

OVERALL/OVERVIEW Specific Aims

ALERT: Introduction sections This application responds to PAR-13-147, which requires for each component a one-page Introduction with responses to the 2008 Summary Statement, separate from the Research Aims and Strategy sections. Electronic submission through the NIH ASSIST system is also required. However, the NIA ASSIST system will not permit the uploading of the Introduction pages. After consultation with John Hsiao, MD, NIA Program Officer for DIAN, and Ramesh Vemuri, PhD, Chief of the Scientific Review Branch at NIA, the Introduction pages for each component in this proposal are accessible to reviewers in the “Research and Related Other Project Information” under “Other Attachments” for each component. We regret any inconvenience reviewers may experience in accessing the Introductions.

This application continues to address the 3 original DIAN hypotheses (abbreviations are explained in Glossary in Strategy). First, AD biomarker changes will identify MCs many years before symptomatic AD develops, thus supporting the concept of preclinical AD. Second, the initial biomarker changes in the preclinical stage of ADAD will involve A β ₄₂, followed by changes related to neurodegeneration, followed by cognitive decline. Third, the clinical and neuropathological phenotypes of ADAD will be similar to, but not identical with, those of “sporadic” LOAD. Although data obtained in the initial budget period provide support for each of these hypotheses, all have yet to be confirmed with longitudinal data analyses. Hence, this application now emphasizes longitudinal data collection and analyses to truly appreciate how biomarkers change over time.

We will examine the hypotheses with the following Specific Aims:

1. Maintain the established international DIAN registry of individuals (MCs and NCs, symptomatic and asymptomatic) who are biological adult children of an affected parent with an *APP*, *PSEN1*, or *PSEN2* mutation causing AD and assess participants every 2 years with the uniform DIAN protocol.
2. Recruit to the registry 50 new asymptomatic participants, both MCs and NCs, in Year 1 of the next budget period to maintain the total DIAN cohort at ~250 individuals. These new participants will include those who are more than 15 years younger than the estimated age of symptomatic onset (EAO) to explore the earliest observable biomarker changes of preclinical AD.
3. Maintain the integrated DIAN database and biospecimen repository to disseminate data and tissue to qualified investigators (within and outside of DIAN) in a user-friendly manner and to permit analyses within, between, and among the various data domains that will include:
 - a. In asymptomatic MCs (using NCs as controls), determine the temporal ordering and rate of intraindividual change in clinical, cognitive, imaging, and fluid biomarkers of AD prior to EAO
 - b. In symptomatic MCs, compare the clinical and neuropathological phenotypes of ADAD to those of LOAD, using datasets such as ADNI (see Letter of Support from Michael Weiner).
4. Utilize the DIAN cohort and its database and biospecimen repository to support new scientific studies, including use of exome chip technology to examine potential modifiers of age at symptomatic onset (see Genetics Core). Other new studies that are funded independently of the DIAN grant but are conducted within the DIAN infrastructure at no cost to DIAN are discussed in the Approach section below.
5. Provide genetic counseling to any and all DIAN participants who wish to learn their mutation status and, for those who decide to learn their status after counseling, provide genetic testing by Clinical Laboratory Improvement Amendments (CLIA)-approved laboratories (i.e., outside of DIAN).

NOTE: Relationship between DIAN, DIAN-TU, and the Pharma Consortium.

Scientifically and budgetarily, this renewal application continues the recruitment, assessment, and longitudinal collection of clinical, cognitive, genetic, imaging, and fluid biomarker data and tissue from the unique DIAN cohort in this multisite observational study. Building on the many strengths of this cohort, the DIAN-TU was developed to design and conduct secondary prevention trials in individuals from ADAD families. Funding for the DIAN-TU is entirely **independent** of the DIAN observational study and includes support from the Alzheimer’s Association and the Pharma Consortium, a group of 10 pharmaceutical companies that contribute candidate drugs and expertise in precompetitive design for the DIAN-TU trials. The trials themselves are directly supported by the companies whose compounds were selected for the therapeutic trials (solanezumab and the BACE inhibitor, LY2886721, from Eli Lilly and gantenerumab from Roche). Although **DIAN-TU and the DIAN observational study are separate entities**, they work together to harmonize protocols and policies and to minimize interference of participants moving from the observational study to the trials and potentially back again. **There is no budgetary overlap between DIAN and DIAN-TU.** Although some personnel are shared between the 2 entities, each mechanism supports the percent effort it receives. Neither entity subsidizes the other. The Pharma Consortium highly values the DIAN observational study (data from DIAN were critical in designing the DIAN-TU trials) and commits to funding specific DIAN science initiatives (see Letters of Support).