Core D: Neuropathology Specific Aims

The **Dominantly Inherited Alzheimer Network-Neuropathology Core** (**DIAN-NPC**) will focus on undertaking a neuropathological assessment of all participants recruited to DIAN who come to autopsy in the 5 year period of this project. Clinical, genetic, neuropsychological, biochemical, and neuroimaging data obtained from DIAN will be correlated with the earliest changes in Autosomal Dominant Alzheimer Disease (ADAD). Although each participating DIAN center will undertake its own neuropathological assessment, each site uses different methods, fixation and staining protocols, and different diagnostic criteria. Therefore, to ensure **standardized methods and uniform assessment** of tissue, the DIAN-NPC will undertake processing and staining and apply uniform diagnostic criteria. From each autopsied individual, a uniform set of fixed blocks and frozen tissue will be forwarded to **DIAN-NPC** which will undertake systematic examination of tissue taken from standard brain areas according to the most recent published neuropathological diagnostic criteria. Using immunohistochemical methods to detect misfolded proteins, the distribution and severity of lesions will be assessed using computerized stereological methods and these data will be correlated with clinical, neuropsychological, and neuroimaging data. These studies will help us to assess the probability and rate that AD progresses within the brain. Using frozen brain tissue, biochemical methods will be used to investigate changes in protein solubility which may offer early and novel targets for therapeutic intervention. Using immunohistochemical and stereological methods the early changes associated with disease will be quantified. Together, these projects will define the earliest pathological and biochemical stages of AD in comparison with healthy brain aging and facilitate unparalleled clinicopathological studies. Thus, the **DIAN-NPC** will add value to those cases recruited and longitudinally assessed through the multi-centered DIAN. Until reliable biomarkers of disease progression are validated, the gold standard for the diagnosis of neurodegenerative diseases remains the neuropathological assessment of CNS tissue at autopsy. To achieve these goals, the aims of the **DIAN-NPC** are:

1. To obtain brain tissue at the time of death from all DIAN participants. Each center will undertake its own brain assessment and forward a standard set of fixed tissue blocks and frozen tissue to DIAN-NPC;
2. To undertake a thorough post-mortem CNS examination and establish a standard and uniform neuropathological diagnosis in each case;
3. To maintain a bank of unfixed frozen and fixed tissues from participants and distribute these samples to participating DIAN investigators and other approved investigators for research;
4. To maintain, with the DIAN Informatics Core, a database of demographic and neuropathological data including diagnoses and banked tissue;

NOTE: When resources permit, we aim also to assess family members of DIAN participants, but the focus of this Core is to assess participants who come to autopsy.