

RESEARCH ARTICLE

Enrichment for clinical trials of early AD: Combining genetic risk factors and plasma p-tau as screening instruments

Xin Wang¹ | Xinran Wang² | Steven D. Edland^{1,2} | Iris J. Broce¹ | Anders M. Dale¹ | Sarah J. Banks¹ | for the Alzheimer's Disease Neuroimaging Initiative

¹Department of Neuroscience, University of California San Diego, La Jolla, California, USA

²Division of Biostatistics, Herbert Wertheim School of Public Health and Human Longevity Science, University of California San Diego, La Jolla, California, USA

Correspondence

Sarah J. Banks, University of California San Diego, 9500 Gilman Drive, m/c 0841, La Jolla, CA 92093, USA.

Email: sbanks@health.ucsd.edu

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

The appendix are from ADNI website: https://cdn-links.lww.com/permalink/wnl/b/wnl_2021_07_03_grothe_1_sdc1.pdf

Funding information

National Institutes of Health, Grant/Award Number: 1R01AG066088; Alzheimer's Disease Neuroimaging Initiative, Grant/Award Number: U01 AG024904

Abstract

INTRODUCTION: Identifying low-cost, minimally-invasive screening instruments for Alzheimer's disease (AD) trial enrichment will improve the efficiency of AD trials.

METHODS: A total of 685 cognitively normal (CN) individuals and individuals with mild cognitive impairment (MCI) from the Alzheimer's Disease Neuroimaging Initiative (ADNI) were grouped according to cutoffs of genetic risk factor (G) polygenic hazard score (PHS) and tau pathology (T) plasma phosphorylated tau-181 (p-tau181) into four groups: G+T+, G-T-, G+T-, and G-T+. We assessed the associations between group level and longitudinal cognitive decline and AD conversion. Power analyses compared the estimated sample size required to detect differences in cognitive decline.

RESULTS: The G+T+ group was associated with faster cognitive decline and higher AD risk. Clinical trials enrolling G+T+ participants would benefit from significantly reduced sample sizes compared with similar trials using only single makers as an inclusion criterion.

DISCUSSION: The combination of two low-cost, minimally-invasive measures—genetics and plasma biomarkers—would be a promising screening procedure for clinical trial enrollment.

KEYWORDS

Alzheimer's disease, clinical trial enrichment, plasma p-tau181, polygenic hazard score

Highlights

- Participants with unimpaired or mildly impaired cognition were grouped based on cutoffs on genetic risk factors (G: polygenic hazardous score [PHS]) and Alzheimer's pathology (T: baseline plasma phosphorylated tau-181 [p-tau181]).
- Participants with high PHSs and plasma p-tau181 levels (G+T+) were at risk of faster cognitive decline and AD progression.
- The combination of PHS and plasma p-tau181 could enhance clinical trial enrichment more effectively than using single biomarkers.

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial](https://creativecommons.org/licenses/by-nc/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2024 The Author(s). *Alzheimer's & Dementia* published by Wiley Periodicals LLC on behalf of Alzheimer's Association.

1 | BACKGROUND

Alzheimer's disease (AD) is a progressive neurodegenerative disease with gradual deterioration of behavioral and cognitive functions. Before the onset of clinical symptoms, pathological changes have already been occurring in the brain for 10–20 years. These early stages (preclinical and prodromal stages) are an important target window for optimal timing of therapeutic intervention.¹ There is an increasing consensus that to bring about significant modifications to AD progression, treatment or intervention must begin at early stages (preclinical or prodromal stages) of the disease. However, due to the clinical heterogeneity of AD, it is a challenge to identify and select asymptomatic individuals who are at risk of faster cognitive decline and AD progression. Therefore, sample enrichment becomes a pivotal component in the design of clinical trials for AD that could reduce the necessary sample size and enhance the likelihood of detecting the effectiveness of a treatment.²

Numerous studies have used neuroimaging techniques such as magnetic resonance imaging (MRI), positron emission tomography (PET), and cerebrospinal fluid (CSF) biomarkers to identify individuals exhibiting abnormal AD pathology for inclusion in clinical trials.³ MRI, allowing a direct measure of regional brain atrophy, has been evaluated as an enrichment biomarker in clinical trials among the amnesic mild cognitive impairment (MCI) population.⁴ Amyloid PET imaging has also been serving as a feasible and effective screening tool to enroll individuals with abnormal amyloid pathology in clinical trials at early stages of AD.⁵ Tau PET imaging has the potential to enrich pre-dementia participants who are at risk of cognitive decline.⁵ Furthermore, CSF biomarkers have also been recommended for clinical trial enrichment and treatment selection.⁶ Studies have identified combinations of these biomarkers that could help to improve the selection of individuals with a high risk of AD progression.^{7–9} However, these measures face limitations due to high cost, the need for invasive procedures such as lumbar puncture, and high dependency on specialized equipment and clinical expertise.

With exciting recent progress in research, plasma biomarkers have been proposed as a cost-effective and easily accessible screening tool for clinical use. Several clinical trials have benefited from more efficient clinical trial recruitment using plasma biomarkers, including TRAILBLAZER-ALZ3 and SKYLINE.¹⁰ Other studies have reported the potential utility of plasma phosphorylated tau (p-tau) as a screening tool for preventive clinical trials.^{11,12} In addition, genetic risk factors are also a promising and affordable assessment instrument for clinical trial enrichment.¹³ The polygenic hazard score (PHS), developed by the Desikan group to evaluate AD genetic risk factors, is associated with the age at onset of AD and can be calculated using epithelial cell DNA that is easily collected with a cheek swab.¹⁴ Although plasma biomarkers identify the current pathological load, the PHS benefits from a predictive component, thereby identifying future risk. Our recent work has proposed that a simple PHS stratification method could contribute to efficient clinical trial design in pre-dementia participants.^{13,15} Logically, combining future potential decline (PHS) with current status

RESEARCH IN CONTEXT

- 1. Systematic review:** We used Google Scholar and PubMed to explore the research on clinical trial enrichment in the preclinical and prodromal stage of Alzheimer's disease (AD). Our investigation uncovered a lack of studies employing multimodal, low-cost, and minimally-invasive screening tools for the prevention and treatment of early-stage AD.
- 2. Interpretation:** The combination of genetic and plasma biomarkers could predict pre-dementia participants at risk of AD progression and enhance clinical trial enrichment more effectively than using single biomarkers.
- 3. Future directions:** This article proposes a possible approach to identifying individuals who could benefit from medications targeting early-stage AD, and could be ideal candidates for clinical trials. We anticipate that this approach could be duplicated in alternative cohorts and applied in forthcoming clinical trials.

(plasma p-tau) might add sensitivity to identify individuals at highest risk for impending decline, who might be the best candidates for trials that target preclinical or prodromal AD. Exploring whether combining genetic risk factors and plasma biomarkers outperforms a model relying on a single diagnostic indicator adds an intriguing dimension to the investigation.

In this study, we aimed to assess how and whether the combination of PHS and plasma p-tau181 would improve the prediction of cognitive decline for enriching clinical trial populations in the pre-dementia stage. We included cognitively normal (CN) and newly symptomatic individuals with MCI, and we assessed whether individuals with high PHS and high baseline plasma p-tau181 were associated with faster cognitive decline and high AD risk. We also investigated how the joint use of two markers as screening instruments improved AD clinical trial enrichment compared to using only one marker.

2 | METHODS

2.1 | Data source

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. For up-to-date information, see www.adni-info.org.

2.2 | Participants

We included participants ($N = 685$) from ADNI who were CN ($N = 270$) or had MCI ($N = 415$) at their baseline plasma p-tau181 measurement, had available calculated Desikan PHS, and had longitudinal cognitive data. Although racial and ethnic minority groups were underrepresented in ADNI, we included only participants who self-identified as non-Hispanic White (NHW), as genetic risk factors differ by group^{16,17} and the PHS is not yet well defined in these other racial and ethnic groups. In addition, we conducted additional analyses by including 20 extra subjects who did not self-identify as NHW ($N = 705$, CN: $N = 281$; MCI = 424).

2.3 | Plasma p-tau181

Plasma p-tau181 was examined by the single-molecule array (Simoa) technique, using an in-house assay developed in the Clinical Neurochemistry Laboratory, University of Gothenburg, Sweden. The assay utilizes a combination of two monoclonal antibodies (tau12 and AT270) and measures N-terminal to mid-domain forms of p-tau181. Details of the assay can be found here.¹⁸

2.4 | PHS determination

Desikan AD PHS was calculated as described previously.¹⁴ Briefly, it was computed based on a Cox proportional hazard regression model combining 31 AD-associated single nucleotide polymorphisms (SNPs) in addition to two apolipoprotein E (APOE) variants ($\epsilon 2/\epsilon 4$). Individuals with high PHS have the highest yearly AD incidence rates.

Participants were grouped according to the previously published cutoffs of PHS at 65th percentile (PHS below 65th: G-; PHS above 65th: G+)¹³ and baseline plasma p-tau181 (p-tau181 < 19.8 pg/mL: T-; p-tau181 \geq 19.8 pg/mL: T+)¹⁹: G+T+, G-T+, G+T- and G-T-.

2.5 | Cognitive measures

Longitudinal cognitive decline was assessed using five outcome measures, the Clinical Dementia Rating scale Sum of Boxes (CDR-SB), the Mini-Mental State Examination (MMSE), the ADNI-modified Pre-clinical Alzheimer's Cognitive Composite (PACC) with Digit Symbol Substitution (mPACCdigits), and the Trails B (mPACCtrailB).

2.6 | Statistical analyses

In the characteristics table, differences in baseline age, education, baseline cognitive measures, PHS, baseline p-tau181, and follow-up time (years since baseline) between different groups were compared (G+T+ vs. G-T-/G-T+/G+T-) using independent t-tests. Pearson's chi-square tests were used to detect group differences (G+T+ vs

G-T-/G-T+/G+T-) in sex, baseline amyloid positivity, and APOE $\epsilon 4$ carriership.

We fit a linear mixed-effects (LME) model with random slopes and intercepts, including an interaction term of time x group, to assess the effects of group levels (G+T+ vs G-T-/G-T+/G+T-) on longitudinal cognitive change over time in CN and MCI separately. In this model, we adjusted for baseline age, sex, and education as potential confounders. In addition, we conducted a sensitivity analysis adjusting for baseline amyloid positivity. Furthermore, we fit the LME model (random slopes and intercepts) to extract participant-specific slopes as cognitive change rates and compared the annual cognitive change between groups using the linear regression model by adjusting for baseline age, sex, and education in CN and MCI separately.

Cox proportional hazards regression models were used to estimate the hazard ratio (HR) of diagnosing incident MCI/AD or AD between groups, adjusting for baseline age, sex, and education. We fit the models separately for CN and MCI. In both LME and Cox models, time was treated as a continuous variable and the group segmentation was treated as a categorical variable with G+T+ as the reference. We also plotted Kaplan-Meier survival curves using the `ggsurvplot` function in R.

In the power analyses, time was rounded to its nearest calendar year to be consistent with the Mixed Models for Repeated Measures (MMRM) analysis plan used in clinical trials. Then we treated the rounded time as a categorical variable and estimated the sample size for a two-arm clinical trial over 1 year and 2 years, designed to detect a 25% reduction in cognitive decline of each outcome (a type I error rate of 5%, power of $\geq 80\%$, and equal allocation to arms). Power calculations used mean change from baseline and residual covariance structure from MMRM fitting to the combined CN and MCI data. Three sample sizes were calculated and compared, one estimating the sample size required for a trial only restricting enrollment to high plasma p-tau181 participants (T+ only), one for a trial restricting to high PHS participants (G+ only), and one for a trial restricting enrollment to participants with both high plasma p-tau181 and high PHS (G+T+).

A significant threshold $\alpha < 0.0125$ (0.05/4) was used for correcting multiple comparisons using Bonferroni's method. All analyses were completed with R version 3.6.1.

3 | RESULTS

3.1 | Participants

Participants' characteristics are presented in Table 1.

In CN, individuals in the G+T+ group were on average older than those in the G-T- and G+T- group. The proportion of women in G+T+ was lower than the ones in G-T-, G-T+, and G+T-. The percentage of APOE $\epsilon 4$ carriers in G+T+ was higher than in G-T- and G-T+ groups. In G+T+, 76% of participants were amyloid positive, which was higher than G-T-, G-T+, and G+T-. There were no significant differences in baseline cognitive performance between the groups.

TABLE 1 Participants characteristics.

	CN			MCI		
	G-T-	G-T+	G+T-	G-T-	G-T+	G+T-
N	141	35	73	145	41	122
BL_age, mean (SD)	74.62 (6.43)*	77.77 (6.45)	72.81 (5.87)**	72.50 (7.92)	76.70 (7.60)**	70.69 (7.80)
Education (years), mean (SD)	16.51 (2.72)	17.03 (2.48)	16.37 (2.55)	16.19 (2.73)	16.02 (2.80)	16.40 (2.58)
Gender, women, N (%)	71 (50.4)*	16 (45.7)	48 (65.8)**	63 (43.4)	15 (36.6)	50 (41.0)
APOE ε4 carriers, N (%)	0 (0.0)**	0 (0.0)**	59 (80.8)	2 (1.4)**	0 (0.0)**	97 (79.5)**
BL_Amyloid positivity, N (%)	34 (24.1)**	14 (40.0)*	33 (45.2)*	49 (33.8)**	22 (53.7)**	70 (57.4)**
BL_MMSE, mean (SD)	29.04 (1.21)	29.14 (1.22)	29.08 (1.20)	28.37 (1.48)**	28.29 (1.68)*	28.17 (1.67)**
BL_CDR-SB, mean (SD)	0.04 (0.17)	0.14 (0.38)	0.09 (0.28)	1.45 (0.91)**	1.22 (0.78)**	1.41 (0.86)**
BL_mPACCdigit, mean (SD)	0.01 (2.85)	0.21 (2.72)	0.14 (2.85)	-4.14 (3.82)**	-4.37 (3.65)**	-4.74 (3.46)**
BL_mPACCtrailsB, mean (SD)	0.05 (2.69)	0.18 (2.31)	0.11 (2.61)	-3.51 (3.53)**	-4.00 (3.39)**	-3.96 (2.94)**
PHS, mean (SD)	-0.37 (0.27)**	-0.32 (0.22)*	0.69 (0.35)	-0.31 (0.23)**	-0.35 (0.24)**	0.88 (0.57)*
BL_ptau181 (pg/mL), mean (SD)	11.10 (4.87)**	31.27 (12.41)	12.81 (3.80)**	12.15 (4.49)**	30.74 (18.00)	12.01 (4.31)**
TIME (years), mean (SD)	5.68 (3.08)	6.51 (3.03)	4.92 (2.86)	5.30 (2.97)**	3.67 (2.60)	4.58 (3.08)**

Note: Group comparisons between G+T+ with the other three groups separately (G-T-, G+T-, and G-T-).

Abbreviations: APOE, apolipoprotein E; BL, baseline; CDR-SB, Clinical Dementia Rating scale Sum of Boxes; CN, cognitively normal; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; mPACCdigit, PACC with digit symbol substitution; mPACCtrailsB, PACC with Trails B; PHS, polygenic hazard score.

* $p < 0.0125$.

** $p < 0.005$.

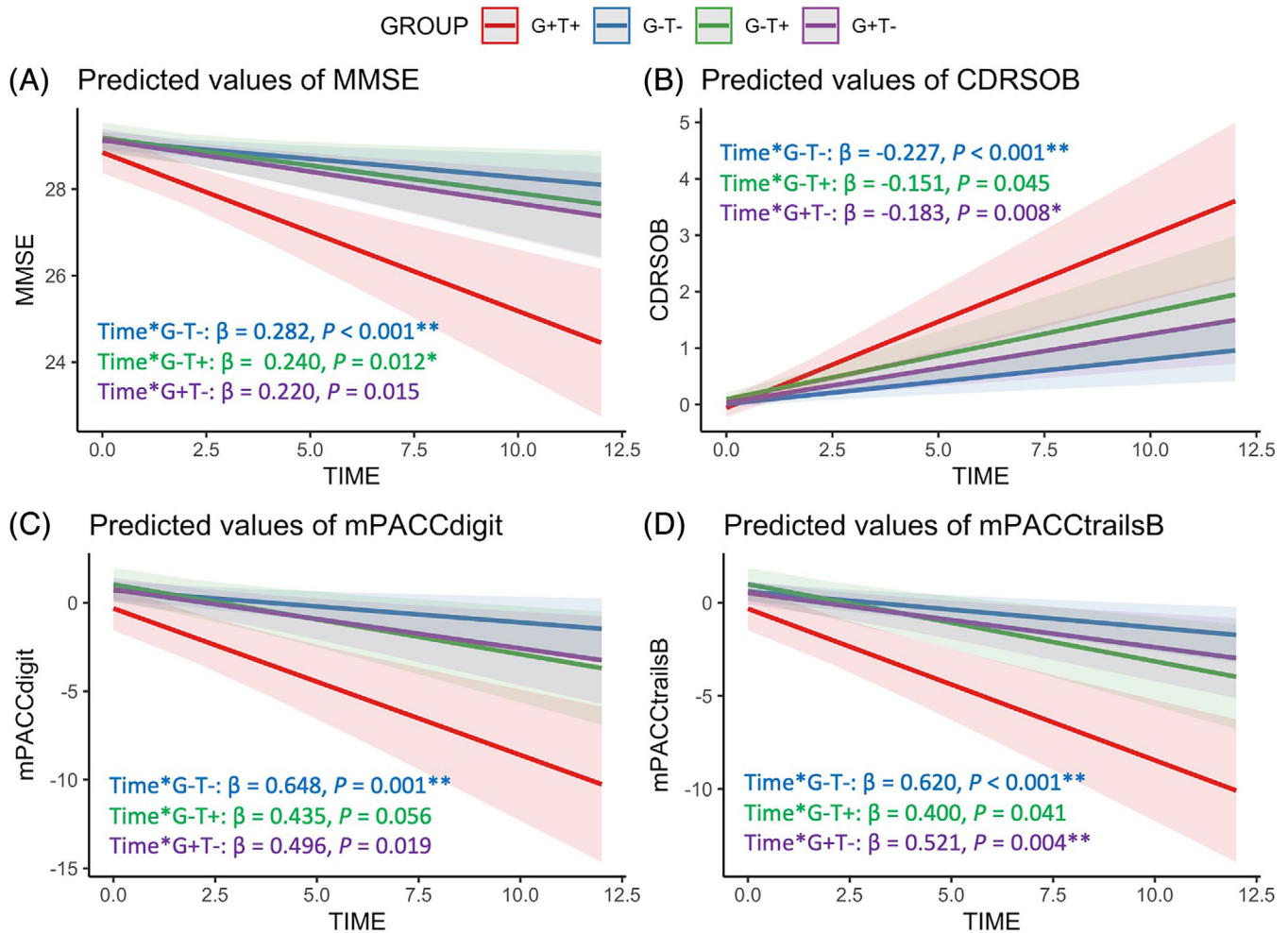


FIGURE 1 LME model with time and group interaction on cognitive outcomes in CN. Interaction plots between time and group on different cognitive outcomes showing the estimated mean cognitive trajectory in CN participants. (A) MMSE; (B) CDR-SB; (C) mPACCdigit; (D) mPACCtrailsB. Interaction coefficients from the LME model (adjusted for baseline age, sex, and education; G+T+ as the reference group) were labeled. * $p < 0.0125$; ** $p < 0.005$. CDR-SB, Clinical Dementia Rating scale Sum of Boxes; CN, cognitively normal; LME, linear mixed-effects; MMSE, Mini-Mental State Examination; mPACCdigit, PACC with digit symbol substitution; mPACCtrailsB, PACC with Trails B.

In MCI, the G+T+ group was generally younger than the G-T+ group. The prevalence of *APOE* $\epsilon 4$ carriers was notably greater in the G+T+ group compared to the G-T- and G-T+, and even the G+T- groups. Within G+T+, 88.8% of individuals tested amyloid-positive, a notably higher percentage compared to those in G-T-, G-T+, and G+T-. Moreover, G+T+ showed the worst baseline cognitive performance compared to the other three groups in four cognitive outcomes.

3.2 | Longitudinal cognitive changes

Among CN, we observed significant time-by-group (G-T- and G-T+) interaction on longitudinal MMSE change (time \times group G-T-: $\beta = 0.282, p < 0.001$; time \times group G-T+: $\beta = 0.240, p = 0.012$), and a marginally significant interaction of time-by-group G+T- on MMSE after the multiple comparison correction (time \times group G+T-: $\beta = 0.220, p = 0.015$) (Figure 1A). The G-T- and G+T- groups inter-

acted significantly with time on the CDR-SB (time \times G-T-: interaction $\beta = -0.227, p < 0.001$; time \times G+T-: interaction $\beta = -0.183, p = 0.008$) (Figure 1B). For mPACCdigit, there were significant interaction effects of time and G-T- (time \times G-T-: interaction $\beta = 0.648, p = 0.001$) (Figure 1C), whereas the interaction of time-by-group G+T- did not survive after multiple comparisons. Additionally, we also detected significant time-by-group (G-T- and G+T-) interactions on longitudinal mPACCtrailsB (time \times G-T-: interaction $\beta = 0.620, p < 0.001$; time \times G+T-: interaction $\beta = 0.521, p = 0.004$) (Figure 1D).

In MCI, there were significant interactions of time and G-T-, G-T+, and G+T- on MMSE, CDR-SB, mPACCdigit, and mPACCtrailsB (p 's < 0.001 , Figure 2).

The results were similar after adjusting for additional baseline amyloid positivity (Figures S1 and S2) and after including participants who were not NHW (Figures S3 and S4).

We then calculated the annual change of cognitive outcomes for individual participants by extracting participant-specific slopes from the LME model and compared the cognitive change rates between

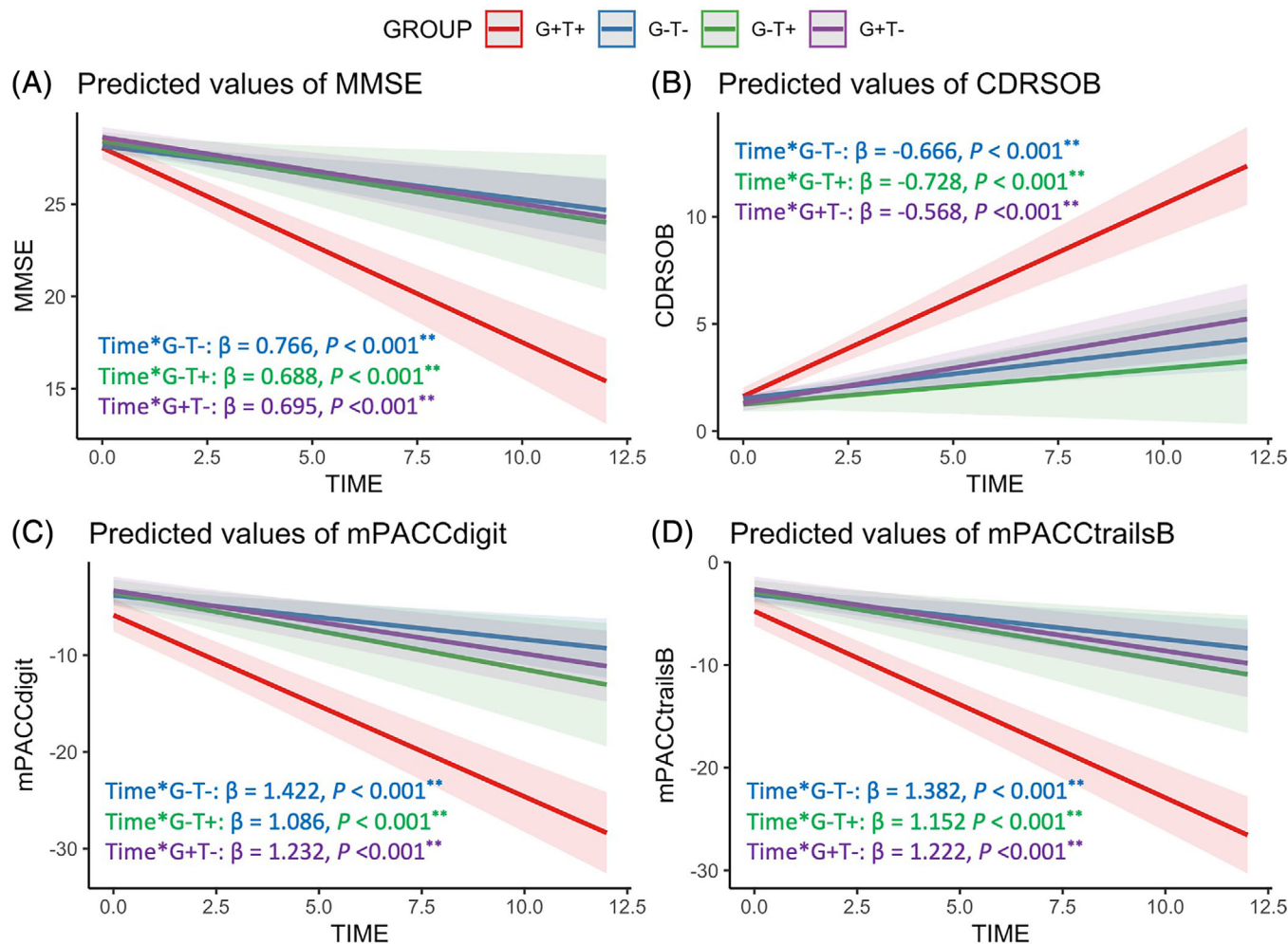


FIGURE 2 LME with time and group interaction on cognitive outcomes in MCI. Interaction plots between time and group on different cognitive outcomes showing the estimated mean cognitive trajectory in participants with MCI. (A) MMSE; (B) CDR-SB; (C) mPACCdigit; (D) mPACCtrailsB. Interaction coefficients from LME model (adjusted for baseline age, sex, and education; G+T+ as the reference group) were labeled. * $p < 0.0125$; ** $p < 0.005$. CDR-SB, Clinical Dementia Rating scale Sum of Boxes; LME, linear mixed-effects; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; mPACCdigit, PACC with digit symbol substitution; mPACCtrailsB, PACC with Trails B.

groups. In CN, G+T+ showed greater rates of decline in MMSE and mPACCtrails than G-T-, G-T+, and G+T- (Figure 3A,D). For CDR-SB and mPACCdigit, G+T+ demonstrated faster cognitive decline than G-T- and G+T- (Figure 3B,C). In MCI, G+T+ exhibited greater cognitive decline rates than G-T-, G-T+, and G+T- in MMSE, CDR-SB, mPACCdigit, and mPACCtrailsB (Figure 4).

3.3 | Survival analyses

Figure 5 shows the HRs, 95% confidence intervals (CIs), and p -values from Cox proportional hazards regression models. In CN, compared to G+T+, G-T- and G+T- were associated with a lower risk of MCI/AD diagnosis (G-T-: HR = 0.255, $p < 0.001$; G+T-: HR = 0.328, $p = 0.010$) (Figure 5 and Figure S5). The G-T+ group is estimated to have a lower risk of AD diagnosis compared to G+T+ (G-T+: HR = 0.386, $p = 0.020$); yet the association did not suggest being statistically significant after correcting for multiple comparisons.

Consistent with what we observed in the longitudinal cognitive changes, in MCI, the G-T-, G+T-, and G-T+ groups were all significantly associated with a lower risk of AD (G-T-: HR = 0.246, $p < 0.001$; G-T+: HR = 0.061, $p < 0.001$; G+T-: HR = 0.391, $p < 0.001$) (Figure 5 and Figure S6).

3.4 | Power analyses

Next, we evaluated whether the combination of PHS and baseline plasma p-tau181 (G+T+) outperformed the single criterion (G+ only or T+ only) in clinical trial enrichment. Table 2 shows the sample size needed for each cognitive outcome in each arm of a two-arm hypothetical trial with combined CN and MCI participants. For each of the cognitive measures, the clinical trial required substantially fewer samples when enrolling based on the combinational criterion of recruiting G+T+ participants. Especially at 2 years, using multiple biomarkers (G+T+) required roughly 70%–80% fewer participants for enrollment

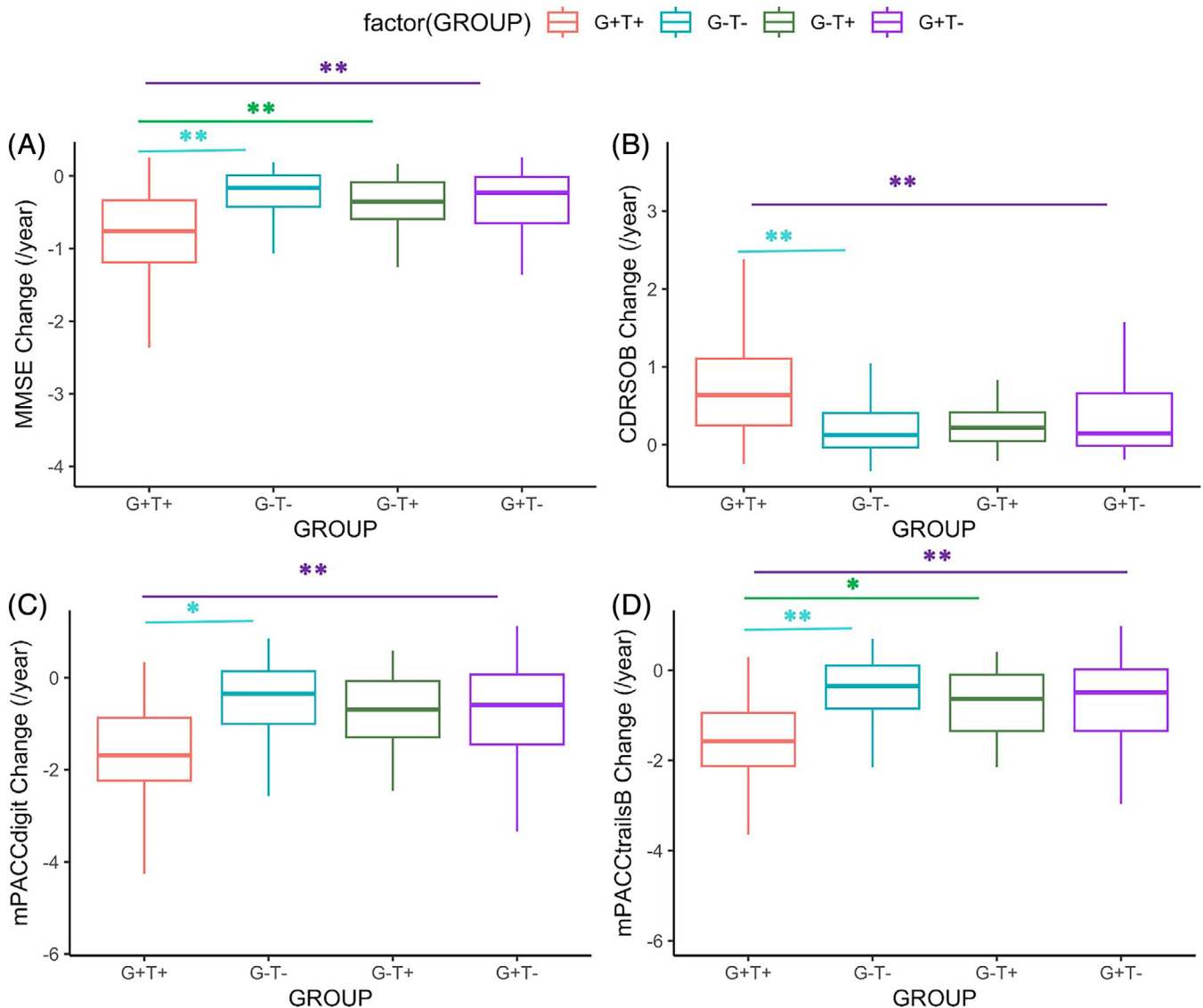


FIGURE 3 Cognitive change comparison between groups in CN. Bar plots showing the comparison between different cognitive outcomes (A) MMSE; (B) CDR-SB; (C) mPACCdigit; (D) mPACCtrailsB between groups in CN (adjusting for baseline age, sex, and education; G+T+ as the reference group). * $p < 0.0125$; ** $p < 0.005$. CDR-SB, Clinical Dementia Rating Scale Sum of Boxes; CN, cognitively normal; MMSE, Mini-Mental State Examination; mPACCdigit, PACC with digit symbol substitution; mPACCtrailsB, PACC with Trails B.

compared to using only G+ and 25%–40% fewer participants compared to using T+ only. The results were similar after adjusting for additional baseline amyloid positivity (Table S1) and including participants who were not NHW (Table S2). Hence, the use of multiple biomarkers as an inclusion criterion is suggested to be more efficient in recruitment.

4 | DISCUSSION

There is growing consensus that for effective AD prevention and treatment, the clinical intervention will benefit from initiation at the early stages including the preclinical and prodromal stages.¹ However, including non-AD participants with slower cognitive decline or

AD progression might reduce the power and sensitivity of treatment detection. In this study, we explored that combining genetic and plasma biomarkers, both being accessible and cost-efficient, could effectively predict participants at risk of faster cognitive decline and AD progression. Power analyses also suggest that the combination could enhance clinical trial enrichment more effectively than using single biomarkers.

Previous work has indicated that PHS and plasma p-tau181 were both associated with amyloid positivity and longitudinal cognitive decline, respectively,^{13,20–23} but most of these studies involved participants with MCI or a combination of CN and MCI. In this study, by combining these two measures, the G+T+ group enabled the prediction of higher amyloid positivity and faster cognitive decline, even in CN. Individuals with only one risk factor (G+T- and G-T+) displayed a lower proportion of amyloid positivity than those in the G+T+. Like

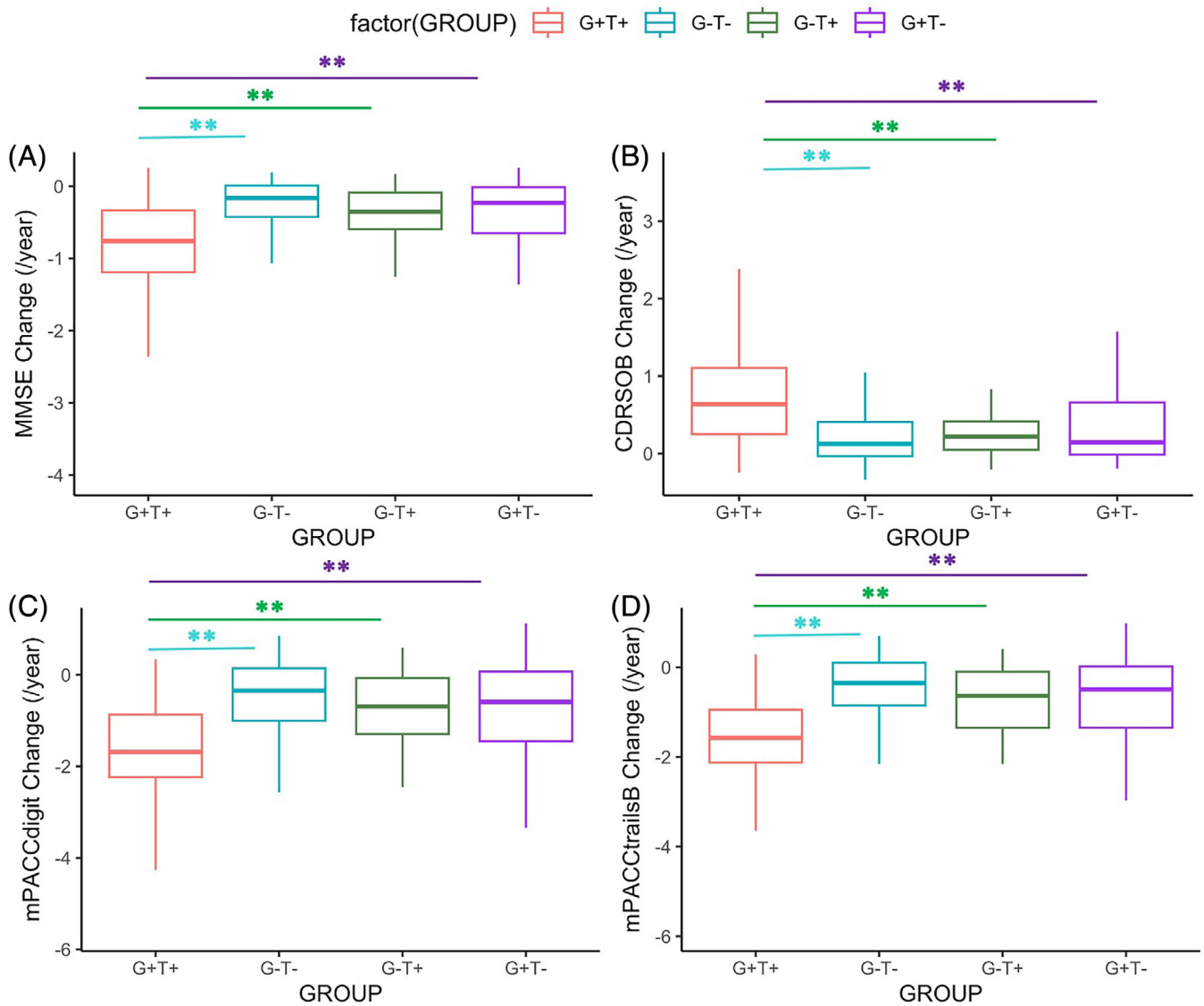


FIGURE 4 Cognitive change comparison between groups in MCI. Bar plots showing the comparison between different cognitive outcomes (A) MMSE; (B) CDR-SB; (C) mPACCdigit; (D) mPACCtrailsB between groups in participants with MCI (adjusting for baseline age, sex and education; G+T+ as the reference group). * $p < 0.0125$; ** $p < 0.005$. CDR-SB, Clinical Dementia Rating scale Sum of Boxes; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; mPACCdigit, PACC with digit symbol substitution; mPACCtrailsB, PACC with Trails B.

G-T-, both G+T- and G-T+ exhibited slower cognitive change compared to G+T+. In addition, survival analyses indicated that G+T- and G-T+ were associated with a lower risk of AD. This suggested the potential clinical utility of using a combination of PHS and plasma p-tau181 for a more accurate assessment of AD risk and cognitive decline in cognitively unimpaired populations. Notably, PHS and plasma p-tau181 have also been reported to benefit clinical trial enrichment individually.^{13,24} Our findings in the power analyses demonstrated that a combination of these two markers (G+T+) is superior to using a single marker (G+ or T+) for enrichment. CN or MCI individuals with high PHS and plasma p-tau181 are at high risk of AD progression and are more likely to benefit from the intervention in clinical trials. Selecting these individuals might enhance the efficiency of trials by reducing the variability within the study population and increasing the likeli-

hood of detecting treatment effects. In future clinical trials, employing a multistep screening process wherein high PHS participants are pre-screened through easily collectible and cost-effective cheek swabs, followed by the measurement of plasma p-tau from blood samples, presents a potential, cost-effective, and widely accessible method for enrichment.

Recent studies have reported that plasma p-tau217 had a stronger association with AD pathology than plasma p-tau181 in preclinical AD and may be diagnostically superior to p-tau181.²⁴ Recent work from the Biofinder group has reported that plasma p-tau217 outperforms p-tau181 in the prediction of cognitive decline.¹² Subsequent research should delve into exploring and comparing the predictive capacities in AD and clinical trial enrichment by incorporating PHS along with measurements of plasma p-tau217 and p-tau181.

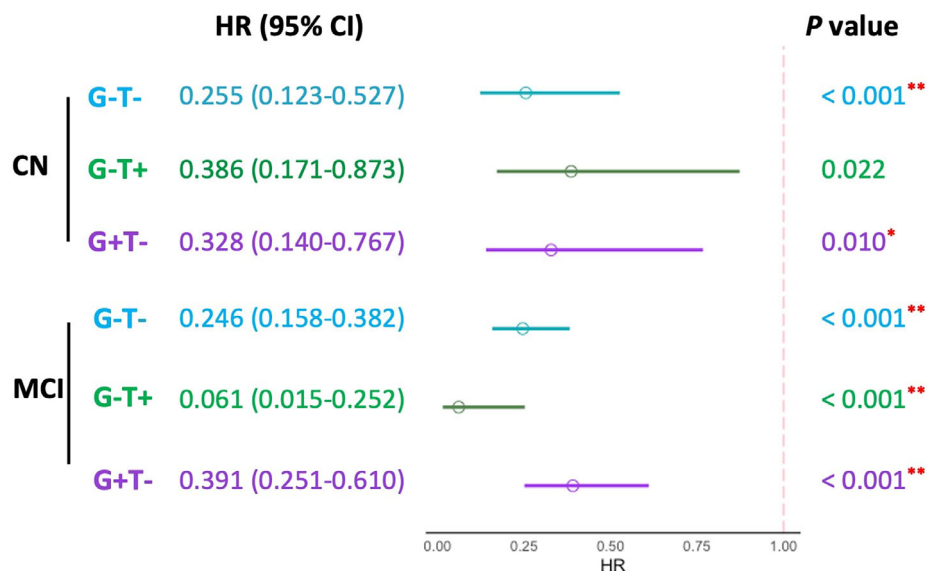


FIGURE 5 HR of MCI/AD conversion from CN and AD conversion from MCI. Cox proportional risk model estimating the HR of MCI/AD in CN and AD in MCI, adjusting for age, sex, and education. * $p < 0.0125$; ** $p < 0.005$. AD, Alzheimer's disease; CN, cognitively normal; HR, hazard ratio; MCI, mild cognitive impairment.

In this study, the power calculation estimates provide insight into the relative efficiency of integrating genetic risk factors with plasma biomarkers. However, the actual necessary sample size may be contingent upon the characteristics of individuals who are targeted for

TABLE 2 Sample size needed in the hypothetical clinical trial (CN + MCI).

	1 year	2 years
MMSE		
G+	7450	4743
T+	3852	1458
G+T+	3273	994
CDR-SB		
G+	5099	3092
T+	3670	1114
G+T+	2479	810
mPACCdigit		
G+	6354	3746
T+	3350	1260
G+T+	2666	872
mPACCtrailsB		
G+	4621	3662
T+	3243	1140
G+T+	1868	658

Note: Sample size estimation and comparison between using G+T+ and only G+ or T+.

Abbreviations: CDR-SB, Clinical Dementia Rating scale Sum of Boxes; CN, cognitively normal; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; mPACCdigits, modified Preclinical Alzheimer's Cognitive Composite with Digit Symbol Substitution; mPACCtrailsB, modified Preclinical Alzheimer's Cognitive Composite with Trails B.

recruitment in future clinical trials. In addition, it is important to note that the chosen cutoff values for PHS and plasma p-tau181 based on prior published work are arbitrary. Furthermore, there is considerable variability in sensitivity and measurement scales among different methods for assessing plasma p-tau. To facilitate future clinical applications, it is imperative to establish standardized measurement methods to ensure consistency across various studies and laboratories.

This study has some other limitations. First, participants in this study are mainly NHW, thereby limiting the generalizability of the study results. The application of the combination may not generalize to non-White populations, since PHS was developed using a sample of White participants of European ancestry and there have been reported differences in plasma p-tau between races. In addition, the application of a combination of PHS and plasma p-tau181 data presented requires validation in an independent sample. Further research will expand this work and these biomarkers beyond this narrow racial/ethnic group and into larger, more diverse cohorts.

In conclusion, the combination of PHS and plasma p-tau181 provides cost-effective and accessible screening tools for AD clinical trials.

ACKNOWLEDGMENTS

This work was supported by the National Institutes of Health ([NIH] grant number 1R01AG066088. Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI; NIH grant number U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie; Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate;

Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd. and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC; Johnson & Johnson Pharmaceutical Research & Development LLC; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California. This study was supported by the National Institute on Aging, R01 AG080663.

CONFLICT OF INTEREST STATEMENT

Dr. Anders M. Dale reports that he was a Founder of and holds equity in CorTechs Labs, Inc., and serves on its Scientific Advisory Board. He is also a member of the Scientific Advisory Board of Human Longevity, Inc. (HLI), and the Mohn Medical Imaging and Visualization Centre in Bergen, Norway. He receives funding through a research agreement with General Electric Healthcare (GEHC). The terms of these arrangements have been reviewed and approved by the University of California, San Diego, in accordance with its conflict-of-interest policies. Dr. Anders M. Dale is supported by the following grants from the National Institutes of Health (NIH): U24DA041123; R01AG076838; U24DA055330; and OT2HL161847. Xin Wang, Xinran Wang, Dr. Edland, Dr. Broce, and Dr. Banks have no relevant disclosures for this article. Author disclosures are available in the [Supporting Information](#).

CONSENT STATEMENT

All participants in this study signed informed consent before participating in this study.

REFERENCES

1. Aisen PS, Jimenez-Maggiore GA, Rafii MS, Walter S, Raman R. Early-stage Alzheimer disease: getting trial-ready. *Nat Rev Neurol*. 2022;18:389-399.
2. Cummings J. Lessons learned from Alzheimer disease: clinical trials with negative outcomes. *Clin Transl Sci*. 2018;11:147-152.
3. Frisoni GB, Boccardi M, Barkhof F, et al. Strategic roadmap for an early diagnosis of Alzheimer's disease based on biomarkers. *Lancet Neurol*. 2017;16:661-676.
4. Yu P, Sun J, Wolz R, et al. Operationalizing hippocampal volume as an enrichment biomarker for amnesic mild cognitive impairment trials: effect of the algorithm, test-retest variability, and cut point on trial cost, duration, and sample size. *Neurobiol Aging*. 2014;35:808-818.
5. Ossenkoppele R, Smith R, Mattsson-Carlsson N, et al. Accuracy of tau positron emission tomography as a prognostic marker in preclinical and prodromal Alzheimer disease: a head-to-head comparison against amyloid positron emission tomography and magnetic resonance imaging. *JAMA Neurol*. 2021;78:961-971.
6. Bouwman FH, Frisoni GB, Johnson SC, et al. Clinical application of CSF biomarkers for Alzheimer's disease: from rationale to ratios. *Alzheimers Dement*. 2022;14:e12314.
7. Ritter A, Cummings J. Fluid biomarkers in clinical trials of Alzheimer's disease therapeutics. *Front Neurol*. 2015;6:186.
8. Wolz R, Schwarz AJ, Gray KR, Yu P, Hill DL, Alzheimer's Disease Neuroimaging I. Enrichment of clinical trials in MCI due to AD using markers of amyloid and neurodegeneration. *Neurology*. 2016;87:1235-1241.
9. Yu P, Dean RA, Hall SD, et al. Enriching amnesic mild cognitive impairment populations for clinical trials: optimal combination of biomarkers to predict conversion to dementia. *J Alzheimers Dis*. 2012;32:373-385.
10. Blennow K, Galasko D, Pernecky R, et al. The potential clinical value of plasma biomarkers in Alzheimer's disease. *Alzheimers Dement*. 2023;19(12):5805-5581.
11. Ferreira PCL, Ferrari-Souza JP, Tissot C, et al. Potential utility of plasma p-tau and neurofilament light chain as surrogate biomarkers for preventive clinical trials. *Neurology*. 2023;101:38-45.
12. Mattsson-Carlsson N, Salvadó G, Ashton NJ, et al. Prediction of longitudinal cognitive decline in preclinical Alzheimer disease using plasma biomarkers. *JAMA Neurol*. 2023;80:360-369.
13. Wang X, Broce I, Qiu Y, et al. A simple genetic stratification method for lower cost, more expedient clinical trials in early Alzheimer's disease: a preliminary study of tau PET and cognitive outcomes. *Alzheimers Dement*. 2023;19:3078-3086.
14. Desikan RS, Fan CC, Wang Y, et al. Genetic assessment of age-associated Alzheimer disease risk: development and validation of a polygenic hazard score. *PLoS Med*. 2017;14:e1002258.
15. Banks SJ, Qiu Y, Fan CC, et al. Enriching the design of Alzheimer's disease clinical trials: application of the polygenic hazard score and composite outcome measures. *Alzheimers Dement*. 2020;6:e12071.
16. Rubin L, Ingram LA, Resciniti NV, et al. Genetic risk factors for Alzheimer's disease in racial/ethnic minority populations in the U.S.: a scoping review. *Front Public Health*. 2021;9:784958.
17. Deters KD, Mormino EC, Yu L, Lutz MW, Bennett DA, Barnes LL. TOMM40-APOE haplotypes are associated with cognitive decline in non-demented Blacks. *Alzheimers Dement*. 2021;17:1287-1296.
18. Karikari TK, Pascoal TA, Ashton NJ, et al. Blood phosphorylated tau 181 as a biomarker for Alzheimer's disease: a diagnostic performance and prediction modelling study using data from four prospective cohorts. *Lancet Neurol*. 2020;19:422-433.
19. Hansson O, Cullen N, Zetterberg H; Alzheimer's Disease Neuroimaging Initiative, Blennow K, Mattsson-Carlsson N. Plasma phosphorylated tau181 and neurodegeneration in Alzheimer's disease. *Ann Clin Transl Neurol*. 2021;8:259-265.
20. Tan CH, Fan CC, Mormino EC, et al. Polygenic hazard score: an enrichment marker for Alzheimer's associated amyloid and tau deposition. *Acta Neuropathol*. 2018;135:85-93.
21. Pereira JB, Janelidze S, Stomrud E, et al. Plasma markers predict changes in amyloid, tau, atrophy and cognition in non-demented subjects. *Brain*. 2021;144:2826-2836.
22. Simrén J, Leuzy A, Karikari TK, et al. The diagnostic and prognostic capabilities of plasma biomarkers in Alzheimer's disease. *Alzheimers Dement*. 2021;17:1145-1156.
23. Lehmann S, Schraen-Maschke S, Vidal JS, et al. Plasma phosphorylated tau 181 predicts amyloid status and conversion to dementia stage dependent on renal function. *J Neurol Neurosurg Psychiatry*. 2023;94:411-419.
24. Gonzalez-Ortiz F, Kac PR, Brum WS, Zetterberg H, Blennow K, Karikari TK. Plasma phospho-tau in Alzheimer's disease: towards diagnostic and therapeutic trial applications. *Mol Neurodegener*. 2023;18:18.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Wang X, Wang X, Edland SD, Broce IJ, Dale AM, Banks SJ; for the Alzheimer's Disease Neuroimaging Initiative. Enrichment for clinical trials of early AD: Combining genetic risk factors and plasma p-tau as screening instruments. *Alzheimer's Dement.* 2024;1-19.
<https://doi.org/10.1002/alz.14284>

APPENDIX**Collaborators**

The Data and Publications Committee, in keeping with the publication policies adopted by the ADNI Steering Committee, here provides lists for standardized acknowledgement. The list consists of three parts: I. ADNI Infrastructure Investigators and Site Investigators; II. DOD ADNI Infrastructure Investigators and Site Investigators; and III. ADNI Depression Infrastructure Investigators and Site Investigators. Infrastructure Investigators represent the names responsible for leadership and infrastructure. Site Investigators represent the names of individuals at each recruiting site. All articles, including methodological studies, should have an acknowledgement list that consists of Infrastructure Investigators plus the FULL list.

I. ADNI I, GO, II and III**Part A: Leadership and Infrastructure**

ADNI began in 2004 under the leadership of Dr. Michael W. Weiner

Principal Investigator

Michael W. Weiner, MD, University of California, San Francisco

ATRI PI and Director of Coordinating Center Clinical Core

Paul Aisen, MD, University of Southern California

Co PI of Clinical Core Ronald Petersen, MD, PhD, Mayo Clinic, Rochester

Executive Committee

Michael W. Weiner, MD, University of California, San Francisco

Paul Aisen, MD, University of Southern California

Ronald Petersen, MD, PhD, Mayo Clinic, Rochester

Clifford R. Jack, Jr., MD, Mayo Clinic, Rochester

William Jagust, MD, University of California, Berkeley

John Q. Trojanowki, MD, PhD, University of Pennsylvania

Arthur W. Toga, PhD, University of Southern California

Laurel Beckett, PhD, University of California, Davis

Robert C. Green, MD, MPH, Brigham and Women's Hospital/Harvard Medical School

Andrew J. Saykin, PsyD, Indiana University

John C. Morris, MD, Washington University St. Louis

Richard J. Perrin, MD, PhD, Washington University St. Louis

Leslie M. Shaw, PhD, University of Pennsylvania

ADNI External Advisory Board (ESAB)

Zaven Khachaturian, PhD, Prevent Alzheimer's Disease 2020 (Chair)

Maria Carrillo, PhD, Alzheimer's Association

William Potter, MD, National Institute of Mental Health

Lisa Barnes, PhD, Rush University

Marie Bernard, MD, National Institute on Aging

Hector González, University of California, San Diego

Carole Ho, Denali Therapeutics

John K. Hsiao, MD, National Institutes of Health

Jonathan Jackson, PhD, Massachusetts General Hospital

Eliezer Masliah, MD, National Institute on Aging

Donna Masterman, MD, Biogen

Ozioma Okonkwo, PhD, University of Wisconsin, Madison

Richard Perrin, MD, Washington University

Laurie Ryan, PhD, National Institute on Aging

Nina Silverberg, PhD, National Institute on Aging

ADNI 3 Private Partner Scientific Board (PPSB)

Adam Fleisher, MD, Eli Lilly (Chair)

Administrative Core—Northern California Institute for Research & Education (NCIRE/The Veterans Health Research Institute)

Michael W. Weiner, MD, University of California, San Francisco

Diana Truran Sacrey, NCIRE/The Veterans Health Research Institute

Juliet Fockler, University of California, San Francisco

Cat Conti, BA, NCIRE/The Veterans Health Research Institute

Dallas Veitch, PhD, NCIRE/The Veterans Health Research Institute

John Neuhaus, PhD, University of California, San Francisco

Chengshi Jin, PhD, University of California, San Francisco

Rachel Nosheny, PhD, University of California, San Francisco

Miriam Ashford, PhD, NCIRE/The Veterans Health Research Institute

Derek Flenniken, NCIRE/The Veterans Health Research Institute

Adrienne Kormos, NCIRE/The Veterans Health Research Institute

Data and Publications Committee

Robert C. Green, MD, MPH, BWH/HMS (Chair)

Resource Allocation Review Committee

Tom Montine, MD, PhD, University of Washington (Chair)

Cat Conti, BA, NCIRE/The Veterans Health Research Institute

Clinical Core Leaders and Key Personnel

Ronald Petersen, MD, PhD, Mayo Clinic, Rochester (Core PI)

Paul Aisen, MD, University of Southern California (Core PI)

Michael Rafii, MD, PhD, University of Southern California

Rema Raman, PhD, University of Southern California

Gustavo Jimenez, MBS, University of Southern California

Michael Donohue, PhD, University of Southern California

Devon Gessert, BS, University of Southern California

Jennifer Salazar, MBS, University of Southern California

Caileigh Zimmerman, MS, University of Southern California

Yuliana Cabrera, BS, University of Southern California

Sarah Walter, MSc, University of Southern California

Garrett Miller, MS, University of Southern California

Godfrey Coker, MBA, MPH, University of Southern California
 Taylor Clanton, MPH, University of Southern California
 Lindsey Hergesheimer, BS, University of Southern California
 Stephanie Smith, BS, University of Southern California
 Olusegun Adegoke, MSc, University of Southern California
 Payam Mahboubi, MPH, University of Southern California
 Shelley Moore, BA, University of Southern California
 Jeremy Pizzola, BA, University of Southern California
 Elizabeth Shaffer, BS, University of Southern California
 Rev February 2021
 Brittany Sloan, BA, University of Southern California

Biostatistics Core Leaders and Key Personnel

Laurel Beckett, PhD, University of California, Davis (Core PI)
 Danielle Harvey, PhD, University of California, Davis
 Michael Donohue, PhD, University of Southern California

MRI Core Leaders and Key Personnel

Clifford R. Jack, Jr., MD, Mayo Clinic, Rochester (Core PI)
 Arvin Forghanian-Arani, PhD, Mayo Clinic
 Bret Borowski, RTR, Mayo Clinic
 Chad Ward, Mayo Clinic
 Christopher Schwarz, PhD, Mayo Clinic
 David Jones, MD, Mayo Clinic
 Jeff Gunter, PhD, Mayo Clinic
 Kejal Kantarci, MD, Mayo Clinic
 Matthew Senjem, MS, Mayo Clinic
 Prashanthi Vemuri, PhD, Mayo Clinic
 Robert Reid, PhD, Mayo Clinic
 Nick C. Fox, MD, University College London
 Ian Malone, PhD, University College London
 Paul Thompson, PhD, University of Southern California School of Medicine
 Sophia I. Thomopoulos, BS, University of Southern California School of Medicine
 Talia M. Nir, PhD, University of Southern California School of Medicine
 Neda Jahanshad, PhD, University of Southern California School of Medicine
 Charles DeCarli, MD, University of California, Davis
 Alexander Knaack, MS, University of California, Davis
 Evan Fletcher, PhD, University of California, Davis
 Danielle Harvey, PhD, University of California, Davis
 Duygu Tosun-Turgut, PhD, University of California, San Francisco
 Stephanie Rossi Chen, BA, NCIRE/The Veterans Health Research Institute
 Mark Choe, BS, NCIRE/The Veterans Health Research Institute
 Karen Crawford, University of Southern California School of Medicine
 Paul A. Yushkevich, PhD, University of Pennsylvania
 Sandhitsu Das, PhD, University of Pennsylvania

PET Core Leaders and Key Personnel

William Jagust, MD, University of California, Berkeley (Core PI)
 Robert A. Koeppe, PhD, University of Michigan

Eric M. Reiman, MD, Banner Alzheimer's Institute
 Kewei Chen, PhD, Banner Alzheimer's Institute
 Chet Mathis, MD, University of Pittsburgh
 Susan Landau, PhD, University of California, Berkeley

Neuropathology Core Leaders and Key Personnel

John C. Morris, MD, Washington University St. Louis
 Richard Perrin MD, Washington University St. Louis
 Nigel J. Cairns, PhD, FRCPATH Washington University St. Louis—Past Investigator
 Erin Householder, MS, Washington University St. Louis
 Rev February 2021
 Erin Franklin, MS, Washington University, St. Louis
 Haley Bernhardt, BA, R. EEG T, Washington University, St. Louis
 Lisa Taylor-Reinwald, BA, HTL (ASCP), Washington University, St. Louis—Past Investigator

Biomarkers Core Leaders and Key Personnel

Leslie M. Shaw, PhD, Perelman School of Medicine, University of Pennsylvania (Co-PI)
 John Q. Trojanowski, MD, PhD, Perelman School of Medicine, University of Pennsylvania (Co-PI)
 Magdalena Korecka, PhD, Perelman School of Medicine, University of Pennsylvania,
 Michal Figurski, PhD Perelman School of Medicine, University of Pennsylvania,

Informatics Core Leaders and Key Personnel

Arthur W. Toga, PhD University of Southern California (Core PI)
 Karen Crawford, University of Southern California
 Scott Neu, PhD, University of Southern California

Genetics Core Leaders and Key Personnel

Andrew J. Saykin, PsyD, Indiana University School of Medicine (Core PI)
 Kwangsik Nho, PhD, Indiana University School of Medicine
 Shannon L. Risacher, PhD, Indiana University School of Medicine
 Liana G. Apostolova, MD, Indiana University School of Medicine
 Li Shen, PhD, UPenn School of Medicine
 Tatiana M. Foroud, PhD, NCRAD/Indiana University School of Medicine
 Kelly Nudelman, PhD, NCRAD/Indiana University School of Medicine
 Kelley Faber, MS, CCRC, NCRAD/Indiana University School of Medicine
 Kristi Wilmes, MS, CCRP, NCRAD/Indiana University School of Medicine

Initial Concept Planning & Development

Michael W. Weiner, MD, University of California, San Francisco
 Leon Thal, MD – Past Investigator, University of California, San Diego
 Zaven Khachaturian, PhD, Prevent Alzheimer's Disease 2020

NIA

John K. Hsiao, MD, National Institute on Aging

Part B: Investigators By Site**Oregon Health & Science University:**

Lisa C. Silbert, MD
 Betty Lind, BS
 Rachel Crissey
 Jeffrey A. Kaye, MD, – Past Investigator
 Raina Carter, BA – Past Investigator
 Sara Dolen, BS – Past Investigator
 Joseph Quinn, MD – Past Investigator

University of Southern California:

Lon S. Schneider, MD
 Sonia Pawluczyk, MD
 Mauricio Becerra, MD
 Liberty Teodoro, RN
 Karen Dagerman, MS
 Bryan M. Spann, DO, PhD – Past Investigator

University of California – San Diego:

James Brewer, MD, PhD
 Helen Vanderswag, RNRev February 2021
 Adam Fleisher, MD – Past Investigator

University of Michigan:

Jaimie Ziolkowski, MA, BS, TLLP
 Judith L. Heidebrink, MD, MS
 Lisa Zbizek-Nulph, MS
 Joanne L. Lord, LPN, BA, CCRC – Past Investigator
 Lisa Zbizek-Nulph, MS, CCRP

Mayo Clinic, Rochester:

Ronald Petersen, MD, PhD
 Sara S. Mason, RN
 Colleen S. Albers, RN
 David Knopman, MD
 Kris Johnson, RN

Baylor College of Medicine:

Javier Villanueva-Meyer, MD
 Valory Pavlik, PhD
 Nathaniel Pacini, MA
 Ashley Lamb, MA
 Joseph S. Kass, MD, LD, FAAN
 Rachelle S. Doody, MD, PhD – Past Investigator
 Victoria Shibley, MS – Past Investigator
 Munir Chowdhury, MBBS, MS – Past Investigator
 Susan Rountree, MD – Past Investigator
 Mimi Dang, MD – Past Investigator

Columbia University Medical Center:

Yaakov Stern, PhD
 Lawrence S. Honig, MD, PhD
 Akiva Mintz, MD, PhD

Washington University, St. Louis:

Beau Ances, MD, PhD, MSc
 John C. Morris, MD
 David Winkfield, BS
 Maria Carroll, RN, MSN, GCNS-BC
 Georgia Stobbs-Cucchi, RN, CCRP – Past Investigator
 Angela Oliver, RN, BSN, MSG – Past Investigator
 Mary L. Creech, RN, MSW – Past Investigator
 Mark A. Mintun, MD – Past Investigator
 Stacy Schneider, APRN, BC, GNP – Past Investigator

University of Alabama—Birmingham:

David Geldmacher, MD
 Marissa Natelson Love, MD
 Randall Griffith, PhD, ABPP – Past Investigator
 David Clark, MD – Past Investigator
 John Brockington, MD – Past Investigator
 Daniel Marson, JD, PhD – Past Investigator

Mount Sinai School of Medicine:

Hillel Grossman, MD
 Martin A. Goldstein, MD
 Jonathan Greenberg, BA
 Effie Mitsis, PhD – Past Investigator

Rush University Medical Center:

Raj C. Shah, MD
 Melissa Lamar, PhD
 Patricia Samuels

Wien Center:

Ranjan Duara, MD
 Maria T. Greig-Custo, MD
 Rosemarie Rodriguez, PhD

Johns Hopkins University:

Marilyn Albert, PhD
 Chiadi Onyike, MD
 Leonie Farrington, RN
 Scott Rudow, BS
 Rottislav Brichko, BS
 Stephanie Kielb, BS – Past Investigator

University of South Florida: USF Health Byrd Alzheimer's Institute:

Amanda Smith, MD
 Balebail Ashok Raj, MD – Past Investigator
 Kristin Fargher, MD – Past Investigator

New York University:

Martin Sadowski, MD, PhD
 Thomas Wisniewski, MD

Melanie Shulman, MD
 Arline Faustin, MD
 Julia Rao, PhD
 Karen M. Castro, BA
 Anasztasia Ulysse, BA
 Shannon Chen, BA
 Mohammed O. Sheikh, MD – Past Investigator
 Jamika Singleton-Garvin, CCRP – Past Investigator

Duke University Medical Center:

P. Murali Doraiswamy, MBBS, FRCP
 Jeffrey R. Petrella, MD
 Olga James, MDRev February 2021
 Terence Z. Wong, MD
 Salvador Borges-Neto, MD – Past Investigator

University of Pennsylvania:

Jason H. Karlawish, MD
 David A. Wolk, MD
 Sanjeev Vaishnavi, MD
 Christopher M. Clark, MD – Past Investigator
 Steven E. Arnold, MD – Past Investigator

University of Kentucky:

Charles D. Smith, MD
 Gregory A. Jicha, MD, PhD
 Riham El Khouli, MD
 Flavius D. Raslau, MD

University of Pittsburgh:

Oscar L. Lopez, MD
 MaryAnn Oakley, MA
 Donna M. Simpson, CRNP, MPH

University of Rochester Medical Center:

Anton P. Porsteinsson, MD
 Kim Martin, RN
 Nancy Kowalski, MS, RNC
 Melanie Keltz, RN
 Bonnie S. Goldstein, MS, NP – Past Investigator
 Kelly M. Makino, BS – Past Investigator
 M. Saleem Ismail, MD – Past Investigator
 Connie Brand, RN – Past Investigator

University of California Irvine IMIND:

Gaby Thai, MD
 Aimee Pierce, MD
 Beatriz Yanez, RN
 Elizabeth Sosa, PhD
 Megan Witbracht, PhD

University of Texas Southwestern Medical School:

Brendan Kelley, MD
 Trung Nguyen, MD
 Kyle Womack, MD
 Dana Mathews, MD, PhD – Past Investigator
 Mary Quiceno, MD – Past Investigator

Emory University:

Allan I. Levey, MD, PhD
 James J. Lah, MD, PhD
 Ihab Hajjar, MD
 Janet S. Cellar, DNP, PMHCNS-BC – Past Investigator

University of Kansas, Medical Center:

Jeffrey M. Burns, MD
 Russell H. Swerdlow, MD
 William M. Brooks, PhD

University of California, Los Angeles:

Daniel H.S. Silverman, MD, PhD
 Sarah Kremen, MD
 Liana Apostolova, MD – Past Investigator
 Kathleen Tingus, PhD – Past Investigator
 Po H. Lu, PsyD – Past Investigator
 George Bartzokis, MD – Past Investigator
 Ellen Woo, PhD – Past Investigator
 Edmond Teng, MD, PhD – Past Investigator

Mayo Clinic, Jacksonville:

Neill R Graff-Radford, MBBCH, FRCP (London)
 Francine Parfitt, MSH, CCRC
 Kim Poki-Walker, BA

Indiana University:

Martin R. Farlow, MD
 Ann Marie Hake, MD – Past Investigator
 Brandy R. Matthews, MD – Past Investigator
 Jared R. Brosch, MD
 Scott Herring, RN, CCRC

Yale University School of Medicine:

Christopher H. van Dyck, MD
 Adam P. Mecca, MD, PhD
 Adam P. Mecca, MD, PhD
 Susan P. Good, APRN
 Martha G. MacAvoy, PhD
 Richard E. Carson, PhD
 Pradeep Varma, MD

McGill Univ., Montreal-Jewish General Hospital:

Howard Chertkow, MD
 Susan Vaitekunis, MD
 Chris Hosein, MEd

Sunnybrook Health Sciences, Ontario:

Sandra Black, MD, FRCPC
 Bojana Stefanovic, PhD
 Chris (Chinthaka) Heyn, BSC, PhD, MD, FRCPCRev February 2021

U.B.C. Clinic for AD & Related Disorders:

Ging-Yuek Robin Hsiung, MD, MHSc, FRCPC
 Ellen Kim, BA
 Benita Mudge, BS
 Vesna Sossi, PhD

Howard Feldman, MD, FRCPC – Past Investigator
Michele Assaly, MA – Past Investigator

St. Joseph's Health Care:

Elizabeth Finger, MD
Stephen Pasternak, MD
Irina Rachinsky, MD
Andrew Kertesz, MD – Past Investigator
Dick Drost, MD – Past Investigator
John Rogers, MD – Past Investigator

Northwestern University:

Ian Grant, MD
Brittanie Muse, MSPH
Emily Rogalski, PhD
Jordan Robson
M.-Marsel Mesulam, MD – Past Investigator
Diana Kerwin, MD – Past Investigator
Chuang-Kuo Wu, MD, PhD – Past Investigator
Nancy Johnson, PhD – Past Investigator
Kristine Lipowski, MA – Past Investigator
Sandra Weintraub, PhD – Past Investigator
Borna Bonakdarpour, MD – Past Investigator

Nathan Kline Institute:

Nunzio Pomara, MD
Raymundo Hernando, MD
Antero Sarrael, MD

University of California, San Francisco:

Howard J. Rosen, MD
Bruce L. Miller, MD
David Perry, MD

Georgetown University Medical Center:

Raymond Scott Turner, MD, PhD
Kathleen Johnson, NP
Brigid Reynolds, NP
Kelly MCCann, BA
Jessica Poe, BS

Brigham and Women's Hospital:

Reisa A. Sperling, MD
Keith A. Johnson, MD
Gad A. Marshall, MD

Stanford University:

Jerome Yesavage, MD
Joy L. Taylor, PhD
Steven Chao, MD, PhD
Jaila Coleman, BA
Jessica D. White, BA – Past Investigator
Barton Lane, MD – Past Investigator
Allyson Rosen, PhD – Past Investigator
Jared Tinklenberg, MD – Past Investigator

Banner Sun Health Research Institute:

Christine M. Belden, PsyD
Alireza Atri, MD, PhD
Bryan M. Spann, DO, PhD
Kelly A. Clark
Edward Zamrini, MD – Past Investigator
Marwan Sabbagh, MD – Past Investigator

Boston University:

Ronald Killiany, PhD
Robert Stern, PhD
Jesse Mez, MD, MS
Neil Kowall, MD – Past Investigator
Andrew E. Budson, MD – Past Investigator

Howard University:

Thomas O. Obisesan, MD, MPH
Oyonomo E. Ntekim, MD, PhD
Saba Wolday, MSc
Javed I. Khan, MD
Evaristus Nwulia, MD
Sheeba Nadarajah, PhD

Case Western Reserve University:

Alan Lerner, MD
Paula Ogrocki, PhD
Curtis Tatsuoka, PhD
Parianne Fatica, BA, CCRC

University of California, Davis – Sacramento:

Evan Fletcher, PhD
Pauline Maillard, PhD
John Olichney, MD
Charles DeCarli, MD
Owen Carmichael, PhD – Past Investigator

Dent Neurologic Institute:

Vernice Bates, MDRev February 2021
Horacio Capote, MD
Michelle Rainka, PharmD, CCRP

Parkwood Institute:

Michael Borrie, MB ChB
T-Y Lee, PhD
Rob Bartha, PhD

University of Wisconsin:

Sterling Johnson, PhD
Sanjay Asthana, MD
Cynthia M. Carlsson, MD, MS

Banner Alzheimer's Institute:

Allison Perrin, PhD
Anna Burke, PhD – Past Investigator

Ohio State University:

Douglas W. Scharre, MD
 Maria Katakai, MD, PhD
 Rawan Tarawneh, MD
 Brendan Kelley, MD – Past Investigator

Albany Medical College:

David Hart, MD
 Earl A. Zimmerman, MD
 Dzintra Celmins, MD

University of Iowa College of Medicine

Delwyn D. Miller, PharmD, MD
 Laura L. Boles Ponto, PhD
 Karen Ekstam Smith, RN
 Hristina Koleva, MD
 Hyungsub Shim, MD
 Ki Won Nam, MD – Past Investigator
 Susan K. Schultz, MD – Past Investigator

Wake Forest University Health Sciences:

Jeff D. Williamson, MD, MHS
 Suzanne Craft, PhD
 Jo Cleveland, MD
 Mia Yang, MD – Past Investigator
 Kaycee M. Sink, MD, MAS – Past Investigator

Rhode Island Hospital:

Brian R. Ott, MD
 Jonathan Drake, MD
 Geoffrey Tremont, PhD
 Lori A. Daiello, Pharm.D, ScM
 Jonathan D. Drake, MD

Cleveland Clinic Lou Ruvo Center for Brain Health:

Marwan Sabbagh, MD
 Aaron Ritter, MD
 Charles Bernick, MD, MPH – Past Investigator
 Donna Munic, PhD – Past Investigator
 Akiva Mintz, MD, PhD – Past Investigator

Roper St. Francis Healthcare:

Abigail O'Connell, MS, APRN, FNP-C
 Jacobo Mintzer, MD, MBA
 Arthur Williams, BS

Houston Methodist Neurological Institute:

Joseph Masdeu, PhD

Barrow Neurological Institute:

Jiong Shi, MD, PhD
 Angelica Garcia, BS
 Marwan Sabbagh – Past Investigator

Vanderbilt University Medical Center:

Paul Newhouse, PhD

Long Beach VA Neuropsychiatric Research Program:

Steven Potkin, PhD

Butler Hospital Memory and Aging Program:

Stephen Salloway, MD, MS
 Paul Malloy, PhD
 Stephen Correia, PhD

Neurological Care of CNY:

Smita Kittur, MD – Past Investigator

Hartford Hospital, Olin Neuropsychiatry Research Center:

Godfrey D. Pearson, MD – Past Investigator
 Karen Blank, MD – Past Investigator
 Karen Anderson, RN – Past Investigator

Dartmouth-Hitchcock Medical Center:

Laura A. Flashman, PhD – Past Investigator
 Marc Seltzer, MD – Past Investigator
 Mary L. Hynes, RN, MPH – Past Investigator
 Robert B. Santulli, MD – Past Investigator, Rev February 2021

Cornell University

Norman Relkin, MD, PhD – Past Investigator
 Gloria Chiang, MD – Past Investigator
 Michael Lin, MD – Past Investigator
 Lisa Ravdin, PhD – Past Investigator
 Athena Lee, PhD, Rev February 2021

II. DOD ADNI**Part A: Leadership and Infrastructure****Principal Investigator**

Michael W. Weiner, MD, University of California, San Francisco

ATRI PI and Director of Coordinating Center Clinical Core

Paul Aisen, MD, University of Southern California
 Co Director Clinical Core Ron Petersen Mayo Clinic

Executive Committee

Michael W. Weiner, MD, University of California, San Francisco
 Paul Aisen, MD, University of Southern California
 Ronald Petersen, MD, PhD, Mayo Clinic, Rochester,
 Robert C. Green, MD, MPH, Brigham and Women's Hospital/
 Harvard Medical School
 Danielle Harvey, PhD, University of California, Davis
 Clifford R. Jack, Jr., MD, Mayo Clinic, Rochester
 William Jagust, MD, University of California, Berkeley
 John C. Morris, MD, Washington University St. Louis
 Andrew J. Saykin, PsyD, Indiana University
 Leslie M. Shaw, PhD, Perelman School of Medicine, University of
 Pennsylvania
 Arthur W. Toga, PhD, University of Southern California
 John Q. Trojanowki, MD, PhD, Perelman School of Medicine, University
 of Pennsylvania

Psychological Evaluation/PTSD Core

Thomas Neylan, MD, University of California, San Francisco

Traumatic Brain Injury/TBI Core

Jordan Grafman, PhD, Rehabilitation Institute of Chicago, Feinberg School of Medicine,
Northwestern University

Data and Publication Committee (DPC)

Robert C. Green, MD, MPH, BWH/HMS (Chair)

Resource Allocation Review Committee

Tom Montine, MD, PhD, University of Washington (Chair)

Clinical Core Leaders and Key Personnel

Michael W. Weiner MD, Core PI

Ronald Petersen, MD, PhD, Mayo Clinic, Rochester (Core PI)

Paul Aisen, MD, University of Southern California (Core PI)

Gustavo Jimenez, MBS, University of Southern California

Michael Donohue, PhD, University of Southern California

Devon Gessert, BS, University of Southern California

Jennifer Salazar, MBS, University of Southern California

Caileigh Zimmerman, MS, University of Southern California

Sarah Walter, MSc, University of Southern California

Olusegun Adegoke, MSc, University of Southern California

Payam Mahboubi, MPH, University of Southern California, Rev February 2021

Lindsey Hergesheimer, BS,

University of Southern California

Sarah Danowski, MA, University of Southern California

Godfrey Coker, MBA, MPH, University of Southern California

Taylor Clanton, MPH, University of Southern California

Jeremy Pizzola, BA, University of Southern California

Elizabeth Shaffer, BS, University of Southern California

Catherine Nguyen-Barrera, MS, University of Southern California

San Francisco Veterans Affairs Medical Center

Thomas Neylan, MD, University of California, San Francisco

Jacqueline Hayes, University of California, San Francisco

Shannon Finley, University of California, San Francisco

Biostatistics Core Leaders and Key Personnel

Danielle Harvey, PhD, University of California, Davis (Core PI)

Michael Donohue, PhD, University of California, San Diego

MRI Core Leaders and Key Personnel

Clifford R. Jack, Jr., MD, Mayo Clinic, Rochester (Core PI)

Matthew Bernstein, PhD, Mayo Clinic, Rochester

Bret Borowski, RT, Mayo Clinic

Jeff Gunter, PhD, Mayo Clinic

Matt Senjem, MS, Mayo Clinic

Kejal Kantarci, Mayo Clinic

Chad Ward, Mayo Clinic

Duygu Tosun-Turgut, PhD, University of California, San Francisco

Stephanie Rossi Chen, BA, NCIRE/The Veterans Health Research Institute

PET Core Leaders and Key Personnel

Susan Landau, PhD, University of California, Berkeley (Core PI)

Robert A. Koeppe, PhD, University of Michigan

Norm Foster, MD, University of Utah

Eric M. Reiman, MD, Banner Alzheimer's Institute

Kewei Chen, PhD, Banner Alzheimer's Institute

Neuropathology Core Leaders

John C. Morris, MD, Washington University, St. Louis

Richard J. Perrin, MD, PhD, Washington University, St. Louis

Erin Franklin, MS, Washington University, St. Louis

Biomarkers Core Leaders and Key Personnel

Leslie M. Shaw, PhD, Perelman School of Medicine, University of Pennsylvania

John Q. Trojanowki, MD, PhD, Perelman School of Medicine, University of Pennsylvania

Magdalena Korecka, PhD, Perelman School of Medicine, University of Pennsylvania

Michal Figurski, PhD, Perelman School of Medicine, University of Pennsylvania

Informatics Core Leaders and Key Personnel

Arthur W. Toga, PhD, University of Southern California (Core PI)

Karen Crawford, University of Southern California, Rev February 2021

Scott Neu, PhD, University of Southern California

Genetics Core Leaders and Key Personnel

Andrew J. Saykin, PsyD, University

Tatiana M. Foroud, PhD, Indiana University

Steven Potkin, MD, UC Irvine

Li Shen, PhD, Indiana University

Kelley Faber, MS, CCRC, Indiana University

Sungeun Kim, PhD, Indiana University

Kwangsik Nho, PhD, Indiana University

Kristi Wilmes, MS, CCRP, NCRAD

Part B: Investigators By Site**University of Southern California:**

Lon S. Schneider, MD

Sonia Pawluczuk, MD

Mauricio Becerra, MD

Liberty Teodoro, RN

Karen Dagerman, MS

Bryan M. Spann, DO, PhD – Past Investigator

University of California, San Diego:

James Brewer, MD, PhD

Helen Vanderswag, RN

Adam Fleisher, MD – Past Investigator

Columbia University Medical Center:

Yaakov Stern, PhD

Lawrence S. Honig, MD, PhD

Akiva Mintz, MD, PhD

Rush University Medical Center:

Raj C. Shah, MD
Ajay Sood, MD, PhD
Kimberly S. Blanchard, DNP, APRN, NP-C
Debra Fleischman, PhD – Past Investigator
Konstantinos Arfanakis, PhD – Past Investigator

Wien Center:

Ranjan Duara MD, PI
Daniel Varon MD, Co-PI
Maria T Greig, HP, Coordinator

Duke University Medical Center:

P. Murali Doraiswamy, MBBS, FRCP
Jeffrey R. Petrella, MD
Olga James, MD – Past Investigator
Salvador Borges-Neto, MD
Terence Z. Wong, MD

University of Rochester Medical Center:

Anton P. Porsteinsson, MD
Bonnie Goldstein, MS, NP
Kimberly S. Martin, RN

University of California, Irvine:

Gaby Thai, MD
Aimee Pierce, MD
Christopher Reist, MD
Beatriz Yanez, RN
Elizabeth Sosa, PhD
Megan Witbracht, PhD

Premiere Research Inst (Palm Beach Neurology):

Carl Sadowsky, MD
Walter Martinez, MD
Teresa Villena, MD

University of California, San Francisco:

Howard Rosen, MD
David Perry

Georgetown University Medical Center:

Raymond Scott Turner, MD, PhD
Kathleen Johnson, NP
Brigid Reynolds, NP
Kelly MCCann, BA
Jessica Poe, BS

Brigham and Women's Hospital:

Reisa A. Sperling, MD
Keith A. Johnson, MD, Rev February 2021
Gad Marshall, MD

Banner Sun Health Research Institute:

Christine M. Belden, PsyD
Alireza Atri, MD, PhD
Bryan M. Spann, DO, PhD

Kelly A. Clark
Edward Zamrini, MD – Past Investigator
Marwan Sabbagh, MD – Past Investigator

Howard University:

Thomas O. Obisesan, MD, MPH
Oyonomo E. Ntekim, MD, PhD
Saba Wolday, MSc
Evaristus Nwulia, MD
Sheeba Nadarajah, PhD, RN

University of Wisconsin:

Sterling Johnson, PhD
Sanjay Asthana, MD
Cynthia M. Carlsson, MD, MS

University of Washington:

Elaine R. Peskind, MD
Eric C. Petrie, MD, MS
Gail Li, MD, PhD

Stanford University:

Jerome Yesavage, MD
Joy L. Taylor, PhD
Steven Chao, MD, PhD
Jaila Coleman, BA
Jessica D. White, BA – Past Investigator
Barton Lane, MD – Past Investigator
Allyson Rosen, PhD – Past Investigator
Jared Tinklenberg, MD – Past Investigator

Cornell University:

Michael Lin, PhD
Gloria Chiang, MD
Lisa Ravdin, PhD
Norman Relkin, MD, PhD – Past Investigator

Roper St. Francis Healthcare:

Abigail O'Connell, MS, APRN, FNP-C
Jacob Mintzer, MD, MBA
Arthur Williams, BS, Rev February 2021

III. ADNI Depression**Part A: Leadership and Infrastructure****Principal Investigator**

Scott Mackin, PhD, University of California, San Francisco

ATRI Coordinating Center Clinical Core

Paul Aisen, MD, University of Southern California
Rema Raman, PhD, University of Southern California
Gustavo Jimenez-Maggiore, MBS, University of Southern California
Michael Donohue, PhD, University of Southern California
Devon Gessert, BS, University of Southern California
Jennifer Salazar, MBS, University of Southern California
Caileigh Zimmerman, MS, University of Southern California
Sarah Walter, MSc, University of Southern California

Olusegun Adegoke, MSc, University of Southern California
Payam Mahboubi, MPH, University of Southern California

Executive Committee

Scott Mackin, PhD, University of California, San Francisco
Michael W. Weiner, MD, University of California, San Francisco
Paul Aisen, MD, University of Southern California
Rema Raman, PhD, University of Southern California,
Clifford R. Jack, Jr., MD, Mayo Clinic, Rochester
Susan Landau, PhD, University of California, Berkeley
Andrew J. Saykin, PsyD, Indiana University
Arthur W. Toga, PhD, University of Southern California
Charles DeCarli, MD, University of California, Davis
Robert A. Koeppe, PhD, University of Michigan

Data and Publication Committee (DPC)

Robert C. Green, MD, MPH, BWH/HMS (Chair)
Erin Drake, MA, BWH/HMS (Director)

Clinical Core Leaders

Michael W. Weiner, MD, Core PI
Paul Aisen, MD, University of Southern California
Rema Raman, PhD, University of Southern California
Mike Donohue, PhD, University of Southern California

Psychiatry Site Leaders and Key Personnel

Scott Mackin, PhD, University of California, San Francisco
Craig Nelson, MD, University of California, San Francisco
David Bickford, BA, University of California, San Francisco
Meryl Butters, PhD, University of Pittsburgh
Michelle Zmuda, MA, University of Pittsburgh

MRI Core Leaders and Key Personnel

Clifford R. Jack, Jr., MD, Mayo
Clinic, Rochester (Core PI)
Matthew Bernstein, PhD, Mayo Clinic, Rochester
Bret Borowski, RT, Mayo Clinic, Rochester
Jeff Gunter, PhD, Mayo Clinic, Rochester
Matt Senjem, MS, Mayo Clinic, Rochester

Kejal Kantarci, MD, Mayo Clinic, Rochester
Chad Ward, BA, Mayo Clinic, Rochester
Denise Reyes, BS, Mayo Clinic, Rochester

PET Core Leaders and Key Personnel

Robert A. Koeppe, PhD, University of Michigan
Susan Landau, PhD, University of California, Berkeley

Informatics Core Leaders and Key Personnel

Arthur W. Toga, PhD, University of Southern California (Core PI)
Karen Crawford, University of Southern California
Scott Neu, PhD, University of Southern California

Genetics Core Leaders and Key Personnel

Andrew J. Saykin, PsyD, Indiana University
Tatiana M. Foroud, PhD, Indiana University
Kelley M. Faber, MS, CCRC, Indiana University
Kwangsik Nho, PhD, Indiana University
Kelly N. Nudelman, Indiana University

Part B: Investigators By Site

University of California, San Francisco:

Scott Mackin, PhD
Howard Rosen, MD
Craig Nelson, MD
David Bickford, BA
Yiu Ho Au, BA
Kelly Scherer, BS
Daniel Catalinotto, BA
Samuel Stark, BA
Elise Ong, BA
Dariella Fernandez, BA

University of Pittsburgh:

Meryl Butters, PhD
Michelle Zmuda, BS
Oscar L. Lopez, MD
MaryAnn Oakley, MA
Donna M. Simpson, CRNP, MPH