## Research Use Statement for Application for Genomic Data from NIAGADS

**Research Use Statement:**

Objective: We have developed a novel and powerful statistical approach to identify genetic variants associated with age-at-onset (AAO) or time-to-event traits. Here, we propose to identify genetic modifiers of AAO of Alzheimer's disease (AD) through genome-wide association testing in large data sets representing different ancestries, followed by replication studies in independent data sets.

Study design: Using the data requested from NIAGADS, we will use genotype imputation and association testing to fine-map loci identified by genome-wide association studies in independent data sets. We will also use these data to perform association testing, identifying variants associated with AD risk or AAO and evaluating their sensitivity to covariates such as *APOE* genotype, sex, and ancestry.

Analysis plan: Data from NIAGADS with be cleaned and aligned to the forward strand and same marker map. Additional genotype data will be imputed using the Michigan Imputation Server and reference data selected to best match the ancestry(s) represented in the data. Association testing will adjust for population structure and genetic relatedness. Variants of interest will be annotated using resources such as the Variant Effect Predictor and the Genotype-Tissue Expression project to facilitate the interpretation of association results. Pathway analyses may be used to better understand potential relationships between implicated genes and genes previously implicated in AD and related disorders. By identifying genetic modifiers of AAO, we will provide further insight into the biology of AD and nominate additional therapeutic targets.

## Non-Technical Summary for Application for Genomic Data from NIAGADS

This project applies novel and complex study design with existing genome-wide marker data to test for association between genotypes and either age-at-onset or risk of Alzheimer's disease. We will perform genome scans in large data sets representing diverse ancestries. We will use imputed genotype data within association signals to fine-map the location of variants associated with Alzheimer's disease. Association testing across independent data sets will be used to replicate these signals. We will use variant annotation to describe the potential relationships between implicated variants and gene function, regulation, and pathways. This work will nominate genes or regulatory regions as modifiers of age-at-onset of Alzheimer's disease or disease risk.