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Authors

Wang, Xin

Wang, Xinran

Edland, Steven D

et al.

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RESEARCH ARTICLE

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

Xin Wang[1] | **Xinran Wang**[2] | **Steven D. Edland**[1,2] | **Iris J. Broce**[1] | **Anders M. Dale**[1] | **Sarah J. Banks**[1] | **for the Alzheimer's Disease Neuroimaging Initiative**

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

[2]Division 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

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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.

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 amnestic 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 (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.

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.

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 (ε2/ε4). 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 ≥ 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 Preclinical 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* ε4 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 ≥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* ε4 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+	G+T−	G+T+
N	141	35	73	21	145	41	122	107
BL_age, mean (SD)	74.62 (6.43)*	77.77 (6.45)	72.81 (5.87)**	78.88 (6.95)	72.50 (7.92)	76.70 (7.60)**	70.69 (7.80)	72.84 (7.10)
Education (years), mean (SD)	16.51 (2.72)	17.03 (2.48)	16.37 (2.55)	17.67 (2.29)	16.19 (2.73)	16.02 (2.80)	16.40 (2.58)	16.20 (2.83)
Gender, women, *N* (%)	71 (50.4)*	16 (45.7)	48 (65.8)**	5 (23.8)	63 (43.4)	15 (36.6)	50 (41.0)	46 (43.0)
APOE ε4 carriers, *N* (%)	0 (0.0)**	0 (0.0)**	59 (80.8)	17 (81.0)	2 (1.4)**	0 (0.0)**	97 (79.5)**	101 (94.4)
BL_Amyloid positivity, *N* (%)	34 (24.1)**	14 (40.0)*	33 (45.2)*	16 (76.2)	49 (33.8)**	22 (53.7)**	70 (57.4)**	95 (88.8)
BL_MMSE, mean (SD)	29.04 (1.21)	29.14 (1.22)	29.08 (1.20)	29.00 (1.18)	28.37 (1.48)**	28.29 (1.68)*	28.17 (1.67)**	27.39 (1.91)
BL_CDR-SB, mean (SD)	0.04 (0.17)	0.14 (0.38)	0.09 (0.28)	0.12 (0.27)	1.45 (0.91)**	1.22 (0.78)**	1.41 (0.86)**	1.82 (1.06)
BL_mPACCdigit, mean (SD)	0.01 (2.85)	0.21 (2.72)	0.14 (2.85)	−1.38 (2.84)	−4.14 (3.82)**	−4.37 (3.65)**	−4.74 (3.46)**	−7.67 (4.73)
BL_mPACCtrailsB, mean (SD)	0.05 (2.69)	0.18 (2.31)	0.11 (2.61)	−1.16 (2.68)	−3.51 (3.53)**	−4.00 (3.39)**	−3.96 (2.94)**	−6.62 (4.18)
PHS, mean (SD)	−0.37 (0.27)**	−0.32 (0.22)*	0.69 (0.35)	0.88 (0.57)	−0.31 (0.23)**	−0.35 (0.24)**	0.88 (0.57)*	1.08 (0.51)
BL_ptau181 (pg/mL), mean (SD)	11.10 (4.87)**	31.27 (12.41)	12.81 (3.80)**	26.86 (6.58)	12.15 (4.49)**	30.74 (18.00)	12.01 (4.31)**	29.24 (10.36)
TIME (years), mean (SD)	5.68 (3.08)	6.51 (3.03)	4.92 (2.86)	5.62 (3.07)	5.30 (2.97)**	3.67 (2.60)	4.58 (3.08)**	3.49 (2.41)

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 Examnation; mPACCdigit, PACC with digit symbol substitution; mPACCtrailsB, PACC with Trails B; PHS, polygenic hazard score.

*$p < 0.0125$.

**$p < 0.005$.

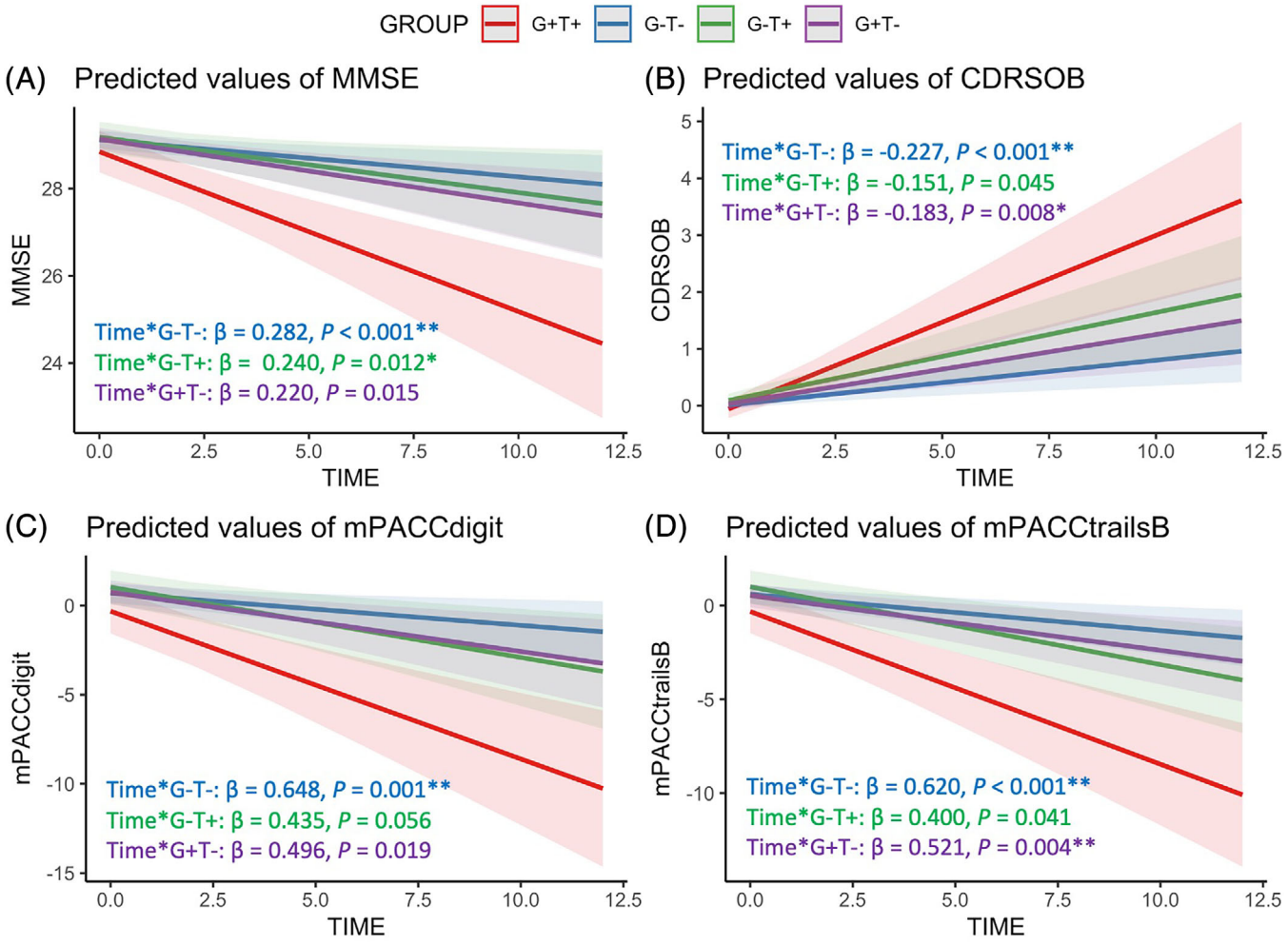

FIGURE 1 LME model with time and group interaction on cognitive outcomes in CN. Interaction plots between time and group on different cognitive outcomes showing the estimated mean cognitive trajectory in CN participants. (A) MMSE; (B) CDR-SB; (C) mPACCdigit; (D) mPACCtrailsB. Interaction coefficients 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* ε4 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 x group G−T−: $\beta = 0.282$, $p < 0.001$; time × 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 × group G+T−: $\beta = 0.220$, $p = 0.015$) (Figure 1A). The G−T− and G+T− groups interacted significantly with time on the CDR−SB (time x G−T−: interaction $\beta = -0.227$, $p < 0.001$; time × G+T−: interaction $\beta = -0.183$, $p = 0.008$) (Figure 1B). For mPACCdigit, there were significant interaction effects of time and G−T− (time x 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 × G−T−: interaction $\beta = 0.620$, $p < 0.001$; time × 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

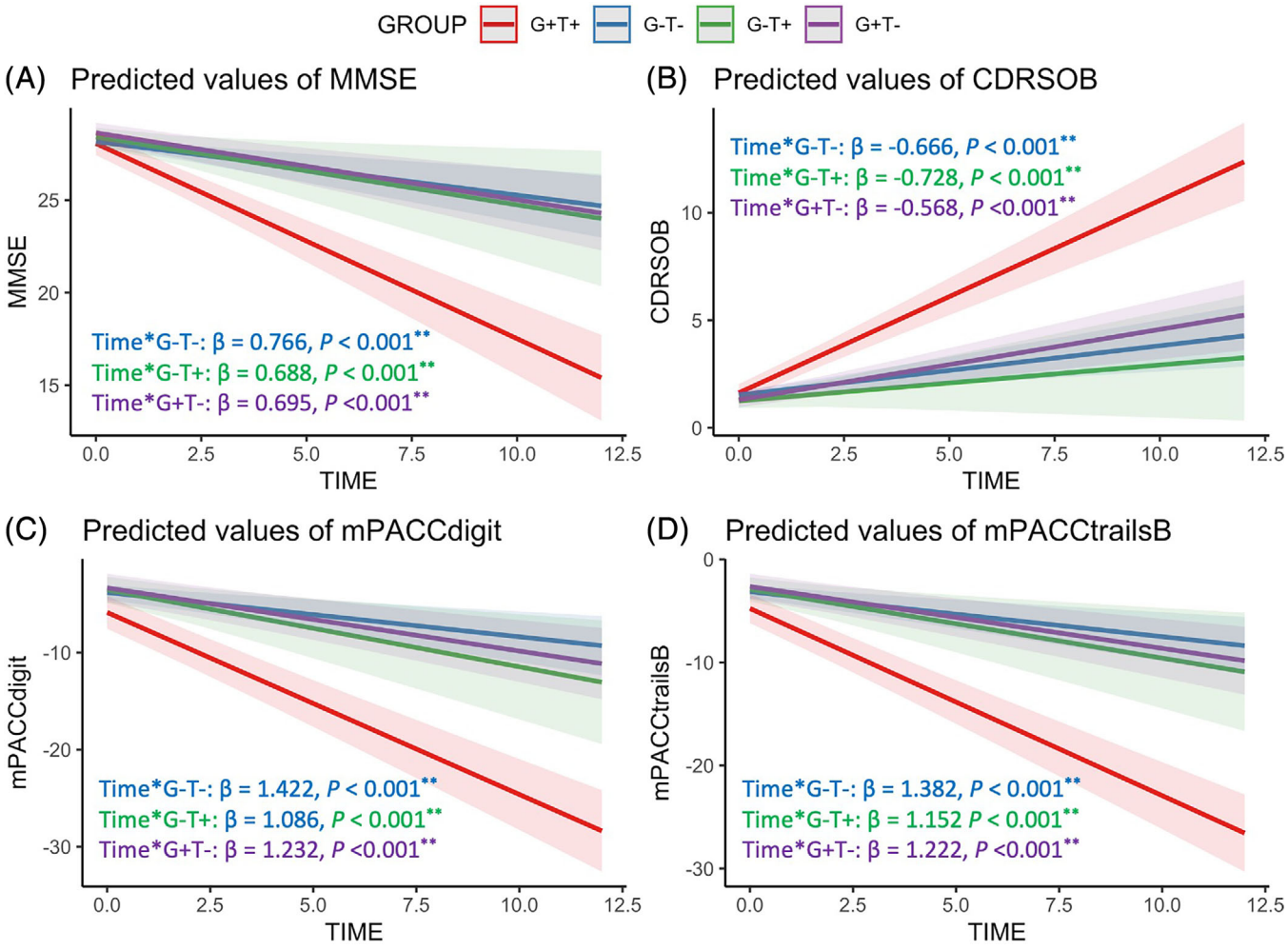

FIGURE 2 LME with time and group interaction on cognitive outcomes in MCI. Interaction plots between time and group on different cognitive outcomes showing the estimated mean cognitive trajectory in participants with MCI. (A) MMSE; (B) CDR-SB; (C) mPACCdigit; (D) mPACCtrailsB. Interaction coefficients 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

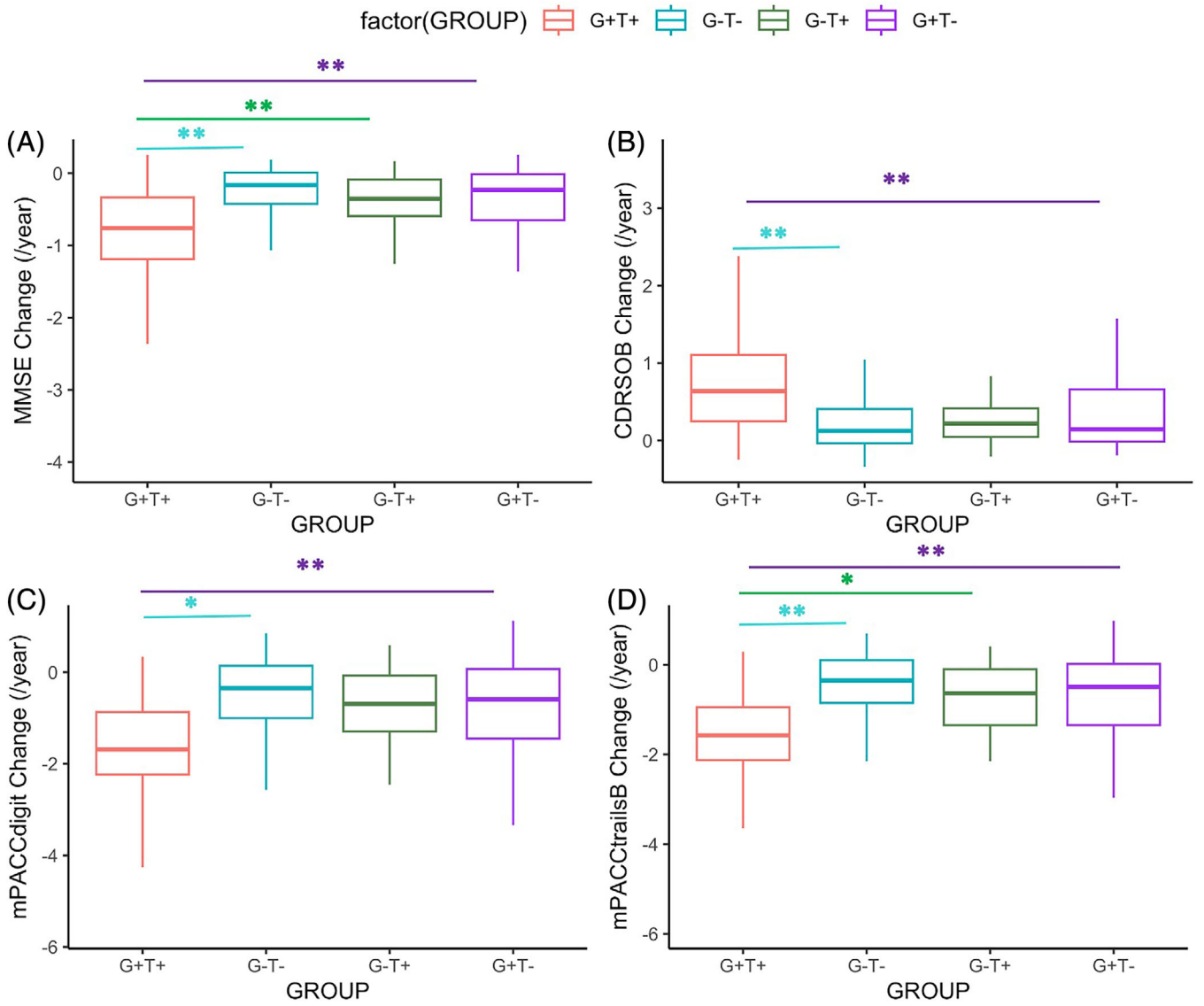

FIGURE 3 Cognitive change comparison between groups in CN. Bar plots showing the comparison between different cognitive outcomes (A) MMSE; (B) CDR-SB; (C) mPACCdigit; (D) mPACCtrailsB between groups in CN (adjusting for baseline age, sex, and education; G+T+ as the reference group). *$p < 0.0125$; **$p < 0.005$. 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

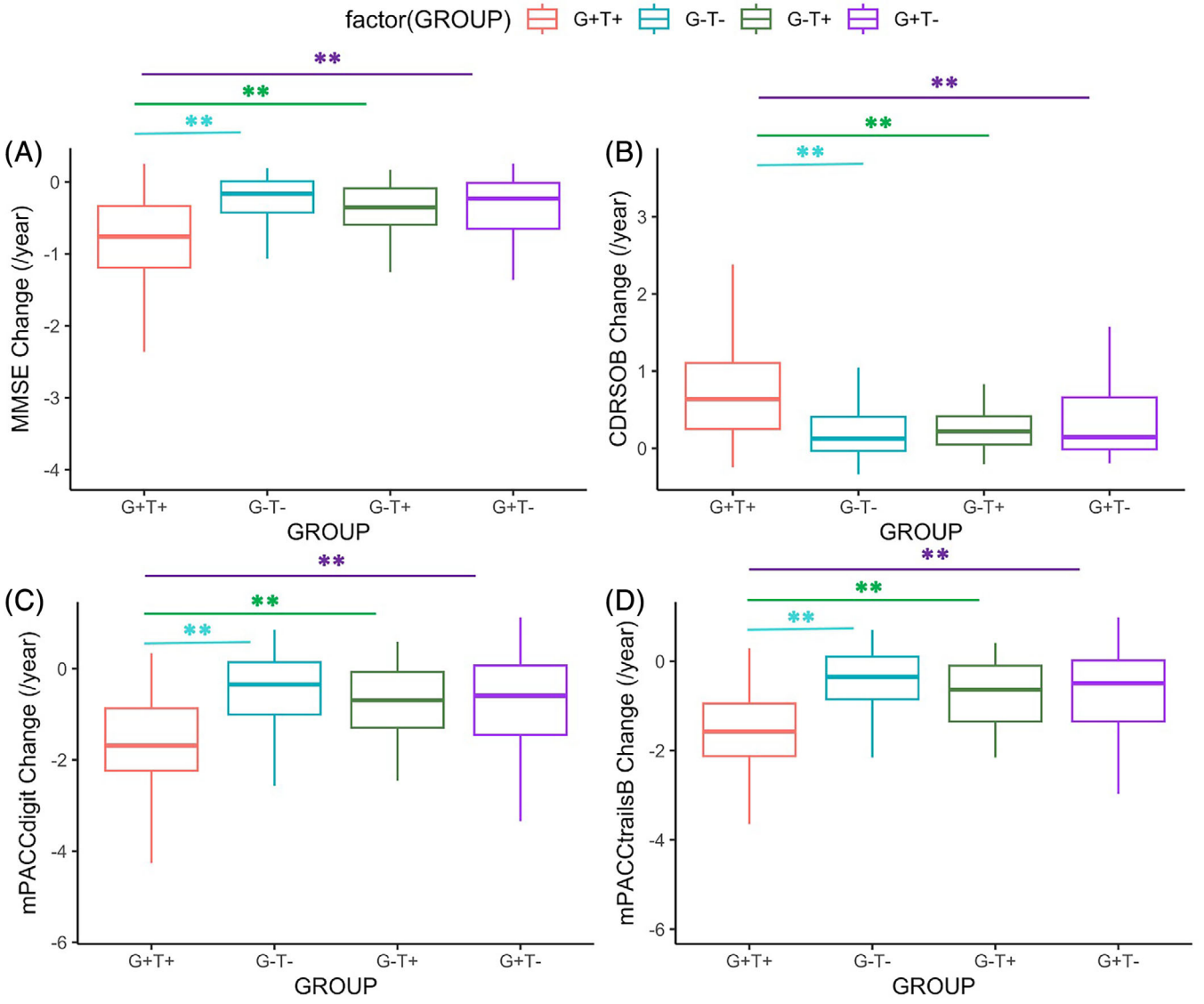

FIGURE 4 Cognitive change comparison between groups in MCI. Bar plots showing the comparison between different cognitive outcomes (A) MMSE; (B) CDR-SB; (C) mPACCdigit; (D) mPACCtrailsB between groups in participants with MCI (adjusting for baseline age, sex and education; G+T+ as the reference group). *$p < 0.0125$; **$p < 0.005$. 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 likelihood of detecting treatment effects. In future clinical trials, employing a multistep screening process wherein high PHS participants are prescreened 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.

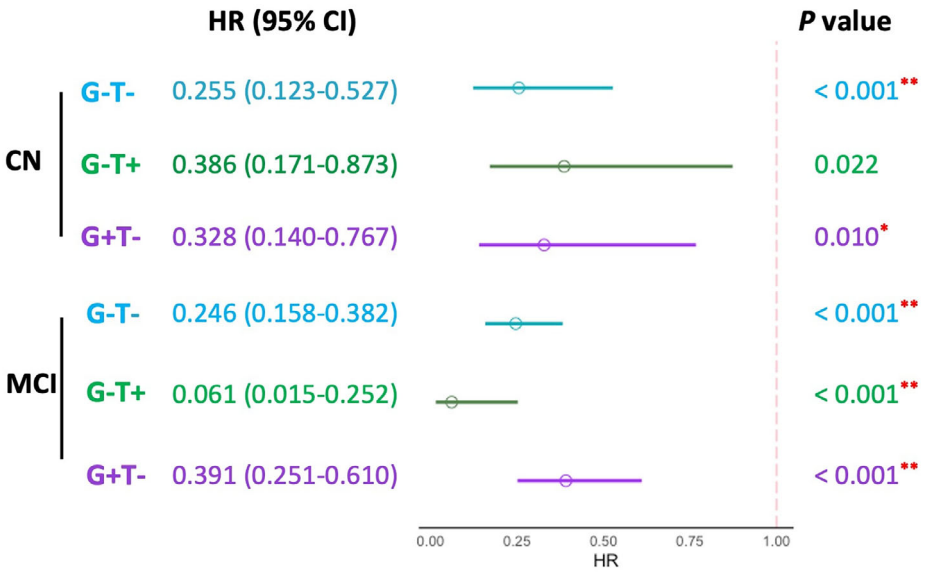

FIGURE 5 HR of MCI/AD conversion from CN and AD conversion from MCI. Cox proportional risk model estimating the HR of MCI/AD in CN and AD in MCI, adjusting for age, sex, and education. *$p < 0.0125$; **$p < 0.005$. AD, Alzheimer's disease, CN, cognitively normal; HR, hazard ratio; MCI, mild cognitive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

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; mPACCtrailB, modified Preclinical Alzheimer's Cognitive Composite with Trails B.

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.

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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.

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SUPPORTING INFORMATION

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

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APPENDIX

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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.

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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

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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
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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

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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 CaliforniaRev 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
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Ian Malone, PhD, University College London
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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
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Evan Fletcher, PhD, University of California, Davis
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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. LouisRev 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. Trojanowki, 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

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Raj C. Shah, MD
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Ranjan Duara, MD
Maria T. Greig-Custo, MD
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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
Anaztasia 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

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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
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Bonnie S. Goldstein, MS, NP – Past Investigator
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M. Saleem Ismail, MD – Past Investigator
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Gaby Thai, MD
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Beatriz Yanez, RN
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Megan Witbracht, PhD

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

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Adam P. Mecca, MD, PhD
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Martha G. MacAvoy, PhD
Richard E. Carson, PhD
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Bojana Stefanovic, PhD
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Ellen Kim, BA
Benita Mudge, BS
Vesna Sossi, PhD

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Michele Assaly, MA – Past Investigator

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Jared Tinklenberg, MD – Past Investigator

Banner Sun Health Research Institute:
Christine M. Belden, PsyD
Alireza Atri, MD, PhD
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Edward Zamrini, MD – Past Investigator
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Owen Carmichael, PhD – Past Investigator

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Michelle Rainka, PharmD, CCRP

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T-Y Lee, PhD
Rob Bartha, PhD

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

Banner Alzheimer's Institute:
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Anna Burke, PhD – Past Investigator

Ohio State University:
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Maria Kataki, MD, PhD
Rawan Tarawneh, MD
Brendan Kelley, MD – Past Investigator

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Jonathan D. Drake, MD

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Donna Munic, PhD – Past Investigator
Akiva Mintz, MD, PhD – Past Investigator

Roper St. Francis Healthcare:
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Jacobo Mintzer, MD, MBA
Arthur Wiliams, 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. Pearlson, 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 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, 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
Oyonumo 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'Connelll, MS, APRN, FNP-C
Jacobo Mintzer, MD, MBA
Arthur Wiliams, 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-Maggiora, 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, BWM/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