Validation and Replication of a Prognostic Machine Learning Model for Enrichment of Cognitive Decliners in Clinical Trials

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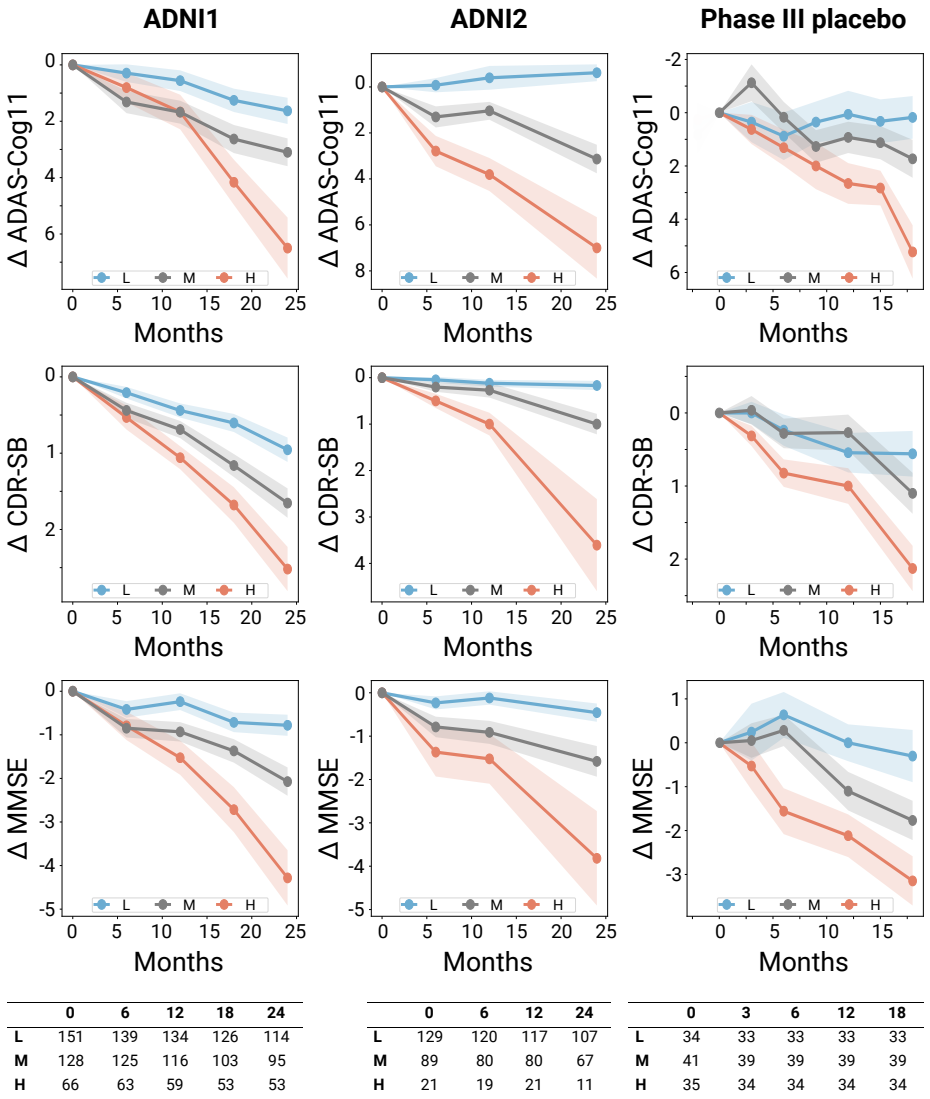
Background:

Identifying individuals who will experience cognitive decline is paramount to evaluating novel treatments in Alzheimer's disease (AD) clinical trials. We propose to use highly specific neuroimaging and genetic signatures that are indicative of the risk of cognitive decline in individuals with mild Alzheimer's disease and mild cognitive impairment (MCI).

Methods:

Baseline measurements of gray matter volumes, from structural magnetic resonance imaging, APOE4 status, age, and sex from healthy controls and AD patients from the AIBL dataset [1] were provided to a machine learning prognostic enrichment solution, Foresight-Cognition from Perceiv Research Inc. Canada [2], to identify signatures of individuals at risk of cognitive decline up to two years of follow-up. The resulting three cohorts of individuals were: (a) low-risk, (b) moderate-risk, (c) high-risk of decline according to the enrichment tool. ADAS-Cog11, CDR-SB, and MMSE were used as clinical endpoints to evaluate the trajectory of each cohort. The prognostic tool was evaluated on three independent datasets: stable and progressive MCI patients from ADNI1 (n=345), stable and progressive MCI patients from ADNI2 (n=238) [3], and mild AD patients from the placebo arm of an 18-month Phase III study (n=110). In ADNI1 and ADNI2, progressive MCI patients received a diagnosis of AD dementia within 36 months of follow-up.



	0	6	12	18	24
L	151	139	134	126	114
M	128	125	116	103	95
H	66	63	59	53	53

	0	6	12	24
L	129	120	117	107
M	89	80	80	67
H	21	19	21	11

	0	3	6	12	18
L	34	33	33	33	33
M	41	39	39	39	39
H	35	34	34	34	34

Figure 1. Cognitive trajectories, measured by ADAS-Cog11, CDR-SB, and MMSE, of 3 groups as labelled by our prognostic model: low (L), moderate (M), and high (H) risk for cognitive decline across 18-24 months in 3 datasets (ADNI1, ADNI2, and a phase III placebo arm). Sample sizes for each group at each timepoint are reported in the tables.

Table 1. Characteristics of the MCI patients at Month 0

ADNI1	All	Low-risk	Moderate-risk	High-risk
N	345	151	128	66
Age (mean)	74.4	74.4	74.4	74.4
% Male	60.0	49.7	62.5	78.8
% APOE4 +	55.4	25.8	75.0	84.8
% CSF Aβ + [4]	75.5	64.7	78.9	100.0
% CSF T-tau + [4]	47.1	42.8	50.0	52.9
% CSF P-tau + [5]	9.43	11.7	7.89	5.88
% True progressors	43.7	25.1	50.0	74.2
ADNI2	**All**	**Low-risk**	**Moderate-risk**	**High-risk**
N	239	129	89	21
Age (mean)	71.4	70.4	71.7	76.1
% Male	50.6	39.5	62.9	66.7
% APOE4 +	47.2	25.6	69.7	85.7
% AV45 + [6]	57.6	42.4	71.6	90.4
% CSF Aβ + [4]	68.4	52.5	81.2	100.0
% CSF T-tau + [4]	36.4	25.0	44.4	66.7
% CSF P-tau + [5]	23.9	20.3	25.0	40.0
% True progressors	24.3	11.6	33.7	61.9

Conclusions:

Our proposed prognostic tool can identify individuals who are at different levels of risk of future cognitive decline across the mild cognitive impairment and mild Alzheimer's dementia spectrum. This tool can help enrich for cognitive decliners, APOE4 carriers, and individuals with AD pathology in clinical trials.

References: **[1]** aibl.csiro.au **[2]** www.perceiv.ai **[3]** adni.loni.usc.edu **[4]** Shaw, et al., 2009. Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. Annals of neurology, 65(4), pp.403-413. **[5]** Tariciotti, et al., 2018. Clinical Experience with Cerebrospinal Fluid Aβ 42, Total and Phosphorylated Tau in the Evaluation of 1,016 Individuals for Suspected Dementia. Journal of Alzheimer's Disease, 65(4), pp.1417-1425. **[6]** Johnson, et al., 2013. Florbetapir (F18-AV-45) PET to assess amyloid burden in Alzheimer's disease dementia, mild cognitive impairment, and normal aging. Alzheimer's & Dementia, 9(5), pp.S72-S83.