A machine learning tool to enrich early Alzheimer's disease clinical trial cohorts

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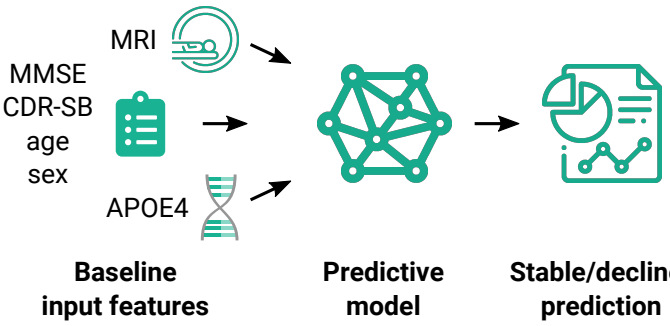
Background

A significant proportion of trial participants will not exhibit cognitive decline during a trial. This can negatively impact a trial's ability to detect differences between placebo and treatment arms, leading to failure to meet its endpoints.

Objective: We aim to improve cohort quality through outcome-based population enrichment by identifying decliners who will experience ΔCDR-SB > 0 at 24 months compared to baseline.

Setup



Results: Stratification of participants

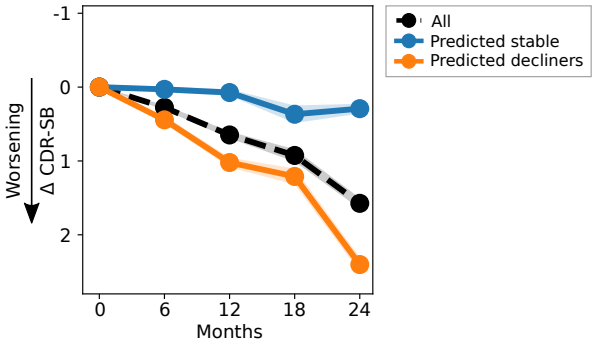


Figure 1. Mean cognitive trajectories of predicted decliners and stable individuals in the discovery dataset (ADNI [1] & NACC [2]) measured by change in CDR-SB. The AUC was 78.7 ± 4.9%.

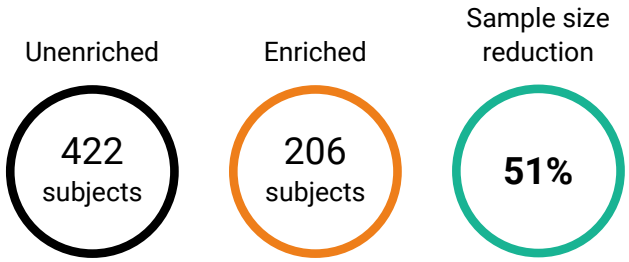
Table 1. Characteristics of the discovery dataset.

	All	Predicted stable	Predicted decliners
N	1151	452	699
Baseline age	73.1 (7.9)	71.1 (7.8)	74.5 (7.6)*
Female %	43.5	43.6	43.5
APOE ε4 carriers %	53.3	33.0	66.5*
Amyloid positive %	67.9	48.9	84.7*
Baseline MMSE	26.3 (3.3)	28.2 (1.6)	25.0 (3.5)*
Baseline CDR-SB	2.31 (1.9)	1.31 (0.8)	2.96 (2.1)*
Change in CDR-SB at endpoint	1.57 (2.4)	0.29 (1.4)	2.40 (2.6)*
True decliners %	64.6	36.5	82.7*

* denotes significant differences (p<0.05, two-sided) between the stable and decliners by Mann-Whitney U and chi-squared tests.

Data were provided by [1] Alzheimer's Disease Neuroimaging Initiative (ADNI), adni.loni.usc.edu, [2] National Alzheimer's Coordinating Center, naccdata.org, NIA/NIH Grant U24 AG072122 and NIA-funded ADRCs, and [3] PharmaCog, www.alzheimer-europe.org/Research/PharmaCog. MRI icon made by LAFS and model and report icons made by Freepik from www.flaticon.com

Results: Reduced sample size per arm



Sample sizes are estimated for 30% treatment effect at 80% power.

Results: External validation in two cohorts

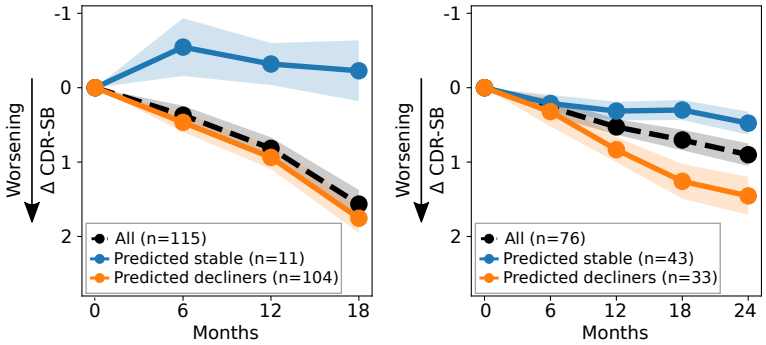


Figure 2. Mean cognitive trajectories of the predicted classes in two extermal validation datasets. Left: Phase 3 trial placebo group (AUC=71.4%). Right: PharmaCog [3] (AUC=72.2%).

Results: Amyloid positive subset

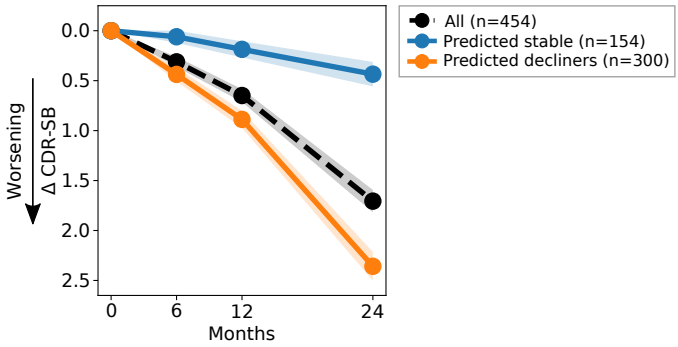


Figure 3. Mean cognitive trajectories of the predicted classes in amyloid positive participants from the discovery dataset.

Conclusion

We designed and externally validated a machine learning tool that can identify participants with early AD who are likely to experience impending cognitive decline from a single baseline time point. Using this tool to specifically recruit enriched cohorts of decliners can **substantially reduce sample sizes and improve trial quality**, thereby increasing trials' likelihood of meeting their endpoints.

Related oral presentation (OC34) on Friday November 12 about enrichment for presymptomatic cohorts