

Predicting Alzheimer's Disease Progression Using NULISAseq CNS Panel Proteomic Signatures

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Background

While the most common experience of Alzheimer's Disease (AD) progression is a gradual transition from Cognitively Normal (CN) to Mild Cognitive Impairment (MCI) and finally to AD, a significant number of patients convert rapidly from CN to AD or do not progress beyond MCI. With current Alzheimer's disease treatment being preventative, there is great interest in predicting the likelihood and rate of cognitive decline to better identify vulnerable individuals who would benefit most from treatment. This study used a data-driven approach to identify panels of blood biomarkers with the aim of improving prediction of AD conversion.

Methods

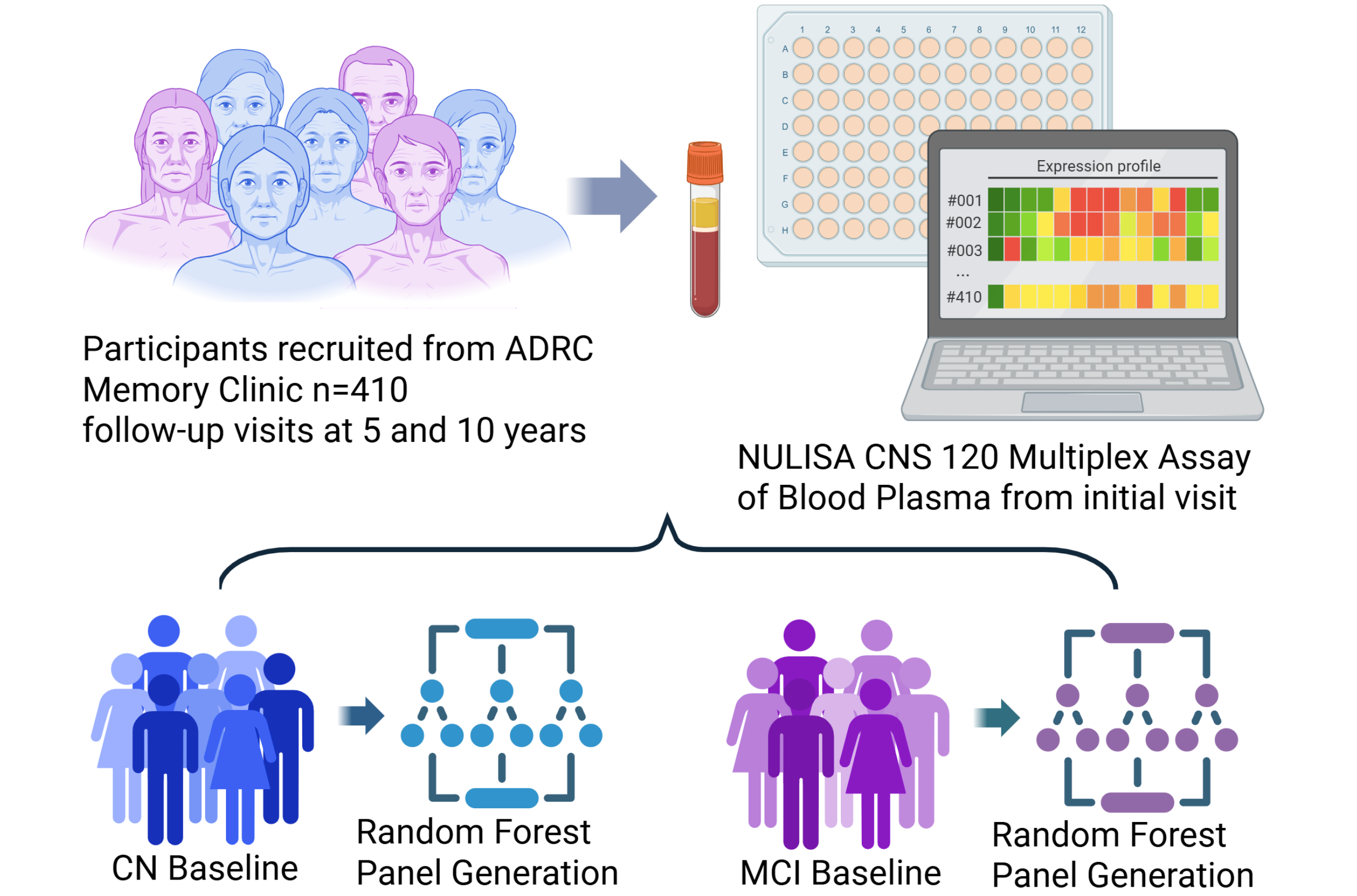
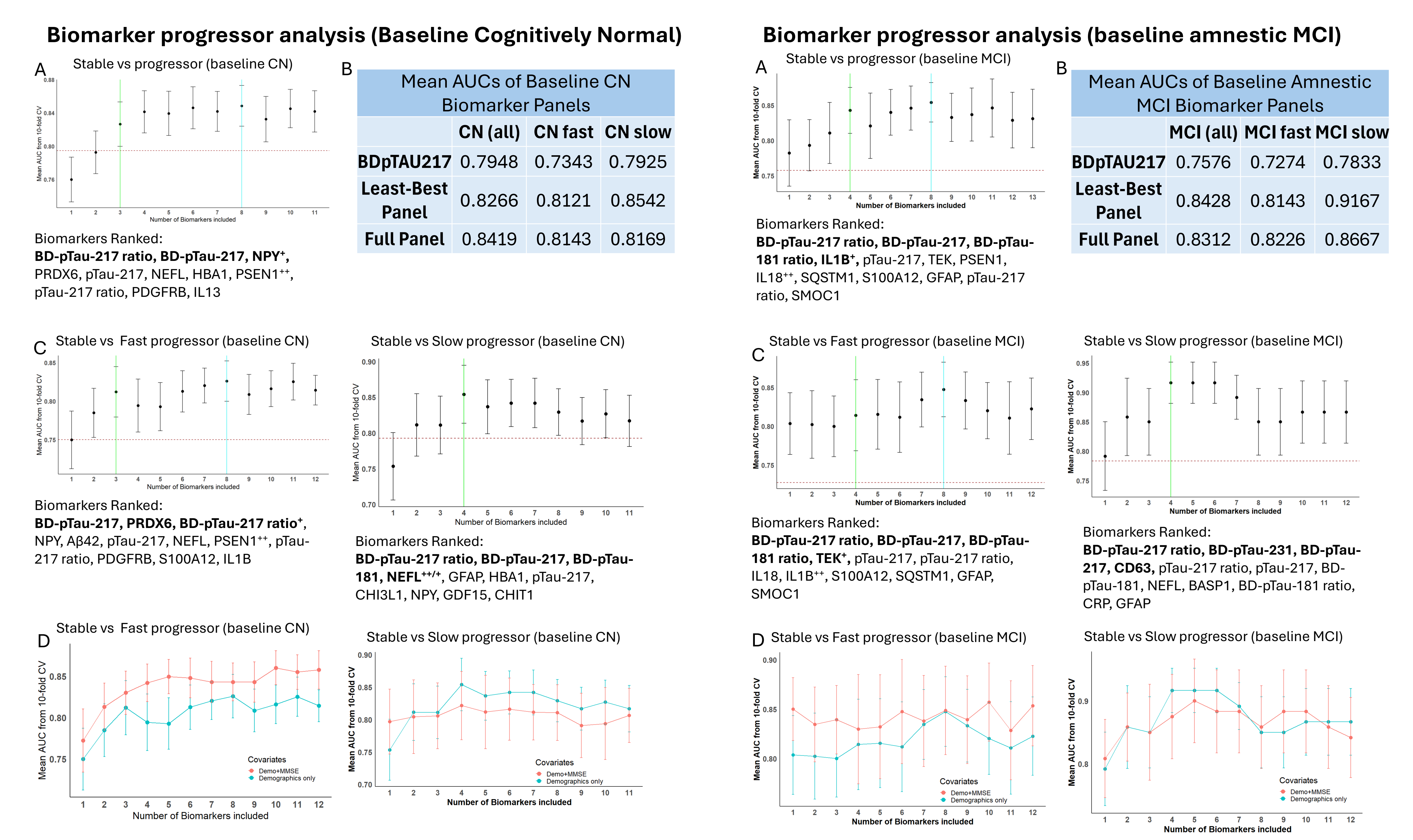


Figure 1. Workflow schematic of study, participants recruited from Alzheimer's Disease Research Center (ADRC) Memory Clinic n=410, patients were tracked through follow-up visits after 5 and 10 years. Plasma samples were analyzed using NULISA CNS Disease Panel 120. Patient data was grouped into baseline cognitively normal (CN) and baseline amnesic mild cognitive impairment (MCI) groups for comparison of progressor vs stable over ten years. Biomarkers were analyzed using random forest classification with 10-fold cross-validation and ranked by mean decrease in Gini. Biomarkers with the top ten Gini importance values were combined into panels. Panel AUC was calculated and least-best panels were determined. Baseline Groups were further divided into fast (≤ 5 years) and slow (5-10 years) progressors and panels were generated using the pipeline described above. Panel AUCs were then re-evaluated with Mini Mental State Examination (MMSE) included.

Baseline Cognitively Normal		Baseline Amnesic MCI	
Conversion status	# participants	Conversion status	# participants
CN $\rightarrow$ MCI ≤ 5 years	54	MCI $\rightarrow$ AD ≤ 5 years	140
CN $\rightarrow$ AD ≤ 5 years	15	MCI $\rightarrow$ non-AD ≤ 5 years	15
CN $\rightarrow$ non-AD ≤ 5 years	2	MCI $\rightarrow$ AD 5-10 years	21
CN $\rightarrow$ MCI 5-10 years	20	MCI $\rightarrow$ non-AD 5-10 years	1
CN to AD 5-10 years	20	Stable over 10 years	22
CN to non-AD 5-10 years	1		
Stable over 10 years	99		

Table 1 Number of participants in each progression status group

Results



Conclusions

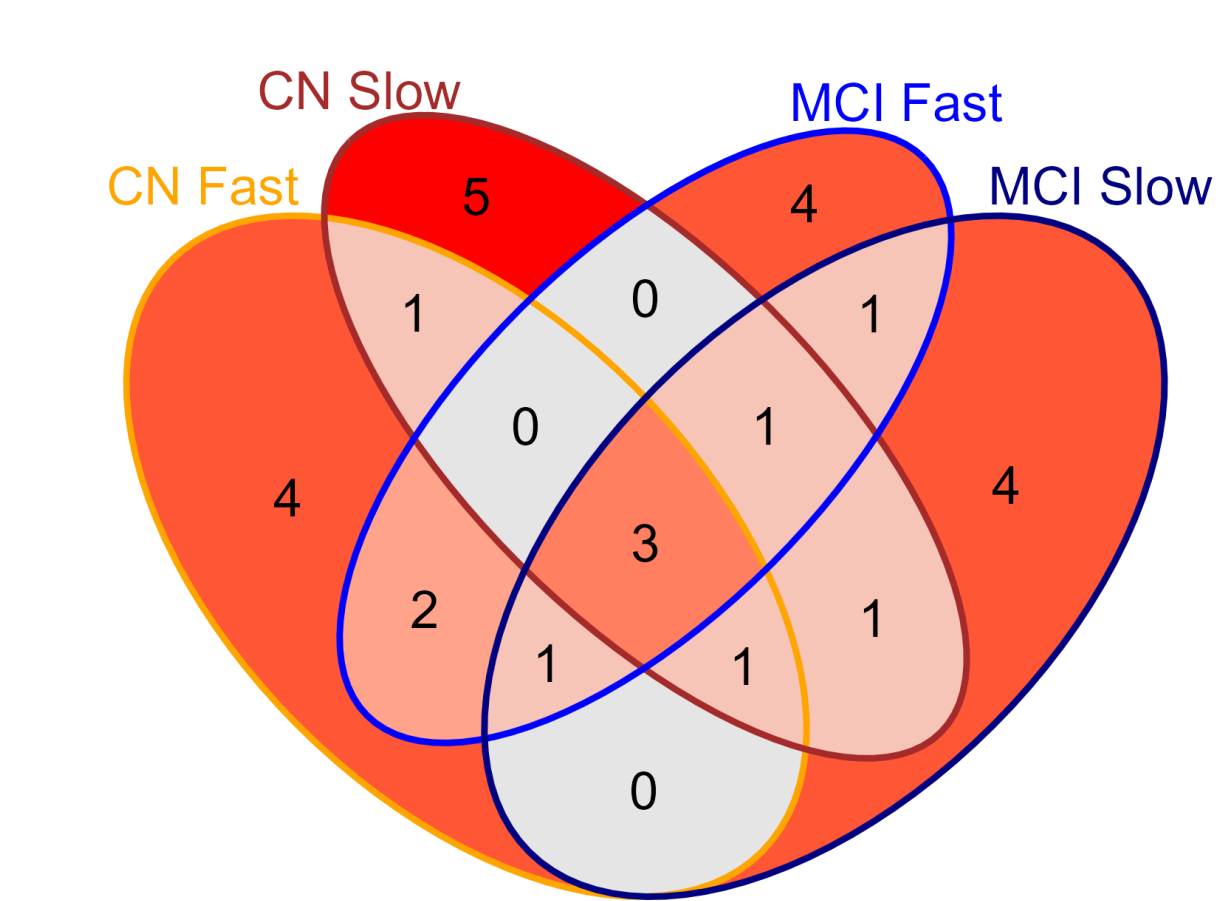


Figure 3. Venn Diagram of Proteins in CN Fast, CN Slow, MCI Fast, and MCI Slow Full Panels

- The least-best panels generated by this data-driven work-flow all consist of three to four biomarkers and improved the AUC of BD-pTau-217 alone by a range of 0.0318 to 0.1334.
- BD-pTau-217 and BD-pTau-217 ratio were in every least-best biomarker panel, and pTau-217 appeared in every top ten ranking.
- Inclusion of MMSE as a covariate decreased AUC of slow progressor panels but increased the AUC of fast progressor panels.
- S100A12 and ILB1 ranked in the top-ten biomarkers of fast progressor groups regardless of baseline status but did not rank highly for slow progressor groups according to mean decrease in Gini.
- BD-pTau-181 ranked in the top-ten of slow progressor groups regardless of baseline status but did not rank highly for fast progressor groups according to mean decrease in Gini.

Acknowledgements: We thank all members of the Karikari Lab, ADRC, and study participants, as well as the generous funding from the NIH R01 AG083874 and P30 AG066468

Disclosures: There are no conflicts of interest related to the research presented in this poster