Core E: Biomarkers Specific Aims

Alzheimer's disease (AD) will become a public health crisis in the near future if left untreated. There are currently no proven treatments that delay the onset or prevent the progression of AD, although several promising candidates are being tested. During therapy development, it will be critical to have biomarkers that identify individuals at high risk for AD in order to target them for clinical trials and to monitor therapy.

Fluid biomarker assessment in DIAN participants carrying autosomal-dominant AD mutations has yielded important insights regarding the estimated trajectories/timing of underlying AD pathologies, especially in the preclinical/asymptomatic stage. Notably, cross-sectional analyses of samples collected at baseline revealed elevated CSF tau and ptau181, markers of neurodegeneration and/or neurofibrillary tangles, 15 years prior to the estimated age of symptomatic onset (EAO -15). Low levels of CSF Aβ1-42, a marker of amyloid plaques, were observed in carriers 10 years prior to estimated symptom onset, but levels appear to decline much earlier (EAO -25) from levels initially higher than non-carriers (Bateman et al., 2012). Consistent with the known stimulatory effect of AD mutations on Aβ1-42 production, plasma Aβ1-42 levels were significant higher in carriers at all cross-sectional time points; however, they did not change as a function of EAO, suggesting plasma Aβ1-42 is not a marker of underlying disease pathology. Despite the fact that mutations account for <1% of AD cases, these cross-sectional data are consistent with models proposed for the more common late-onset form (LOAD). We hypothesize that continued analysis of samples collected from DIAN participants at defined points in their disease course, an assessment that is not possible in LOAD, will permit characterization of the timing of underlying disease processes during the preclinical period. The ultimate goal of the DIAN renewal is to determine the timing and pattern of biomarker trajectories within individuals over time, especially during the preclinical period. Such information will be critical for the design and evaluation of clinical trials intended to prevent the onset of cognitive decline in at-risk individuals.

In the present renewal application, we will build upon our success by continuing to collect and measure these core AD fluid markers in new and existing DIAN participants, as well as expand our panel to include two novel analytes that have recently shown robust diagnostic and prognostic utility in LOAD. Given the critical importance of within-subject analyses in the setting of a biomarker field challenged by limitations in assay stability and reproducibility, we propose an additional Core aim designed to optimize the analytical parameters of such longitudinal evaluations. The three Specific Aims of the current DIAN renewal include:

1. Maintain and grow the biorepository of DIAN plasma and CSF samples and coordinate the distribution of samples to qualified investigators for approved discovery studies. Serum will no longer be collected due to lack of scientific interest. Samples will be obtained at study entry for new recruits and at follow-up visits at defined intervals for all DIAN participants (specified in Core B). Biomarker Core (BM) functions will include sample receipt, processing, aliquotting, storage and inventory management. In addition, upon approval by the DIAN Resource Allocation and Steering Committees, the BM Core will implement sample selection (in collaboration with Cores B and H), shipping, tracking, inter-lab correspondences, and electronic database management functions that are required for sample distribution to qualified investigators.

2. Obtain fluid analyte measures for evaluation in DIAN cross-sectional analyses. Plasma will continue to be assayed for Aβ1-40, Aβx-40, Aβ1-42 and Aβx-42, and CSF for Aβ1-42, total tau, and ptau181 via bead-based multiplexed immunoassay. Two novel biomarker candidates showing diagnostic/prognostic utility in LOAD (CSF VILIP-1, a marker of neurodegeneration, and tau seeding activity in CSF and plasma) will also now be evaluated at no cost to DIAN (see Letters of Support from Drs. Ladenson and Diamond.

3. Develop and implement procedures for analysis of DIAN longitudinal fluid samples, including analytical protocols and quality control testing. CSF samples collected longitudinally within individual DIAN participants over time will be (re)analyzed for Aβ1-42, tau and ptau181 (and VILIP-1 and tau seeding activity, if promising) on the same assay plate at certain intervals. In collaboration with Core C, resultant biomarker trajectories will be compared to those estimated from the same samples evaluated in Aim 2 as cross-sectional measures. Thus, this standardization effort by DIAN will be a major contribution to quality control efforts worldwide.