OVERVIEW

A glossary of commonly used abbreviations in this application is provided here.

Grants:

DIAN Dominantly Inherited Alzheimer Network (this application); the database for this Network is the DIAN Central Archive (**DCA**)

ACS Adult Children Study program project (P01 AG026276; JC Morris, PI) to study antecedent biomarkers of Alzheimer's disease

FACS Familial Adult Children Study (P01 AG026276-S1), supplement to the ACS to enroll presymptomatic children of parents with a causative mutation for Alzheimer's disease (led by R. Bateman)

ADRC Alzheimer Disease Research Center (P50 AG05681; JC Morris, PI)

HASD Healthy Aging and Senile Dementia program project (P01 AG03991; JC Morris, PI)

ADNI Alzheimer Disease Neuroimaging Initiative (U01 AG24904; MW Weiner, PI), a consortium to evaluate imaging and biomarker changes in Alzheimer's disease; DIAN uses ADNI protocols

ADNI-NPC ADNI Neuropathology Core (U01 AG24904S1), established in 2007 and led by JC Morris and NJ Cairns

ADCS Alzheimer Disease Cooperative Study (U01 AG10483; PS Aisen, PI), a consortium to advance treatment trials for Alzheimer disease; the ADCS serves as the clinical core for ADNI and also will serve as the DIAN Clinical Coordinating Center (**CCC**)

NACC National Alzheimer's Coordinating Center (U01 AG016976, W Kukull, PI), the data repository for the federally funded Alzheimer's Disease Centers (**ADCs**)

Definitions:

DAT Dementia of the Alzheimer type, clinically diagnosed AD syndrome

AD Alzheimer's disease, the histopathological disorder

ADAD Autosomal Dominant Alzheimer Disease, defined by family history and validated by known causative mutations for AD

Preclinical AD Histopathological AD in cognitively normal individuals (i.e., in the absence of even mild cognitive impairment, or **MCI**)

Aβ amyloid-beta protein, a 38 to 43 amino acid product of the amyloid precursor protein

***APOE*/ApoE** The gene and protein, respectively; the ε4 allele polymorphism increases AD risk

PSEN1 The gene most commonly mutated in ADAD (~164 pathogenic mutations)

PSEN2 A homologue of *PSEN1,* ~10 pathogenic mutations causing ADAD

APP The gene for amyloid precursor protein with ~28 pathogenic mutations causing ADAD

Procedures:

UDS Uniform Data Set, the clinical and cognitive batteries in use at all federally-funded ADCs for the standard and uniform longitudinal assessment of nondemented individuals and those with MCI and DAT

CDR Clinical Dementia Rating, staging instrument for dementia severity

LP Lumbar puncture

MRI Magnetic resonance imaging

PET Positron emission tomography

PIB Pittsburgh Compound-B, a [^{11}C] benzothiazole amyloid imaging agent

FDG [^{18}F]fluorodeoxyglucose

A. SPECIFIC AIMS

This U01 application is in response to RFA-AG-08-002 to establish an "international network for identification, evaluation, and follow-up of families with early-onset dominantly inherited Alzheimer's disease." Although dominantly inherited Alzheimer's disease (AD) represents less than 1% of all cases of AD, it is an attractive model for study because the responsible mutations have known biochemical consequences that are believed to underlie the pathological basis of the disorder. The opportunity to determine the sequence of imaging and biomarker changes in presymptomatic gene carriers who are destined to develop AD may reveal critical information about the pathobiological cascade that culminates in symptomatic disease. Because the clinical and pathological phenotypes of dominantly inherited AD appear similar in many respects to those for the far more common late-onset "sporadic" AD, the nature and sequence of brain changes in autosomal dominant AD (ADAD) also may be relevant for late-onset AD. However, ADAD individuals are limited in number and are geographically dispersed worldwide. Research efforts with this population have been limited

to a few academic centers, each studying relatively small numbers of individuals with site-specific protocols. A multi-center, systematic effort to identify individuals with ADAD and enroll them in a patient registry larger than any single site can accomplish has yet to be realized. Moreover, current differences in assessment protocols, collection methods for imaging and biomarker data, and assays used by individual sites often preclude direct comparison of research findings. There thus is an urgent need to develop a worldwide ADAD network and establish a central repository of harmonized clinical, cognitive, imaging and biological data and samples obtained from ADAD individuals. This application to establish a Dominantly Inherited Alzheimer's Network (DIAN) directly addresses these needs.

We will test three major hypotheses in this application. First, we hypothesize that there is a period of preclinical (presymptomatic) AD in individuals who are destined to develop dementia (mutation carriers) that can be detected by changes in biological fluids and in neuroimaging measures in comparison with individuals who will not develop dementia (noncarriers). Second, because all identified causative mutations for AD affect the normal processing of amyloid precursor protein (APP) and increase brain levels of $A\beta_{42}$, we hypothesize that the sequence of preclinical changes initially will involve $A\beta_{42}$ (reduced levels in CSF), followed by evidence for cerebral deposition of $A\beta_{42}$ (amyloid imaging), followed by altered cerebral metabolic activity (functional imaging), and finally by regional atrophy (structural imaging). Clinical and cognitive changes also may occur. Finally, we hypothesize that the phenotype of symptomatic ADAD is similar to that of late-onset "sporadic" AD.

We propose the following specific aims to test these hypotheses:

1. Establish an international, multicenter registry of individuals (mutation carriers and noncarriers; presymptomatic and symptomatic) who are biological adult children of a parent with a known causative mutation for AD in the *APP*, *PSEN1*, or *PSEN2* genes in which the individuals are evaluated in a uniform manner at entry and longitudinally thereafter with instruments to include:
   a. The clinical and cognitive batteries that comprise the Uniform Data Set (UDS) of the ADCs, to be supplemented by the development of web-based neuropsychological tests.
   b. The ADNI structural, functional, and amyloid imaging protocols.
   c. In accordance with the ADNI protocols, collection of biological fluids (blood; CSF) for DNA analysis and assays of putative biomarkers of AD, including $A\beta_{42}$ and tau.
   d. Uniform histopathological examination of cerebral tissue in individuals who come to autopsy.
2. In presymptomatic individuals, compare mutation carriers and noncarriers to determine the order in which changes in clinical, cognitive, neuroimaging, and biomarker indicators of AD occur prior to the occurrence of dementia.
3. In symptomatic individuals, compare the clinical and neuropathological phenotypes of ADAD to those of late-onset "sporadic" AD (using the data sets established by ADNI and by NACC).
4. Maintain the DCA, an integrated data base incorporating all information obtained from individuals in the registry to permit analyses within, between, and among the various data domains and also to disseminate the data to qualified investigators in a user-friendly manner.
5. Provide genetic counseling to all DIAN participants and, for those who after counseling wish to learn their mutation carrier status, provide genetic testing by Clinical Laboratory Improvement Amendments-approved laboratories.

Washington University serves as the Coordinating Center (Administrative Core) for this U01 application; it also will serve as a performance site. Based on factors such as access to adequate numbers of individuals from ADAD families, experience with ADNI and other imaging and biomarker protocols, and commitment to the goals of this proposal, six other performance sites were selected to join DIAN: Brigham and Women's Hospital/Massachusetts General Hospital/Brown University Consortium (R Sperling, site leader); Columbia University (R Mayeux, site leader); Indiana University (B Ghetti, site leader); University of California, Los Angeles (J Ringman, site leader); University College of London, Institute of Neurology (M Rossor, site leader); and the Australian Early Onset AD Collaboration (P Schofield, site leader). Total enrollment from the 7 performance sites into the DIAN registry will be 240 ADAD individuals (50% mutation carriers, 50% noncarriers); we estimate that from the status of individuals currently enrolled at the sites about 80% will be without cognitive symptoms (e.g., before the age of onset of dementia for their family) and 20% will be symptomatic. We anticipate including additional sites after DIAN is established.

ADDENDUM: Budgets for all components of this application are based on the award limits provided in the RFA. These limits constrained the number of performance sites that could be included and the number of ADAD individuals to be enrolled; they also resulted in insufficient cost coverage for some of the work to be performed (e.g., processing of blood samples by the Genetics Core in Budget Year 04). The Principal Investigator (PI) of the application ensures that all the work proposed will be completed. In this regard, the PI

has secured commitments from an anonymous foundation to supplement the National Institute on Aging (NIA) award with an additional $600,000 over the initial 3 years of the DIAN grant, if it is awarded (see Letter from M Morton) and from GE Healthcare to assist with hardware, software, and personnel resources in the interpretation of imaging data (see Letter from S Sirohey). Both of these commitments were received just days before the application was submitted and well after the budget for this application was finalized. **Thus, the benefits they will bring to DIAN are not reflected in the application other than here.** However, the supplemental funds provided by the foundation not only will optimize the completion of all proposed work but also will permit the enrollment of an additional 60 ADAD participants into DIAN, for a total sample size of 300. These commitments represent appreciation of the invaluable insights about AD to be gained from DIAN and testify to the ability of the PI to ensure the success of this initiative.

B. BACKGROUND

B.1. Rationale for DIAN at Washington University

Investigations of AD at Washington University began in 1979 with a longitudinal study of "senile dementia" in comparison with healthy aging (R01 MH 31054) that evolved in 1984 into the HASD program project grant that addressed the clinical, cognitive, behavioral, and biomedical correlates of AD in its mildest symptomatic stages in comparison with nondemented aging. The ADRC was awarded in 1985 and like HASD has been continuously funded by the NIA. Results from a series of careful clinicopathological studies led by JL Price and the PI of this application led to the hypothesis that AD is characterized by a long preclinical period where cerebral changes gradually accumulate and eventually result in DAT. The preclinical AD hypothesis is based on the observation that up to 40% of nondemented individuals 75 years or older have neuropathologic AD.[1] These individuals do not manifest cognitive impairment or decline[2] and have little or no neuronal loss in brain areas vulnerable to AD, such as the entorhinal cortex.[3,4] When the earliest symptoms of AD appear, at a stage characterized elsewhere as "mild cognitive impairment", or MCI, there already is substantial loss of neurons in layer II of the entorhinal cortex and in CA1 of the hippocampus.[4] We interpreted these findings as consistent with a preclinical stage of AD in which lesions develop in the brain many years before symptoms occur. When densities of amyloid plaques and neurofibrillary tangles reach a threshold, operate over a sufficient period of time, and/or are triggered by unknown factors, neuronal[4] and synaptic[5] degeneration occurs and the earliest symptomatic stage of AD is expressed.[6] The importance of this hypothesis is that by the time DAT can be detected, even when symptoms are so mild that they fail to meet criteria for MCI,[7] substantial neuronal damage already is present. It is possible that, to be truly effective, potential "disease-modifying" therapies now in development will need to be introduced prior to the substantial loss of neurons and before DAT, MCI, or even preMCI can be diagnosed. To identify the preclinical stage of AD, biomarkers are needed.

The current funding cycle (Jan 2004-Dec 2008) of HASD is devoted to the evaluation of biomarkers that occur antecedent to the appearance of cognitive deficits. The clinical, cognitive, neuroimaging, and biochemical features identified in previous funding cycles that distinguish very mild DAT from nondemented aging now are being evaluated in cognitively healthy older adults to determine their prevalence and predictive ability for the development of DAT during longitudinal follow-up. Potential antecedent biomarkers being investigated include the absence of a learning effect on serially administered neuropsychological tests,[8] measures of attentional control,[9,10] volumetric and shape changes in whole brain, medial temporal lobe, and other brain structures as determined by MRI,[11-14] evidence of cerebral amyloid deposits with PET PIB,[15] and changes in CSF levels of relevant proteins, including Aβ and tau.[16,17] Preliminary work has shown that several of these biomarkers appear to identify those nondemented older adults who will develop DAT within a few years.[11,13,18] It is unknown when during the lifespan these biomarkers can be detected or the sequence in which they occur. Determining these aspects will notably improve understanding of the earliest pathogenesis of AD and the temporal course of the resulting molecular, cellular, and biochemical abnormalities.

B.2. Principal Investigator

John C. Morris, MD, is the PI for DIAN. He successfully leads the ADRC and the two program projects, HASD and ACS, that are the "parents" of the DIAN application. He is recognized for his clinical research in AD (over 250 peer-reviewed publications) and for his ability to harmonize the clinical evaluation of DAT across multiple sites and investigators. He was the Clinical Task Force leader for the Consortium to Establish a Registry for Alzheimer's Disease (CERAD; U01 AG06790) and developed and implemented the Clinical Assessment Battery across all participating CERAD sites for uniform administration.[19] He standardized the Clinical Dementia Rating (CDR) for multicenter studies and trained and certified all ADCS investigators in its use.[20] To address the heterogeneity in assessment protocols at the ADCs, the NIA convened a Clinical Task Force (CTF) in 2002 and appointed Morris as Chair. The CTF, working closely with NACC, developed assessment procedures to characterize individuals with mild AD and MCI in comparison with nondemented

aging. This common set of standardized clinical and cognitive data elements is the UDS[21] and since 2005 is collected longitudinally in a uniform manner at all ADCs (over 12,500 individuals assessed with the UDS have been contributed to the NACC database). The UDS has detailed guidelines for administration and standard definitions and terminology as well as training protocols for clinicians and neuropsychologists.

Morris also is recognized for his scientific leadership abilities. He chairs the External Advisory Committees for 10 of the 29 ADCs, as well as for several program projects and R01s that address aging and dementia. He recently completed two terms as a Director for the National Alzheimer's Association and currently serves on its Medical and Scientific Advisory Council. He serves on the Steering Committee for NACC. In 2007 he completed a 6-year term as Editor-in-Chief for *Alzheimer's Disease and Associated Disorders*. He is a member of the NIA's National Advisory Council on Aging and chairs its Working Group on Program. Dr. Morris' record of scholarly contributions, effectiveness in standardizing clinical assessments for AD across large multi-site studies, and leadership experience demonstrate his ability to lead DIAN.

C. PRELIMINARY STUDIES

C.1. ACS/FACS

To address the chronology and order of preclinical changes, we recently initiated the ACS program project. This study examines potential clinical, cognitive, genetic, imaging, and biochemical indicators of AD in cognitively normal individuals, age 45y-74y, in two groups: those with a parent with AD (age of onset before 80y) and those for whom neither parent had AD (lived to at least 70y). The ACS participants are assessed longitudinally; structural neuroimaging, PET PIB, and CSF are obtained in all participants. Implementation of the ACS was facilitated by the existing ADRC and HASD infrastructure and leadership. (The organization and interrelationships of these three grants is provided in the Appendix.) All have similarly structured administrative, clinical, data management and biostatistical, and neuropathological components led by the same investigators, ensuring consistency and stability across the entire program. Moreover, participants in all three grants are assessed with identical protocols, administered in a uniform manner, to facilitate comparison of data derived from the separate cohorts. The ACS has benefited from the environment provided by the ADRC and HASD: we anticipated completion of enrollment (n=240) by the end of Budget Year 3, but from initial funding on 9/30/05 through 10/1/07 already 208 participants have been enrolled. Of these, 157 have completed their LP with the remainder to be scheduled.

The ACS correlates longitudinal data from several different biomarker modalities. Positive cerebral cortical PIB binding, even in cognitively normal individuals,[15] correlates remarkably well with low CSF levels of $A\beta_{42}$, indicating that this CSF biomarker is a sensitive and specific marker for the presence of cerebral amyloid deposits.[17] In cognitively normal individuals followed longitudinally, CSF biomarkers predict the development of DAT.[18] ACS participants also have contributed to proteomic approaches to identify novel candidate biomarkers for AD[22] and to the use of CSF biomarkers to identify novel genetic risk factors for AD.[23]

A supplement to the ACS has been awarded and establishes our Familial Adult Children Study (FACS) that extends the ACS in two important ways: 1) it selectively recruits and enrolls members of kindreds with dominantly inherited AD with a known causative mutation; and 2) its adds an innovative analysis of the fractional rates for the synthesis and clearance of $A\beta_{42}$ (and other CSF proteins) in humans.[24]

As noted in **Core B: Clinical**, 6 presymptomatic individuals from a kindred with a *PSEN1* mutation traveled to St. Louis within the past 12 months to inaugurate the FACS. All 6 completed the comprehensive assessment protocol proposed for DIAN, including clinical and cognitive assessments, blood draw for DNA, MRI, PET PIB, and LP for CSF assays (one individual was excluded from LP because of spina bifida). Although they did not have FDG PET, the 5 individuals eligible for LP underwent the hourly collection of CSF (through an indwelling lumber catheter) and blood over 36 hours to measure Aβ production and clearance in the central nervous system.[24] The willingness of these individuals to undergo all assessments, requiring a 4-day visit to Washington University, is typical for members of ADAD kindreds in our experience. An earlier study at our ADRC involving clinical and cognitive assessments, MRI, and LP for CSF assays in another ADAD kindred had a participation rate of 96% (27 completers of 28 eligible family members).

The ACS and subsequently the FACS supplement are directly descended from HASD and ADRC (see organizational chart in the Appendix). The overarching goal is to identify indicators and biomarkers of AD in cognitively normal individuals, and the unique ACS cohort permits an exploration of whether these markers may occur even many years before the onset of DAT. We are successfully addressing the relevant issues and developing the appropriate methods and procedures to identify antecedent biomarkers of AD. We recognize the potential power (as well as the appropriate cautions) of extending these studies to ADAD individuals. Our experience with the ACS/FACS, and the supportive infrastructure provided by the ADRC and HASD, ideally position us to respond to the RFA-AG-08-02.

C.2. Washington University experience with ADAD

The PI is experienced with the identification of and characterization of dominantly inherited dementias and related genetic studies. [25-35] The leader of the DIAN **Core F: Genetics**, Alison Goate, reported the first causative mutation for ADAD.[36] The ADRC's Genetics Core, led by Dr. Goate, was formally established in 2001 and has obtained DNA samples and ApoE genotypes in over 3000 individuals (including from ADRC participants). It sequences the major dementia-causing genes for mutations and polymorphisms from many individuals in families with autosomal dominantly inherited dementia, including perhaps the largest *PSEN1* kindred yet identified.[37,38] The Genetics Core follows the largest known kindred of frontotemporal lobar degeneration[34] and has pioneered the use of CSF biomarkers as an endophenotype to identify novel mutations in an ADAD kindred followed by the ADRC's Clinical and Genetics Cores.[23] Drs. Morris and Goate have worked and published together since 1994 and continue to do so.[23,35]

C.3. Interactions and Protocols

C.3.a. The leadership of the DIAN components is shown in Figure 1(Appendix). The DIAN core leaders and the PI have worked productively together for years in the ADRC, HASD, and now ACS/FACS. Drs. Holtzman and Goate, Associate Directors for DIAN, also are Associate Directors for the ADRC and meet weekly with Dr. Morris and the Executive Director, Dr. Buckles, to monitor and discuss programmatic and scientific issues. This meeting will be extended to include DIAN. The DIAN Associate Directors and Core leaders are members of the ADRC Executive Committee which meets formally with Dr. Morris every 2 months. In practice, Dr. Morris interacts at least weekly with each DIAN Core leader for both administrative and academic purposes. The Washington University ADRC is recognized for its tradition of intramural collaboration, as these recent publications attest.[15,18,34,39-42]DIAN will follow the ADRC model of a highly interactive, interdisciplinary team.

C.3.b. The Washington University ADRC is recognized also for its extramural collaborations. Table 1 (Appendix) shows our current tissue sharing record for external investigator-initiated projects. Tissue also is provided to multicenter studies, including those led by Richard Mayeux (Columbia University; LOAD Genetics Initiative) and the National Cell Repository for Alzheimer's Disease (NCRAD). The ADRC also participates in the ADCS and ADNI (the initial ADNI participant was enrolled at our ADRC). As of October 1, 2007, the ADRC had contributed to the NACC database 636 Initial Visit UDS Packets (second highest among the 29 ADCs) and 317 Follow-up Visit UDS Packets (highest).

The ADRC offers public access to its clinical and imaging data from over 600 ADRC participants processed with the software platform, Extensible Neuroimaging Archive Toolkit (XNAT; www.xnat.org). This open source application and related public data sharing projects, including OASIS (www.oasis-brains.org), make available structural neuroimages from individuals with and without AD (See **Core H**: **Informatics**) and have notably stimulating research outside of Washington University (see Letters from M Greicius and R Buckner). Our commitment to extramural collaboration and data sharing will carry forward to and benefit DIAN.

C.3.c. The leader of each performance site will serve on the DIAN Steering Committee and thus will play key roles in decisions about the definitions, procedures, and measures to be used in DIAN, monitoring its progress, and coordinating its work. Subcommittees will support the Steering Committee and all site leaders will actively engage in this work. Three key Subcommittees will be led by DIAN investigators outside of Washington University: Richard Mayeux, Datasharing and Publication Subcommittee; Bernandino Ghetti, Expansion Subcommittee; and Martin Rossor, Participant Liason and Protection Subcommittee. The Steering Committee and the Subcommittees are further described below in **D. Methods**.

C.3.d. The full UDS is included in the Appendix for **Core B: Clinical**. The clinical and cognitive measures in the UDS are listed in Tables 2 and 3 (Appendix). The UDS has several attributes to recommend its use as the basic clinical and cognitive instrument for DIAN. These attributes include: 1) It already has been adopted by five DIAN performance sites (Brigham and Womens Hospital, Columbia University, Indiana University, UCLA, and Washington University) and is in use as their standard clinical assessment instrument for nondemented control individuals and persons with MCI and mild AD; 2) The UDS has versions for both initial and follow-up visits; 3) The UDS incorporates standard definitions for dementia and clinical diagnostic criteria for MCI, AD, and other dementias; 4) It includes an informant interview to ascertain whether an individual's cognitive, behavioral, and functional abilities have declined from previously attained levels, which may allow the detection of intraindividual decline even prior to the demonstration of objective cognitive deficits, especially in highly educated and high functioning individuals;[43] 5) It capitalizes on commonly used measures and scales; 6) It provides an experienced clinician with sufficient information to determine the presence or absence of dementia and, when present, its probable cause or causes; and 7) Detailed guidebooks and training protocols

have been developed and implemented to ensure that the UDS data are collected in a standard and uniform manner across all sites. (See Letter from W. Kukull)

The UDS will facilitate comparison of the clinical phenotype and course of ADAD in comparison with late-onset "sporadic" AD as typically evaluated in the ADCs. Younger ADC participants also have been evaluated with the UDS; for example, 202 individuals below the age of 60 years have been administered the immediate and delayed recall measure from the Wechsler Memory Scale-Revised in the UDS neuropsychological battery. As noted in **Core B: Clinical**, the UDS will be supplemented with additional measures to more stringently assess cognition in the younger DIAN cohort.

Yet another advantage for the UDS is that it has been translated into Spanish. The Spanish UDS has been implemented in the ADCs since April 2007. Two DIAN performance sites (Columbia University; UCLA) have large numbers of Spanish-speaking ADAD individuals. DIAN will initiate operations with English-speaking individuals to simplify its start-up, but once it is established the UDS will enable the enrollment of Spanish-speaking ADAD persons.

C.3.e. ADNI serves as a tremendously important resource for DIAN (see Letter from MW Weiner). The 5 US DIAN sites also are ADNI sites and thus already have been certified on the ADNI protocols. ADNI's standardization, start-up process, and qualification will be extended to the non-US sites under the direction of ADNI for DIAN image data (see **Core G: Imaging** and the subcontracts with ADNI leaders C Jack for MRI, R Koeppe for PET, and C Mathis for [^{11}C]PIB). Moreover, ADNI will perform continuous quality control for DIAN on the MRI and PET images. The image data will be collected using existing ADNI protocols. The DIAN data thus will represent the standards in the field and will be directly comparable with ADNI data.

The collection of biological fluids (blood; CSF) will be in accordance with ADNI biomarker protocols (see **Core E: Biomarker**, and Letter from L Shaw and JQ Trojanowski), allowing the DIAN biomarker data to be directly comparable with ADNI data. The ADCS serves ADNI as its clinical coordinating center. DIAN has subcontracted with ADCS to perform similar duties for DIAN, including the coordination of all clinical and neuropsychological evaluations and monitoring the acquisition of imaging studies and collection of biological fluids at all DIAN performance sites. Specific duties include: 1) Develop clinical protocols, case report forms, and procedures manual (ADNI's clinical protocol is an extended version of the UDS, so this largely is accomplished); 2) Monitor the recruitment and retention of DIAN participants to meet goals; 3) Develop and approve regulatory documents at all DIAN sites; 4) Track collection of biological fluid samples (blood, CSF); 5) Assist in scheduling and tracking DIAN participants undergoing the imaging protocols; 6) Perform data entry and transfer of all clinical and cognitive data to DIAN **Core H: Informatics**; 7) Perform quality control on clinical and cognitive data; 8) Monitor the DIAN sites; and 9) Generate invoices for work performed at the DIAN sites.

C.3.f. ADNI also will provide DIAN sites with protocols developed by its Neuropathology Core (ADNI-NPC) for obtaining voluntary provisional consent for autopsy and will provide a uniform neuropathological assessment, using state of the art immunohistochemical methods, in accordance with standard diagnostic criteria for all DIAN participants who come to autopsy during the study period. <u>These neuropathological services will be provided at no cost to the DIAN budget</u>. This is possible because of ADNI's support for the DIAN initiative (see Letter of Support from MW Weiner), because the number of autopsied DIAN cases are expected to average fewer than 5 per year, and because the ADNI-NPC is led by Dr. Morris and Dr. Cairns, leader of **Core D: DIAN-Neuropathology Core**. The DIAN Neuropathology Core (DIAN-NPC) will be an extension of the ADNI-NPC. It will provide and implement training materials and protocols to assist each DIAN site in obtaining voluntary consent for autopsy in DIAN participants. Because individual DIAN sites differ in their neuropathological methods and application diagnostic criteria, thus precluding comparison of findings across sites, the DIAN-NPC will provide uniform neuropathological assessments and standard diagnoses in accordance with widely-accepted criteria. The DIAN-NPC assessment is in addition to (and will not interfere with) site-specific neuropathology evaluations. The DIAN-NPC will maintain a state-of-the-art resource for fixed and frozen brain tissue from the autopsied DIAN participants and facilitate the process wherein investigators may access the tissue and data for research purposes.

D. METHODS

D.1. Overall Approach

DIAN will study dominantly inherited AD in individuals for whom the diagnosis is certain (mutation carriers) in comparison with their noncarrier siblings, who serve as naturally occurring control group. Advantages of this cohort include the collection of relevant information and specimens from presymptomatic stages through symptomatic stages and the absence of confounding age-associated illnesses that may influence the onset and course of DAT. The value of the DIAN cohort will be enhanced because it will provide

a sample size larger than can be achieved by any site alone, because all DIAN participants will be assessed longitudinally with comprehensive and state-of-the-art clinical, cognitive, genetic, imaging, and biomarker protocols, and because all data will be collected in a standard and uniform manner for entry into a central repository. This research database will be harmonized with other databases (ADNI; NACC) that use methods and protocols identical to DIAN, and will serve to promote data sharing within and without DIAN.

DIAN will capitalize on existing programs, resources, and infrastructures to optimize the successful completion of its goals. We modeled DIAN on the ACS/FACS program project (which in turn is supported by our ADRC and HASD program project) that is successfully enrolling, evaluating, and following young and middle aged, cognitively normal individuals for antecedent biomarkers of AD. These individuals are at increased genetic risk for AD because they have an affected parent with DAT (ACS) or are a member of an ADAD kindred (FACS). We thus already developed, implemented, and gained valuable experience with the study design, assessment protocols, methods, and procedures proposed for DIAN.

DIAN is substantially supported by ADNI and ADCS. This support notably strengthens DIAN's goal to obtain data in a standard and uniform manner by providing clinical and cognitive monitoring of all DIAN sites, providing uniform neuropathologic assessments of autopsied DIAN cases, and extending the standardized procedures to image and biomarker data collection and quality control through established ADNI protocols.

DIAN will train and standardize all performance sites on the assessment and data collection protocols and their uniform administration. Following standardization, the sites will recruit, enroll, and follow individuals from ADAD kindreds to reach a total sample size of 240 individuals. Surveys of the DIAN performance sites indicate that over 400 DIAN-eligible participants presently are enrolled in site-specific research studies, and this pool will be targeted for recruitment to DIAN. As noted in **Core B: Clinical**, our experience is that ADAD individuals already participating in research are highly motivated and committed to completing even the comprehensive assessments, including LP, proposed for DIAN. We will also be able to identify and recruit ADAD individuals who learn of DIAN through its website and through our listing with eFAD on the Alz Forum (www.alzforum.org) (see Letter from J Kinoshita). Other potential organizations that can be used to aid recruitment include the NIA's Alzheimer Disease Education and Referral Center, the Alzheimer's Association, and Alzheimer-based research programs that are not current DIAN performance sites (see Letter of Support from T Bird). Many ADAD individuals who participate in research do not live in the city where the research program is based, but travel to the program for their assessments. Should these individuals also wish to participate in DIAN (without compromising the original program's research studies or causing undue burden on the participant), they would be eligible to do so and would only need to travel to a DIAN site.

Based on the DIAN survey, of the 400+ individuals currently being studied at the prospective DIAN performance sites, approximately 80% are cognitively normal (presymptomatic) and have yet to reach the age at onset (AAO) of their affected parent. The remaining 20% either have developed DAT (symptomatic) or remain cognitively normal past the parent's AAO. We anticipate that the DIAN cohort will be similar in composition (about 80% presymptomatic, 15-20% symptomatic). Given autosomal dominant inheritance, 50% of the presymptomatic sample will be mutation carriers and 50% will be noncarriers. Virtually all ADAD mutations are fully penetrant (penetrance in rare *PSEN2* mutations may be incomplete). Confirmation of a *PSEN1*, *PSEN2*, or *APP* mutation (or any additional ADAD-causing mutations that may be discovered) is required to avoid contamination by nonAD disorders that mimic the DAT phenotype.[44]

The follow-up interval will be determined by the age of the individual in relation to the parent's AAO. The follow-up scheme is a compromise between the intent to assess individuals more frequently as they approach the threshold of conversion from presymptomatic to symptomatic stages versus the burden on the participants (some will travel to a DIAN performance visit for a visit of several days to permit completion of protocols, necessitating arrangements to align vacation days, family obligations, and the like with the DIAN visit) and the finite resources available to DIAN. Also, because the age at which biomarker changes can be detected in individuals destined to develop AD is not known, it is important to include in DIAN some participants who may be decades younger than the AAO of their parent. The AAO within an ADAD kindred may vary widely. In a large Colombian kindred with a E280A *PSEN1* mutation, the AAO ranged from 35 to 62 years and varied as a function of genetic (ApoEε4 status) and environmental (educational level) factors.[38] Other mutations show a range for AAO from 5-15 years[45-47] and yet others (albeit generally those with small numbers of affected individuals) within 1-5 years.[33,48] For DIAN, we propose to use the affected parent's AAO as the index for the frequency of assessments as follows: 1) annual assessments for participants within 3(+/-) years of AAO; 2) assessments every 3 years for participants between >3-10 years younger than AAO; 3) assessments every 5 years for participants >10 years younger than AAO. Participants more than 3 years older than the parent's

AAO will be evaluated at 5y beyond the AAO. All participants not seen annually will have a yearly telephone interview; if concerns about cognitive decline are triggered, they will be converted to annual assessments.

The assessments at each visit are described in **Core B: Clinical**. All participants must complete the UDS clinical and cognitive assessments and (at entry) provide blood to remain active in the DIAN cohort. The other protocols (MRI, FDG PET, PET PIB, LP) are not mandatory but participation in them at each time of assessment will be strongly encouraged. Our experience with the ACS/FACS cohorts is that almost all of these individuals will complete all protocols, including at follow-up, if the rationale, risks, benefits and protections are carefully explained (and if there are no contraindications). DIAN will develop methods and materials for use at all sites to facilitate participation in these protocols. Similar methods used by ADNI in individuals with sporadic AD resulted in a voluntary rate of 60% for LP (versus the 25% expected), and almost certainly this rate will be higher in the committed DIAN participants.

All participants also will be encouraged to have independent genetic counseling (available at all performance sites) with costs to be covered by the grant. After counseling, should they choose to proceed to independent genetic testing, those costs also will be covered by DIAN. The DIAN informed consent, however, will clearly state that findings from the individual's research participation, including sequencing results, will not be provided.

We are prepared to address the consequences of disclosure of the diagnosis of DAT. We examined 90 ADRC participants (both demented and nondemented) and their collateral sources before and after ADRC diagnosis for changes in depression and anxiety. No significant changes in depression were noted for the participants or their companions, regardless of whether the diagnosis was no dementia (31%) or dementia (69%), even at the very mild stage elsewhere characterized as MCI. Anxiety was substantially reduced in all groups after disclosure of the diagnosis.[49] We also reviewed our experience since 1979 with catastrophic outcomes following disclosure of dementia diagnosis. Of 2883 participants (1127 men, mean age at entry=74 years), 2 men attempted suicide (1 was successful). Both were well educated, had preserved insight into their very mild DAT, and endorsed suicidality; neither meet criteria for depression.[50] Two suicide attempts in 28 years corresponds to a rate of 6 per 100,000 per year, notably less than the 2005 national annual rate of 32 per 100,000 for all men 65 years or older, as reported by the National Center for Health Statistics. Hence, although catastrophic responses to the disclosure of a dementia diagnosis can occur, they are quite rare in the ADRC setting.

DIAN will monitor participants and their families for behavioral and psychological consequences related to knowledge of mutation carrier status. Disclosure of genetic risk for familial cancer syndromes resulted in no change in measures of anxiety or depression for mutation carriers and reduced anxiety for noncarriers.[51] Factors associated with increased risk for a catastrophic event (suicide, suicide attempt, psychiatric hospitalization) after genetic testing for Huntington disease included a psychiatric history prior to testing and being unemployed; the rate of catastrophic events in 4527 participants was 1%.[52] A study of 251 persons at risk for autosomal dominantly inherited AD or frontotemporal dementia found that only 8.4% elected to proceed with genetic counseling and testing when it was offered; no psychiatric hospitalizations or suicides resulted in those who completed testing.[53] Based on these studies and our experience, it appears that disclosure of dementia diagnosis and of genetic test results can be successfully accomplished in the context of a supportive environment that offers ongoing follow-up and genetic counseling, as will be provided in DIAN. However, all DIAN investigators and clinicians will be trained in methods to communicate these results to participants and families and in the recognition of risk factors for possible catastrophic events. DIAN also will monitor potential long-term effects, including for marriage and family planning.

D.2. Variables of interest

The DIAN investigators, operating through the Steering Committee during the start-up phase of DIAN, will propose, discuss, and determine the specific variables to be examined in the study. Additional variables can be considered by the Steering Committee throughout the study as new knowledge is gained. Published data to guide DIAN in addressing its three major hypotheses are relatively sparse, as there have been few, if any, large-scale longitudinal studies of ADAD to evaluate whether antecedent biomarkers can be detected in mutation carriers (Hypothesis 1), determine whether the chronology and sequence of the appearance of biomarkers proceeds from biochemical abnormalities to cerebral amyloid deposition to cerebral hypometabolism to cerebral atrophy (Hypothesis 2), or assess the phenotypic comparability of ADAD with late-onset "sporadic" AD. A review of selected studies provides some basis to support examination of the following variables. Both cross-sectional and longitudinal analyses will be supported by DIAN, as change over time may provide predictive information even when absolute values are within the normal range.

1) Clinical and cognitive features

a) Onset and course: Comparison of early onset sporadic AD (below the age of 65 years) with late onset sporadic AD revealed no differences in gender distribution or duration of symptoms but found the early onset group to be better educated, perform more poorly on attentional measures, more likely to present with language impairment, and to have greater **rates of dementia progression**.[54,55] **AAO** is heterogeneous even for nondominant AD. The mean AAO for individuals (n=60) with *PSEN*1 mutations was 44 years (range: 30-69 years), for individuals (n=13) with an *APP* mutation was 49 years (range: 39-59 years), and for individuals (n=17) with a *PSEN2* was 59 years (range: 45-73 years).[56] **Time to death** averaged 10 years for *PSEN1*, 12 years for *APP*, and 11 years for *PSEN2* mutations. The **presenting symptom** for ADAD individuals typically is memory loss, but disturbances of mood behavior, and language may accompany the memory decline.[33,37] Other than AAO, the presenting clinical phenotype of ADAD often is indistinguishable from sporadic AD.[57]

b) Neurological features: **Myoclonus** and generalized **seizures**,[58,59] **pyramidal signs** including spastic paraparesis,[47,60]and **extrapyramidal dysfunction**[33] often develop during the course of ADAD.

c) Neuropsychology: Deficits on **cognitive measures** in symptomatic ADAD generally are typical of sporadic AD,[37,61]and feature impaired **verbal and nonverbal memory** as well as deficits in **verbal fluency**, **language** comprehension, **naming**, and constructional praxis. **Cognitive decline**, particularly in verbal memory, has been reported to occur 2-3 years before the appearance of symptoms in ADAD.[62] **Visuospatial impairment** has been demonstrated in presymptomatic *PSEN2* mutation carriers[63] and nondemented carriers of *PSEN1* mutations perform more poorly than noncarriers on measures of episodic memory, **executive function**, and visuospatial ability.[64]

2) Neuropathology: Although **Lewy body** pathology frequently accompanies ADAD,[33,65] the hallmark neuropathological features (**amyloid plaques, neurofibrillary tangles**) are similar in **density and distribution** between ADAD and sporadic AD.[66,67]

3) Imaging: **Hipppocampal and whole brain atrophy** develops before the appearance of symptoms in *APP* and *PSEN1* mutation carriers.[68,69] Presymptomatic ADAD individuals carrying *PSEN1* mutations demonstrate global **cerebral cortical hypometabolism**.[70] A 20 year old *PSEN1* mutation carrier (AAO for the family was 48 years) exhibited increased memory-related brain activity on functional neuroimaging.[71] Preliminary analysis from our study of a single presymptomatic mutation *PSEN1* carrier indicates increased **PIB retention** 10 years prior to AAO for the family (see Figure 4, **Core G: Imaging**).

4) CSF: Presymptomatic *PSEN1* mutation carriers, compared to neurological controls, had decreased **CSF levels of $A\beta_{42}$** 4-12 years before the age at which their parent developed DAT.[72] Other CSF proteins, including **tau and phospho-tau**, will be assayed.

5) Blood: In our experience with sporadic AD, **plasma levels of $A\beta_{40}$ and $A\beta_{42}$** have not been informative as preclinical biomarkers for AD [18] but other studies suggest more promise.[73,74] **Genetic variants**, including *APOE* and *SORL1,*[75]may influence AAO or other features of ADAD.

6) Other: DIAN will be prepared to incorporate novel markers as identified by emerging technologies, including microassay analysis of biological fluids.[76]

D.3. Governance

D.3.a. Steering Committtee

The PI, Associate Directors, Executive Director, Core Leaders, Dr. Weiner (ADNI), and all performance site leaders (n=7) will be joined by a bioethicist, an ADAD family representative, a representative from the Food and Drug Administration, and appropriate staff from the NIA to form the Steering Committee (SC) for DIAN. The bioethicist and family representative will be chosen from nominees suggested by the other members of the SC and with the approval of NIA staff. The SC has the responsibilities of governing DIAN, including finalizing the definitions, procedures, and measures proposed in this application. Once these are finalized, the SC will coordinate the development by the Cores and the Clinical Coordinating Center of the DIAN Manual of Operations to guide all DIAN functions and performance sites. The SC will designate Subcommittees to address specific topics and operations; a proposed initial roster of Subcommittees is shown in Table 4 (Appendix).

The proposed Tissue and Biospecimen Subcommittee will oversee the allocation and distribution of biological specimens generated by DIAN. This Subcommittee will establish procedures by which investigators can request access to the biospecimens and, with the PI and NIA staff, nominate members to form the Resource Allocation Review Committee (RARC). The RARC will be composed of individuals who are not directly involved with DIAN and have no relevant conflicts of interest. It will review applications for use of the DIAN biospecimens and provide their recommendation for approval or disapproval to the SC.

The SC will meet every 2 months (6 times a year). One meeting each year will be “face-to-face”. To minimize costs and inconvenience, whenever possible the face-to-face meeting will be held in conjunction with

another meeting that normally is attended by many DIAN personnel (e.g., International Conference on Alzheimer's Disease, annual meeting of the American Academy of Neurology). The other 5 meetings each year will be held by teleconference. Given the 15 hour difference in time zones between London and Sydney, we may need to alternate the inclusion of each site in the teleconferences. However, the site (London or Sydney) not included in a particular teleconference will be asked to comment and contribute to the agenda in advance of the meeting and will of course review the minutes. Dr. Aisen (ADCS) or another representative from the CCC will participate in the SC meetings. Matters requiring attention prior to a scheduled SC meeting will be addressed by electronic mail, telephone, or FAX.

D.3.b. External Advisory Committee

If DIAN is awarded, with the advice of the Steering Committee and NIA staff an External Advisory Committee (EAC) will be recruited by the PI. EAC members will be from outside the participating DIAN institutions and will be selected based on expertise relevant to the various Cores and functions of DIAN. The responsibilities of the EAC include visiting the DIAN Coordinating Center (Washington University) annually to evaluate progress, assess the effectiveness of communications among the DIAN components, and ensure that the conduct of the studies is of the highest possible quality. NIA staff will be invited to attend the EAC meetings, and DIAN investigators outside of Washington University will have the opportunity to participate in person or by teleconference. The EAC will generate a report of its findings each year.

D.4. Training and Standardization

Dr. Morris developed and implemented training and standardization meetings for clinicians and neuropsychologists at all ADCs in regard to the UDS,[21] and will coordinate the same training for DIAN sites who have not yet been standardized on the UDS. Similar training and standardization protocols have been developed and implemented by ADNI for its imaging and biomarker studies. The process by which non-ADNI DIAN sites will be qualified by the ADNI imaging subcontractors is discussed in **Core G: Imaging**. The non-ADNI sites also will be trained with the ADNI Biofluid Protocol for the collection, processing, and storage of biological fluids (**Core E: Biomarkers**). Procedures for quality control for DIAN data collection will be developed by the Steering Committee unless they already are in place (e.g., the CCC for clinical and cognitive data; image data through ADNI subcontractors).

The inaugural SC meeting will plan the Training and Standardization meeting for all performance sites. Clinicians, neuropsychologists, and study coordinators from each performance site, in addition to the site leader, will attend this meeting.

D.5. Data Access/Data Sharing

DIAN is committed to placing its clinical, cognitive, imaging, and biomarker data in the public domain where they will be available to qualified scientific investigators by a defined process and at time intervals to be determined by the SC, in accordance with NIH policy. The plan is discussed in **Core A: Administration**.

D.6. Interactions with other programs

We anticipate that DIAN will have a large impact. Many more institutions that could be accommodated budgetarily expressed interest in becoming as a DIAN performance site. Once DIAN is established and fully operational, the Expansion Subcommittee and the SC will consider how additional qualified sites worldwide may be included. Three major factors will need to be addressed: 1) the ability and willingness of the candidate site to adopt DIAN's standardized protocols for uniform administration to DIAN participants; 2) translation issues for languages other than English and Spanish; and 3) costs.

Although not a goal of the RFA, the DIAN cohort may be very attractive for the evaluation of potential therapies for AD. The possibility of clinical trials in DIAN with agents now in development already have been explored by several pharmaceutical companies preliminarily with the PI. The SC, working with the participant Liaison and Protection Subcommittee, will develop a process wherein formal proposals to conduct clinical trials or other studies in the DIAN cohort are evaluated and approved. Such proposals will need to be funded outside of the DIAN grant.

D.7. Timeline-The DIAN Timeline is provided at the end of **Core A: Administration**.

E. HUMAN SUBJECTS RESEARCH-Please see **Core B: Clinical** for the Human Subjects Research section.

F. VERTEBRATE ANIMALS – Not applicable

G. SELECT AGENT RESEARCH – Not applicable

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I. MULTIPLE PI LEADERSHIP PLAN – Not applicable

J. CONSORTIUM/CONTRACTUAL ARRANGEMENTS.

Five conventional subcontracts will be part of the DIAN organization:

1. Core A: Administration – Northern California Institute for Research and Education, to support effort of Dr. Michael Weiner in DIAN.
2. Core B: Clinical – University of California, San Diego, Dr. Paul Aisen, PI, to support the DIAN Clinical Coordinating Center

Core G: Imaging

3. Mayo Clinic-Rochester, Dr. Clifford Jack, PI, to support MRI image pre-processing services.
4. University of Michigan, Dr. Robert Koeppe, PI, to support PET image pre-processing services
5. University of Pittsburgh, Dr. Chester Mathis, PI, to support PET PIB problem-solving for sites inexperienced with PET PIB.

If DIAN is successfully funded, clinical performance contracts will be established on a per-participant payment basis with 6 institutions/consortiums to perform the DIAN evaluations. See Core A: Administration for more detail.

K. RESOURCE SHARING-See Core A: Administration for DIAN Resource Sharing Plan.

L. CONSULTANTS.-

Core A: Administration – To be determined Steering Committee and External Advisory Committee
Core B: Clinical – Dr. Susan Embretson
Core C: Biostatistics – Dr. John Rice
Core H: Informatics – Dr. Cynthia Csernanski