Research Use Statement

Analyzing postmortem phenotype and genomics data from ~1100 human brain samples with machine learning, Vivid Genomics, Inc., has developed prototype genetic biomarker assays that predict the presence of amyloid plaques, Lewy body pathology and cerebral amyloid angiopathy. The objective is to increase subject numbers with similar data available through NIAGADS and NACC, along with datasets from several individual academic centers, to further optimize and validate our assays for neurodegenerative/cerebrovascular lesion types including tau, TDP-43, hippocampal sclerosis and microinfarcts, and for predicting rate of cognitive decline. NIAGADS datasets requested are ADC1-7 and NG00041; data use limitations from these do not exclude our proposed usage. Outcome variables will include the following NACC data fields: SEX; HISPANIC; RACE; CDRGLOB; DECAGE; MMSE; MOCATOTS; NORMCOG; DEMENTED; NACCTMCI; ADMUT; PROBAD; NACCAGB; NACCNIHR; NPDAGE; NPBRWT; NPADNC; NPBRAAK; NPNEUR; NPDIFF; NPVASC; NACCINF; NPLINF; NPMICRO; NPOLD; NPLAC; NPSCL; NPAVAS; NPARTER; NPWMR; NPAMY; NACCLEWY; NPLEWY; NPPICK; NPCORT; NPPROG; NPPDXB; NPFTD; NPGENE; NPAPOE; NPTHAL; NPALSMND; NPFTDTDP; NPPDXP; NPPDXQ. We are targeting >3000 subjects in total to be used for optimization of this model. We will focus on SNP selection and test the effects of different analysis strategies: 1) changing SNP p-value cutoffs 2) using LD-filtered representative SNPs with full genome coverage 3) testing the value of stratifying by *APOE* genotype 4) determining if it is better to add other covariates including age and sex. A fraction of the genetic data (~30%) will be withheld for validation. Optimization is defined as an area under the curve (AUC) of 80% and positive predictive value (PPV) of 80%, as well as R^2 >0.75 for all assays. Values within 10% of this will be considered a successful validation. Through these assays, this project will benefit those suffering from Alzheimer's disease and other neurodegenerative disorders by increasing clinical trial efficiency through more precise subject selection and/or stratification.

Non-Technical Summary

Vivid Genomics is dedicated to developing genetic tests, typically done from DNA obtained from blood, that will predict, for any given older person, the likelihood that they have, or might develop when they become old, the characteristic brain changes of Alzheimer's disease as well as other brain changes that affect thinking in older people. These changes include amyloid or senile plaques, tangles or tau, amyloid angiopathy, Lewy bodies, TDP-43 pathology, hippocampal sclerosis and brain infarcts (strokes). The objective of this study is to improve upon initial tests developed by Vivid, and to also develop genetic tests to predict the rate at which older people's thinking ability decreases over time. To do this, Vivid Genomics requests human subject DNA analysis data stored at NIAGADS. The DNA analysis data will be compared to brain change and thinking progression data on the same human subjects through another NIH-funded agency, the National Alzheimer's Coordinating Center. Through these new genetic tests, Vivid hopes to benefit those suffering from Alzheimer's disease and other brain diseases of aging by allowing better selection of subjects for clinical trials of these diseases, which would increase the chances of clinical trials finding useful new treatments.