzer/Aβ-elecsys immunoassay kits. The validation study focuses on $A\beta_{1-42}$, with t-tau and p-tau_{181} soon to follow. Our validation plan for the Roche automated platform in our laboratory uses non-ADNI CSF aliquots from routine clinic residual samples and 70 AD (autopsy confirmed) and 70 age-matched cognitively normal subject CSF samples provided by the Penn AD Core Center led by John Trojanowski the Co-CL here. The overall study includes systematic precision and accuracy studies and parallel analyses of all CSF samples by the Roche method, AlzBio3 immunoassay and mass spectrometry candidate reference method. Once completed the Biomarker Core will analyze ADNI1, GO and 2 CSF samples and use a variety of approaches to assess cutpoint values including mixture modelling [37]. Implementation of these accuracy-based methods will provide CSF biomarker data, that together with the existing AlzBio3 xMAP RUO Luminex-based immunoassay (Fujirebio-Europe, Ghent, Belgium) data will add an unprecedented level of certainty to future assessments of the interrelationships between these biomarkers and imaging, genomic, metabolomics, memory, cognitive and functions of daily living scores**.**

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OMB Number: 4040-0001
Expiration Date: 06/30/2016

APPLICATION FOR FEDERAL ASSISTANCE

SF 424 (R&R)

5. APPLICANT INFORMATION **Organizational DUNS*:** 6133387890000

Legal Name*: NORTHERN CALIFORNIA INSTITUTE FOR RESEARCH AND EDUCATION
Department:
Division:
Street1*: 4150 CLEMENT STREET (151-NC)
Street2:
City*: SAN FRANCISCO
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 941211545

Person to be contacted on matters involving this application

Prefix:	First Name*:	Middle Name:	Last Name*:	Suffix:
	Azarah	Sr. Grant Specialist	Wong	

Position/Title:
Street1*: 4150 CLEMENT STREET (151-NC)
Street2:
City*: SAN FRANCISCO
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 941211545
Phone Number*: 415-750-6954 x 23891 Fax Number: 415-750-9358 Email: cgawards@ncire.org

7. TYPE OF APPLICANT* M: Nonprofit with 501C3 IRS Status (Other than Institution of Higher Education)

Other (Specify):
Small Business Organization Type ❍ Women Owned ❍ Socially and Economically Disadvantaged

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
Genetics Core

12. PROPOSED PROJECT

Start Date*	Ending Date*
08/01/2016	07/31/2021

OMB Number: 4040-0010
Expiration Date: 06/30/2016

Project/Performance Site Location(s)

Project/Performance Site Primary Location

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: The Trustees of Indiana University
Duns Number: 6030079020000
Street1*: 355 W. 16th St.
Street2: GH 4100
City*: Indianapolis
County:
State*: IN: Indiana
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 46202-2207
Project/Performance Site Congressional District*: IN-007

Project/Performance Site Location 1

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: University of California, Irvine
DUNS Number: 0467058490000
Street1*: 5251 California Ave
Street2: Suite 240
City*: Irvine
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 926970000
Project/Performance Site Congressional District*: CA-045

File Name

Additional Location(s)

Genetics Core: Abstract The overarching goals are to support sample banking and analysis to identify variants associated with Alzheimer's disease (AD) phenotypes that have the potential to enhance clinical trial design and serve as potential therapeutic targets, as well as to provide an organizational framework to foster collaboration on genomic studies within ADNI. During ADNI2, the core banked DNA, RNA, and lymphoblastoid cell lines and provided genome-wide data sets facilitating rapid research progress resulting in over 300 publications from groups worldwide. Whole exome and whole genome sequencing (WES, WGS) and blood gene expression profiling data were also generated through collaborations with industry, private non-profit organizations, and academic partners and provided to the scientific community. A major focus of studies by the core and other groups has been genetic association analyses of quantitative AD endophenotypes including MRI, PET, CSF, and cognitive measures. Recent studies have incorporated systems biology network and pathway approaches as late onset AD is a complex disease with multiple determinants. Examples of genetic findings relevant for clinical trial design include identification of variation in the cholinergic gene *BCHE* as a predictor of baseline amyloid burden on PET and variation in the immune gene *IL1RAP* as associated with rate of amyloid accumulation. These gene effects were moderately large and independent of *APOE*, suggesting potential for genetic enrichment to enhance efficiency and targeting of clinical trials. Specific Aims for ADNI3: 1) Continue sample collection, processing, banking, curation, and dissemination. PBMC banking for iPSC development and other applications has been added in response to strong interest from academic and industry investigators; 2) Continue to provide genome-wide and *APOE* genotyping data to the scientific community; 3) Continue to perform and facilitate bioinformatics analyses of ADNI genetics and quantitative phenotype data. Several hypotheses will be assessed including H1: Efficiency of clinical trials can be improved by enrichment with genetic markers beyond *APOE*; H2: 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; H3: Variation in the *MAPT* gene and other neurodegeneration pathways will be associated with [^{18}F]AV-1451 tau PET; and, H4: Genetic variation influences proteomic and metabolomic biomarker assays and controlling for genetic effects will improve their performance in predicting disease progression and outcomes; and, 4) Continue to provide organization, collaboration, and support for further development of genomic studies of quantitative biomarker phenotypes and outcomes in ADNI through the core's working groups (WGS, RNA Analysis, Epigenomics, Systems Biology, and Functional Genomics) and regular conference calls. These aims are expected to impact the field by helping to improve clinical trials and support the development of precision diagnostic and therapeutic medicine for AD.

PROFILE - Senior/Key Person

Prefix: First Name*: TATIANA Middle Name M. Last Name*: FOROUD Suffix:

Position/Title*: Professor and Director of HD Division
Organization Name*: The Trustees of Indiana University
Department: DEPARTMENT OF MEDICAL AND MOLE
Division: Hereditary Genomics
Street1*: 410 W. 10th St
Street2: HS 4000
City*: INDIANAPOLIS
County:
State*: IN: Indiana
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 462020000

Phone Number*: 317-278-1291 Fax Number: 317-278-1100 E-Mail*: tforoud@iu.edu

Credential, e.g., agency login: tforoud

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: PHD,MS,BS Degree Year:

File Name
Attach Biographical Sketch*: Core_E_Biosketch_Foroud.pdf
Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: LI Middle Name Last Name*: SHEN Suffix:

Position/Title*: Associate Professor
Organization Name*: The Trustees of Indiana University
Department: Radiology and Imaging Sciences
Division:
Street1*: 355 W. 16th Street, Suite 4100
Street2:
City*: Indianapolis
County:
State*: IN: Indiana
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 462020000

Phone Number*: 3179637504 Fax Number: E-Mail*: shenli@iu.edu

Credential, e.g., agency login: li_shen

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: PHD Degree Year:

File Name
Attach Biographical Sketch*: Core_E_Biosketch_Shen.pdf
Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: LIANA Middle Name G Last Name*: APOSTOLOVA Suffix:

Position/Title*: Visiting Professor
Organization Name*: The Trustee of Indiana University
Department: School of Medicine
Division:
Street1*: 355 W. 16th Street
Street2: Suite 4700
City*: indianapolis
County:
State*: IN: Indiana
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 462022285

Phone Number*: 317-963-7436 Fax Number: E-Mail*: lapostol@iu.edu

Credential, e.g., agency login: apostolova2

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: MD,MS Degree Year:

File Name
Attach Biographical Sketch*: Core_E_Biosketch_Apostolova.pdf
Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: Sungeun Middle Name Last Name*: Kim Suffix:

Position/Title*: Assistant Professor
Organization Name*: The Trustees of Indiana University
Department: Radiology and Imaging Sciences
Division:
Street1*: 355 W. 16th Street
Street2:
City*: Indianapolis
County:
State*: IN: Indiana
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 462022207

Phone Number*: 3179637505 Fax Number: E-Mail*: Sk31@iupui.edu

Credential, e.g., agency login: sungeunkim

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: Degree Year:

File Name
Attach Biographical Sketch*: Core__E_Biosketch_Kim.pdf
Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: Kwangsik Middle Name Timothy Last Name*: Nho Suffix:

Position/Title*: Assistant Professor
Organization Name*: The Trustees of Indiana University
Department: Radiology and Imaging Sciences
Division:
Street1*: Center for Neuroimaging
Street2: 355 West 16th Street, GH, Ste 4100
City*: Indianapolis
County:
State*: IN: Indiana
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 460320000

Phone Number*: 317-963-7503 Fax Number: E-Mail*: knho@iupui.edu

Credential, e.g., agency login: kwangsiknho

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: PHD,MS,BS Degree Year:

File Name

Attach Biographical Sketch*: Core_E_Biosketch_Nho.pdf

Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: SHANNON Middle Name L Last Name*: RISACHER Suffix:

Position/Title*: Assistant Research Professor
Organization Name*: Indiana University
Department: Radiology and Imaging Sciences
Division:
Street1*: 355 West 16th Street, GH Suite 4100
Street2:
City*: INDIANAPOLIS
County:
State*: IN: Indiana
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 462020000

Phone Number*: 317-963-7513 Fax Number: 317-274-8744 E-Mail*: srisache@iupui.edu

Credential, e.g., agency login: srisache

Project Role*: Consultant Other Project Role Category:

Degree Type: PHD,BS Degree Year:

File Name

Attach Biographical Sketch*: Core-E_Biosketch_Risacher.pdf

Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: Rima Middle Name F Last Name*: Kaddurah-Daouk Suffix:

Position/Title*: Professor
Organization Name*: Duke University Medical Center
Department:
Division: Behavioral Medicine
Street1*: DUMC 3903
Street2: Blue Zone South
City*: DURHAM
County:
State*: NC: North Carolina
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 277100000

Phone Number*: 919-684-5175 Fax Number: 919-684-6278 E-Mail*: rima.kaddurahdaouk@duke.edu

Credential, e.g., agency login: KADDU001

Project Role*: Consultant Other Project Role Category:

Degree Type: PHD,MS,BS Degree Year:

File Name

Attach Biographical Sketch*: Core_E_Biosketch_Kaddurah-Daouk.pdf

Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: STEVEN Middle Name G Last Name*: POTKIN Suffix:

Position/Title*: Professor
Organization Name*: University of California Irvine
Department: Psychiatry & Human Behavior
Division:
Street1*: 5251 California Ave
Street2:
City*: IRVINE
County: Orange
State*: CA: California
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 926977600

Phone Number*: 949-824-8040 Fax Number: 949-824-2094 E-Mail*: sgpotkin@uci.edu

Credential, e.g., agency login: spotkin

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: MD Degree Year:

File Name

Attach Biographical Sketch*: Potkin_Biosketch_2015.ADNI3.pdf

Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: Fabio Middle Name Last Name*: Macciardi Suffix:

Position/Title*: Professor
Organization Name*: University of California Irvine
Department: Psychiatry & Human Behavior
Division:
Street1*: 5251 California Avenue, suite 240
Street2:
City*: Irvine
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 926970000

Phone Number*: 9493514756 Fax Number: E-Mail*: fmacciar@uci.edu

Credential, e.g., agency login: fmacciardi

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: MD,PHD Degree Year:

File Name
Attach Biographical Sketch*: Macciardi_Biosketch.pdf
Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: Theodorus Middle Name G.M. Last Name*: van Erp Suffix:

Position/Title*: Assistant Professor in Residence
Organization Name*: University of California, Irvine
Department: Psychiatry & Human Behavior
Division:
Street1*: 5251 California Avenue
Street2: Suite 240C
City*: Irvine
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 926170000

Phone Number*: 949-824-3331 Fax Number: 949-824-3324 E-Mail*: tvanerp@uci.edu

Credential, e.g., agency login: tvanerp

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: PHD,MA Degree Year:

File Name
Attach Biographical Sketch*: VanerpNIH_biosketch_ADNI3.pdf
Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: ANDREW Middle Name J Last Name*: SAYKIN Suffix:

Position/Title*: Professor & Director of Neuroimaging
Organization Name*: Indiana University
Department: Radiology and Imaging Sciences
Division:
Street1*: Center for Neuroimaging/Radiology
Street2: 355 W. 16th St, Suite 4100
City*: Indianapolis
County:
State*: IN: Indiana
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 462020000

Phone Number*: 317-963-7501 Fax Number: 317- 274-1067 E-Mail*: asaykin@iupui.edu

Credential, e.g., agency login: saykin

Project Role*: Other (Specify) Other Project Role Category: Genetics Core Lead

Degree Type: PSYD,MS,BA Degree Year:

	File Name
Attach Biographical Sketch*:	Core_E_Biosketch_Saykin.pdf
Attach Current & Pending Support:	

Genetics Core: Specific Aims

The overarching goal of the core is to identify and validate genetic markers for use in clinical trials. Although AD is highly heritable [1], the main practical contribution of genetics to AD clinical trials has been stratification by *APOE* status which influences onset age [2, 3], amyloid beta deposition/clearance [4, 5], and susceptibility to adverse effects of anti-amyloid treatment [6]. The challenge is to leverage the major technical advances in genetics and related -*omics* to discover, validate, and implement novel markers that can improve the precision and power of AD clinical trials. During ADNI-2, the core collected, processed, banked, and disseminated lymphoblastoid cell lines (LCL) and DNA and RNA samples from blood, as well as extensive derived data sets downloaded 1000's of times. *APOE* and genome-wide association study (GWAS) genotyping, whole exome and whole genome sequencing (WES, WGS), and most recently gene expression profiling, have all been generated and provided to the scientific community. The impact of genetic studies enabled by ADNI is reflected by over 300 publications since 2010 [7]. Many of the first applications of quantitative endophenotype association studies in MCI and AD employed ADNI data, including some of the earliest GWAS and pathway-based studies of fluid biosamples, of MRI and PET imaging biomarkers, and of clinical and cognitive variables. Other contributions include among the first copy number variation (CNV) and WES/WGS data sets and reports in MCI, AD, and controls. Several susceptibility and protective loci associated with clinical diagnosis of MCI/AD or AD biomarker values have been identified and/or replicated using ADNI data. Despite these successes, *APOE* remains the only widely used genetic marker in trials for late onset AD (LOAD). In ADNI-3, additional data collection will increase statistical power, new phenotypes will enable novel questions, and new bioinformatics strategies will analyze growing multi-omics and longitudinal data. To better address the complexity inherent in AD, *systems biology* modeling approaches incorporating immune, mitochondrial, cell cycle/fate, and other biological processes, in addition to amyloid and tau, will be implemented. In the next phase of ADNI, longitudinal analyses of *metabolome* changes will help elucidate dynamic metabolic processes underlying preclinical and prodromal stages of disease. Ultimately, the core will facilitate design of more efficient clinical trials through genetic enrichment and foster discovery of novel targets for drug development.

Specific Aims:

1) Continue sample collection, processing, banking, curation, and dissemination as in ADNI-2. This includes longitudinal DNA and RNA collection, processing, quality control (QC), and banking at the National Cell Repository for AD (NCRAD). In ADNI-3, the core will begin banking PBMCs for use by the scientific community for development of induced pluripotent stem cells (iPSCs), functional drug development related assays, or other scientific purposes approved by the *Resource Allocation Review Committee (RARC)*.

2) Continue to provide genome-wide genotyping data, including *APOE*, to the scientific community. The leading cost effective GWAS platform in 3 years will be used (Illumina arrays were used in ADNI-1/GO/2).

3) Continue to perform and facilitate bioinformatics analyses of ADNI genetics and quantitative phenotype data and test scientific hypotheses related to the goals of ADNI-3.

H1: 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.
H2: 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.
H3: Variation in the *MAPT* and other neurodegeneration pathways is associated with [^{18}F]AV-1451 tau PET.
H4: Genetic variation influences proteomics and metabolomics biomarker assays and controlling for genetic effects will improve the performance of –*omics* biomarkers in predicting disease progression and outcomes.

4) Continue to provide organization, collaboration, and support for further development of genomic studies of quantitative biomarker phenotypes and outcomes in ADNI. The core will collaborate with the other ADNI cores and industry and academic partners to leverage resources with other national/international consortia. The core will continue to facilitate new data acquisition and knowledge generation through organized working groups (WGS, RNA Analysis, Epigenomics, Systems Biology, and Functional Genomics) and regular conference calls working with the Biostatistics core in these efforts. Several future directions have been identified that will require additional support before they can be fully realized, but within available resources, work will continue to develop these potentially important areas: A) Work with other parties to find resources for WGS, transcriptome and epigenetic profiling of ADNI's longitudinal DNA and RNA samples; B) Provide a framework for consensus building and planning for return of research results to participants; C) Work with the Clinical Core to develop new call back and family studies of ADNI participants; D) Facilitate replication studies with other cohorts/data sets; E) Collaborate with academic and industry partners on *molecular validation* of novel targets and characterization of mechanisms via *functional validation* follow-up studies in model systems; and F) Collaborate with the Neuropathology Core to relate differential pathological features to genetic variation.

Genetics Core: Research Strategy

A. Significance

Genetic factors serve a critical role in AD research on multiple levels including design of clinical trials. Rare mutations in *APP, PSEN1*, and *PSEN2* are highly penetrant for early-onset autosomal dominant forms of AD and these discoveries have informed knowledge of pathophysiological mechanisms [8-11] and now serve as a basis for interventional trials. In sporadic late-onset AD (LOAD), the *APOE* (apolipoprotein E) ε4 allele has been robustly replicated as a susceptibility gene associated with amyloid beta and other AD pathologies through mechanisms that are not yet fully understood [12]. *APOE* and the adjacent gene *TOMM40* are being employed for enrichment in ongoing clinical trials [13, 14]. With the advent of large-scale genome-wide association studies (GWAS) conducted by multi-study consortia, a current list of approximately 20 genes has emerged and are now undergoing further investigation to identify the biological basis of their risk or protective roles in LOAD [15]. In ADNI, *APOE* and GWAS genotyping has been completed and DNA and lymphoblastoid cell lines (LCL) have been banked on all participants, permitting ADNI to contribute to several large and important GWAS studies [15-17]. Notably, most of these large well-powered meta-analytic GWAS are case-control studies. A unique aspect of ADNI is the systematic longitudinal collection of biomarker data that can serve as quantitative endophenotypes for GWAS. Using quantitative endophenotypes as target measures has been found to improve detection power relative to case-control designs with similar sample sizes, as well as to avoid using arbitrary or potentially error prone cut-offs to define case status [18, 19]. Recognizing the value of these quantitative trait loci (QTL) investigations in AD, the ADNI Genetics core was established at the beginning of the ADNI-GO/2 phase [20] with the ***prior specific aims*** of: (1) blood sample processing, genotyping, and dissemination; (2) genome-wide analysis of multidimensional phenotypic data collected on the ADNI cohort; and, (3) serving as a central resource, point of contact, and planning group for genetic studies in ADNI. The first GWAS of an ADNI quantitative phenotype (hippocampal volume) was published in 2009 [21] and rapid progress has been made as groups worldwide analyzed the readily available ADNI genetic data. In two recent reviews, Shen et al. [22] provided a detailed report of results from ADNI genetic studies through 2012 and Saykin et al. [7] updated the results through 2014 and discussed future plans, implications for clinical trial design, and systems biology approaches to study key pathways in MCI and AD. In the ***Innovation*** and ***Progress Report*** sections, we briefly and selectively provide a further update of key results through mid-2015 and discuss future directions to maximally leverage this important growing data set.

B. Innovation

ADNI has been at the forefront of validating biomarkers for clinical trials in AD. The Genetics core has contributed to this innovation by generating and disseminating one of the largest, earliest, and most comprehensive genomics data sets in a targeted disease area. The core provided leading-edge analyses and assisted numerous investigators around the world in performing novel, scientifically informative analyses. Recent contributions by the core present new innovative opportunities to evaluate their utility for clinical trial enrichment and for Pharma to assess potential a targets for novel therapeutic development. Examples include identification of novel risk (*PARP1*, *CARD10*) and protective (*REST*) variants associated with rate of hippocampal atrophy using WES in MCI [23-26]. Using [^{18}F]florbetapir PET, *BCHE* was associated with baseline amyloid deposition [27] and *IL1RAP* was associated with rate of amyloid accumulation [28]. Other examples include the discovery of *SPON1* as a new brain connectivity gene influencing dementia severity [29] and rate of cognitive decline in AD [30] and identification of *FASTKD2* as associated with memory and hippocampal structure [31]. Another innovative aspect is the use of pathway-based approaches and a systems biology framework to understand cognitive, imaging, and biomarker changes in MCI, AD, and related conditions, particularly in the context of genetics [27, 32-36]. Other innovative use of ADNI genetic material and data generated are described in [7, 22] and in the ***Progress Report***. An Endnote file with references to all publications using ADNI genetic data through 03/2015 was published [7]. ***In ADNI-3, innovation will be enhanced by (1) A focus on genetic enrichment strategies to improve clinical trials; (2) Analyses to identify the genetic architecture of important new phenotypes (tau patterns on PET, metabolomics analytes provided by the AD Metabolomics Consortium R01, novel CSF biomarkers, etc.); (3) New bioinformatics strategies including network and pathway analyses; and (3) PBMC banking enabling iPSC and functional assays for new mechanistic/drug development efforts by the scientific community.***

C. Approach

Core Organization and Response to 2010 Review: The core benefitted from the excellent suggestions made by reviewers who raised concerns regarding several areas. Overall issues are discussed here with others addressed under the most relevant *Aim.* *Core leadership* is multidisciplinary with experts in genetics and biomarkers of AD and complex disease from neuropsychology/neuroimaging (core leader (CL)), genetics (co-

CL), psychiatry (co-CL), bioinformatics and computational biology (co-CL and 2 co-investigators (I)), neurology (2 co-Is), and imaging genetics (all members). All investigators have NIH funding related to AD genetic studies, have collaborated for many years [7, 22] (for reviews), and have expertise in quantitative AD phenotypes. Previous reviewers noted that "*CL publications reflect … imaging techniques to a much greater extent than genetics."* During the 2010-2015 funding period, Dr. Saykin (CL) served as first/senior author on at least 25 AD genetics publications [7, 20, 22-25, 27, 28, 32-48]. Dr. Foroud (co-CL and Dept. Chair of Genetics at IU) is a statistical geneticist and expert on biobanking who directs the biosample lab functions of the core. Dr. Shen (co-CL) is a computer scientist and associate director of the IU Center for Computational Biology and Bioinformatics and leads the bioinformatics aspects of the core. Dr. Potkin (co-CL) is an expert in imaging genetics/clinical trials. *Duties and operations*: Drs. Nho and Kim are highly experienced in genetic data QC, integration, and bioinformatics, and perform most of the outreach and support. Dr. Risacher updates and integrates all ADNI clinical, cognitive, and biomarker phenotypes regularly. Core members meet weekly to plan, prioritize, update, and coordinate data QC, organization, analysis, and reporting, and to liaison with collaborating teams and projects. Decisions are made by consensus. The CL schedules regular conference calls (weekly to monthly as needed) with each of the core's working groups. *Cross core integration*: See Aim 4. *Data access & authorship*: All ADNI data, including genetic, is available to the scientific community without embargo. For core led papers, investigators performing the most work serve as lead authors with early career members encouraged to lead projects. *Power & analytic issues:* See Aim 3 for genetic models, power considerations, multiple comparisons, and systems biology modeling considerations.

Aim 1: Continue sample collection, processing, banking, curation, and dissemination as in ADNI-2. *Ongoing collection*: The Genetics core will accomplish Aim 1 as before in collaboration with the NIA-sponsored National Cell Repository for Alzheimer's Disease (NCRAD; http://ncrad.iu.edu/). Methods and standard operating procedures (SOPs) for blood collection for lymphoblastoid cell line (LCL) development, serial DNA and RNA collections, sample processing (DNA and RNA extraction), QC, and secure banking for genome, transcriptome, and epigenetic studies were recently published [7]. Detailed lab level SOPs and updates are available from the Genetics core whenever requested. *Quality control:* QC will continue to be a key consideration of the core and will continue to include evaluation of DNA and RNA quantity and integrity metrics, robotic plating and sample identity confirmation (sex, *APOE*, independent "fingerprint" SNPs), and concordance across techniques and platforms. To date, such issues have been rare but the core previously found and retested a few samples where site labeling did not match sample properties. All were resolved with the sites and/or by repeating genotyping. All corrections were documented, forwarded to the Clinical, Biostatistics, and Informatics cores, and posted to users. This level of strict QC and documentation will be continued in ADNI-3. For RNA, quality is assessed and only samples with good quality (RIN) will be used. *Peripheral blood mononuclear cell (PBMC) collection (new in ADNI-3)* will be used to support future development of *induced pluripotent stem cells (iPSCs)* or other uses by the scientific community with approval from the RARC. NCRAD protocols are in place for PBMC collection, processing, and banking. ADNI's partners strongly recommended this collection given the importance of iPSCs that can be differentiated into specific cell lines (neuronal, glial, immune, etc.) and utilized for functional studies of disease mechanism, drug development, and transplantation. Alternative approaches were discussed with experts at stem cell research laboratories. PBMC rather than fibroblast collection was based on participant and clinical site burden.

Aim 2: Continue to provide genome-wide genotyping, including *APOE*, to the scientific community. *Organize, QC, and disseminate ADNI GWAS data*. We will analyze, facilitate, and support analyses by the community of GWAS data on all new and current subjects. GWAS and other data will undergo QC as described in [7] and applied in [24, 25, 27, 28]. GWAS data will be imputed (1000 Genomes reference panel) and made available on the ADNI web site in commonly used formats. *GWAS and Imputing*: In ADNI-2, we used the *Illumina OmniExpress* array and *HumanOmni2.5-4v1* for the WGS subsample. We will again use the *OmniExpress* but note that a superior choice is likely to be available in 2-3 years when ADNI-3 is fully enrolled. Following core protocol, our extended team of experts and advisors will achieve consensus on the most appropriate technology. In general, we have tried to harmonize methods with other collaborating NIA genetics initiates (e.g., ADGC, ADSP). MaCH [49], Minimac [50], and haplotype patterns from the 1000 Genomes Project reference panel were used to impute SNP genotypes not directly assayed by the GWAS arrays in previous reports [24, 27]. These or updated methods and reference panels will be used in the future.

Aim 3: Continue to perform and facilitate bioinformatics analyses of ADNI genetics and quantitative phenotype data and test scientific hypotheses related to the goals of ADNI-3. In this aim we briefly outline the goals and bioinformatics approaches to be employed to achieve the major objectives of the core.

Enhancing clinical trials through enrichment: We will focus efforts on variants (and polygenic sets of variants) that can identify individuals enriched for risk of AD and more rapid progression. This will aid the development of more powerful, efficient, shorter, and less expensive clinical trials ([7], p.13). As the field moves to embrace *precision medicine* and *tailored therapeutics* with the goal of getting the "right drug to the right patient at the right time," collection and analysis of genetic data is recommended and becoming routine for clinical trials [51] and international standards have been proposed for such data [52]. The FDA has provided draft guidance to the pharmaceutical industry regarding development of enrichment strategies for clinical trials that include genetic markers [53] and for clinical pharmacogenomics [54] analyses that relate to drug PK/PD, safety, and efficacy. The FDA draft guidance on enrichment [53] discusses three strategies that can increase power and effect sizes and decrease study population size requirements including: (1) Decreasing patient heterogeneity including inter- and intra- patient variability, 2) Prognostic enrichment by choosing patients with a greater likelihood of substantial worsening, and 3) Predictive enrichment by choosing patients more likely to respond to a drug treatment than other patients with the condition. This early FDA guidance will be considered in analytic strategies for ADNI data. Genetic factors may be most immediately applicable to strategies 1-2 as ADNI does not include an intervention but ultimately may be important for strategy 3 as well. Analyses will be performed in collaboration with the Biostatistics core with whom we are working on a modeling framework to quantitate the increased efficiency of clinical trials based on genetic enrichment from candidate variants and polygenic risk scores [55]. The ADNI Systems Biology Working Group will also investigate network-derived enrichment scores. Several hypotheses will be evaluated that are related to clinical trial enhancement:

Hypothesis 1: 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. The first step in this process is to identify variants that improve prediction of disease trajectory (i.e., onset, course, and outcome). Models: *Predicted outcomes* will include conversion along the NL-SMC-MCI-AD continuum and longitudinal progression using optimized composite cognitive/functional outcome scores determined by the Biostatistics core. Appropriate covariates will be included in models including age, sex, education, *APOE* status, family history of AD, and other variables as appropriate. Additive genetic models will be the starting point for most analyses. In some cases sample sizes and MAF will predicate use of dominant models. Hierarchical approach: We will begin with AD candidate genes nominated by large GWAS [15], sequencing studies (e.g., *TREM2* [56-59], *PLD3* [60]), prior studies of AD endophenotypes in ADNI [7, 22] and other studies, followed by GWA (e.g., [27, 28, 39]). Common variants (MAF $\geq$ 5%) will be analyzed using PLINK [61, 62] and other software as needed for GWAS data on the entire ADNI-1/GO/2/3 cohort. Analyses will be performed with baseline endophenotypes (e.g., amyloid PET [27]) and repeated with longitudinal phenotype models as follow-up data becomes available (e.g., [28]). Theoretical considerations and multivariate analysis: We hypothesize that variants associated with biomarkers may yield clues to biological mechanisms and serve as potential targets for enrichment or therapeutic development. However, we note that a reviewer in 2010 expressed concern regarding whether *"…analysis of multiple different phenotypes in a single set of data…actually shed light on underlying causal mechanisms, when the phenotypes are correlated with one another and the major genetic influence (APOE itself) may well play a role across the spectrum of clinical and imaging measures."* We view this as an interesting and important empirical question that ADNI data is ideally-suited to address at multiple levels: a) *APOE* is being intensively studied with all ADNI phenotypes (e.g., [41, 42]), b) analyses typically include *APOE* in the model and assess epistasis, c) multivariate phenotype GWAS studies will continue [63], d) multivariate biomarker clustering and profiling can identify phenotype subgroups [64] for GWAS, and e) recent GWA & WES results suggest unique insights from biomarker QTL analyses that complement case-control designs [23-25, 27, 28, 33, 36, 39, 41]. A recent report [63] showed increased power with multivariate compared to univariate GWAS and the best analytic performance was by PLINK [61, 62], SNPTEST [65], MultiPhen [66], and BIMBAM [67, 68] packages. Bioinformatics tools: A wide array of additional bioinformatics tools are available for imputation [49, 50] and QC of common and rare variants from GWAS and NGS [62, 69, 70], expression profiling [71-74], methylation arrays [75, 76], structural variants including CNVs [77-79], multivariate phenotype GWAS [63, 66], epistasis [80-84], family data [85], replication and meta-analysis [83, 86], and network analysis [35, 87] as needed. Power and sample size considerations: Moderately large genetic effect sizes have the potential to improve clinical trial design through enrichment for single variants. Preliminary data from ADNI-2 indicates the likelihood of detecting appropriately large effects. Examples of candidate trial enrichment markers that will be further studied in ADNI-3 include *BCHE* [27] and *IL1RAP* [28]. ADNI GWAS of amyloid PET phenotypes detected genome-wide significant effects in these genes accounting for 15% of baseline amyloid burden (*APOE* 10.7%, *BCHE* 4.3%) [27] and 10.5% of rate of accumulation (*IL1RAP* 7.1%, *APOE* 3.4%) [28] with samples of 555

and 495, respectively. Additional data in ADNI-3 will enhance power by increasing participants with complete longitudinal data (and the range of phenotypes). Detailed calculations and simulations by the Biostatistics core (C1.6) indicate that we will have power to detect moderate to large gene effects on change in biomarkers and cognitive/functional status. In simulating enrichment based on rate of amyloid change for an anti-amyloid agent trial, a gene or gene combination (e.g., *IL1RAP* and *APOE4*) that identifies 10% of the overall sample as "high-risk" and the remaining 90% as "low-risk" would lead to at least a 4.5-fold reduction in required sample size to detect change targeting 25% or 50% reduction of accumulation rate at a fixed power and alpha. With only a few common gene variants this would be very cost effective as a screening strategy for such a trial. Multiple Comparisons challenge all highly multivariate and multidimensional studies. Our group is funded to address these types of methodological challenges (R01 LM011360, "*Bioinformatics Strategies for Multidimensional Brain Imaging Genetics*") and the principles extend to other biomarkers and *–omics* analyses. Standard steps are to determine the actual number of independent comparisons, apply dimensionality reduction strategies, and threshold results by Bonferroni, false discovery rate (FDR) [88-90], or family-wise error rate (FWER) adjustments [91]. The software tools discussed above have these features. Step down [92] and sequential designs based on prior knowledge and prioritization, as proposed above, are also useful in maintaining power while controlling FDR [93]. *Interpretive considerations* include a) biological plausibility of obtained findings, and where available, b) results of molecular and functional validation, c) independent replication, and d) meta-analysis with increased power through collaboration with other cohorts.

Hypothesis 2: 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. Reviewers in 2010 suggested including systems biology modeling approaches. We, and others, have published reviews of methods and applications related to gene network and pathway-based analysis in neurodegenerative disease [34, 35]. Network biology and systems pharmacology methods have been applied to baseline and longitudinal biomarker data sets in ADNI [27, 32-36]. New tools and concepts are evolving and new research faculty devoted to systems biology affiliated with the IU Network Sciences Institute (IUNI) and the Center for Computational Biology and Bioinformatics at IU are dedicated to working on AD with special emphasis on ADNI data. *This synergistic support from IUNI leverages and extends resources in the proposed core budget.* In brief, gene network analyses will be performed through functionally annotated gene sets (e.g., those from specific biological pathways and networks) to identify larger effects that may be overlooked in SNP-level studies [35]. These high level analyses (e.g., [94]) can also yield results with better replication potential and biological interpretation to aid the design of clinical trials. Selected approaches: Epistasis tools (e.g., PLINK [62], MDR [95], BOOST [96], and SIXPAC [97]) will be used to search for interaction effects. Polygenic networks of risk genes will be analyzed through graph theory software (e.g., iGraph [98], Cytoscape [99]) and enrichment tools (e.g., Enrichr [100], Metacore [101], dmGWAS [102]) for annotation of biological significance. Overlap between disease-related gene networks and others inferred from transcriptome, proteome, or metabolome profiling will be determined using WGCNA [87] and SEBINI [103]. Power Considerations for Networks and Epistasis: Polygenic scores aggregate small effects to yield a larger influence. This is an active area of investigation and, while more exploratory than using one or two genes with large effects, there have been significant applications in cancer and cardiovascular research and clinical trials as noted by the FDA guidance document on enrichment strategies [53]. Theory and methodology for statistical power analysis in gene network analyses are not yet well-developed. However, available estimates from research on power to detect epistasis effects [104] can provide a useful foundation (networks are larger sets of interacting genes) and indicate that the ADNI sample is sufficient to detect medium-to-large gene-gene interactions. This is consistent with our published preliminary data on epistasis in amyloid PET [84]. An empirical comparison of statistical methods for gene network analysis [105] demonstrated that accuracy in analyzing gene networks (using 1344 genes) increased with sample size but appeared asymptotic as N approached 1,000 [105]. The increased sample in ADNI-3 will be advantageous for larger-scale networks. Multiple comparison issues were discussed above. FDR-based strategies for networks will be employed. Significant dimension reduction will be achieved using polygenic scores and network enrichment scores.

Hypothesis 3: Genetic variation in the MAPT gene pathway and other relevant neurodegeneration pathways will be associated with [^{18}F]AV-1451 tau PET. The *MAPT* gene codes for tau. Using the hierarchical strategy described above, we will begin with analysis of a manually curated *MAPT* pathway (prepared by K. Deters, PhD student in the CLs lab focusing on tau) that is ready for network analysis [106-108] when PET data are available. This will be followed by inclusion of other neurodegeneration associated pathways [34, 36] and then GWAS, as performed for amyloid PET [28, 109]. Power is discussed in Aims 1-2.

***Hypothesis 4*: Genetic variation influences proteomics and metabolomics biomarker assays and controlling for genetic effects will improve the performance of –omics biomarkers in predicting disease progression and outcomes.** *Proteomics:* Profiling of plasma and CSF are available on the ADNI-1 sample using the Myriad-RBM Luminex Discovery platform and a MS-based approach (the Biomarker Consortium). Dr. Kim (co-I) reported that many analyte levels are heavily influenced by genetic variation [37] and thus, will pursue this further in ADNI and via "*Novel Strategies for Blood-based Biomarkers for AD: Role of Genetic Variation in a Multivariate Framework"* (R03AG050856-01). *Metabolomics profiling data*. Recent reports have indicated significant cross-sectional and longitudinal associations of several metabolite classes with AD [110, 111] but the role of genetic variation has not been systematically addressed. Thus, such analyses will be completed by the core in collaboration with the *AD Metabolomics Consortium* led by Rima Kaddurah-Daouk (collaborator, see Biosketch) with funding by a supplement U01 AG024904-09S4 for baseline profiling, as well as "*Metabolic Networks and Pathways In Alzheimer's Disease"* (R01 AG046171-01) and "*Metabolic Signatures Underlying Vascular Risk Factors For Alzheimer-Type Dementias"* (RF1 AG051550-01) which fund profiling of longitudinal plasma data. The core will investigate the relationship of targeted metabolites to specific gene sets and networks using the bioinformatics tools described above. Secondary exploratory analyses will be directed toward novel metabolome-genome associations relevant to AD and using multivariate mGWAS approaches [112-114] developed by the consortium. *Gene-environment interactions* (e.g., effects of drugs, diet, and other interventions) will be modeled as emerging evidence indicates their impact on metabolic readouts (e.g., fish oil, a dietary supplement, alters multiple lipidomic metabolites). We will assess whether adjusting proteomics and metabolomics analytes for genetic influence improves performance (e.g., R^2, AUC) as potential AD biomarkers. Biological insights regarding gene/protein/metabolite relations in AD will inform future studies.

Aim 4: Continue to provide organization, collaboration, and support for further development of genomic studies of quantitative biomarker phenotypes and outcomes in ADNI. *Collaboration with other cores and industry/academic partners:* Cross-core interactions include work with the: Clinical core on maximal utilization of genomic material and on optimized methods for quantifying cognitive complaints [41, 115]; MRI core on imaging genetic association studies [20, 23-25, 29, 31, 41, 42, 116]; PET core on studies of amyloid and [^{18}F]FDG PET [27, 28, 36, 41, 42, 47]; Biomarker core on gene-analyte studies [31, 37, 41, 42, 47, 117]; Biostatistics core on specialized analyses [41, 118-123]; and f) Informatics core on dissemination of GWAS/WGS data, as well as collaboration on specific analyses [7, 22, 28, 29, 31, 116, 118, 120-124]. Collaboration with PPSB partners will continue to be productive and informative [7, 22, 37, 47, 117, 123]. The core will continue to facilitate collaboration, new data, and knowledge through organized working groups (WGS, RNA Analysis, Epigenomics, Systems Biology, and Functional Genomics) holding regular conference calls and including Biostatistics and other cores as needed.

Future Directions: *Several areas have been identified that will require additional support before they can be fully realized, but within available resources, the core will work to develop these potentially important areas:* A) *Identify resources for additional genomics profiling*: We will work with other interested parties in academia and industry to find resources for sequencing, transcriptome, and epigenetic profiling of ADNI's longitudinal DNA and RNA samples. In ADNI-2 these efforts were successful in obtaining WGS and expression arrays. Methylation profiling on a subsample is pending release by mid-2016. Brief overview of evolving projects: A.1 *Sequencing*: Initial methods for NGS have been published [23-25]. This is a rapidly evolving area and the core is collaborating with the NIA AD Sequencing Project (ADSP) by participating in working groups related to case-control analysis, structural variants, and annotation. The ADSP has the full set of ADNI realigned and called BAM and VCF files and will combine the ADNI-2 data with other contributed data. The Broad Institute's Genome Analysis Toolkit (GATK) best practices guidelines will be employed. The ADSP WES/WGS data sets processed through the same pipelines will be accessed via NIAGADS and dbGaP for replication as large sample sizes are needed to detect low frequency and rare variants. ADNI genomes will contribute to larger datasets within the ADSP where gene-based tests that aggregate information across rare variants within a gene, including SKAT-O [69, 70], MiST [125], and other burden tests [126], will be performed first using AD candidate genes and curated pathways followed by discovery-oriented exploration with replication in independent sets. *A.2 RNA analysis*: Expression profiling methods using Affymetrix arrays were reported [7]. For future longitudinal analyses RNA-seq would be preferable as it is more comprehensive and accurate and enables analysis of expression of sequence variants, detection of novel RNAs, and discrimination of transcripts' splicing isoforms [127]. Costs are decreasing [128] and statistical methods are well-established [89, 129] (discussed in Aim 3). A.3 *Epigenetic analysis:* AbbVie, Biogen and Eisai are providing initial methylation profiling on DNA samples from 376 ADNI-2 subjects who also have WGS, GWAS, and expression data, as well as full MRI, PET, and two-year clinical outcome data. We will use the Illumina *Infinium*

HumanMethylation450 BeadChip for these initial epigenetic analyses which should be completed by mid-2016. This array, used in AD previous studies [130-132], interrogates more than 450K methylation sites across the genome, covering 99% of RefSeq genes and 96% of CpG islands with greater than 98% reproducibility[133]. Drs. Saykin & Apostolova each have R01 cohorts with the same methylation array permitting rapid replication.
B) *Return of research results (RORR) to participants:* The issue of potentially actionable genetic findings, alone or in conjunction with other test results, is important as discussed in [7]. Dr. Robert Green (also ADNI DPC Chair), a policy expert regarding RORR and incidental findings in studies and biobanking [134-136] will lead efforts to provide a framework for consensus and planning for RORR. ADNI policy is to not disclose genetic or biomarker data. New knowledge, competing trials, and evolving practices may require revisiting this policy.
C) *Call back and family studies:* There is great scientific value in availability of participants for future *–omics* and biomarker studies, as well as potential recruitment of relatives for family studies, especially where there is enrichment for LOAD (i.e., family history) or where GWA studies suggest the participant may be carrying informative risk or protective variants. We will work with the Clinical and Biostatistics cores to design and facilitate these studies. The ADNI-3 draft consent form has been updated to reflect this future direction which may include inviting family members to join BrainHealthRegistry.org and to provide saliva kits for DNA banking.
D) Facilitate replication studies with other cohorts/data sets. The core will continue to identify independent replication data sets. To date, we have partnered with ROS/MAP [28, 30, 31], NIA ADC cohorts including the Indiana Memory and Aging Study (IMAS) [28, 31, 32, 37, 40], the NIA HRS [31, 32, 40], MIRAGE [20, 22-25, 30], the Pittsburgh CHS [2, 3, 137-139], and AddNeuroMed [23-25, 31, 140]. AIBL is another promising opportunity for replication analyses in a longitudinal at-risk cohort with serial amyloid imaging as AIBL is now completing GWAS and WES.
E) *Molecular and functional validation:* Prior reviewers in 2010 suggested the core "*facilitate targeted molecular follow up … at least on a limited basis".* *Molecular validation* of novel variants identified by imputed SNPs from GWAS will be confirmed by deep sequencing (e.g., [28]), performed or facilitated by the core through sequencing services, in-house laboratories at IU, or by ADNI partners. *Functional validation* of novel loci through mechanistic follow-up studies is indicated for promising variants identified by GWA. The core will facilitate these studies in appropriate academic or industry labs to help ensure follow-up of promising leads.
F) *Neuropathological correlation with genetic variation:* Autopsy numbers are growing with 42 cases with both pathological diagnoses and GWAS or WGS data available for analysis at this time. We plan targeted analyses with replicated using larger-scale pathology-GWAS data sets including ROS/MAP (AMP-AD) [141], TGen [45], and others. *See the NP Core for power.* Later, correlation of brain and blood markers will be possible.
D. Progress Report (see Publication List): Aim 1 (Biosamples & Assays): As of 8/31/15, 809 ADNI-1, 128 ADNI-GO, and 780 ADNI-2 participants have a DNA sample stored at NCRAD; 288 ADNI-1, 128 ADNI-GO, and 779 ADNI-2 participants at least 1 RNA sample. See [7] for details regarding the GWAS, Illumina WGS (n= 812), and RNA profiling (Affymetrix U219 Array) contributed by BMS (n=811). There have been 26 DNA set requests fulfilled by NCRAD; 7739 DNA samples were used for *APOE* and genotyping, *TOMM40* Poly-T typing, WES, WGS, replication of genetic findings from other cohorts, and other studies. Aims 2: (Data Use, Analyses, Publications): By 12/2014, ADNI genetic data were downloaded approximately 107,000 times. 16 sets of the extensive (~150 TB) WGS raw data (BAM files) have been disseminated. Over 300 published studies used ADNI genetic data from 2010-2014. A complete list is available as an Endnote file (see Supplement) [7]. Papers published from 2009-2012 are summarized in detail in [22] and have continued to increase rapidly in 2013-2015. ***Timeline of major accomplishments and innovations:* 2010:** First GWAS of CSF markers [38, 142] and whole-brain MRI GWAS [43, 124]; First GWAS of longitudinal hippocampal MRI [20]; Among first AD studies of mitochondrial DNA [143]. **2011:** Replication sample in very large-scale AD GWAS [16, 17]; Among the first reports of CNV in AD/MCI [45, 46, 48, 144]. **2012:** Contributed to large-scale genetic meta-analyses of MRI (ENIGMA) [145, 146]; First gene pathway analysis of amyloid PET [36]; Among the first gene pathway analyses of memory impairment [33-35]. **2013:** Sample in the large-scale genetic AD meta-analysis [15]; First GWAS of amyloid PET identifying *BCHE* in plaque burden [27]; First MRI study of recently discovered *TREM2* variant [59]; First WES study in MCI (first extreme MRI phenotype in MCI) [23, 24]; Demonstrated genetic influence on plasma biomarker proteins [37]; First large scale AD/MCI WGS data set released [7]; First GWAS of the human structural connectome/discovery of *SPON1* gene [29, 30]. **2014:** Largest GWAS of memory discovered a role of *FASTKD2* [31, 40]; AD Metabolomics-genetics collaboration launched. **2015:** Whole-exome sequencing study in MCI identified *REST* as a neuroprotective gene [25]; Contributed to largest imaging GWAS with N>30,000 (ENIGMA-2, [116]); ADNI GWAS & WGS identifies novel *IL1RAP* variant related to amyloid accumulation rate [28]; RNA expression data released [7]. Aim 3: (Collaboration, Organization, Support): *See above & publication list.*

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OMB Number: 4040-0001
Expiration Date: 06/30/2016

APPLICATION FOR FEDERAL ASSISTANCE

SF 424 (R&R)

5. APPLICANT INFORMATION **Organizational DUNS*:** 6133387890000

Legal Name*: NORTHERN CALIFORNIA INSTITUTE FOR RESEARCH AND EDUCATION
Department:
Division:
Street1*: 4150 CLEMENT STREET (151-NC)
Street2:
City*: SAN FRANCISCO
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 941211545

Person to be contacted on matters involving this application

Prefix:	First Name*:	Middle Name:	Last Name*:	Suffix:
	Azarah	Sr. Grant Specialist	Wong	

Position/Title:
Street1*: 4150 CLEMENT STREET (151-NC)
Street2:
City*: SAN FRANCISCO
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 941211545
Phone Number*: 415-750-6954 x 23891 Fax Number: 415-750-9358 Email: cgawards@ncire.org

7. TYPE OF APPLICANT* M: Nonprofit with 501C3 IRS Status (Other than Institution of Higher Education)

Other (Specify):

Small Business Organization Type ❍ Women Owned ❍ Socially and Economically Disadvantaged

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
Neuropathology Core

12. PROPOSED PROJECT

Start Date*	Ending Date*
08/01/2016	07/31/2021

OMB Number: 4040-0010
Expiration Date: 06/30/2016

Project/Performance Site Location(s)

Project/Performance Site Primary Location

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:	Washington University
Duns Number:	0685522070000
Street1*:	660 South Euclid Ave.
Street2:	Campus Box 8111
City*:	St. Louis
County:	
State*:	MO: Missouri
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	63110-1093
Project/Performance Site Congressional District*:	MO-001

File Name

Additional Location(s)

Neuropathology Core: Project Summary/Abstract

The overall goal of the Neuropathology Core is to validate the clinical, CSF biomarker, and neuroimaging data of participants collected during the period of the grant. Specifically, the Neuropathology Core will: 1) foster and facilitate a voluntary brain autopsy for each ADNI participant at each site; 2) provide a uniform neuropathologic assessment of all cases that are autopsied; 3) maintain a repository of frozen and fixed brain tissue from ADNI participants in order to facilitate ADNI and non-ADNI investigator-led research; 4) test the hypothesis that comorbidities (Lewy bodies, TDP-43 proteinopathy, vascular disease, hippocampal sclerosis, and tau astrogliopathy) contribute to the variance in clinical, CSF biomarker, and neuroimaging data; and 5) characterize the relationships between neuropathology and genomic data in multimodal studies of ADNI participants. The Neuropathology Core infrastructure has been successful in promoting brain donation at participating sites, shipping of tissues to the ADNI Neuropathology Core at Washington University School of Medicine in St. Louis, and undertaking standardized neuropathologic assessments in 52 participants (as of August 1, 2015, 3 cases are pending shipment of tissue). The diagnostic accuracy for AD is 45/47 (number of cases with neuropathologic AD/number of cases with DAT = 95.7%; two cases had argyrophilic grain disease only). A noteworthy finding is that age-related comorbidities (Lewy bodies, hippocampal sclerosis, tau astrogliopathy, argyrophilic grain disease, vascular disease and infarcts) are found in more than half of cases indicating that cognitive impairment may not be due solely to AD. In collaboration with the Biomarker and MRI Cores we have undertaken a preliminary multimodal study which revealed that comorbid Lewy bodies impact CSF biomarkers and MRI imaging. These are important observations because they indicate that the presence of comorbidity in a trial will impact CSF biomarker, MRI imaging, and clinical outcome measures. We propose to expand these studies to include multimodal analyses in a larger cohort of cases and to include the recently available genomic data in collaboration with the Genetics Core.

PROFILE - Senior/Key Person

Prefix: First Name*: Nigel Middle Name John Last Name*: Cairns Suffix: Ph.D

Position/Title*: Professor
Organization Name*: Washington University
Department: Neurology
Division: School of Medicine
Street1*: 660 South Euclid Ave.
Street2: Campus Box 8118
City*: Saint Louis
County:
State*: MO: Missouri
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 631100000

Phone Number*: 314 362 2386 Fax Number: E-Mail*: cairns@wustl.edu

Credential, e.g., agency login: NIGEL_CAIRNS

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: PHD Degree Year:

File Name
Attach Biographical Sketch*: Core_H_Biosketch_Cairns_v2.pdf
Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: JOHN Middle Name Last Name*: MORRIS Suffix:

Position/Title*: Professor
Organization Name*: Washington University
Department: Neurology
Division: School of Medicine
Street1*: 660 South Euclid Ave.
Street2: Campus Box 8111
City*: ST. LOUIS
County:
State*: MO: Missouri
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 631082293

Phone Number*: (314) 286-2881 Fax Number: (314) 286-2763 E-Mail*: MORRISJ@ABRAXAS.WUSTL.EDU

Credential, e.g., agency login: j_morris

Project Role*: Other (Specify) Other Project Role Category: Neuropathology Core Lead

Degree Type: MD,BA Degree Year:

File Name
Attach Biographical Sketch*: Core_H_Biosketch_Morris_v2.pdf
Attach Current & Pending Support:

Neuropathology Core: Specific Aims

The Alzheimer's Disease Neuroimaging Initiative (ADNI) was established to determine the relationships among the clinical, cognitive, imaging, genetic and biochemical biomarker characteristics of the entire spectrum of Alzheimer disease (AD) as the pathology evolves from normal aging to dementia. The major significance of this Core is our demonstration in ADNI participants that AD is heterogeneous and that comorbidities (e.g., Lewy bodies and vascular disease) impact biomarker (CSF and neuroimaging) values and outcome measures which may be used in clinical trials. The proposed Core continues our neuropathologic validation of the clinical/cognitive and biomarker information from the currently funded ADNI (ADNI2), a public/private collaboration between academia and industry to study biomarkers of AD (http://www.adni-info.org/).

To achieve the goals of ADNI3, the Neuropathology Core is essential to validate the clinical classifications and diagnoses. Our neuropathologic validation makes it very clear which of the ADNI databases contain individuals who do not have AD, or, more commonly, comorbidities such as vascular disease and non-AD neurodegenerative disorders. Therefore, a single Neuropathology Core site is necessary because different neuropathologists use different processing and staining methods, as well as different antibodies and interpret diagnostic criteria differently. Even for the neuropathologic diagnosis of AD, not all sites use the same sets of criteria. A single Neuropathology Core ensures uniformity and fidelity of staining and application of diagnostic criteria to all ADNI participants who come to autopsy.

Specific Aim 1: Provide training materials and protocols to assist clinicians at ADNI sites in obtaining voluntary consent for brain autopsy in ADNI participants. As there may be personnel changes at ADNI performance sites over time, there is a continuing need to monitor each site to ensure that training and protocols for obtaining autopsies are in place. Therefore, it is essential to maintain a dedicated NPC Coordinator to ensure these functions are performed over the period of the grant.

Specific Aim 2: Maintain a central laboratory to provide uniform neuropathological assessments in all autopsied ADNI participants in accordance with standard criteria and to promote clinical-neuroimaging-neuropathological correlations. Neuropathologic assessment at a single NPC site is essential to maintain staining standards and uniform neuropathologic diagnoses. In addition, the ability to have neuropathology helps determine the sequence of biomarker changes. Based on autopsied ADNI cases to date (n=52), preliminary data indicate that the ADNI population is neuropathologically heterogeneous and that comorbidity may confound or explain variance in the data generated by the different ADNI Cores.

Specific Aim 3A: Maintain a state-of-the-art resource for fixed and frozen brain tissue obtained from autopsied ADNI participants to support ADNI's biomarker studies and make available to ADNI-approved investigators access to the tissue and data for research purposes. Fixed brain tissue/paraffin sections will be made available from cases that have come to autopsy. These and frozen brain samples will facilitate the validation of clinical, imaging, and biomarker data obtained during the course of the disease**.**

Specific Aim 3B: Interact with ADNI's Data Coordinating Center to ensure appropriate entry of the Core's data into ADNI's database, promote data sharing and collaborative research, and integrate the ADNI3-NPC with all ADNI3 components to support its administration, operations, and progress toward goals. Data generated by the ADNI3-NPC will be transmitted securely to USC for upload to LONI according to the ADNI3 procedures. These de-identified data will be available with the relevant clinical, biological and imaging data on the Informatics Core web site (LONI) and will be made available to all qualified investigators.

Specific Aim 4: To test the **hypothesis** that comorbidities including Lewy bodies (synucleinopathy) and TDP-43 proteinopathy contribute to the variance in clinical, CSF biomarker, and neuroimaging data) we will correlate molecular pathologic heat maps with neuroimaging and CSF biomarker data using the methods previously developed by Dr. Toledo and colleagues (Biomarkers Core).

Specific Aim 5: Using the methods developed to correlate PET-PiB Aβ data with neuropathologic Aβ burden observed at autopsy, we will undertake correlation analyses using PET-tau (T807) SUVR data with regional tau burden measured in postmortem brain tissue. We will assess, using stereological methods (Stereo Investigator, MicroBrightField), the burden of different forms of tauopathy (neurofibrillary tangles, neuritic plaques, neuropil threads, and glial tauopathy) in both gray and white matter. We predict that PET-tau will be a better predictor of cognitive decline than other imaging and CSF biomarkers.

Specific Aim 6: In collaboration with the Genetics Core we aim to undertake comprehensive integrative genomics and bioinformatics analyses using ADNI genome sequencing data and neuropathology variables including synucleinopathy and other comorbidities.

Neuropathology Core: Research Strategy

SIGNIFICANCE

The Alzheimer's Disease Neuroimaging Initiative (ADNI) was established to determine the relationships among the clinical, cognitive, imaging, genetic and biochemical biomarker characteristics of the entire spectrum of Alzheimer disease (AD) as the pathology evolves from normal aging to dementia (1;2). The major significance of this Core is our demonstration in ADNI participants that AD is heterogeneous and that comorbidities (e.g., Lewy bodies and vascular disease) impact biomarker (CSF and neuroimaging) values and outcome measures which may be used in clinical trials (3). The proposed Core continues our neuropathologic validation of the clinical/cognitive and biomarker information from the currently funded ADNI (ADNI2), a public/private collaboration between academia and industry to study biomarkers of AD (http://www.adni-info.org/).

The goals of ADNI3 will be accomplished by: 1) continuing annual clinical/cognitive/MRI follow-up of normal controls [for numbers in each cohort see Sample Size Tables in Overview], participants with subjective memory concerns, early MCI, late MCI, and mild AD dementia together with rollover participants from ADNI1, ADNI GO, and ADNI2; 3) performance of F18 amyloid PET on all participants, together with F18 tau (T807) PET, lumbar puncture for CSF, clinical/cognitive measurements and MRI, and neuropathology on all cases that come to autopsy. All collected data will be processed, analyzed by ADNI investigators including the Biostatistics Core, and made available to all qualified scientists in the world who request a password, and without embargo.

To achieve the goals of ADNI3, the Neuropathology Core is essential to validate the clinical classifications and diagnoses (3). Our neuropathologic validation makes it very clear which of the ADNI databases contain individuals who do not have AD, or, more commonly, comorbidities such as vascular disease and non-AD neurodegenerative disorders. Therefore, a single Neuropathology Core site is necessary because different neuropathologists use different processing and staining methods, as well as different antibodies and interpret diagnostic criteria differently. Even for the neuropathologic diagnosis of AD, not all sites use the same sets of criteria. A single Neuropathology Core ensures uniformity and fidelity of staining and application of diagnostic criteria (16) to all ADNI participants who come to autopsy.

APPROACH

In ADNI3, the Neuropathology Core (NPC) will enhance the existing infrastructure put in place during ADNI1, ADNI GO, and ADNI2 to: (1) improve the overall autopsy rate at ADNI sites; (2) improve the neuropathologic assessment of cases to include site, size, and nature of vascular lesions, and to assess the presence of comorbidities including TDP-43 proteinopathy, non-AD neurodegenerative disease, and age-related tau astrogliopathy (ARTAG); and (3) facilitate multidisciplinary research on those cases that have come to autopsy.

In this application, we use conservative death rate estimates because the demanding ADNI3 protocols may result in healthier participants. We thus assume annual death rates of 1% for non-demented ADNI3 participants, 1% for MCI individuals, and 5% for AD individuals. From surviving ADNI1, ADNI GO, and ADNI2 and newly enrolled participants, and assuming an autopsy rate of 75% over the proposed funding cycle for ADNI3 (2016-21), we anticipate that at the minimum there will be 10 autopsies in year 1 of the next funding period, 10 in year 2, 20 in year 3, 25 in year 4, and 28 in year 5.

Specific Aim 1: Provide training materials and protocols to assist clinicians at ADNI sites in obtaining voluntary consent for brain autopsy in ADNI participants.

As there may be personnel changes at ADNI performance sites over time, there is a continuing need to monitor each site to ensure that training and protocols for obtaining autopsies are in place. Therefore, it is essential to maintain a dedicated NPC Coordinator to ensure these functions are performed over the period of the grant (4).

To obtain consent for an autopsy, the ADNI site physician will lead a discussion about autopsy with all participants (demented and non-demented) at their initial assessment (study partners and families are welcomed in the discussion and required for AD participants). There are 3 objectives of the discussion: 1) to convey information about the value of brain autopsy in confirming the clinical diagnosis and advancing knowledge regarding MCI and AD; 2) to initiate consideration of the individual's wishes concerning an autopsy; and 3) to answer questions, misconceptions, or concerns about autopsy. The involvement of the physician in these discussions emphasizes the importance of autopsy. The discussions are repeated on an annual basis if the individual has not decided about autopsy, but are terminated once a decision is reached. There is no pressure on an individual to decide; they are encouraged to involve family members, clergy, physicians, or other appropriate persons in their decision-making. Participants are assured that a decision not to have autopsy does not in any way jeopardize their research participation or any other patient rights.

When voluntary consent is granted, more detailed information is provided about procedures to follow at time of death, including telephone numbers to call and other guidelines (sample forms available in the NPC

appendix and on line at http://www.adni-info.org/). Participants are strongly encouraged to share this information with next-of-kin, a person who holds a Durable Power of Attorney (DPOA), and private physicians. In many states, final legal authorization by the Legally Authorized Representative (LAR) or next-of-kin must be obtained at time of death.

Each ADNI site is encouraged to establish an autopsy coordinator (typically a research nurse or coordinator) who processes the autopsy consent form, provides information as needed, and monitors the need to update any information (e.g., change in residence) at the participant's longitudinal assessments. The coordinator also will develop procedures for that site to facilitate autopsies outside of usual hours (e.g., evenings and weekends). The actual procedures are expected to vary in accordance with local needs and resources (one model used by many ADCs is to provide 24-hour telephone access).

At the time of death, the autopsy coordinator (or a suitable representative) facilitates arrangements to ensure the completion of the autopsy. The coordinator will notify the ADNI3-NPC, which in turn verifies that the site neuropathologist has the dissection protocol and necessary materials to send the required tissues to the ADNI3-NPC.

The ADNI3-NPC, in addition to instructing site personnel at each ADNI Steering Committee Meeting in these procedures, will be available at any time to answer questions. Contact information, including a 24-hour pager, is available. ADNI3 sites that already have ADRC/ADC neuropathology services will continue to follow their own existing protocols. For ADNI3 sites that do not have established neuropathology services, transportation costs from point of death to the autopsy location, costs of the autopsy procedure, and shipment of materials will be covered by ADNI3-NPC so that the decedent's family and the individual ADNI site do not incur extra expense.

Once the Participant has given consent (provisional or otherwise) for a brain donation, the Acknowledgement of Autopsy Authorization letter (see Appendix)and supporting documentation will be sent to the following: Participant and/or family and/or applicable other (e.g. Durable Power of Attorney), nursing home, and funeral home/transport service (as requested), and the Participant's private physician (as requested).

Specific Aim 2: Maintain a central laboratory to provide uniform neuropathologic assessments in all autopsied ADNI3 participants in accordance with standard criteria and to promote clinical-neuroimaging-neuropathologic correlations.

Where possible, each site will undertake its own brain assessment and forward a standard set of fixed tissue blocks or sections and frozen tissue to the ADNI3-NPC (see below) (3). For sites that do not routinely undertake neuropathologic studies, a separate brain removal protocol is available (see http://www.adni-info.org/). **Financial assistance with block sampling, preservation, and shipping costs:** The ADNI3-NPC will fund all costs in shipping frozen and fixed tissue samples to St. Louis, MO. To assist participating sites and neuropathologists with the costs of obtaining frozen tissue blocks and/or formalin-fixed paraffin wax-embedded tissue the following costs will be reimbursed, if requested: (1) harvesting of frozen tissue and/or formalin-fixed paraffin wax-embedded tissue blocks (*see list of brain regions below): $300; (2) harvesting formalin-fixed paraffin wax-embedded tissue sections or frozen sections (*see list of brain regions below): $100. Resources to defray the costs of sampling, tissue, processing, administration, and transport will be made available to each center already undertaking neuropathology. These resources are to facilitate the provision of the standard set of blocks for ADNI3-NPC. To minimize the burden on participating sites, formalin-fixed, paraffin wax-embedded tissue blocks from the following 16 areas from the left cerebrum will be forwarded to the ADNI3-NPC: middle frontal gyrus, superior and middle temporal gyri, inferior parietal lobe (angular gyrus), occipital lobe to include the calcarine sulcus and peristriate cortex, anterior cingulate gyrus at the level of the genu of the corpus callosum, posterior cingulate gyrus and precuneus at the level of the splenium, amygdala and entorhinal cortex, hippocampus and parahippocampal gyrus at the level of the lateral geniculate nucleus, striatum (caudate nucleus and putamen) at the level of the anterior commissure, lentiform nucleus (globus pallidus and putamen), thalamus and subthalamic nucleus, midbrain, pons, medulla oblongata, cerebellum with dentate nucleus, and spinal cord, when available.

In the unusual situation where it is impractical to forward a tissue block (e.g., if the block is used for stereology), 10 paraffin wax sections (4-8 μm) from each block will be provided to ADNI3-NPC for systematic neuropathology and diagnosis.

To provide tissue for biochemical studies and to advance the aims of the Biomarkers Core, snap frozen tissue will be dissected, frozen, and sent to ADNI3-NPC. The following **coronal hemibrain slices** (0.5 to 1cm thick), where possible, will be taken: (1) frontal lobe to include striatum; (2) frontal and temporal lobe at the level of the mammillary body; (3) temporal and parietal lobes at the level of the lateral geniculate nucleus; (4) occipital lobe to include the calcarine sulcus; and (5) cerebellum to include the dentate nucleus.

Histology: In all cases, the following stains will be performed at the ADNI3-NPC laboratory on the blocks indicated above, and/or as requested by the neuropathologist: hematoxylin and eosin and modified Bielschowsky silver impregnation. Briefly, routine immunohistochemistry will be performed using the following antibodies: phospho-tau (PHF1, a gift of Dr. P. Davies), β-amyloid (10D5, Eli Lilly), and phospho-α-synuclein (Cell Applications), and phospho-TDP-43 (Cosmo Bio); other stains and primary antibodies will be used as appropriate. 3,3'-Diaminobenzidine will be used as the chromogen for IHC and sections will be counterstained with hematoxylin.

Histology Review: Dr. Cairns will review the histological slides in a systematic manner. The data will be entered into the NACC Neuropathology Data Form (currently Version 10) and transmitted to the Laboratory of Neuroimaging (LONI) at the University of Southern California. The final neuropathologic diagnosis and neuropathologic report will be forwarded to the site that made available the tissue. The ADNI3 Site Leader or qualified clinician may relay the findings to the participant's family. Dr. Cairns is available to assist with this process when requested.

Neuropathologic Assessment and Diagnostic Criteria: The operational criteria for the classification of AD and other pathologies defined by NACC will be applied to all ADNI3-NPC cases (5-15). The neuropathologic diagnosis will be determined by Dr. Cairns and Dr. Robert Schmidt (Head of the Division of Neuropathology, WUSTL) using consensus neuropathologic criteria for AD, and for non-AD disorders. Briefly, for each case, multiple pathologies are recorded as described in the NACC Neuropathology Data Form (currently Version 10). For each brain area (n=16), a semiquantitative assessment of neuronal loss, gliosis, small vessel disease, infarcts, hemorrhages, and any other focal lesions is recorded. Immunohistochemistry is performed on all brain areas (n=16) and the severity of beta-amyloidosis, tangle and neuritic plaque density, Lewy body disease, and TDP-43 proteinopathy are recorded using established rating scales (4-15). This spatial distribution of quantitative neuropathology enables the generation of 'pathological heat maps' (for example, see Figure 1 and ref. 16) and facilitates direct comparison with spatial structural and functional neuroimaging data. This will allow investigators maximal utility in applying the neuropathological diagnoses and spatial pathologic data in the most appropriate way to support their research aims**.**

Specific Aim 3A: Maintain a state-of-the-art resource for fixed and frozen brain tissue obtained from autopsied ADNI participants to support ADNI's biomarker studies and make available to ADNI-approved investigators access to the tissue and data for research purposes.

The ADNI1-NPC purchased a -80°C freezer with 23 cubic feet capacity with CO_2 back-up and telephone alarm which is now full. We envision that a second freezer will be required during the next period to accommodate the projected number of harvested cases in ADNI3. ADNI3-NPC will maintain a neuropathology computerized database in concert with Biostatistics and Clinical Cores of the Washington University Neuroscience Blueprint Interdisciplinary Center Core (P30-NS057105). Information stored will include macroscopic images of fresh and fixed brain, demographic data, diagnoses, semi-quantitative morphometric data, neuropathology reports (in collaboration with Dr. Schmidt), bibliographic information, and data relevant to Core tissue banking activities. In addition, neuropathology data will be transferred by the ADNI3 Coordinating center for upload to the Laboratory of Neuroimaging LONI database.

As the number of brain autopsies performed (n=52 to date) increases, so too does the demand for ADNI postmortem brain tissues. As the autopsy rate increased to >70% in the preceding year (9-1-13 through 8-31-14), we envisage that the numbers of autopsies will increase during the period of the ADNI3 grant and will generate sufficient samples for multi-modal studies, similar to one which we have already undertaken. To ensure that all participating sites are aware of the archived ADNI tissue, each site will be contacted individually and annually to alert each site of this resource and to solicit feedback on the Neuropathology Core. In addition, a link to the Neuropathology Core will be made available on the ADNI website which describes the procedure for qualified investigators to obtain tissue samples. So that ADNI investigators and the Private Partner Scientific Board (PPSB) may be informed of tissue availability and project development, a bi-annual teleconference will be held with the NPC's PPSB representative.

Specific Aim 3B: Interact with ADNI's Data Coordinating Center to ensure appropriate entry of the Core's data into ADNI's database, promote data sharing and collaborative research, and integrate the ADNI3-NPC with all ADNI components to support its administration, operations, and progress toward goals.

Data generated by the ADNI3-NPC will be transmitted securely to USC for upload to LONI according to the ADNI3 procedures. These de-identified data will be available with the relevant clinical, biological and imaging data on the Informatics Core web site (LONI) and will be made available to all qualified scientists in the world who request a password, without embargo. Applications for biospecimens, including brain tissue, will follow the format of NIH R01 limited to 5 pages. Only manuscripts accepted for publication, published manuscripts, and

submitted grants will be considered as appendix material. Applications will be sent to the Chairman of the Resource Allocation Review Committee (RARC; Thomas J. Montine, MD, PhD, Chairman, Department of Pathology, University of Washington, Seattle, WA). The criteria used by RARC will be: scientific merit, feasibility, appropriateness of principal investigator qualifications, burden on ADNI samples, and appropriateness to ADNI goals/themes.

Specific Aim 4: To test the hypothesis that comorbidities including Lewy bodies (synucleinopathy) and TDP-43 proteinopathy contribute to the variance in clinical, CSF biomarker, and neuroimaging data, we will correlate molecular pathologic heat maps with neuroimaging and CSF biomarker data using the methods previously developed by Dr. Toledo and colleagues (16). Total pathology burden (e.g., β-amyloidosis, synucleinopathy, tauopathy) will be correlated separately with last cognitive assessment (ADAS COG), clinical assessment (CDR-SB), CSF biomarker (Aβ, tau, Ptau), MRI (hippocampus and ventricle volume), and PET SUVR (amyloid, FDG) using linear regression, adjusted for covariates as described in the Biostatistics Core. With at least 100 total brains by the end of the next grant cycle, we will have 80% power to detect a correlation coefficient accounting for 8% of variation ($r=\pm 0.28$).

Specific Aim 5: Using the methods in development to correlate PET-PiB Aβ data with neuropathologic Aβ burden observed at autopsy, we will undertake correlation analyses using PET-tau (T807) SUVR data with regional tau burden measured in postmortem brain tissue. We will assess, using stereological methods (Stereo Investigator, MicroBrightField), the burden of different forms of tauopathy (neurofibrillary tangles, neuritic plaques, neuropil threads, and glial tauopathy) in both gray and white matter. We predict that PET-tau will be a better predictor of cognitive decline than other imaging and CSF biomarkers. Tau SUVR will be correlated with post-mortem measures described above using linear regression, adjusted for covariates as described in the Biostatistics Core. With ~50 brains from individuals who have undergone PET-tau in the next grant cycle, we will have 80% power to detect any association accounting for as little as 15% of variation ($r=\pm 0.39$).

Specific Aim 6: In collaboration with the Genetics Core we aim to undertake comprehensive integrative genomics and bioinformatics analyses using ADNI genome sequencing data and neuropathology variables including synucleinopathy and other comorbidities. Hypothesis-driven analyses of the relationship between neuropathology and genetics will focus on polygenic and pathway scores, to ensure adequate power with the relatively small sample size (total of approximately 100 brains by the end of the next grant cycle). The power for testing pre-specified hypotheses about the association between a systems-biology driven score and a proposed summary measure will be similar to that for Aim 4. Hypothesis-generating searches of larger groups of genes and proteins will be informed, as much as possible, by systems biology, in order to increase power and reduce the risk of false discovery; we will also use standard internal and external cross validation and false discovery rate error correction to control for the large number of candidate predictors.

INNOVATION:

The Neuropathology Core has undertaken preliminary multimodal studies of clinical, biomarker (CSF and neuroimaging), genetic, and multimodal studies of ADNI participants who are neuropathologically well characterized (16). A comparison of neuropathologic findings with cases of autosomal dominant AD (ADAD; DIAN cohort) indicates that the late-onset AD of ADNI is different from that of ADAD. Late-onset AD (LOAD) cases from ADNI are characterized by frequent age-related comorbidity (Lewy body disease, hippocampal sclerosis, vascular disease and infarcts, other non-AD neurodegenerative diseases, and age-related tau astrogliopathy) (3). The presence of significant comorbidity in LOAD indicates that the pathology in this cohort is heterogeneous and likely influences biomarker outcomes and the design of clinical studies. To test the hypothesis that tau imaging is a better predictor of cognitive change we will use stereologic methods to determine tau burden in participants who have undergone tau (T807) PET imaging. Specifically, we will correlate the spatial organization of tau burden in postmortem brain with SUVR data obtained from T807 tau imaging in collaboration with the PET Core.

PROGRESS REPORT:

Progress since 09-30-2010: The overall impact of the Neuropatholgy Core has been the demonstration that some ADNI participants diagnosed with AD antemortum do not have AD pathology and also that a large fraction of ADNI participants have mixed pathologies. Taken together with the rich antemortem phenotyping with clinical/cognitive evaluations, MRI, PET, CSF biomarkers, and genetics etc, these provides a very rich data set for vaidation of biomarkers for AD clinical trials. A highly motivated ADNI-NPC Research Coordinator, Mrs. Erin Franklin, has contacted all participating ADNI sites to implement the protocols established for obtaining autopsy consent and performing neuropathology services. Mrs. Franklin continuously monitors the sites to encourage and facilitate autopsy consent in ADNI participants. In addition, all ADNI-NPC documentation is available at the ADNI website. Where autopsy procedures do not exist locally, arrangements have been put in place with the Site Leader and local hospital to harvest brain tissue and forward to the ADNI-

NPC in St Louis. At all ADNI Executive Committee teleconferences and at the annual ADNI Steering Committee, the NPC leadership (Morris and/or Cairns) reports on the NPC's progress and promotes the goals of the Core.

The overall autopsy rate (number of deaths/number of autopsies) for ADNI 1, ADNI GO, and ADNI2 is 61% since the inception of the ADNI Neuropathology Core and 57% including the time period of 9-1-05 to 8-31-07 before the Core was formed. The autopsy rate for the progress reporting period of 9-30-2010 through 8-5-15 is 62% (41 autopsies/66 deaths) (Table 1). Of 52 autopsies, tissue has been received for 49 cases. Of the 49 cases, 43 cases have fresh frozen tissue available. Tissues from three participants that came to autopsy late in the reporting period remain to be shipped from the ADNI2 sites that performed the autopsies. Of the 49 cases received, the average age is 81.6 (age range: 59-93). During the progress reporting period the average age of those that have come to autopsy is 81.7 (age range: 59-93). Overall, 10 females and 39 males have come to autopsy.

Table 1. Autopsy rates for ADNI1, ADNI GO, and ADNI2.

ADNI	ADNI-NPC	Deaths	Autopsies	Autopsy Rate (%)
Funding Period				
9-1-05 to 8-31-07	NO	6	0	0
9-1-07 to 8-31-08	YES	7	2	28
9-1-08 to 8-31-09	YES	8	8	100
9-1-09 to 8-31-10	YES	4	1	25
9-1-10 to 8-31-11	YES	13	6	46
9-1-11 to 8-31-12	YES	4	3	75
9-1-12 to 8-31-13	YES	15	8	53
9-1-13 to 8-31-14	YES	20	13	65
9-1-14 to 8-5-15	YES	14	11	79
Total (2005-2015)	-	91	52	57
Total since NPC established	**-**	**85**	**52**	**61**

The mean post mortem interval (mean time from death to tissue snap freezing) for ADNI autopsies is 12.8h (range: 2-76h). The overall average brain weight of ADNI participants that have come to autopsy is 1,209g (range: 860g-1430g). *APOE* ε4 frequencies in 45/49 cases were obtained: 2 ε4 = 17.8% (n = 8); 1 ε4 = 46.7% (n = 21); 0 ε4 = 35.6% (n = 16). At the time of expiration, Clinical Dementia Ratings (CDR) were: CDR 0, n = 0; CDR 0.5, n = 5; CDR 1, n = 3; CDR 2, n = 8; CDR 3, n = 22. The ADNI-NPC was unable to obtain an estimate of the CDR at death in 11 cases. Of the 57 ADNI 2 sites 42 are fully operational to obtain autopsy consent and brain donation. 3 ADNI2 sites have refused or opted out of participation in obtaining autopsy consent and brain donation. 12 ADNI2 sites are either actively in the process of becoming operational for the neuropathology portion of ADNI 2 or remain undecided.

Neuropathologic assessment of ADNI participants

The clinical diagnostic accuracy of AD dementia is high (45/47; 95.7%); two cases of clinically diagnosed AD had AGD at autopsy (Table 2). As in previous studies, comorbid disease was a common finding in LOAD. The identification of cases with comorbid pathology is important for determining the potential contribution of other non-AD pathologies to the clinical phenotype. The presence of cases with an additional molecular pathology in this sample, although representative of other larger series, indicates that the contribution of tauopathy, alpha-synucleinopathy, and TDP-43 proteinopathy, and possibly other proteinopathies, will need to be assessed in the ADNI series as more cases come to autopsy. If the neuropathologic sample is representative of the total ADNI cohort of dementia patients, these preliminary data indicate widespread comorbidity which contributes to variance in the data obtained by the different Cores (16). Together with the Biomarkers Core (16) we have undertaken multimodal studies of CSF and neuroimaging biomarkers and correlated these data with the spatial distribution of molecular pathology as 'pathologic heat maps' (Figure 1). There is good correlation between PET Aβ burden at last assessment and Aβ burden determeined at autopsy. We plan to extend these studies to include the PET tau ligand (T807, Lilly).

Table 2. Clinical and neuropathologic diagnoses at expirartion.

Clinical Diagnosis	Neuropathologic Diagnosis [N (%)]											
	AD	AD +DLB	AD +TDP	AD +DLB +TDP	AD+DLB +TDP+AGD	AD +ALB	AD + AGD	AD +HS	AD+TDP +Infarcts	AGD	Pending	TOTAL (%) ^
AD	18*	12**	2	2		2	1	3†	1	2¶		43 (83)
AD +DLB				1	1	2‡						4 (8)
Pending											5	5 (10)
TOTAL (%) ^	18 (35)	12 (23)	2 (4)	3 (6)	1 (2)	4 (8)	1 (2)	3 (6)	1 (2)	2 (4)	5 (9)	52 (100)

AD, Alzheimer disease (NIA-AA score: A1, B0, C0 or greater); ALB, AD with amygdala Lewy bodies; DLB, dementia with Lewy bodies; AGD, argyrophilic grain disease; TDP, AD with TDP-43 proteinopathy in medial temporal lobe; HS, hippocampal sclerosis.

Notes:*One case had additional infarcts; **One case had additional AGD and one case had additional age-related tau astrogliopathy; †One case had additional AGD and one case had additional TDP-43 proteinopathy; ‡One case had additional TDP-43 proteinopathy; ¶Both cases had additional primary age-related tauopathy. ^Figures are rounded and may not equal 100%. Small vessel disease (arteriolosclerosis and cerebral amyloid angiopathy) was a feature of all cases.

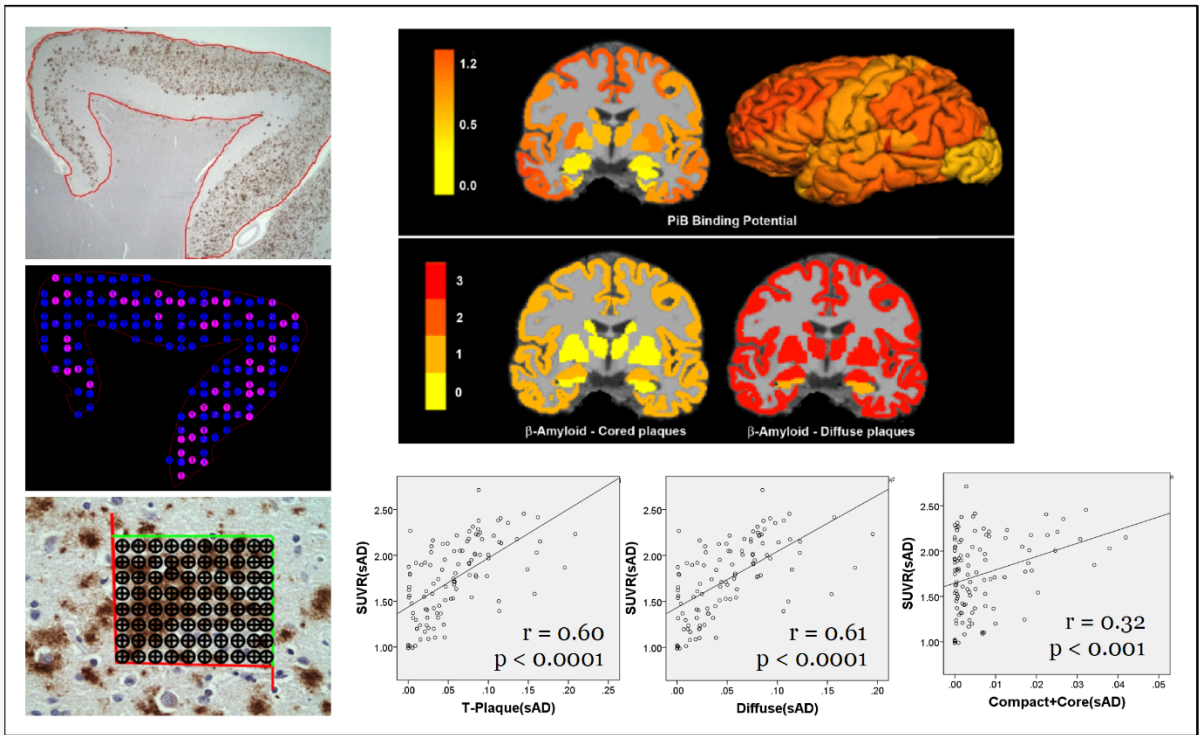

Figure 1. Neuropathologic validation of PET-PiB β-amyloid imaging. Computerized stereologic methods are used to assess Aβ burden detected by IHC. A region of interest (ROI) is outlined in the frontal lobe (left upper panel). Stereo Investigator software uses the Area Fraction Fractionator probe to randomly sample the cortex (left center panel) and Aβ load is calculated using a sampling probe (lower left panel) in 19 nuclei/regions to generate neuropathologic heat maps (right upper panel, lower half) which are compared with PET-PiB SUVR (right upper panel, upper half). There is good correlation between total Aβ burden in postmortem brain and PET-PiB at last assessment (lower right panels).

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OMB Number: 4040-0001
Expiration Date: 06/30/2016

APPLICATION FOR FEDERAL ASSISTANCE

SF 424 (R&R)

5. APPLICANT INFORMATION **Organizational DUNS*:** 6133387890000

Legal Name*: NORTHERN CALIFORNIA INSTITUTE FOR RESEARCH AND EDUCATION
Department:
Division:
Street1*: 4150 CLEMENT STREET (151-NC)
Street2:
City*: SAN FRANCISCO
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 941211545

Person to be contacted on matters involving this application

Prefix:	First Name*:	Middle Name:	Last Name*:	Suffix:
	Azarah	Sr. Grant Specialist	Wong	

Position/Title:
Street1*: 4150 CLEMENT STREET (151-NC)
Street2:
City*: SAN FRANCISCO
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 941211545
Phone Number*: 415-750-6954 x 23891 Fax Number: 415-750-9358 Email: cgawards@ncire.org

7. TYPE OF APPLICANT* M: Nonprofit with 501C3 IRS Status (Other than Institution of Higher Education)

Other (Specify):

Small Business Organization Type ❍ Women Owned ❍ Socially and Economically Disadvantaged

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
Biostatistics Core

12. PROPOSED PROJECT

Start Date*	Ending Date*
08/01/2016	07/31/2021

OMB Number: 4040-0010
Expiration Date: 06/30/2016

Project/Performance Site Location(s)

Project/Performance Site Primary Location

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:	Regents of the University of California (UC Davis)
Duns Number:	0471200840000
Street1*:	One Shields Ave.
Street2:	MS1C
City*:	Davis
County:	Yolo
State*:	CA: California
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	95616-8638
Project/Performance Site Congressional District*:	CA-003

File Name

Additional Location(s)

Biostatistics Core: Project Summary/Abstract
The goal of the Biostatistics Core is to ensure that sound designs and statistical analyses are used to address the aims of ADNI3, which are to validate biomarkers for Alzheimer's disease (AD) clinical trials. ADNI1, ADNI-GO, and ADNI2 have created an extensive combined database with rich longitudinal data on the biological, cognitive, and functional changes that take place across the spectrum from normal aging (NL) through mild cognitive impairment (MCI) to AD. The Biostatistics Core has contributed to the design and analysis of ADNI since its inception, in close collaboration with all the other ADNI Cores. Our work has set a pattern for describing the trajectory over time of ADNI biomarkers, characterizing their association with other features of disease progression, and assessing their potential for use in standardized clinical trial designs. The Biostatistics Core will continue these analyses in ADNI3 with new biomarkers and outcome measures (tau-PET measures, network measures from diffusion tensor imaging, MTL subregions, CogState.) We will test hypotheses proposed by other Cores to validate new biomarkers: that baseline levels predict biological, cognitive, and functional change, and that changes in biomarkers correlate with other AD-related changes and disease progression. We will carry out formal comparisons of biomarker performance as potential screening tools for clinical trials, by estimating improvements in efficiency of trial design. We will make use of the very long-term follow-up from the combined ADNI data to model the earliest measurable changes and the sequence and timing of changes. We will develop new statistical methodology as needed for these models of multiple trajectories of biomarker and clinical data, especially when some measurements of interest (amyloid and tau PET) have been introduced partway through the ADNI studies or are available only at some occasions of measurement (planned missingness or dropout from some study components.) The very large number of potential biomarkers and measurements in ADNI means that no one group can analyze all available data. We will therefore work with other ADNI Cores to select biomarkers for our group to analyze. We will follow best practices of literate coding and reproducible research to develop our analyses as templates for other investigators, and we will share code through LONI and a dedicated GITHub.

PROFILE - Senior/Key Person

Prefix: First Name*: Danielle Middle Name J. Last Name*: Harvey Suffix: Ph.D

Position/Title*: Associate Professor
Organization Name*: University of California, Davis
Department: Public Health Sciences
Division: School of Medicine
Street1*: One Shields Avenue
Street2: MS1C
City*: DAVIS
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 956165200

Phone Number*: 5307522075 Fax Number: (530) 754-6008 E-Mail*: djharvey@ucdavis.edu

Credential, e.g., agency login: djharvey

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: PHD Degree Year:

File Name
Attach Biographical Sketch*: CoreG_Biostatistics_Biosketch_Harvey_v2.pdf
Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: LAUREL Middle Name A Last Name*: BECKETT Suffix:

Position/Title*: Professor and Division Chief
Organization Name*: University of California, Davis
Department: Public Health Science
Division:
Street1*: One Shields Way
Street2: MS1C
City*: Davis
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 956160000

Phone Number*: 530-754-7161 Fax Number: E-Mail*: labeckett@ucdavis.edu

Credential, e.g., agency login: labeckett

Project Role*: Other (Specify) Other Project Role Category: Biostatistics Core Lead

Degree Type: PHD,BA Degree Year:

File Name
Attach Biographical Sketch*: CoreG_Biostatistics_Biosketch_Beckett.pdf
Attach Current & Pending Support:

Biostatistics Core: Specific Aims

The overall goal of the Biostatistics Core is to ensure that sound designs and statistical analyses are used to address the aims of ADNI3, which are to validate biomarkers for Alzheimer's disease (AD) clinical trials. ADNI1, ADNI-GO, and ADNI2 have created together one of the richest and most complex databases in the world, to tackle exceptionally difficult questions about the biological, cognitive, and functional onset, progression, and potential treatment of Alzheimer's disease (AD). The Biostatistics Core has the technical expertise to take full advantage of the richness of the ADNI data, and the demonstrated experience to handle the many complexities of this database.

During the past decade, the Biostatistics Core has played a critical role in ADNI. We have helped to establish the "industry standard" for validated measurements of imaging and fluid biomarkers. We have provided analytic expertise as co-authors for 66 ADNI-related papers (47 since the beginning of ADNI2) and advice on numerous others. We have developed longitudinal methodology to characterize simultaneously the trajectories of biological and clinical measures and standardized ways to compare biomarkers from different domains. We have set an example for reproducible research by sharing data and code, and our work has provided a foundation for other analyses of ADNI data. We have shared our work through talks, publications, LONI postings, and monthly calls with ADNI and industry biostatisticians.

We will continue and extend these efforts in ADNI3, with our primary goal being the systematic characterization of biomarker behavior, relationships, and potential to improve clinical trial design. **Specific Aims**:

Aim 1: To carry out interim and final analyses of ADNI3 data, separately and in combination with data from previous phases, for 5 analytic sub-aims validating the potential of a subset of key clinical, functional, magnetic resonance imaging (MRI), positron emission tomography (PET), cerebrospinal fluid (CSF), and genetic biomarkers. In collaboration with other ADNI leaders we will designate these biomarkers, and for each biomarker we will:

Aim 1.1: Characterize baseline biomarker distribution and performance as a predictor of clinical, functional, and biological change, of progression from cognitively normal (NL) to mild cognitive impairment (MCI) and MCI to AD, and of post-mortem findings;

Aim 1.2: Characterize baseline biomarker potential for use in clinical trials for inclusion/exclusion, screening, stratification, covariate adjustment.

Aim 1.3: Characterize longitudinal biomarker change (rate, between- and within-person variation, non-linearity) and its association with clinical, functional, and other biomarker change, and post-mortem findings.

Aim 1.4: Characterize longitudinal biomarker potential for use in clinical trials as an outcome measure.

Aim 1.5: Compare candidate biomarkers' performance as predictors (1.1) and outcomes (1.4)

Aim 2: To provide design and analytic support for new initiatives in ADNI3, including assay validation and calibration sub-studies, discovery analyses to identify potential new biomarkers and biomarker combinations, and supplemental biomarkers that may be added during the course of ADNI3;

Aim 3: To develop new biostatistical methodology supporting ADNI3 goals and analyses; three planned sub-aims that will extend our previous work include:

Aim 3.1 Development of models for disease progression and the association between biomarker change, clinical change, and risk factors using multiple trajectories and incorporating heterogeneity;

Aim 3.2 Methods for modeling the relationship between clinical change and biomarkers with structural missing data (e.g. tau imaging or amyloid imaging starting in later phases of study, or with planned skipped times.)

Aim 3.3 Methods for structured comparison of biomarkers for their potential for improving clinical trial designs by targeted patient selection, covariate adjustment, or better outcome measures;

Aim 4: To provide intellectual leadership and foster communication among academic and industry biostatisticians interested in ADNI, including sharing of code through LONI and a public Git repository.

As ADNI's experts in biostatistical methods, we will collaborate with other ADNI leaders on analyses for each research theme: characterizing change, identifying predictors, improving clinical trial design, and discovery. We will focus on a limited number of candidate biomarkers in each domain (cognitive/functional, MRI, PET, fluid biomarker, genetic), designated by Core leaders. We will carry out the analyses in Aims 1.1-1.5 for each key target biomarker. We will use best practices of reproducible research and data sharing so that our analyses can serve as templates for our colleagues and other investigators to build on our work in new analyses of ADNI data, with additional biomarkers, additional targets for prediction, and additional clinical trial designs.

Biostatistics Core: Research Strategy

A. SIGNIFICANCE

Overall Significance of the Biostatistics Core: The primary goals of ADNI are to use our understanding of the clinical and biological disease progression to improve AD clinical trial design, and to develop and share datasets to guide future trial designs and research. The Biostatistics Core has been an integral part of ADNI since its beginning. We have led design and analysis efforts across all Cores and Specific Aims. Our Core has made unique contributions in three areas: integrated assessment and comparison across multiple Core domains of biomarker potential for prediction and measurement of change[1]; innovative longitudinal data analysis to characterize simultaneously the biological and clinical patterns of change across the disease spectrum[2, 3]; and guidance and templates enabling other users to access and analyze ADNI's complicated database[4-6]. Our foundation longitudinal paper[7] has been widely cited for how to characterize change in biomarkers and clinical measures in ADNI and assess their usefulness in clinical trials. The Biostatistics Core will continue to play a critical role in the analysis and dissemination of ADNI data.

Significance of Analysis Contributions: The combined ADNI database is one of the largest and most complex studies of AD that is publicly available, and the analytic challenges are formidable. ADNI3 adds new biomarkers that will need internal and external validation and calibration. We will update and extend our models that link and correlate trajectories of longitudinal change in biomarker data with clinical change[2, 8, 9] adding new biomarkers (e.g. tau PET) and computer-based cognitive testing. We have developed a systematic approach to assess and compare the performance characteristics of biomarker and clinical measures as predictors and clinical trial outcomes[10] and will extend this approach to compare performance as trial covariates and as stratification or selection tools. ADNI3 will also draw on systems biology approaches to further improve clinical trial design, and biostatistics will be an important component of this effort.

Significance of Biostatistics Integration and Communication: The Biostatistics Core is a critical resource not only for ADNI leadership and other cores, but also for industry and government partners and outside researchers. Our monthly biostatistics calls reach over 20 biostatisticians from industry, academia, and government. Our analyses serve as templates, with shared code reflecting best practices, for adaption and extension by other researchers. Our workshops, online tutorials[5, 6], and shared code[4] enable collaborators and outside researchers to access ADNI data, merge datasets, and define variables for analysis. We will add a "shared code" hub to allow robust version control, documentation, and issue tracking for ADNI3.

Significance of New Statistical Methodology: The primary analytic challenges of ADNI3 are 1) developing statistical methods to model complex heterogeneous biological and clinical processes that underlie and represent the cognitive and functional decline of AD and related dementias, and 2) using these to improve clinical trial design. Past efforts to improve the signal-to-noise characteristics of cognitive and functional outcomes to increase study power or decrease required sample size have yielded only modest improvements[11]. New computer-based tests in ADNI3 may improve on existing tests not only as outcomes, but also for screening. The amyloid positive subset of MCI, whether defined by PET imaging or CSF, has greater risk of clinical progression and faster decline[12]; this finding, combined with development of amyloid-targeting agents, has led to dramatic changes in trial design[13]. New approaches are still needed to identify either high-risk or low-risk subsets, as well as predictors and potential targets. Finally, the growing body of high-throughput assay data offers many daunting statistical challenges in ADNI. A systems biology approach can help to link our best outcomes with biologically-driven predictors and change models.

B. INNOVATION

ADNI3 will be one of the largest and most complex studies of AD ever conducted due to number of participants, length of follow-up, and richness of cognitive, functional, clinical, imaging, and fluid biomarkers. ADNI3 will require corresponding statistical innovation in: 1) models for multiple longitudinal processes, combining multiple scales, non-linearity, and heterogeneity; 2) rigorous approaches to validation, calibration, and comparison of biomarkers; 3) improving clinical trials, by better outcome measures, covariate adjustment, stratification, and patient selection or exclusion; 4) sharing not only data in real time but also our methods and code to provide online help to investigators wanting to access and analyze ADNI data.

C. APPROACH

C.0 Overview: The Biostatistics Core includes Drs. Beckett and Harvey and staff at UC Davis, along with Dr. Donohue at the Clinical Core, and Mr. Insel at the Administrative Core. Dr. Beckett is responsible for overall operations, including setting priorities in collaboration with ADNI leaders, design and analysis activities, and communication of progress and findings. We communicate via weekly meetings of the UC Davis group and monthly teleconferences with Core members and industry and government biostatisticians. Our approach will focus on support of ADNI3's goals of discovering and validating biomarkers to improve clinical trial design.

Analyses will address each of ADNI's 5 themes: description of biological and clinical change; identifying predictors of change; validation of biomarkers; improving clinical trial design; and discovery.

Previous reviews noted the highly qualified team, the development of innovative methods that provide a level of sophistication to address foundational issues in ADNI, and the experience and progress of the Core in the first years but raised four concerns. 1. Reviewers asked for more clarity on which analyses the Core would do and how priorities are set, given the vast expanse of ADNI data and relatively limited staff. *Response*: In collaboration with each Core, we will identify key biomarkers of interest, for which we will conduct interim and final analyses related to sub-aims 1.1-1.5. Methods and code for these analyses will be made publicly available so that other researchers may build on our work. 2. Reviewers asked for more details on specific modeling issues. *Response*: We give details below and in other Cores. 3. Reviewers were concerned about basis for power for new initiatives. *Response*: We use available ADNI data for power calculations below. 4. Reviewers asked about interactions with the new Genetics Core. *Response*: We are working with the Genetics Core[14], and with its Systems Biology subgroup to develop hypothesis-driven polygenic and pathway scores with adequate power to assess their potential role as predictors and in trial design.

C.1 Specific Aim 1: To carry out analyses of ADNI3 data, separately and in combination with data from previous phases, for 5 analytic sub-aims validating the potential of key clinical, functional, MRI, PET, CSF, and genetic biomarkers. Our Core will do analyses for a focused subset of potential biomarkers, outcomes, and trial designs, selected by ADNI leaders. This uses our limited resources toward foundation publications for each sub-aim and best-practice templates, so other ADNI researchers can build on our work.

We will use two main analytic datasets. First, the ADNI3 cohort (those recruited for ADNI3 combined with rollover participants from ADNI2) will provide information on cognitive and biomarker change in all current measures. The newly recruited participants are critical to ensure adequate numbers of pre-clinical and prodromal AD patients who have complete tau-PET and other new measures from the youngest ages and earliest stages of disease onset. Second, we will also analyze merged data from all ADNI, spanning many years. Analyses will inform on the natural history of AD and timing of biomarker changes. Key carryover clinical outcome variables include ADAS, CDR-Sum of Boxes (CDR-SB), MMSE, and FAQ, while new outcomes include CogState; carryover biomarkers include CSF Aβ and tau, MRI markers (hippocampal volume, TBM-SyN, boundary shift integral), and amyloid PET markers (cortical amyloid SUVR). The major new markers are tau-PET measures of Braak ROIs, and the cerebral tau index. In addition, we will analyze network measures from diffusion tensor imaging, MTL subregions, and centiloid results for amyloid-PET,. Additional markers may be identified during ADNI3. Power will be discussed following analysis sections.

C.1.1 Characterize baseline biomarker distribution and performance as a predictor of cognitive, functional, and biological change, of progression from NL to MCI and MCI to AD, and of post-mortem findings. Baseline characteristics will be summarized graphically and numerically, separately for baseline diagnostic categories (NL, MCI, AD). Longitudinal change in cognitive, functional, and biological measures will be characterized using linear mixed models for continuous measures (most MRI, PET, and fluid biomarker measures; most cognitive and functional performance measures, possibly transformed to deal with floor or ceiling effects, nonlinearity, practice effects, nonnormality, or heteroscedasticity.) These models allow for data missing at random. Informative missingness on longitudinal data will be addressed by sensitivity analysis and by incorporating covariates from non-missing data (e.g. if test score is missing but clinical progression is noted.) Approaches for planned skipped data are discussed in C.3. Generalized linear models will be considered for measures such as CDR-SB and MMSE. Baseline biomarker level will be assessed as a predictor in these models (Clinical Core (CC) hypotheses 1-3; MRI Core hypotheses 5a-5d; PET Core hypothesis b; Biomarker Core (BC) hypothesis 4a; Genetics Core (GC) aims 2.2-2.3). We build models systematically. We first check associations among the target predictor and all potential covariates (age, sex, ApoE4 status) and deal with high collinearity by eliminating or combining variables appropriately. Next, we add the predictor as a main effect and as a modifier of slope. Finally, we add potential covariates and confounders, with attention to the possibility that variables may be in a causal pathway. To assess biomarker performance as predictors of clinical progression, we will use proportional hazard models, building models similarly. To address interval censoring, we will also consider the use of accelerated failure time models. Finally, to assess predictors of postmortem findings, we will build linear or generalized linear models with a postmortem measure as the outcome, pooling NL, MCI and AD for power. Very long-term follow-up in the full ADNI dataset will allow modeling nonlinear trajectories, transitions within diagnostic categories (e.g. to CDR 0.5), and potential target times for early intervention (see Clinical Core for analytic details).

C.1.2 Characterize baseline biomarker potential for use in clinical trials for inclusion/exclusion, screening, stratification, covariate adjustment. Biomarker potential for use in trials will be addressed by quantifying the

reduction in sample size or study duration that could be achieved by incorporating the biomarker for screening, inclusion/exclusion, stratification, or as a covariate for outcome analysis. We will use standard clinical trial design paradigms for assessment of biomarkers, e.g. two-year follow-up of ADAS in MCI, α=0.05, 80% power to detect 25% reduction in annual rate of change, or two-year follow-up to detect risk of progression from MCI to AD. We will consider not only individual markers but also combinations. Combinations are especially relevant for the Genetics Core; to increase biomarker viability for clinical trials, we will consider polygenic and pathway scores developed by the Systems Biology group as summary biomarkers.

C.1.3 Characterize longitudinal biomarker change (rate, between- and within-person variation, non-linearity) and its association with clinical, functional, and biomarker change and post-mortem findings. We will fit longitudinal models as in C.1.1 to estimate annualized rates of change, between- and within-person variation, and the correlation between baseline levels and rates of change for biomarkers. Extensions of these models allow for the simultaneous modeling of change in multiple outcomes for estimating correlation between change in multiple biomarkers or change in a biomarker with cognitive and functional change[8, 9] (CC hypothesis 2; MRI hypotheses 6a-6d; PET hypotheses c, e; BC hypothesis c). Analyses will generally be stratified by baseline diagnosis, to reflect clinical trial design considerations. Additional models will explore the patterns of change for participants with very long-term data collection, e.g. NL and MCI continued from ADNI1 and 2, and test for nonlinearity and change points, onset sequences, and heterogeneity of trajectories.

C.1.4 Characterize longitudinal biomarker potential for use in clinical trials as an outcome measure. We will assess biomarker potential as an outcome measure by calculating the sample size required to detect meaningful reduction in biomarker change, under various standard study designs, as in C.1.2. Comparison of required sample sizes will be systematic, accounting for correlated data, as described in C.1.5.

C.1.5 Compare candidate biomarkers' performance as predictors (1.1), screening or covariate tools (1.2), and outcomes (1.4) (MRI hypotheses 5a-5d, 6a-6d; PET hypotheses b, c, d; BC hypothesis b; GC aim 2.2). Comparison of biomarker performance for this and other aims will use a systematic approach[7, 10]. Biomarkers' performance in trials (as screening tool, covariate, or outcome) will be quantified by improvement in required sample size. Evaluation of biomarkers as predictors will assess clinical validity and will consider correlations with cognitive or functional change or differences between a group that progresses clinically and one that remains stable. Biomarker performance will be operationalized as a correlation (for predictor) or required sample size for a clinical trial (screening tool/outcome). Our comparison strategy first identifies dimension-free participant-level contributions to the correlation or to the formula for sample size. We compare biomarkers with Friedman's rank test to account for patient-level blocking, followed by pairwise comparisons adjusted for multiple comparisons. This approach will also be used in collaboration with the PET Core to determine the best strategy for summarizing the tau-PET data (Braak ROIs, category based on Braak ROI with highest tau ligand uptake, other ROI; see PET Core for more details on potential metrics).

C.1.6: Power considerations for ADNI3 The primary analytic goal of ADNI3 is to develop and assess biomarkers that can be used to improve clinical trial design. ADNI3 will have adequate numbers of people and visits per person in each diagnostic category to a) identify strong predictors of rate of change or time to progression and b) characterize biomarker and outcome change, thus allowing us to enhance clinical trial design by identifying optimal outcome measures and inclusion/exclusion criteria.

Table 1 shows the projected number of ADNI3 participants with baseline and follow-up clinical visits, accounting for 2nd year enrollments and attrition, from CC budget justification, and the expected number of progressions, based on prior ADNI data. See CC for numbers for other measurements. All calculations are for 2-sided tests, level α=0.05, 80% power, using all ADNI3 data.

Table 1. ADNI3 study design: projected sample sizes (clinical visit) by diagnostic group x visit. See CC budget justification tables for projected numbers for MRI, amyloid and tau PET, and CSF.

BL Diagnosis	Baseline	12 m	24 m	36 m	48 m	Progressions at 24 m, 48 m
NL	428	177	289	254	282	31, 54
MCI	425	391	360	331	243	98, 154
AD	215	193	174	X	X	X

Power for predictors of cognitive or functional decline. We examine power for detecting outcome differences between two groups identified by baseline biomarker as high-risk and low-risk. Expected overall mean change/yr of ADAS is 0.31 (1.92, 5.65) points/yr in NL (MCI, AD). For a 50-50 split using a baseline biomarker, we would have 80% power to detect a difference between high-risk and low-risk groups of 0.43 (0.96, 2.28) points/yr for NL (MCI, AD). For clinical trials in NL (MCI), this would allow excluding a low-risk group declining 0.10 (1.44) pts/yr and inclusion of a high-risk group getting 0.53 pts (2.40) pts worse per year, a clinically relevant

selection strategy. Mean detectable differences are comparable for MMSE relative to annualized rate of change, and somewhat smaller (i.e. better power) for FAQ, across all diagnostic groups. For small high-risk groups (10% prevalence, e.g. genetic markers) we can detect differences of 0.72 (1.60, 3.79) for NL (MCI, AD).

Power for detecting group differences in progression. Using a life-table approach, Table 1 numbers, and ADNI progression rates, we project 54 progressions from NL by 48 months and 154 from MCI. For predictors of progression in MCI, we would be able to detect a difference between annual progression rates of 17.7% (worst 50% of participants on a marker) and 10.5%/yr. In NL we would be able to detect a difference between 6.1%/yr (worst 50%) and 2.2% (best 50%). Detectable differences would be greater as we move to 25%-75% or 10%-90% splits based on biomarkers. Subsets with differences this large in prognosis (rate of progression) would reduce substantially the sample size required for clinical trials.

Power for detecting cross-sectional correlations. At baseline, regression models correlating MRI measures and tau PET ligand uptake or other PET markers will have over 80% power to detect any association accounting for as little as 2% of variation ($r=\pm0.14$) in NL and MCI and as little as 3.6% of variation ($r=\pm0.19$) in AD.

Power for detecting correlation in change between biomarkers and cognitive and functional change. Projected sample sizes over time are based on the Schedule of Events in the CC Budget Justification and the PET Core (MRI: (386, 391, 193) (NL, MCI, AD); amyloid-PET: (386, 371, 180); tau-PET: (337, 310, 174); CSF: (240, 225, 107)). Models correlating change between MRI or amyloid-PET biomarkers and cognitive and functional change will have ≥80% power to detect correlations as small as 0.15 (in magnitude) in NL and MCI and 0.21 in AD (correlating with change in tau: 0.16 (NL, MCI), 0.21 (AD); correlating with change in CSF markers: 0.19 (NL, MCI), 0.27 (AD)). Markers truly tracking clinical progression should have much larger correlations, so we will have sufficient power to detect biomarkers with meaningful clinical validity. Comparison of MRI or amyloid-PET markers will have ≥80% power ($\alpha=0.01$ to account for multiple comparisons) to detect differences in correlation with cognitive and functional decline between, for example, 0.8 and 0.69 or 0.6 and 0.42 (NL, MCI) and 0.8 and 0.62 or 0.6 and 0.34 (AD) assuming changes in the biomarkers have a correlation of 0.2 (comparison with change in tau-PET: 0.8 and 0.67 or 0.6 and 0.4 (NL, MCI) and 0.8 and 0.62 or 0.6 and 0.33 (AD); comparison with change in CSF: 0.8 and 0.65 or 0.6 and 0.37 (NL, MCI) and 0.8 and 0.56 or 0.6 and 0.25 (AD)); the detectable difference in correlation decreases as the correlation between biomarkers increases.

Power for detecting association with neuropathology outcomes. NL, MCI, and AD will be pooled, for an estimated 90 autopsies during ADNI3 and 142 combined with previous autopsies. Regression models correlating ADNI3-specific measurements (e.g. tau-PET derived) with neuropathology (e.g. synucleinopathy) will have 80% power to detect any association accounting for as little as 8% of variation ($r=\pm0.29$) while models correlating measures available across all ADNI phases (e.g. cognitive, MRI) with neuropathology will have 80% power to detect associations accounting for 5% of variation ($r=\pm0.23$).

Power for designing novel trial outcomes. Improvement in efficiency of clinical trials is measured by the required sample size for a given trial design. To assess accuracy of sample size estimates in ADNI3, we simulated longitudinal ADNI3 data (including projected attrition) based on prior ADNI data and preliminary tau data from PET Core. From simulations, we calculated the estimated sample size and 95% confidence intervals. Two examples of simulation results illustrate adequate power to detect clinically important improvements. A trial in MCI with 3 annual visits, to detect 25% reduction in change, would require an estimated 2538 people for ADAS (95% CI 2089-3154) and 1015 for hippocampal volume (95% CI 877-1103).

C.2: Specific Aim 2: To provide design and analytic support for new initiatives in the planning and design of ADNI3. These include: assay validation and calibration sub-studies, discovery analyses to identify potential new biomarkers and biomarker combinations. For assay validation (e.g. new bioassay platforms) and calibration (e.g., conversion to centiloid units[15]), we will advise on experimental designs including required sample sizes for necessary precision and estimation of variance components from aliquots, lots, labs, and longitudinal shifts. When possible, study designs will include internal validation, e.g. split samples of CSF, use of two amyloid imaging agents, correlation of amyloid imaging with CSF amyloid. Calibration to a common scale will allow use of multiple platforms or agents in the same statistical analysis. We will collaborate closely with the Genetics and Biomarker Cores on analyses of high throughput assay results (proteomics, metabolomics, gene expression data) as potential predictors or correlates of cognitive and functional outcomes. We will advise on best practices for avoiding false discovery, including internal and external cross-validation and adequate control of error rates. Our primary contribution will be our expertise in ADNI outcome models and our tools for comparison of impact on clinical trial design. Our primary role in this area has been advisory but in ADNI3 we will carry out Genetics Core analyses to assess the performance of selected genes,

polygenic scores, and pathway scores as predictors of clinical outcome and as selection criteria for clinical trials.

C.3. Specific Aim 3: To develop new biostatistical methodology supporting ADNI3 goals and analyses; three planned sub-aims that will extend our previous work include:

C.3.1 Development of models for disease progression and the association between biomarker change, clinical change, and risk factors using multiple trajectories and incorporating heterogeneity. We will build on previous work[2] that developed models placing multiple biological and clinical markers on a common percentile scale and mapping their dynamic evolution over time (See Progress Report D5, Figure 1). New plans include the addition of tau-PET data and extension of the model to capture heterogeneity among sub-populations in the order of marker progression. A second approach[3] will extend the use of generalized Mallows models, treating longitudinal data as partial rankings, to estimate the most likely sequence of progression events and its variation within and between sub-populations.

C.3.2 Methods for modeling relationship between clinical change and biomarkers with structural missing data (e.g. tau imaging or amyloid imaging starting in later phases of study, or with planned skipped times.) Modeling the association between simultaneous change[8] in a biomarker and a clinical outcome is complicated when the biomarker is measured only at a limited number of pre-planned times compared to the clinical measure, or even solely at post-mortem. Some candidate mixed models are not identifiable, and care is required both in model specification and estimation. We will develop guidelines for building simultaneous trajectory models to incorporate amyloid and tau PET data into the full range of longitudinal data for ADNI3 participants (including historical data from carry-over), with constraints to ensure identifiability. Second, we will develop similar guidelines to allow us to model the impact of brain damage that is only measured post mortem on longitudinal cognitive and biomarker trajectories. Both approaches will be illustrated using key biomarkers (Aim 1).

C.3.3 Methods for comparison of biomarkers for their potential for improving clinical trial designs by targeted patient selection, covariate adjustment, or better outcome measures. The systematic approach described in C.1.5 and [10] allows formal comparison of biomarkers as predictors of quantitative outcomes (operationalized by comparing correlations) and as inclusion/exclusion criteria for trials (operationalized by comparing required sample size for fixed design), for a balanced design with all biomarkers measured for all individuals. We will extend this by developing operational criteria for time to clinical progression, accounting for individuals who remain stable or are lost to follow-up; predictors of cognitive or functional decline after adjustment for covariates and potential confounders; and allowing for an unbalanced design, in which not all measures are acquired on all participants. This will extend the Friedman test framework summarized in C.1.5.

C.4. Specific Aim 4: To provide intellectual leadership and foster communication among academic and industry biostatisticians interested in ADNI, including sharing of code through LONI and a dedicated GITHub. We will continue communication via monthly conference calls with ADNI, industry, and government biostatisticians. We will continue posting our code and providing advice and support to other biostatisticians interested in analysis of ADNI data. We plan a new section of the LONI website to bring together in one place the shared code for data preparation (ADNI-MERGE), basic data analysis (currently in our training materials), and publications with shared code. We follow and encourage best practices of literate programing and reproducible research including version control and documentation of all steps from data download through data processing, analysis, and preparation of graphics, tables, and other parts of our papers.

D. PROGRESS REPORT

Overview: During this five-year review period, the Biostatistics Core has overseen the statistical quality of the data, informed design of ADNI3, led analyses that utilize data across all ADNI Cores, collaborated with other Cores on influential projects in the field of Alzheimer's disease and clinical trials, assisted outside users with the complexity of ADNI data, and developed new statistical methodology in the context of Alzheimer's disease research[16]. We review for each aim in ADNI2.

D.1. Aim 1: To provide analytic support for the planning and design of ADNI2 and oversee statistical quality of the data. At least twice a year, the Biostatistics Core generated standard reports summarizing the distribution of values at each visit as well as rates of change on selected clinical, imaging and fluid biomarker measures. Suspicious data points were queried directly to the responsible lab for checking and correction. Monthly reports for the MRI and PET Cores tracked scans submitted, processed, summarized, and uploaded, so pipeline delays could be addressed quickly. In collaboration with the MRI Core, we established best practices for analyzing ADNI MRI data[17]. Finally, in preparation for ADNI3[18], we simulated the impact on precision of estimates for various study designs (omitting a year, stratified sampling); these simulations allowed a modified design that will obtain almost identical precision at substantial cost savings.

D.2. Aim 2: To carry out interim and final analyses of ADNI data. During the past 5 years, the Biostatistics Core has led some analyses of ADNI data, collaborated with other Cores, and provided analytic expertise and templates to other investigators. Our longitudinal models in ADNI1[7] became a standard for description of short-term change in cognition, MRI, and FDG-PET measures, and for comparing their potential as outcomes in clinical trials[19-21]. We extended this work to take advantage of longer follow-up and more variables in ADNI2[1]. We identified a subgroup of ADNI normal controls with atrophy and cognitive decline associated with vascular damage[22] and ADNI MCI subgroups including 2 that were non-AD like[23]. In collaboration with the CC, we developed outcome measures[24] and study designs for preclinical AD clinical trials[13]. We evaluated the self- and participant-reported ECog [25]. The PET Core consulted with us on best strategies for modeling to evaluate associations between cognitive, functional, and FDG-PET measures of decline.[26] PET Core researchers then used our approach to examine other PET markers and cognitive decline[12]. Similarly, the MRI Core consulted with us in order to evaluate change in white matter hyperintensities and cognition[27-29]. We provided analytic and database expertise to additional co-authored papers in imaging and fluid biomarkers[30-36]. Dr. Beckett's ADNI analyses formed part of the CAMD work on European biomarker qualification of hippocampal volume for use in clinical trials[37]. Dr. Beckett continues to provide advice and analyses to CAMD on ADNI data to support extension to CSF biomarkers and to qualification by the FDA.

D.3. Aim 3: To participate in ongoing ADNI2 operations. Dr. Beckett participates in Executive Committee calls and Genetics Core/Systems Biology Workgroup call. Dr. Harvey participates in monthly MRI and PET Core calls. Monthly reports on available scans for each type of scan as well as those processed by each lab were generated for the MRI and PET Cores.

D.4. Aim 4: To provide intellectual leadership and foster communication. The Biostatistics Core holds a monthly conference call to which 20+ academic, industry and government biostatisticians are invited. These calls provide other biostatisticians with updates on data and our analyses, and address their questions and concerns. Drs. Beckett and Harvey were faculty at the 2011 Advanced Psychometrics Workshop in Friday Harbor that focused on ADNI, and were co-authors on 3 papers: the development of composite memory[38] and executive function[39] scores and modeling the sequence of biomarkers for Alzheimer's disease[40]. Dr. Beckett was co-leader of a conference in September, 2015, bringing together academic and industry biostatisticians interested in the analysis of AD data, with plans for a special journal issue built around conference papers. We also serve as a major resource for the greater community working with ADNI data, curating an active google group of 73 members and growing (https://groups.google.com/forum/ - !forum/adni-data). In 2013, we held a web-conference that provided an overview of the data, tips, and code[5, 6]. We developed and shared on LONI R, SAS, SPSS, and Stata packages that merge commonly used data tables into a single analysis-ready file of longitudinal data[4]. This ease of access contributed to high access and publication by non-ADNI researchers.

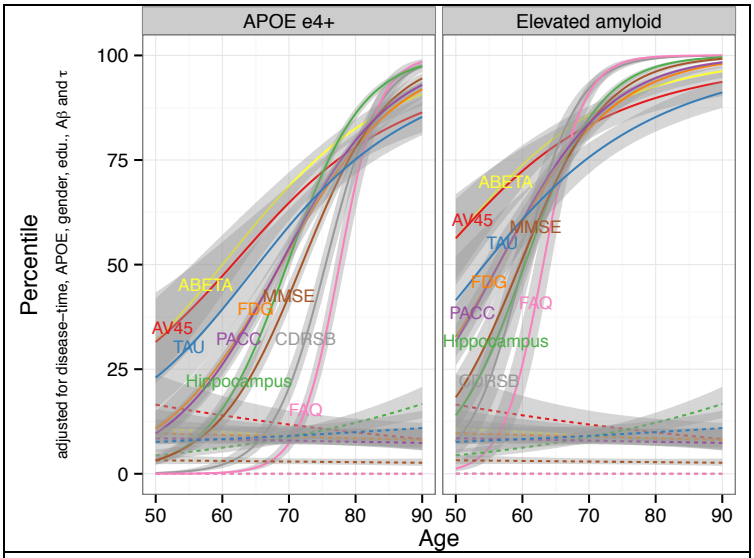

Figure 1. Long-term trajectories from least affected (0th percentile) to most affected (100th percentile), estimated for high-risk and low-risk patients, from age 50 to 90 years (Beckett et al 2015).

D.5. Aim 5: To develop new statistical methodology. We showed the relative efficiency of time-to-threshold change and rate of change in longitudinal data[41] and developed methods for modeling long-term disease dynamics from preclinical to dementia[2] (Figure 1). Dr. Beckett developed methods for partially ranked data that were used to show heterogeneity of modal sequences in the ADNI data[3]. Drs. Harvey and Beckett developed a standardized framework for evaluating biomarkers on precision and clinical validity[10]. Finally, Drs. Harvey and Beckett supervised 5 doctoral students who worked on ADNI–related projects: 1) modeling patterns of amyloid deposition cross-sectionally and over time; 2) estimating time of onset of abnormal levels of a marker based on panel data; 3) developing an information-theoretic approach to evaluate biomarkers; 4) extending the disease dynamics model of Dr. Donohue; and 5) developing a framework for correlating trajectories where one measure has a planned structural missingness pattern (such as post-mortem data).

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OMB Number: 4040-0001
Expiration Date: 06/30/2016

APPLICATION FOR FEDERAL ASSISTANCE

SF 424 (R&R)

5. APPLICANT INFORMATION **Organizational DUNS*:** 6133387890000

Legal Name*: NORTHERN CALIFORNIA INSTITUTE FOR RESEARCH AND EDUCATION
Department:
Division:
Street1*: 4150 CLEMENT STREET (151-NC)
Street2:
City*: SAN FRANCISCO
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 941211545

Person to be contacted on matters involving this application

Prefix:	First Name*:	Middle Name:	Last Name*:	Suffix:
	Azarah	Sr. Grant Specialist	Wong	

Position/Title:
Street1*: 4150 CLEMENT STREET (151-NC)
Street2:
City*: SAN FRANCISCO
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 941211545
Phone Number*: 415-750-6954 x 23891 Fax Number: 415-750-9358 Email: cgawards@ncire.org

7. TYPE OF APPLICANT* M: Nonprofit with 501C3 IRS Status (Other than Institution of Higher Education)

Other (Specify):

Small Business Organization Type ❍ Women Owned ❍ Socially and Economically Disadvantaged

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
Informatics Core

12. PROPOSED PROJECT

Start Date*	Ending Date*
08/01/2016	07/31/2021

OMB Number: 4040-0010
Expiration Date: 06/30/2016

Project/Performance Site Location(s)

Project/Performance Site Primary Location

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:	University of Southern California
Duns Number:	0729333930000
Street1*:	2001 N. Solo St. Suite 102
Street2:	
City*:	Los Angeles
County:	
State*:	CA: California
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	90032-3600
Project/Performance Site Congressional District*:	CA-034

File Name

Additional Location(s)

Tracking Number:

Informatics Core: Project Summary/Abstract

The ADNI *Informatics Core* (IC) will serve as the central data management and data-sharing arm for the ADNI 3 study. The Informatics Core objective is 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. We will provide a platform to securely store and disseminate image, clinical, and genetic data collected from the ADNI 3 initiative. We will work with each of the other ADNI Cores to ingest data collected or generated as part of their efforts. We have established standards and quality control processes during ADNI 1 and ADNI 2 and these will be extended for data collected as part of ADNI 3. The informatics platform will be expanded to incorporate a data harmonization effort in order to form a consistent and searchable representation that characterizes the considerable breadth of data that exists in ADNI. The harmonization effort will include development of new data mapping tools to define data transformation rules for the archived data and to automatically apply the transformations on new data as it arrives. We will directly utilize the harmonized ADNI data by mapping it into our data exploration interface and integrating it into our informatics infrastructure so that newly archived data will automatically be mapped and made viewable and searchable after it arrives. This will enable investigators to visualize data correlations and trends across all phases of ADNI. New search capabilities will be developed for searching the harmonized dataset and for selecting data matching research goals. New data downloading mechanisms will be developed to streamline data transfers of large datasets. We will develop functionality to test the speed and reliability of investigators' network connection and provide recommended download methods based on the test results. Our team is ideally suited to oversee and manage the data management and coordinate data storage and all open data sharing activities.

PROFILE - Senior/Key Person

Prefix: First Name*: ARTHUR Middle Name W Last Name*: TOGA Suffix:

Position/Title*: Provost Professor
Organization Name*: University of Southern California
Department: Ophthalmology
Division:
Street1*: 2001 N. Soto Street, SSB1-102
Street2:
City*: Los Angeles
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 900323600

Phone Number*: (323) 442-7246 Fax Number: (310) 206-5518 E-Mail*: toga@loni.usc.edu

Credential, e.g., agency login: toga22

Project Role*: Other (Specify) Other Project Role Category: Informatics Core Lead

Degree Type: PHD,MS,BS Degree Year:

File Name

Attach Biographical Sketch*: 17_CoreF_Biosketch_Toga.pdf

Attach Current & Pending Support:

Informatics Core: Specific Aims

The primary objective of the ADNI Informatics Core in ADNI 1 and ADNI 2 was 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, particularly in order to support validation of biomarkers for clinical trials. Our objectives in ADNI 3 will continue these efforts, but with new aims centered on improving the data sharing landscape through the development of components that address the problem of data complexity and enable ADNI investigators from all backgrounds to better explore, understand and use the continually expanding array of raw and derived data that includes clinical/cognitive, imaging, genetic, biofluid and -omic data. These developments will involve data harmonization and improved search interfaces for exploring, visualizing, comparing, selecting and downloading data. Our specific aims are:

Specific Aim 1: *Archive, curate, secure and disseminate data acquired in ADNI 3.* We will enhance and provide continuous support for our informatics infrastructure to securely de-identify, receive, integrate, store and disseminate the image, clinical, and genetic data collected from the ADNI 3 initiative including new types of imaging data such as tau PET and new types of computerized cognitive testing data. This includes providing support to the image acquisition sites, integrating different data types and formats, providing search and download functionality to share data with approved ADNI investigators and supporting and enhancing the ADNI website.

Specific Aim 2: *Harmonize ADNI 3 data with data produced by ADNI 1, ADNI GO, and ADNI 2.* We will harmonize data collected in ADNI 3 with data of previous ADNI phases forming a consistent and searchable representation that characterizes the considerable breadth of data that exists in ADNI. We will utilize the new data-mapping tool developed in specific aim 4 to define data transformation rules for the archived data and to automatically apply the transformations on new data as it arrives. We will also generate and assign labels for tagging data when their data descriptions lack sufficient detail for queries.

Specific Aim 3: *"Validation-ready" searching and downloads.* We will bridge the gap that exists between the way ADNI data is acquired and the ways ADNI investigators analyze the data by refactoring data elements into a representation more conducive to validating biomarkers for clinical trials and other analyses. We will redefine the existing paradigm where an investigator downloads and self-processes multiple data spreadsheets by developing a new query interface that enables the investigator to select and search for subject data based upon a specific research question. Once the result set is determined, the investigator can simultaneously download both image and clinical data formatted according to the search criteria (not according to how the data was acquired).

Specific Aim 4: *Map data from all ADNI phases into our interactive data visualization platform.* We will directly utilize the harmonized ADNI data from specific aim 2 by mapping it into our data exploration interface. This will enable investigators to visualize data correlations and trends across all phases of ADNI and support validating biomarkers for clinical trials. The mapping tool developed in specific aim 6 will be integrated into our informatics infrastructure so that newly archived data will automatically be mapped and made viewable and searchable after it arrives. We will also incorporate SNP data in order to facilitate data discovery between clinical, imaging and genetic variables.

Specific Aim 5: *Data download options and support for data aggregation efforts*. We will provide new options for downloading and/or obtaining ADNI data offering flexibility for different types of users. This approach will also support data initiatives such as GAAIN (Global Alzheimer's Association Interactive Network), national data-thons, hack-a-thons, and other organized investigations. We will develop functionality to test the speed and reliability of investigators' network connections and provide recommended download methods based on the test results. We will create data sets for and support the efforts of organizations that sponsor multi-discipline events aimed at finding new methods for mining and processing ADNI data. We will do so using technologies that respect the data ownership concerns and policies set forth by the ADNI data sharing committee.

Specific Aim 6: *Data mapping tool.* We will design and construct a data-mapping tool to visually transform ADNI data that is stored in database tables. This will enable us to combine data from different ADNI phases and/or other AD related data sources into a harmonized data representation suitable for analysis-ready searching (specific aim 3) and incorporation into the data visualization platform (specific aim 4).

Informatics Core: Research Strategy

SIGNIFICANCE

Overall Significance of the Informatics Core: The overarching goal of the Informatics Core (IC) is to secure, link and disseminate all ADNI data coming from the participating sites and the other ADNI cores providing a resource for validating biomarkers for clinical trials. This involves de-identifying and receiving imaging data from the sites, integrating clinical data from the Clinical Core, incorporating analysis results from other cores, managing the data access systems utilized by the Data Publication and Sharing Committee, providing user interfaces to explore, visualize, interpret and download ADNI data and providing comprehensive information about the ADNI study through the public website. The Informatics Core has provided ongoing systems and support for achieving this goal and for sharing ADNI data with thousands of investigators worldwide. The Informatics Core has provided leadership in the design and deployment of the ADNI data-sharing model and has been instrumental in the data sharing effort.

Data Sharing. Sharing research data in a broad and easily accessible manner that follows principles of transparency and active dissemination has a positive impact on scientists, research funders, and the public good (Arzberger et al. 2004). The consequence of such approaches can be seen in the effective re-use of data extending beyond the original intent for which it was collected. Data sharing maximizes financial investment by making data available for new research and minimizing duplicate data set collections (Ross et al. 2013). The ADNI Informatics Core repository supports secure, reliable deposition and open sharing of ADNI raw data, analysis results and methods with a large, global community of researchers. Our approaches have been implemented in other studies of neurological and psychiatric diseases and have served as the catalyst and gold standard for numerous other efforts at NIDA, NIMH, and NICHD, among others. The success of ADNI has significantly impacted Alzheimer's disease research and served as a model for large multi-site efforts. Across its different funding cycles, ADNI 1, ADNI GO, and ADNI 2, necessary and advantageous modifications and additions have been made resulting in, for example, different cognitive assessments, new scanning protocols, and new types of biospecimen analyses. This history is not readily discernible by new ADNI investigators who have applied for and been granted access to the ADNI data set, and so more than just access to the data is required. Many investigators who download ADNI data lack expertise in various aspects, and are confused by the multiple ways the same data is analyzed (for example structural MRI measured in different ways). A harmonized view of data across ADNI phases and cores can remove obstacles impeding use and improve its utility to research. We will harmonize ADNI 3 data with the data archived for the ADNI 1, ADNI GO, and ADNI 2 phases so that investigators will not have to search and merge multiple data sets together. We will map all ADNI data into our interactive data exploration platform so that investigators can visualize all the ADNI phase data together and seamlessly view trends and correlations within and across ADNI phases. We will also provide "validation-ready" searching so that downloaded data is formatted for immediate use by ADNI investigators and they can immediately start analyzing the data instead of spending time preprocessing it for their analysis.

Data Exploration. Exploring and navigating complex, heterogeneous, longitudinal data can be difficult, even when data are extensively harmonized. There are several other database solutions that have emerged in recent years. These include XNAT (Marcus et al., 2007), LORIS (Das et al., 2011), COINS (Bockhold et al., 2009), NDAR (Hall et al., 2012) and others, but these are generally repositories only and do not include visualization and exploration functionality. Similarly, there are several data exploration applications such as tranSMART (Athey et al., 2013), Cortellis Data Fusion (Thompson Reuters) but these do not provide the extent of data archiving, provenance and dissemination proposed here. Seeing data directly within the database at different levels of detail (overview, summary, detail) helps to orient data seekers to the data, provides contextual information for understanding relationships and supports discovery of hidden insights within the underlying data. The data exploration interface proposed here unites the benefits of a graphical data representation and comprehensive harmonized data to support the information needs of investigators allowing them to create cohorts of subjects sharing traits and to search, select, compare and download data meeting their research objectives. This directly supports biomarker validation by providing the means to look at biomarkers in the different groups (CN, MCI and AD) at baseline and lonigitudinally.

Genetic data has Unique Requirements. Genetic data has become increasingly important in Alzheimer's disease research augmented by large meta-analyses combining genotypic and phenotypic data pulled from multiple studies. To date, more than 300 studies incorporating ADNI genetic data have been published (Saykin et al. 2015). The output formats of genotyping and sequencing are typically large binary files or structured text files requiring specialized software. Data sizes can exceed ¼ petabyte, depending on format,

and require alternative distribution strategies. The IC proposes a menu of packaging options and solutions to satisfy those who intend on BAM files for sequence realignment or merely interested in snp associations. The infrastructure and data transfer and dissemination needs vary considerably and our plans accommodate all. Providing a mechanism to extract specific genetic data from large files and to and incorporate it into search and data exploration activities would enable investigators to look for trends and/or compare population differences in different cohorts and be helpful in selecting data of interest to download for further analysis.

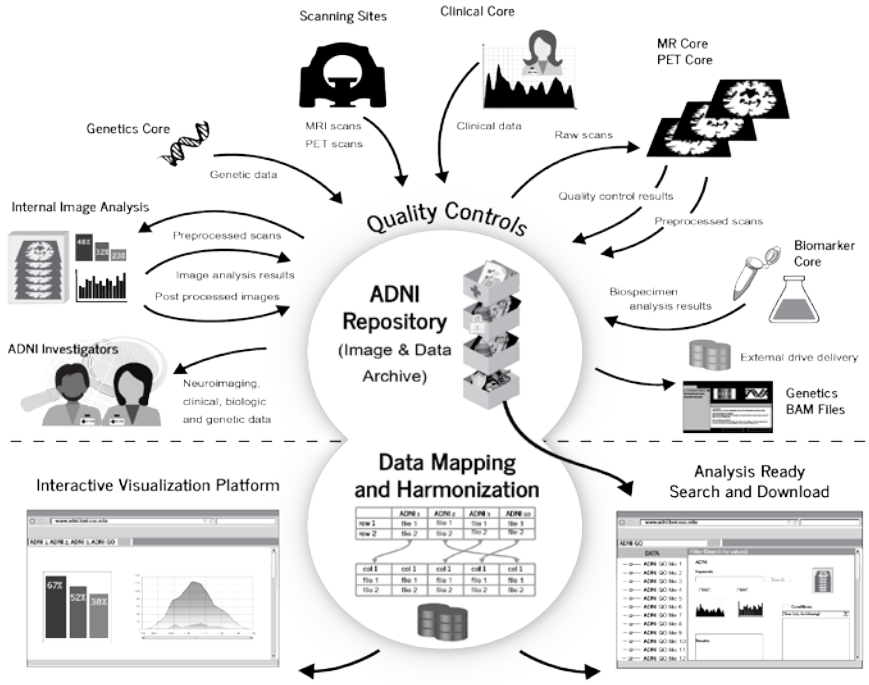

Figure 1 Data mapping and transformation produced a harmonized data set for searching and exploring.

Data Dissemination. Transferring large quantities of data over the Internet is slow and subject to unreliable networks. Many ADNI investigators, especially those who are new, find it necessary to download large quantities of data such as thousands of MR or PET scans, genetic sequencing and other data. Some data files, particularly large whole genome sequencing data, are so large that downloading the complete set using standard internet transfer protocols is all but impossible. Solutions to management and transfer of very large data sets will continue to grow in importance as additional ADNI data are collected and investigators move toward leveraging increasingly large and diverse genetic, phenotypic, -omic and other data. Developing streamlined mechanisms for managing and downloading data will remove some of the hurdles to obtaining data providing more time for research and less on manipulating data files. We will create a mechanism to test users' network speeds and reliability and provide a set of data download options tailored for different network environments including a comprehensive 'ADNI on a drive' distribution method for those that want a snapshot of the entire data set delivered on a external drives.

The significance of these efforts for ADNI 3 data and forging new tools to improve data exploration and usability is to maximize the potential of the collected data and bridge the gap between the acquisition complexities of archived ADNI data and the data views used by ADNI investigators for their analyses.

INNOVATION

Beyond the typical functionality of a common data repository (storing and disseminating data), we believe an advanced data repository must show investigators what information has been collected without exposing them to the details of how it was collected. For example, the year, month, and day on which a cognitive exam is administered is saved as an "exam date" when a subject's exam score is recorded, but that information by itself is meaningless to an investigator. It is only useful when determining how much time has elapsed between when the exam was administered and when other information was collected, e.g., an MRI scan.

Our first innovation is to provide an interactive and visual view of the entire ADNI data set. By uniting the terminologies and data definitions of the previous ADNI phases (ADNI 1, ADNI GO, and ADNI 2) with new definitions in ADNI 3, we will harmonize all the ADNI data into a uniform data model. We will map this harmonized data into our data exploration interface and this will enable investigators to visualize data correlations of biomarkers with clinical outcomes and trends across all phases of ADNI from a basic web browser. This will provide investigators an essential tool to ask questions about, and get answers on ADNI data without requiring them to download and process the data themselves.

Our second innovation is to provide a search interface that allows download of ADNI data without extensive preprocessing before incorporating it into subsequent analyses. We will develop a new query interface that enables ADNI investigators to select and search for data based upon a research question. In

addition to searching individual data values of the harmonized ADNI data set, we will enable searching across data values using time differences and data categories. Once the search results are determined, the image, clinical and other data will be downloaded and formatted according to the search criteria and ready for biostat and validation analyses (not according to how the data was acquired).

Our third innovation is to develop rules for assigning labels and/or tags to collected data that provide intuitive terms used for searching the data. We have already applied this approach to PET scans using novel tracers (Neu et al. 2012) and will extend this approach to other types of data.

Our fourth innovation is to develop a transformation tool to handle the complexities of ADNI data. We will design and construct interactive web interfaces to visually transform ADNI data stored in database. This will play a key role in the harmonization of data across ADNI phases, by supporting automatic updates when data from ADNI 3 is archived and by mapping the harmonized ADNI data into our data exploration interface.

APPROACH

The development and evaluation of the entire system will follow a professional, systematic, software development cycle inclusive of needs analysis, software architecture, user interface design, testing (beta, usability), and a performance review, and approval process.

Aim 1: Archive, curate, secure and disseminate data acquired in ADNI 3. The existing informatics system, the LONI IDA, provides an efficient and secure data repository platform that facilitates data de-identification, deposition, integration, search, visualization and download. Functionalities include 1) image data de-identification, protocol detection and data deposition, 2) clinical, biomarker, quality assessment and analysis results data integration, 3) processing of quality assessment results to release quarantined images, 4) mapping of a subset of ADNI data attributes into a common schema for use in search and visualization interfaces, 5) interfaces to search, select and download data, 6) a visualization interface for inspecting and comparing data, and 7) a comprehensive website containing study-related information such as protocols, announcements and a knowledgebase wherein investigators post questions and receive answers from ADNI experts. We will incorporate new data for ADNI 3 into the existing system, including tau PET scans and data from computerized cognitive tests, providing immediate and uninterrupted access to data from all ADNI phases. We will also develop new sections of the website, in coordination with the Biostatistics Core, to improve information on best practices. We will incorporate ADNI 3 data into the harmonization and mapping described in Aims 2 and 4.

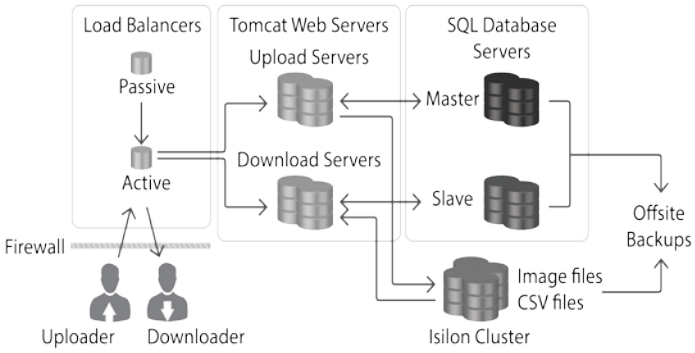

Figure 2. Elements of the Informatics Core Infrastructure.

The IC platform relies on an infrastructure (Figure 2) comprised of fail-safe, redundant and secure components. The underlying network infrastructure has no single points of failure employing multiple physical and Internet backbone connections. Redundant web, application and database servers ensure service continuity in the event of a single system failure and provide improved performance through load balancing across machines. Data backup mechanisms are in place to protect the integrity of the ADNI data. We will continue to provide a secure and reliable information infrastructure for ADNI 3.

Testing and evaluation: We monitor system performance to ensure operation and availability. Each upload and data transfer is logged including the date, time and email address of the individual performing the upload or data transfer. Information about each data download is likewise captured including data transfer speeds.

Aim 2: Harmonize ADNI 3 data with data produced by ADNI 1, ADNI GO, and ADNI 2. One of the most frequent questions posed by investigators seeking assistance with using ADNI data stems from difficulty discovering each subject's diagnosis at any time point. Current diagnosis data was captured differently for ADNI 1 than for ADNI GO and ADNI 2 due to necessary changes in the data collection instrument. Other differences exist between region of interest (ROI) measurements produced by image analysts using different methods, naming conventions, definitions and units of measure. We want investigators to be able to simply ask, "Which subjects who converted from MCI to AD showed a decrease in the size of the left hippocampus?" To accomplish this we will redefine the common data model to encompass all of the ADNI data and map data from each of the ADNI phases into the common model. We will apply transformations on the data to render it consistent across all ADNI phases. This common model will be comprised of a common database schema, data dictionary and code lists. We will use the mapping tool developed in Specific Aim 6 to map and transform data from each of the ADNI phases into the common model.

Testing and evaluation: We will engage subject matter experts from the other cores to provide input into and validation of our transformation plans. We will also perform standard statistical checks of transformed data against source data. In addition, we will provide the mapping and transformation details so data consumers are fully apprised of transformation particulars.

Aim 3. *"Validation-ready" searching and downloads.* A common use case for obtaining ADNI data involves the following steps:

1. Searching for and collecting image data using an online search interface.
2. Downloading the collection of image data.
3. Downloading all the clinical data in spreadsheet form.
4. Reading the ADNI data dictionary to understand the clinical data fields.
5. Matching the clinical data fields to the downloaded image data.
6. Processing the clinical data to find subject data for an analysis.

This workflow is due in part to the way ADNI data is collected. The image data is initially archived separately from the clinical data at different ADNI informatics core sites and combined later. Our approach for streamlining this workflow is to build a search interface for querying both image and clinical data together and to provide search capability that produces search results similar to the data sets used by investigators for their analyses. Figure 3 illustrates a scenario with practical applications. In the top section, the search will find all subjects with a baseline MCI diagnosis who are amyloid positive and had both tau PET and fMRI scans at three or more visits in a three year period. The total number of subjects satisfying the search criteria is seen before the search details are shown to provide feedback to the investigator, who may wish to adjust the search parameters before proceeding. This search enables the investigator to search across data fields, which is commonly done when choosing data variables for a validation or correlation analysis. For data fields that are sparse the investigator may choose "any MCI baseline DX" (i.e., either eMCI, lMCI or MCI) to increase the number of subjects that satisfy the search. These scenarios provide useful information to the investigator, who must otherwise download and process the data in order to determine how much of the desired data exists. Once the result set is determined, the investigator will simultaneously download both image, clinical and other data formatted according to the search criteria, which alleviates the need to process multiple spreadsheets to derive the same information and facilitates the process of validating biomarkers for clinical trials and other analyses.

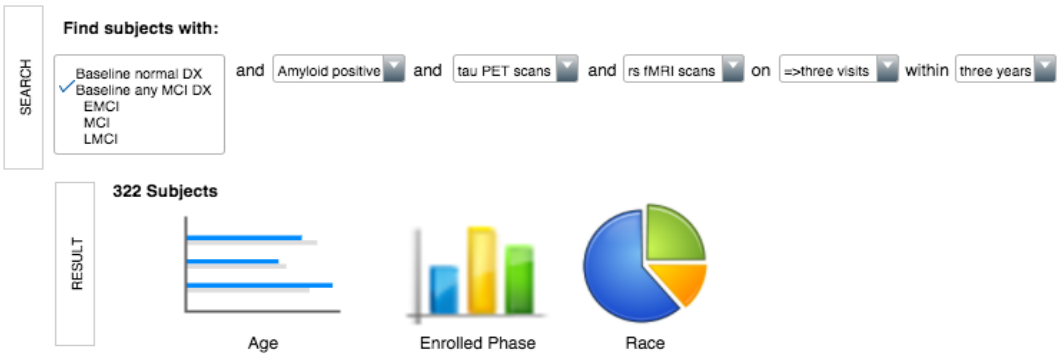

Figure 3. Search criteria reflect what investigators are looking for rather than how the data were collected. Results are summarized in numerical and chart form showing the makeup of the results set.

Testing and evaluation: We will conduct A/B testing with different groups of researchers that represent the different data needs of ADNI investigators. This will provide us feedback so we can determine the most effective combination of search options to use with ADNI data.

Aim 4: Map data from all ADNI phases into our interactive data visualization platform. ADNI data has different phases and has rich, high dimension levels of detail. As such, exploring and navigating through the full data set poses challenges, especially in providing investigators with tools that are easy to use and comprehend. Visualizing data helps orient investigators and provides contextual information for understanding relationships and discovering hidden insights within the underlying data. Although in recent years database solutions have emerged to collect this type of data, they do not provide visualization or exploration functionality. Applications such as tranSMART offer some analytic capability but require data to be laboriously imported and are not automatically updated when new data are archived. The LONI IDA data visualization interface unites the benefits of visual representations of data with a comprehensive harmonized data set and allows creation of subject cohorts and to search, compare, and download data.

We will use the mapping tool developed in specific aim 6 to import the harmonized ADNI data set created in specific aim 2 into the LONI IDA data visualization interface. This will enable investigators to visualize data correlations and trends across all phases of ADNI, including correlations of biomarkers with clinical outcomes, using a single interface and without requiring them to download and import data into an external application.

All newly collected data in ADNI 3 will be immediately and automatically mapped and made available for data exploration using the rules created from the mapping tool. Further, we will incorporate SNP data from ADNI genetic data files and this will enable ADNI investigators to interact with and visualize relationships between imaging, clinical, and genetic information to validate biomarkers for clinical trials.
Testing and evaluation: We will seek and respond to feedback from ADNI investigators on our data exploration interface by conducting usability testing with a target group of experienced users.
Aim 5: Data download alternatives and support for data aggregation efforts. Many ADNI investigators, especially those who have newly applied for access, are interested in downloading large quantities of ADNI data. To date, the total size of all the MRI and PET image scans collected by ADNI is about 5 terabytes. In ADNI 3, this number will grow as large image acquisitions such as DTI scans continue to be added to the ADNI data set. Some data files, particularly the whole genome sequencing data, are so large that downloading the complete set via standard Internet transfer protocols is all but impractical. The limiting factors that make the transfer of large data sets over Internet connections difficult are the speed and reliability of the network used for the data transfer. Currently in the LONI IDA, we have in place several mechanisms to alleviate some of these difficulties, including compressing data before sending it out, automatic retries to continue data transfers after connections fail, and CRC checking to guarantee that data does not arrive corrupted. We also keep a record of each data download so investigators will not accidentally download data they have previously downloaded. Specific aims 3 and 4 address large download limitations by providing search functionalities that help ADNI investigators reduce the size of the data sets they are downloading by allowing them to uniquely identify specific data of interest. This is an important strategy that frees investigators from the need to search through downloaded bulk data in order to obtain a desired subset of data. ADNI investigators use a wide range of Internet connection speeds, from slow wireless connections to Broadband/DSL connections to much faster gigabit connections found in large institutions. In order to assist ADNI investigators as they download data from the LONI IDA, we will add to our current download web pages a function that automatically tests the speed of each investigator's network connection. After an investigator has created an ADNI data set for downloading, we will compute the total size of the download and use the connection speed to display the estimated time it will take to download the data over the connection. We will recommend a data transfer method from a list of available options. We will evaluate open source and commercial solutions for downloading large amounts of data (e.g., Aspera) and suggest these solutions whenever the speed of the download connection is too slow. When commercial solutions are insufficient, we will offer ADNI investigators the option to obtain predefined subsets of ADNI data on a purchasable external drive via mail.
Testing and evaluation: We will monitor user satisfaction from questions and feedback. We will support comparative initiatives in which ADNI data is used in collaborations that attempt to aggregate big data (e.g., GAAIN) or apply data mining and/or new data processing techniques (e.g., data-thons). This involves hosting software from federated networks (e.g., GAAIN) and instances of data sets (e.g., TranSMART virtual machines) in compliance with the ADNI data sharing committee policies.
Aim 6: *Data Mapping Tool*. The ADNI data set contains thousands of data fields and there are significant differences in the data definitions and nomenclature used across ADNI phases (ADNI 1, ADNI GO, and ADNI 2) and data sources. There are many ETL (Extract, Transform, and Load) tools available to integrate data, including Oracle Data Integrator (Hecksel, D., 2012), Microsoft SQL Integration Services (SSIS) (Knight et al., 2012), and SAS Data Integration Studio (Grasse et al., 2006), but they all lack some necessary functionality.
Transform data values, not data tables. In most ETL tool displays, data transformations are constructed by drawing lines to connect data tables. Each line represents a transformative operation that either moves data between tables or applies a function that changes the data value. One disadvantage to this approach is that for complicated workflows the display quickly becomes cluttered with hundreds of intersecting lines and it becomes difficult to understand the logic behind the workflow. We will graphically show how data values are transformed after the application of each new function. Data columns and functions are draggable objects combined to transform data values. Unlike most ETL tools that require the workflow to be executed before results can be viewed, our approach provides immediate feedback and eliminates bundles of intersecting lines.
Automatic data type conversions. Many ETL tools require that data types be explicitly defined and managed. This slows down transformation development because often conversions have to be specified to switch between data types. In our approach we will internally manage only 3 data types: character (e.g., "ABC"), number (e.g., 123), and boolean (true/false). Further, we will implement internal conversions between these data types so that our data transformations will work automatically between different data types.
Compute data element summaries. The first question asked is, "What did I get?" The investigator must search through the data in order to reconcile whether or not the data meets expectations or simply to obtain a better

idea of what data was collected. Most conventional ETL tools are not designed for this type of data investigation. In our approach, we will provide functionality for determining sets and ranges of data values and allow the results to be easily integrated into transformations.
Testing and evaluation: The data mapping tool will only be used internally to map ADNI. Therefore, the primary target group of users providing feedback will be highly experienced database programmers.

PROGRESS REPORT
The ADNI Informatics Core provides a central hub for ADNI data and information comprised of a comprehensive website and a secure data repository. Combined, they deliver a host of information, materials, data and services supporting the needs of the ADNI community. Specific aims for ADNI 2 were the integration of new data types, enhanced search capabilities, direct access to ADNI data from within the LONI Pipeline workflow environment and new means of providing training and support to users.
Summary of progress. Within the ADNI data repository we integrated data collected from sites and produced through the efforts of the other ADNI cores. This has involved de-identification and ingestion of raw and processed neuroimaging data, integration of clinical, biospecimen and genetic data, performance of data quality control and the comprehensive data sharing activities that support the global ADNI research community in meeting diverse informational needs. The repository now contains more than 206,000 raw and processed MRI and PET scans, 410 clinical and results datasets and 90 genetics datasets. Over 6,000 applications for ADNI data access have been received from 80 countries via the automated systems managed within the IC. This number has dramatically increased from less than 200 applications received in 2006 to over 1,200 received in 2014. Using systems developed and managed by the ADNI IC, investigators have downloaded more than 6.5 million data sets (imaging, clinical, genetic, biologic) and have submitted more than 900 manuscripts for review by the ADNI Data Sharing and Publications Committee (DPC). Whole genome sequencing data has been shared with 16 investigative teams in 5 countries. Each copy of the dataset, which exceeds 90 terabytes, has been provided without charge to investigators who provide their own hardware to hold the data. Further, ADNI data has been used as base data for several competitive efforts including a hackathon sponsored by the Organization for Human Brain Mapping in 2013 and the SAGE Bionetworks competition on predicting Alzheimer's conversion in 2014. During ADNI 2 we incorporated additional attributes into the search interfaces, developed a new data visualization interface (Figure 4), and in coordination with the MR Core created standardized collections of MR data and promoted their usage in order to support comparisons of image analysis methods across the same source data (Wyman et al. 2013). The ADNI website provides comprehensive information about the ADNI study, such as documents, contact information, important links, ADNI publications, a listing of active ADNI investigators and support tools. Enhancements to the website include:

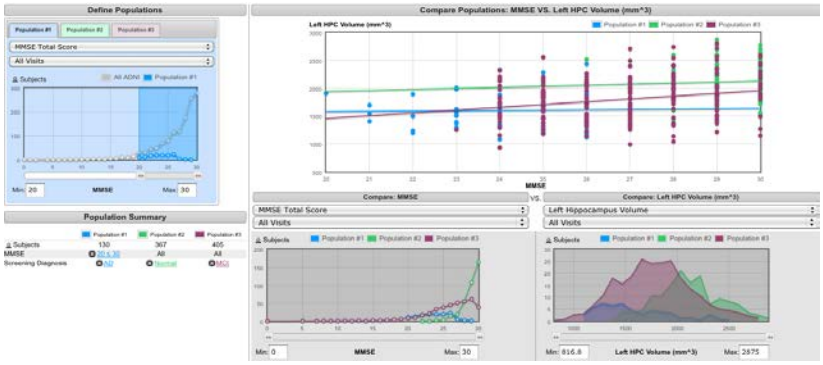

Figure 4. The Visualization interface allows investigators to define cohorts and compare clinical and biomarker data among them, helping bring to light trends and correlations.

1. Ask the Experts Knowledgebase: Users may pose questions to any of the ADNI cores through the Ask the Experts forum. Email distribution lists route questions to the appropriate core(s). Answers provided by each core's experts become part of the knowledgebase that all users may access, thus building a comprehensive, expanding base of knowledge built upon the expertise drawn from all of the ADNI cores.
2. Searchable data dictionary: The combined contents of the ADNI 1, ADNI GO and ADNI 2 data dictionaries are accessible via an online search system. This provides investigators with a useful tool to ascertain whether specific data were collected and if so, in which dataset(s) they may be found. This resource provides immediate, public access to the contents of the ADNI database allowing novice and advanced users to quickly and easily find data of interest to their research activities.
3. RSS Service: Investigators can subscribe to receive news updates via RSS.

In 2013 the Informatics Core PI, Arthur Toga, and the Laboratory of Neuro Imaging successfully moved from UCLA to USC from where the ADNI Informatics Core currently operates.

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