Certificate of Action

Board Action Date: 08/19/2026	**Work Order Number**: 1-1982874-1
Sponsor: Prevention Research Consortium Corporation	**Protocol Approval Expires**: 03/25/2027
Sponsor Protocol Number: None **Amended Sponsor Protocol Number:**	**Continuing Review Frequency**: Annually
IRB Tracking Number: 20260518	
Protocol Title: Assessing Tools that Predict and Stage Mild Cognitive Impairment	

THE FOLLOWING ITEMS ARE APPROVED:
Advertisement - Email - Dear (Contact First Name), GeneMatch is partnering #46856428.0 - As Submitted (source: predictpredementia_email invite)
Advertisement - Summary - The Predict Predementia Study is #46856429.0 - As Submitted (source: predictpredementia_study summary)
Advertisement - Telephone PreScreening Script - Hello, may I please speak #46962963.0 - As Submitted (source: PREDICT_05_Telephone_PreScreening_Script)
Advertisement - Web Description - The Predict Predementia Study is #46856427.0 - As Submitted (source: predictpredementia_web description (1))
Results Disclosure and Genetic Counseling Plan #46962962.0 (source: PREDICT_04_Results_Disclosure_and_Genetic_Counseling_Plan)
Revised Protocol (08-10-2026) (source: clean Revised Protocol (4-10-2026))
SITE SPECIFIC Participant Information Sheet Telephone Pre-Screening #46986523.0 - As Submitted (source: PREDICT-03 Participant Information Sheet Telephone Pre-Screening (HRP-512))
Template Consent Form - Screening and HIPAA [S0]
Template Consent Form [S1]

Please note the following information about this review:
Please have all future participants sign the Consent Form(s) specified in this approval. This is the Board's minimum expectation - Sites can choose to inform or reconsent additional participants

The Board found that this research meets the requirements for a waiver of consent under 45 CFR 46 116(f)[2018 Requirements] 45 CFR 46.116(d) [Pre-2018 Requirements]

ALL WCG IRB APPROVED INVESTIGATORS MUST COMPLY WITH THE FOLLOWING:

- Ensure the consenting process included in the submission is being followed. Any changes to this process must be submitted to the IRB for review
- For research subject to continuing review:
  - Submit continuing review reports when requested by the IRB (you will receive Continuing Review Report forms from WCG IRB when the expiration date is approaching).
- Consistent with AAHRPP's requirements in connection with its accreditation of IRBs, the individual and/or organization submitting shall promptly communicate or provide, and where necessary cause each investigator to promptly communicate or provide, the following information relevant to the protection of human participants to the IRB in a timely manner:
  - Upon request of the IRB, a copy of the written plan between sponsor or CRO and site that addresses whether expenses for medical care incurred by research participants who experience research related injury will be reimbursed, and if so, who is responsible in order to determine consistency with the language in the consent document.
  - Any site monitoring reports that directly and materially affects participant safety or their willingness to continue participation. Such reports will be provided to the IRB within 5 days.

This is to certify that the information contained herein is true and correct as reflected in the records of WCG IRB. WE CERTIFY THAT this IRB IS IN FULL COMPLIANCE WITH GOOD CLINICAL PRACTICES AS DEFINED UNDER THE U.S. FOOD AND DRUG ADMINISTRATION (FDA) REGULATIONS, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) REGULATIONS, AND THE INTERNATIONAL CONFERENCE ON HARMONISATION (ICH) GUIDELINES.

    - Any findings from a closed research study when those findings materially affect the safety and medical care of past participants. Findings will be reported for 2 years after the closure of the research.
- Submit through the translations process any advertisements or participant material that contain both English and translated content to have the translated content approved.
- If this study includes a data monitoring committee/data safety monitoring board, please note that the reports of all meetings of this committee should be submitted to the IRB even if the outcome of the meeting results in no changes to the study.

Additional information regarding IRB review:

- For Investigator's Brochures, an approval action indicates that the IRB has the document on file for the research.
- When the Board approves participant materials and/or advertisements, any redline changes that were provided by the submitter or required by the Board for approval will remain visible in the outcome document(s); however, recipients are expected to accept the tracked changes in the document before using. Do not make any additional modifications (including font size and visual effects) to the approved materials.

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Investigator List

The following PIs received some or all of the approvals specified in this Certificate of Action (COA). Please review the COA for each PI listed below to confirm which approvals apply for each PI.

Carr, Foster

Certificate of Action

Investigator Name: Foster Carr, MD	**Board Action Date:** 08/19/2026
Investigator Address: 2534 State Street 305 San Diego, CA 92103, United States	**Approval Expires:** 03/25/2027 **Continuing Review Frequency:** Annually
Sponsor: Prevention Research Consortium Corporation **Institution Tracking Number:**	**Sponsor Protocol Number:** None **Amended Sponsor Protocol Number:**
Study Number: 1405909	**IRB Tracking Number:** 20260518
Work Order Number: 1-1982874-1	
Protocol Title: Assessing Tools that Predict and Stage Mild Cognitive Impairment	

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Consent Form - Screening and HIPAA [U0-0]
Consent Form [Cal1-0]

Please note the following information:
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The Board found that this research meets the requirements for a waiver of consent under 45 CFR 46 116(f)[2018 Requirements] 45 CFR 46.116(d) [Pre-2018 Requirements]

THE IRB HAS APPROVED THE FOLLOWING LOCATIONS TO BE USED IN THE RESEARCH:
Foster P Carr MD, 2534 State Street 305, San Diego, California 92101

ALL IRB APPROVED INVESTIGATORS MUST COMPLY WITH THE FOLLOWING:
As a requirement of IRB approval, the investigators conducting this research will:

- Comply with all requirements and determinations of the IRB.
- Ensure the consenting process included in the submission is being followed. Any changes to this process must be submitted to the IRB for review
- Protect the rights, safety, and welfare of participants involved in the research.
- Personally conduct or supervise the research.
- Conduct the research in accordance with the relevant current protocol approved by the IRB.

This is to certify that the information contained herein is true and correct as reflected in the records of WCG IRB. WE CERTIFY THAT WCG IRB IS IN FULL COMPLIANCE WITH GOOD CLINICAL PRACTICES AS DEFINED UNDER THE U.S. FOOD AND DRUG ADMINISTRATION (FDA) REGULATIONS, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) REGULATIONS, AND THE INTERNATIONAL CONFERENCE ON HARMONISATION (ICH) GUIDELINES.

- Ensure that there are adequate resources to carry out the research safely.
- Ensure that research staff are qualified to perform procedures and duties assigned to them during the research.
- Submit proposed modifications to the IRB prior to their implementation.
    - Not make modifications to the research without prior IRB review and approval unless necessary to eliminate apparent immediate hazards to participants.
- For research subject to continuing review
    - Submit continuing review reports when requested by the IRB. (you will receive Continuing Review Report forms from WCG IRB when the expiration date is approaching).
    - If research approval expires, stop all research activities and immediately contact the IRB.
- Submit a closure form to close research (end the IRB's oversight) when:
    - The protocol is permanently closed to enrollment
    - All participants have completed all protocol related interventions and interactions
    - For research subject to federal oversight other than FDA:
        - No additional identifiable private information about the participants is being obtained
        - Analysis of private identifiable information is completed
- Promptly (within 5 days) report to the IRB the information items listed in the IRB's "Prompt Reporting Requirements" available on the IRB's Web site.
- Not accept or provide payments to professionals in exchange for referrals of potential participants ("finder's fees.")
- Not accept payments designed to accelerate recruitment that are tied to the rate or timing of enrollment ("bonus payments") without prior IRB approval.
- When required by the IRB ensure that consent, permission, and assent are obtained and documented in accordance with the relevant current protocol as approved by the IRB.
- Promptly notify the IRB of any change to information provided on your initial submission form.
- Submit through the translations process any advertisements or participant material that contain both English and translated content to have the translated content approved.
- If this study includes a data monitoring committee/data safety monitoring board, submit reports from all meetings of this committee to the IRB even if the outcome of the meeting results in no changes to the study.
- Consistent with AAHRPP's requirements in connection with its accreditation of IRBs, the individual and/or organization shall promptly communicate or provide, the following information relevant to the protection of human participants to the IRB in a timely manner:
    - Upon request of the IRB, a copy of the written plan between sponsor or CRO and site that addresses whether expenses for medical care incurred by research participants who experience research related injury will be reimbursed, and if so, who is responsible in order to determine consistency with the language in the consent document.
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- If the IRB approved an e-consent process that involves uploading the approved consent form to an e-consent platform, please ensure that the consent form(s) approved for your site is the version of the consent form that gets uploaded to the platform.
- Once the board approves a change of Principal Investigator - Once approved, the new Principal Investigator is authorized by WCG IRB to carry out the study as previously approved for the prior Principal Investigator (unless the Board provides alternate instructions to the new Principal Investigator). This includes continued use of the previously approved study materials. The IRB considers the approval of the new PI a continuation of the original approval, so the identifying information about the study remains the same.
- If your research site is a HIPAA covered entity and has not otherwise been approved for a waiver of authorization, the HIPAA Privacy Rule requires you to obtain written authorization from each research participant for any use or disclosure of protected health information for research. If your IRB-approved consent form does not include such HIPAA authorization language, the HIPAA Privacy Rule requires you to have each research participant sign a separate authorization agreement.

Thank you for using WCG IRB to provide oversight for your research project.

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Foster Carr, MD, Foster P Carr MD
Gary Strobe, Prevention Research Consortium Corporation

Title: Assessing Tools that Predict and Stage Mild Cognitive Impairment
Principal Investigator: Foster Carr MD

Sponsor: Prevention Research Consortium Corporation

Resubmit Date to WCG IRB: 8/10/2026

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1. Study Overview

1.1 Background and rationale

Late-onset Alzheimer's disease (LOAD) develops over a long preclinical period during which cognitively normal (CN) individuals accumulate Alzheimer's pathology and subtle cognitive changes before reaching mild cognitive impairment (MCI) and dementia. Plasma and CSF pTau217 have emerged as highly accurate biomarkers for Alzheimer's pathology and for predicting conversion from MCI to Alzheimer's dementia, with reported AUCs in the 0.8–0.9 range for progression and for detection of underlying pathology. Clinical Dementia Rating Sum of Boxes (CDR-SB) has been extensively validated for staging from normal cognition through very mild impairment and MCI, and small changes in CDR-SB (0.5–1 point) correspond to clinically meaningful transitions. However, this neurocognitive assessment needs an informant to be present with the patient and is not part of the standard primary care process for evaluating individuals who are cognitively normal. Our study will utilize an Oura Ring Data Risk Assessment, a self-administered Digital Cognitive Assessment, Speech Biomarker Assessment, Lifestyle History Questionnaires, and EMR risk assessments scoring for the initial screening of Cognitively Normal Subjects for any evidence of existing Cognitive Impairment and Assess their expected Risk of Progressing to SCD/MCI after the inclusion of proteogenomic risk scores..

We are currently performing Insilco work to validate proteogenomic progression and risk (P&R) models .)[6,7,8] The current data suggests that integration of An Ancestry and Sex normalized Polygenic Risk Score (PRS) with proteomic profiles can predict near-term conversion probability of CN subjects to AD-MCI with clinically useful AUC-ROC values. These Insilco models were developed in existing cohorts of CN and MCI participants with proteogenomic biomarker data, and will be used to select the best performing model that is able to integrate with EMR risk data (that includes lifestyle risk information and wearable data), into a multimodal (P&R) model that categorizes low, medium, and high risk of conversion to pTau217 positive MCI from Cognitively Normal Individuals with specific risk factors. It is also designed to

categorize SCD subjects with low, medium, and elevated risk of conversion probability to pTau217 positive MCI). The model and pilot data will be used to estimate annual conversion rates from CN to AD-MCI, which will in turn inform sample size and follow-up duration of the 2 year proof of concept studies

Polygenic risk scores (PRS) in Alzheimer's disease

Late-onset Alzheimer's disease (AD) is highly polygenic, with common variants of small effect across the genome contributing to risk in addition to APOE ε4. Polygenic risk scores (PRS) aggregate the weighted effects of large numbers of AD-associated single nucleotide polymorphisms (SNPs), typically using effect sizes from genome-wide association studies (GWAS), to generate an individual-level measure of inherited susceptibility. In AD, such scores, especially when combined with APOE, can identify individuals at markedly elevated odds of developing disease and earlier age at onset compared to those in the lowest PRS strata. [1]

Several large GWAS and meta-analyses have now demonstrated that AD PRS discriminate cases from controls with AUC values commonly in the 0.70–0.80 range, and that individuals in the highest PRS percentiles can have more than a ten-fold higher odds of AD compared to those in the lowest percentiles when stratified by APOE genotype. PRS performance has been replicated across independent European and non-European cohorts and shows a stepwise relationship with incident AD dementia, age at symptom onset, and amyloid deposition. These data support the feasibility of using PRS, in conjunction with APOE and biomarker measures, for risk stratification and enrichment of preclinical and prodromal AD cohorts. [2]

In addition to traditional GWAS-based scores, recent work has explored integrative or "multi-domain" polygenic scores that combine loci implicated in neurodegenerative and vascular pathways, as well as deep-learning–based approaches to optimize SNP weighting and capture non-linear effects. Such integrative scores can improve prediction of dementia onset and may better reflect the heterogeneous biology of AD, including vascular and metabolic components. Together, this literature motivates the use of a validated, APOE-aware PRS as one input into a broader proteogenomic risk (PR) model to stage cognitively normal (CN) individuals along a preclinical AD continuum in this study. [3]

This protocol describes a FIH 2-year observational study to evaluate the Incident Prediction & Risk model's ability to predict conversion among ApoE4-positive adults,

with intensive plasma proteomic, genomic risk assessment, , neurocognitive assessments, and wearable device data. l,

1.2 Objectives and specific aims

This first-in-human observational study is primarily designed as a pilot feasibility and prospective validation of a pre-specified proteogenomic Progression and Risk (P&R) model for predicting conversion from cognitively normal (CN) or very mildly impaired status to pTau217-positive mild cognitive impairment (MCI) in ApoE4-positive older adults. Secondary and exploratory aims evaluate additional omic and digital measures, as well as the practical scalability and cost of the assessment protocol.

Primary aims

1. Validate the fixed P&R model's ability to discriminate participants who convert to pTau217-positive MCI Stage I within 24 months from those who remain non-converted, among ApoE4-positive adults aged ≥55 years.
2. Assess the feasibility and acceptability of the multimodal assessment protocol over 24 months, including recruitment of ApoE4-positive individuals with existing genomic data, completion of scheduled visits and biospecimen collections, and adherence to Oura Ring and digital cognitive assessments.

Secondary aims

3. Compare the prognostic performance of the P&R model with simpler baseline models (e.g., APOE + PRS only, or clinical + cognitive only) for predicting CN → pTau217-positive MCI conversion over 24 months.
4. Estimate, with appropriate uncertainty, short-term (2–5-year) conversion probabilities derived from the P&R model and explore how these inform projected longer-term (up to ten-year) risk in this population, recognizing that extrapolations will be preliminary and supported by external cohorts.
5. Evaluate the practical scalability and relative cost of alternative sampling and visit strategies, including venous versus capillary (fingerstick) blood collection and varying degrees of in-clinic versus remote assessment, using simple per-participant and per-conversion cost summaries.
6. Assess the incremental predictive value, beyond the core P&R model, of selected digital and wearable measures (e.g., Oura-derived sleep and activity metrics, brief speech, and digital cognitive features) for detecting CN → MCI conversion events.

7. Determine the relationship between an Oura Ring–based exposome risk score and proteogenomic risk scores and cognitive-functional measures.

Exploratory aims

8. Evaluate the performance of the P&R model within subsets of CN participants at higher predicted near-term risk (e.g., upper P&R risk strata) to explore whether focusing on such high-risk groups could improve time-to-signal and statistical power for future larger studies.
9. In a subset of participants and as data and budget permit, explore how combinations of plasma pTau217, other plasma markers, and optional measures (such as amyloid PET, retinal hyperspectral imaging, and provoked EEG, when available from clinical care) refine staging and prediction beyond the core P&R model.

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2. Study Design

2.1 Overall design

Longitudinal retro and prospective , observational cohort study of up to 90 ApoE4-positive adults (age ≥55) followed for 24 months, with in-person visits every 6 months and continuous remote monitoring with Oura Ring and a subset of 10 subjects. No investigational drug or device is administered. Participants will undergo venous or capillary blood collection, CSF collection as part of this study are not performed, digital cognitive and speech biomarker assessments,(EEG, retinal imaging or MRIs may be performed outside of this study if ordered by referrals and shared by agreement with this study. Particularly in subjects that convert during this study.

Samples and data will be used to (a) apply and refine the Insilco-derived P&R model for conversion prediction, and (b) compare model-predicted risk with the study observed conversion events.

Definition and components of the PRS

The AD polygenic risk score used in this protocol will be derived from genome-wide SNP data using effect sizes from large, externally validated AD GWAS and meta-analyses, excluding the APOE locus so that APOE genotype can be modeled separately. Briefly, after standard quality control and ancestry checks, we will compute a PRS as the sum across selected SNPs of the number of risk alleles carried by the individual (0, 1, or 2) multiplied by the corresponding log-odds ratio for AD from the discovery GWAS. SNP selection and clumping will follow published best practices (e.g., linkage disequilibrium pruning and p-value thresholding) to balance predictive performance and parsimony.[4]

The components of the PRS therefore include:

- Common autosomal SNPs associated with AD risk in prior GWAS, weighted by their reported effect sizes. [1]
- Explicit separation of APOE ε2/ε3/ε4 genotype, which will be modeled as an independent covariate (e.g., ε4 dose), consistent with evidence that optimal AD risk prediction treats APOE separately from the polygenic background.
- Optional incorporation of loci from integrative dementia scores (e.g., vascular, and neurodegenerative pathways) if they improve prediction in the pre-FIH Insilco phase; any such additions will be documented in the statistical analysis plan.[5]

The raw PRS will be standardized (z-score) within an ancestry-matched reference population (e.g., external dataset plus early enrollees) and then categorized based on prespecified quantiles (e.g., lowest ~25%, next lowest 25%, next highest 25%, and highest ~25%), following prior work stratifying AD risk by PRS percentiles. These categories will be used for recruitment targeting (approximate balance of low, average, and high PRS) and for prespecified subgroup analyses of conversion risk.[2]

Personalized MCI and AD Hazard Ratio Determination

In a Cox model with 5 covariates $X_1, \ldots, X_5$, the hazard at time t is

$$h(t|X) = h_0(t)\exp(\beta_1 X_1 + \cdots + \beta_5 X_5),$$

so the **combined** hazard ratio for a profile $(X_1, \ldots, X_5)$ versus a reference $(X_1^*, \ldots, X_5^*)$ is

$$\mathrm{HR} = \exp\left[\beta_1(X_1 - X_1^*) + \cdots + \beta_5(X_5 - X_5^*)\right].$$

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Equivalently, if each factor's hazard ratio (per unit) is $\mathrm{HR}_k = \exp(\beta_k)$, and the difference from the reference is ΔX_k, then

$$\mathrm{HR} = \prod_{k=1}^{5} \mathrm{HR}_k^{\Delta X_k}.$$

Practical use

- Fit a multivariable Cox model with one or more of the following predictors-X.
    - Polygenic Risk score - stratified to 5 ApoE Genotyped Categories
    - EMR-Lifestyle Risk Score = Dementia Risk Score
    - Proteomic Risk Score - stratified to 5 ApoE Genotype Categories
    - mDNA Risk score
    - Proteome Structure Based Risk Score
    - circRNA based Risk Score
    - MRI based Risk Score
    - PET Scan based Risk Score
    - EEG based Risk Score
    - Neurocognitive based Risk Score
    - Metabolome based Risk Score
- Use the estimated coefficients (or per-unit HRs) to compute the linear predictor for each subject.
- Exponentiate that linear predictor to get a single combined hazard ratio relative to a chosen reference profile; this can then be scaled or categorized as a "risk score." or some may call an Aging Score.

2.2 Insilco and in vitro lead-in (pre-FIH phase)

Mahdi Mogri and Carlos Cruchaga are currently conducting Insilco analyses using existing, independently collected cohorts that include whole-genome sequencing (for APOE and PRS), plasma proteomics including pTau217, imaging, and longitudinal cognitive/clinical outcomes. The data referenced here already have IRB approval and participant consent, and no additional contact with participants will take place during this phase.

The goal of the Insilco work is to develop and calibrate a proteogenomic Progression and Risk (P & R) model that estimates the short-term hazard of conversion from cognitively normal (CN) or very mildly impaired to pTau217-positive MCI due to AD. The model integrates:

- A polygenic risk score (PRS) for AD (APOE-excluded) plus APOE genotype.
- Plasma proteomic features selected from prior multi-omic studies of dementia and brain health.
- DNA methylation features associated with proteomic and cognitive/brain phenotypes.
- Key plasma AD biomarkers (pTau217, Aβ42/40, GFAP, NfL).
- Standardized Baseline cognitive and functional measures.

Model development and comparison
We will develop and compare at least two classes of time-to-event models:

1. A proteogenomic P & R model, which combines PRS + APOE with a parsimonious panel of plasma proteins including pTau217 and grounded with cognitive-functional tests.
2. A proteo-methyl-genomic model grounded with cognitive-functional tests.
3. A proteo-methyl-genomic - emr-lifestyle risk - oura ring data risk model, - grounded with cognitive-functional tests.

For each model, we will:

- Split source cohorts into training and internal validation sets or use cross-validation.
- Fit Cox proportional hazards or related survival models with time to conversion to MCI/AD or pTau217-positive MCI as the outcome.
- Derive a continuous risk score (linear predictor) and estimate discrimination (Harrell's C, AUC/ROC at fixed horizons such as 2–5 years) and calibration (calibration plots, Brier scores).
- Compare models using C-index/AUC and pragmatic criteria (assay cost, number of markers, ease of clinical implementation) to select a single P & R model for the FIH study.

Derivation of CN and SCD 4 risk groups and their expected transition event rates
Using the selected P & R model, we will apply the fitted risk equation to CN participants in the external cohorts and estimate their predicted near-term hazard of conversion. We will then:

- Define 4 Categories CN individuals whose predicted 2–5-year conversion risk to MCI lies above a prespecified percentile cut-off (25 % lowest risk quartile, 25% next to lowest risk quartile, 25% next to highest risk quartile, and 25% highest risk quartile)
- Define 4 Categories of SCD whose predicted 2–5-year conversion risk to MCI lies above a prespecified percentile cut-off (25 % lowest risk quartile, 25% next to lowest risk quartile, 25% next to highest risk quartile, and 25% highest risk quartile)
- Estimate annual conversion rates within these model-defined groups (CN vs SCD), which are expect to differ by several-fold based on prior work showing strong stratification by proteomic , cognitive assessment, and multi-omic risk scores.
  These estimated event rates (number of pTau217 positive MCI conversions per patient-years) are then used to justify the future FIH longitudinal sample size and follow-up duration described in Sections 1.2 and 3.2.

Fixed model for the FIH cohort
Once selected, the P & R model will be locked (fixed coefficients and included markers) before analysis of the FIH cohort. For each enrolled participant, we will calculate the P & R risk score at baseline and use it to:

- Assign CN participants to 4 CN Risk Levels and 4 SCD Risk Levels (per the thresholds derived above).

- Generate individual predicted hazards of conversion for comparison with observed events (primary and secondary analyses).
  The FIH study itself is thus a prospective validation of a pre-specified P & R model developed entirely from existing data.

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3. Study Population

3.1 Target population

ApoE4-positive adults aged ≥55 years, cognitively normal or with very mild cognitive changes (digital cognitive assessment equivalent of CDR 0–0.5), including a subset staged SCD/MCI/CDR <0.5 and pTau217 negative at baseline.

3.2 Sample size

The initial target is ten subjects starting with subjects that have Oura Rings and then expanding to one hundred total for the full 2-year study starting in September 'twenty-six. The targeted composition is:

- CN ApoE4 carriers with a range of polygenic risk scores (PRS): Initial target of three low PRS, 3 average PRS, 4 high PRS (later expanding to 33% in each category when the enrollment expands to a total of 100 subjects)
- Participants with MCI/CDR <0.5 and pTau217-positive at baseline will not continue enrollment in the study and will be referred to a Neurologist. These numbers may be adjusted if external sponsors join the project and support expanded enrollment. The size will be adjusted with more data on the annual CN to AD-MCI conversion rates from Insilco analyses and financial feasibility of intensive longitudinal assessments.

3.3 Inclusion criteria

- Age ≥55 years at enrollment.

- At least one ApoE4 allele documented by prior testing (e.g., prior genetic panel, research cohort genotyping, clinical ApoE testing).
- Whole-genome sequencing (WGS) data previously completed and participants willing to provide existing WGS data files (e.g., VCF, FASTQ, or equivalent) to the study team for polygenic risk score (PRS) calculation.
- If WGS is not available but targeted genotyping arrays covering AD risk loci are available, participants willing to provide these data for PRS calculation (the study will assess feasibility of array-based PRS on a case-by-case basis)
-
- Cognitively normal or very mildly impaired at baseline, defined by:
    - The Punto Test and digital cognitive assessment equivalent of a Global CDR 0 or 0.5, and no clinical diagnosis of dementia.
    - For CN and SCD, P&R model staging criteria will be applied (combining PRS, biomarker, and cognitive data).
- Subjects that do not currently qualify for MCI status. (ie with the equivalent of a g CDR 0.5 - 1.0 , and plasma or CSF pTau217 level above a validated cut-off for AD-MCI pathology.
- Ability to provide informed consent and to comply with study procedures.
- Willingness to wear/keep digital devices for continuous monitoring (e.g., smartphone app, wearable sensors, sleep device).
- Note on genetic testing: This protocol does not perform ApoE genotyping or whole-genome sequencing as a research procedure. Eligible participants must already have these tests completed through prior clinical care, prior research studies, or commercial/direct-to-consumer services, and must be willing to share the results and raw genomic data files with this study. Screening will confirm that (a) prior ApoE genotype shows at least one ε4 allele, and (b) WGS or suitable array data exist and can be obtained for PRS calculation. Individuals without documented ApoE4 carrier status or without available genomic data for PRS are ineligible for this protocol.

3.4 Exclusion criteria

- Diagnosis of dementia (any cause) at baseline.
- Major neurological disorders that confound cognitive assessment (e.g., Parkinson's disease, stroke with residual deficits, epilepsy with frequent seizures).
- Major psychiatric illness (e.g., uncontrolled major depression, schizophrenia) that, in investigator judgment, interferes with participation or data interpretability.

- Uncontrolled systemic medical illness (e.g., unstable cardiac, hepatic, or renal disease) that may limit life expectancy to <3 years.
- Use of investigational drugs or disease-modifying Alzheimer's therapies within 6 months prior to baseline that could confound biomarker trajectories.
- Contraindications to EEG, retinal imaging, or MRI/PET (if clinically indicated), such as implanted incompatible devices or severe claustrophobia.
- Inability or unwillingness to use required digital monitoring tools (e.g., no smartphone access, unwillingness to carry/wear devices, or severe hearing/vision impairment precluding their use).
- Absence of prior ApoE genotype results or refusal to share existing ApoE/genomic data and EMR data with this study.
- MCI pTau217 positive subjects will not continue to be enrolled in the study. They will be referred to a Neurologist.

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4. Study Procedures

4.1 Schedule of events

Each participant will have:

- Baseline visit (Month 0) with full assessments and biospecimen collection.

pTau217 MCI positive subject will be referred to a Neurologist while the main CN group will have:

- Follow up visits on Months 6, 12, 18, and 24 (±2 months) with repeat biospecimens, neurocognitive testing, and safety review.
- Continuous or frequent digital monitoring (passive and active) throughout the 24 months. (or until they turn MCI positive)
- Optional "triggered" visits or remote assessments in response to signs of cognitive or functional decline detected by digital systems, participant report, or clinical assessment. (If blood biomarkers become positive then these subjects will be referred to a Neurologist and discharged from the study.

Total biospecimen collections per participant: 1 at baseline + 4 follow-ups = 5 (if they do not convert to MCI positive)

Biofluid: venipuncture and/or capillary collections every 6 months for 2 years.

4.2 Screening and baseline

Screening (may coincide with baseline):

- Verification that participant has prior ApoE genotype results showing at least one ApoE4 allele (documentation from prior clinical or research testing required).
- Verification that the participant has prior whole-genome sequencing (WGS) data or equivalent high-density genotyping array data suitable for PRS calculation.
- Participants sign data release authorization allowing the study to obtain WGS/genomic data files from prior testing laboratory, research biobank, or direct-to-consumer service (if applicable).
- Optional Approval to Access past and /or future Oura Ring Data.
- Medical, neurologic, and psychiatric history; medication review.
- Physical and neurologic examination, including vital signs (partly collected from wearable device).
- Review of prior cognitive assessments, imaging, and biomarker results if available.

Baseline assessments:

- Cognitive and functional assessment: CDR (global and CDR-SB) and standard neuropsychological tests consistent with MCI trials (e.g., memory, executive function, language).
- Digital cognitive battery from Punto Health (or equivalent), including tasks sensitive to subtle CN → MCI transitions.
- Collection of blood (venous and/or fingerstick) for:
    - Plasma pTau217 and other AD plasma biomarkers (e.g., pTau181, Aβ42/40, GFAP, NfL).
    - Proteomic and methylome profiling per validated in vitro assays.
    - Clinical laboratory safety tests (e.g., CBC, CMP) if needed.
- Optional CSF collection (lumbar puncture) when clinically indicated (e.g., to resolve diagnostic uncertainty), analyzed for pTau217, amyloid, and other AD markers.
- EEG: resting EEG and a provoked EEG paradigm designed to probe memory and attention circuits (e.g., oddball or task-based paradigms).
- Retinal hyperspectral imaging to assay retinal signatures of amyloid and neurodegeneration were available.
- Amyloid PET scan if clinically indicated (per treating clinician) and standard-of-care in the setting; images/results will be captured for research use.
- Digital sensing initiation: participants receive and are trained on wearable devices and smartphone applications used to track smell (smell tests), location/mobility, activity, speech patterns, and sleep.

Baseline staging:

- Calculate P&R model-derived risk for the following prodromal AD stages(CN, SCD, MCI Stage I, etc.).
- Assign participants to CN and MCI risk strata (low, average, high PRS or four quantile-based categories)

Cerebrospinal fluid (CSF):

This protocol does not require any research-mandated lumbar punctures or CSF collection. If a participant undergoes lumbar puncture purely for clinical reasons outside the study (e.g., to resolve diagnostic uncertainty as part of routine care), and if the clinical team and participant agree, residual CSF may be shared with the study for exploratory biomarker assays under a separate biobanking consent. No lumbar puncture will be performed solely for research purposes, and participation in the study is not contingent on undergoing a lumbar puncture.

4.3 Follow-up visits (Months 6, 12, 18, 24)

At each follow-up:

- Interval history, adverse events, and medication changes.
- CDR (global and CDR-SB) and a selected neuropsychological battery to detect MCI criteria and progression.
- Repeat digital cognitive assessments (Punto Health).
- Blood collection (venous and/or fingerstick) for plasma pTau217 and other biomarkers, plus proteomic/methylome panels as budget permits.
- Update on digital monitoring adherence and troubleshooting of devices.
- EEG and retinal imaging at selected visits (e.g., baseline and Month 24 for all, optional intermediate visits in a subset depending on resources).
- Additional imaging (MRI or amyloid PET) only when clinically indicated or available as standard-of-care.

Trigger-based assessments:

- If continuous monitoring or participant self-report suggests cognitive decline (e.g., sustained changes in speech patterns, activity, or sleep; decline in digital cognitive tasks), a targeted evaluation will be scheduled, including repeat CDR, brief neuropsychological testing, and biomarker sampling when feasible.

4.4 Biospecimen handling and storage.

- All blood (venous and fingerstick) samples will be processed according to standardized SOPs used in AD biomarker studies (e.g., timely centrifugation, aliquoting, storage at -80°C, minimal freeze-thaw cycles) to ensure pre-analytical quality.
- Biospecimens will be stored in a secure biobank under coded identifiers, with a link to identifiers maintained separately in a secure master key file.
- Samples will be used for the planned proteomic, methylome, and biomarker analyses and may be stored for future IRB-approved research if participants provide separate permission for future use.
- If any clinically-indicated CSF is shared with the study, those samples will be handled and stored under the same SOPs as other biospecimens but are entirely optional and not required for participation.

4.5 Table 1: Schedule of Assessments

To improve feasibility and proportionality for this first-in-human observational study, study procedures are organized into three tiers. Core procedures are required for all enrolled participants at specified timepoints and include clinical evaluations, brief cognitive and digital assessments, and blood sampling for key AD plasma biomarkers sufficient to Predict and Stage AD. Optional procedures are performed only when clinically indicated (e.g., amyloid PET, MRI, lumbar puncture ordered as part of routine care) or when participants elect to share such data with the study. Sub-cohort procedures (e.g., extended omics panels, EEG, retinal imaging) are limited to smaller subsets of participants as funding and logistics allow and are explicitly not required for participation. This tiered structure is intended to ensure that the protocol remains practical and cost-conscious while still enabling exploratory analyses that may inform future, larger studies.

X = core required assessment for all participants
O = optional or sub-cohort assessment (performed as clinically indicated or as budget allows)

Assessment / Procedure	Screening	Baseline (Month 0)	Month 6 (±2 mo.)	Month 12 (±2 mo.)	Month 18 (±2 mo.)	Month 24 (±2 mo.)	Triggered visit†

Informed consent	X						
Inclusion / exclusion criteria	X	X	X	X	X	X	X
Medical / neurological / psychiatric history	X						
Medication review	X	X	X	X	X	X	X
Physical and neurologic examination		X				X	O
Vital signs (clinic or wearable)	X	X	X	X	X	X	X
Documentation of prior ApoE genotype and WGS / array data	X						
PRS calculation & stratification (once data available)		X					

CDR (global and CDR-SB, no-informant version)		X	X	X	X	X	X
Digital cognitive battery and brief speech measures (Punto Health)		X	X	X	X	X	O
BIOFLUID COLLECTION (core)							
Venous or capillary blood (pTau217 + core panel for P&R model)		X	X	X	X	X	X
Additional plasma markers (extended AD panel, as budget permits)		O	O	O	O	O	O
Blood methylome / other discovery omics (sub-cohort only)		O	O	O	O	O	O

Clinical labs from EMR or PCP (CBC, CMP, etc.)	O	O	O	O	O	O	O
CSF collection (clinically indicated lumbar puncture only)		O					O
Resting / provoked EEG (sub-cohort, if available clinically)		O				O	O
Retinal hyperspectral imaging (if available clinically)		O				O	O
Amyloid PET (standard-of-care only, if ordered by clinician)		O	O	O	O	O	O
MRI / structural imaging (standard-of-care only)		O	O	O	O	O	O

Digital devices and monitoring							
Oura Ring data linkage / device confirmation	O	X					
Continuous Oura monitoring (sleep, activity, HR metrics)		X	X	X	X	X	X
Digital monitoring adherence check (Oura + cognitive app)		X	X	X	X	X	X
Risk score calculation and staging							
Calculate P&R risk score and risk level		X	X	X	X	X	X
Update CN / SCD / MCI Stage I status and event determination		X	X	X	X	X	X

† Triggered visits or remote assessments will occur when digital monitoring, participant report, or clinical assessment suggests possible cognitive decline or functional change; they may include focused cognitive testing and repeat blood sampling for key biomarkers (e.g., pTau217) and will prompt referral to a neurologist if criteria for MCI with positive biomarkers are met.

Notes:

- Total in-clinic visits: 5 required (Baseline + 4 follow-ups at 6, 12, 18, 24 months), plus optional triggered visits.
- Total biospecimen collections: 5 venipuncture/capillary sessions minimum (Baseline + 4 follow-ups), plus optional triggered samples

Duration of participation: 24 months from baseline with continuous remote monitoring

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5. Outcomes and Definitions

5.1 Primary outcome

Conversion from CN pTau217-positive MCI Stage I over the twenty-four-month follow-up, defined as:

- Meeting consensus diagnostic criteria for MCI due to AD, including objective cognitive decline on standardized tests and CDR global ~0.5 with CDR-SB in the “questionable impairment” to very mild dementia range; and
- Plasma pTau217 exceeding a validated cut-off for AD pathology using a clinically validated assay.
- CSF pTau217, if available from clinically-indicated procedures outside the study, may be analyzed exploratorily, but CSF collection is not required by this protocol.

A subset analysis will focus on CN0.9 at baseline to assess time to conversion within this higher-risk group.

5.2 Secondary outcomes

- Time to conversion from CN to MCI Stage I (regardless of pTau217 status) and from CN to pTau217-positive status (biomarker conversion).
- Estimated ten-year conversion rates from CN to MCI Stage I, extrapolating from observed two-year data using survival/hazard modeling informed by external cohorts.

- Hazard ratios for LOAD associated with P&R model-derived risk scores, PRS categories, and biomarker trajectories.
- Cost per participant and per conversion event detected for different sampling strategies (fingerstick vs venous; frequency of in-person visits vs reliance on digital monitoring).
- Incremental predictive value (AUC-ROC, net reclassification improvement) of continuous digital monitoring features (smell, location, activity, speech, EEG, sleep) beyond traditional risk factors and biomarkers.

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6. Statistical Considerations

6.1 General approach

Data analyses will be primarily exploratory and hypothesis-generating given the FIH nature and modest sample size, but key performance metrics (e.g., AUC-ROC) will be estimated with confidence intervals. Observational protocol templates recommend prespecifying primary analyses and sensitivity analyses for observational cohorts.

Analyses:

- Compute AUC-ROC for the P&R model and alternative models for predicting conversion to pTau217-positive MCI Stage I within 24 months.
- Compare AUC-ROC across models (proteogenomic vs proteo-methylome-genomic) using DeLong's test or similar.
- Use Cox proportional hazards models to estimate hazard ratios for time to conversion as a function of baseline P&R risk, PRS, ApoE4 dose, and biomarker levels.
- Use logistic regression and time-dependent ROC analyses for binary conversion endpoints over fixed time horizons.
- Incorporate digital monitoring variables as covariates and evaluate incremental predictive performance.
- For cost-effectiveness, compare costs and detection yield of different biospecimen and monitoring strategies using simple decision-analytic models (incremental cost per correctly predicted conversion).

Missing data will be handled using appropriate methods (e.g., multiple imputations, mixed-effects models) depending on pattern and mechanism of missingness. Sensitivity analyses will evaluate robustness of results to missing data assumptions.

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7. Data Management and Confidentiality

7.1 Data collection and storage

- Data will be collected in a secure, 21 CFR Part 11-capable electronic data capture system (e.g., REDCap or equivalent).
- Each participant will be assigned a unique study ID; direct identifiers will be stored separately in a secure linkage file.
- Digital device data (location, activity, speech metrics, sleep) will be transmitted via encrypted channels and stored on secure servers with role-based access controls.
- Access to identifiable data will be limited to authorized study personnel; analysts will work primarily with coded datasets.

7.2 Confidentiality protections

- All study staff will complete human subjects and HIPAA training.
- Any reports or publications will present aggregated or de-identified data only.
- Data sharing with collaborators and sponsors will occur in de-identified form under data use agreements consistent with IRB and institutional policies.

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8. Risks and Benefits

8.1 Risks

- Venipuncture and fingerstick: transient discomfort, bruising, rarely infection or vasovagal reactions.
- Lumbar puncture (if clinically indicated): headache, back pain, very rarely bleeding or infection.
- EEG and retinal imaging: minimal risk, possible mild discomfort, or fatigue from procedures.
- Amyloid PET scans (if clinically indicated): radiation exposure within clinical standards, potential anxiety about results.
- Digital monitoring: privacy concerns such as information on location, activity, and speech data collection; risk of data breach if security were compromised.
- Psychological risks: anxiety, distress, or altered self-image related to information about genetic risk, biomarker status, and early cognitive changes.

These risks are typical of observational Alzheimer's biomarker studies and continuous monitoring protocols when appropriate safeguards are applied.

8.2 Risk mitigation

- Use trained personnel and SOPs for venipuncture and lumbar puncture; monitor for adverse events.
- Use minimal necessary imaging and adhere to clinical indications and radiation safety guidelines.
- Apply robust cybersecurity measures, encryption, and strict access controls for digital data.
- Provide pre- and post-test counseling for genetic and biomarker information as appropriate; offer referrals to counseling services.
- Allow participants to opt out of specific optional components (e.g., CSF, certain digital features) while remaining in other parts of the study when feasible.

8.3 Potential benefits

- Participants may gain early insights into cognitive status and risk factors, which may inform future clinical decision-making though direct clinical benefit is not guaranteed.
- Society may benefit from improved models for early detection and staging of AD, more scalable biomarker strategies, and evaluation of continuous monitoring for CN → MCI transitions.

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9. Informed Consent Process

- Informed consent will be obtained by qualified study personnel in a secluded setting before any study-specific procedures.
- The consent process will explain:
    - Study purpose, procedures, duration, and follow-up.
    - Risks and benefits.
    - Alternatives (non-participation, standard clinical care).
    - Confidentiality protections and data sharing plans.
    - Voluntary nature of participation and right to withdraw at any time without affecting clinical care.
    - Handling and potential disclosure of genetic and biomarker results (including whether individual results will be returned and under what conditions).

- For digital monitoring, consent will explicitly address what types of data are collected (e.g., GPS, accelerometry, speech features not content), how they are used, and participants' options to pause or discontinue monitoring.

Consent documents will follow institutional templates for observational studies and genetic/biomarker research.

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10. Safety Monitoring and Reporting

- The principal investigator (PI) will oversee ongoing safety monitoring.
- Given the minimal-to-moderate risk and observational nature, a formal external Data Safety Monitoring Board is not initially planned but may be added if required by the IRB or sponsors.
- Unanticipated problems involving risk to participants or others and serious adverse events (SAEs) related to study procedures (e.g., complications from lumbar puncture) will be reported to the IRB aper institutional policy.
- Annual continuing review reports will summarize enrollment, retention, adverse events, and protocol deviations.

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11. Privacy, HIPAA, and Data Sharing

- This study involves collection of protected health information (PHI); a HIPAA authorization will be incorporated into the consent, or a waiver will be sought as appropriate.
- PHI will be limited to the minimum necessary.
- Data sharing with external collaborators and potential industry sponsors will use de-identified or limited datasets under data use agreements that prohibit attempts at re-identification and require appropriate safeguards.
- Any future use of stored biospecimens and data beyond the current protocol will require either explicit participant consent or appropriate IRB/HIPAA determinations.

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12. Vulnerable Populations and Special Considerations

- The study does not specifically target children, prisoners, or pregnant individuals; these populations will be excluded.

- Older adults with subtle cognitive changes are included; consent capacity will be formally assessed when there is concern, and legally authorized representatives may be involved if institutional policy allows and the IRB approves this approach.

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13. Dissemination of Results

- Findings will be disseminated via peer-reviewed publications and conference presentations.
- Results will be reported in aggregate; any case-level descriptions will be de-identified.
- Participants will be offered a lay-language summary of overall study findings at study completion if desired.

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15. Abbreviations

Aβ42/40: Amyloid-beta 42/40 ratio

AD: Alzheimer's Disease

AD-MCI: Alzheimer's Disease- MCI
APOE: Apolipoprotein E
AUC-ROC: Area Under the Curve-Receiver Operating Characteristic
AUCs: Areas Under the Curve
CBC: Complete Blood Count
CDR: Clinical Dementia Rating
CMP: Comprehensive Metabolic Panel
CN: Cognitively Normal
CSF: Cerebrospinal Fluid
EEG: Electroencephalogram
EMR: Electronical Medical Record
GFAP: Glial Fibrillary Acidic Protein
GPS: Global Positioning System
GWAS: Genome Wide Association Studies
HIPAA: Health Insurance Portability and Accountability Act
HR: Hazard Ratio
IRB: Institutional Review Board
LOAD: Late Onset Alzheimer's Disease
MCI: Mild Cognitive Impairment
mDNA: methylated Deoxyribonucleic Acid
MRI: Magnetic Resonance Imaging
NfL: Neurofilament Light
PET: Positron Emission Tomography
PI: Principal Investigator
P & R: Progression and Risk
PHI: Personal Health Information
PRS: Polygenic Risk Score
pTau217: phosphorylated Tau 217
REDCap: Research Electronic Data Capture
SAE: Serious Adverse Events
SOPs: Standard Operating Procedures
SCD: Subjective Cognitive Decline
SNP: Single Nucleotide Polymorphism
WCG: WCG Institutional Review Board
WGS: Whole Genome Sequencing

16. RECRUITMENT, SCREENING, AND RETURN OF INDIVIDUAL RESULTS

16.1 Overview

Enrollment in PREDICT proceeds through four sequential stages. No research procedure is performed at any stage before the consent applicable to that stage has been obtained and documented as specified below.

Stage	Activity	Consent basis
0	Registry listing and self-referral	Registry's own IRB-approved materials
1	Telephone or email pre-screening	Verbal agreement under waiver of documentation of consent (45 CFR 46.117(c))
2	Screening: cognitive assessment, genotyping and plasma p-tau217	Signed Screening Consent and HIPAA Authorization

Stage	Activity	Consent basis
3	Main study enrollment	Signed Main Study Informed Consent

Clinical screening procedures performed solely to determine research eligibility are research procedures requiring prior informed consent. Accordingly, no genotyping, cognitive assessment, biospecimen collection, or laboratory requisition occurs before completion of Stage 2 consent.

16.2 Stage 0: Recruitment sources and registry referral

Participants are identified through the following approved sources: (a) listings with recruitment registries, including the Alzheimer's Prevention Registry administered by Banner Alzheimer's Institute; (b) the ClinicalTrials.gov record for NCT07516119; (c) the study website; (d) IRB-approved advertisements and community outreach materials; and (e) physician and self-referral. Where a recruitment registry is used, the registry contacts its own registrants using materials approved by the registry's IRB, and interested individuals self-refer to the Sponsor. Under this design no protected health information is disclosed by the registry to the Sponsor before the individual has initiated contact. Should any recruitment architecture require pre-consent disclosure of identifiable information to the Sponsor, such disclosure will occur only under the partial waiver of HIPAA authorization described in Section 16.8.

All recruitment materials, including registry listing text, advertisements, emails, the study website, and the study landing page, are submitted for IRB review and approval before use, and are not modified after approval without further IRB review.

16.3 Stage 1: Telephone or email pre-screening

16.3.1 Procedure

Individuals who self-refer are contacted by a trained research coordinator who conducts a scripted telephone pre-screening interview of approximately 10 minutes. The approved Pre-Screening Script and Pre-Screening Information Sheet govern this interaction.

Before any eligibility question is asked, the coordinator: (a) identifies themselves as a research coordinator and not a treating clinician; (b) states the purpose of the call; (c) states that no test, blood draw, or genetic testing will occur on the basis of the call; (d) provides or reads the Pre-Screening Information Sheet; (e) states that participation is voluntary, that any question may be skipped, that the call may be ended at any time without giving a reason, and that neither refusal nor ineligibility affects the individual's medical care or standing with any referring registry; and (f) obtains affirmative verbal agreement to proceed.

Pre-screening collects self-reported age, state of residence, general health status, subjective cognitive concerns, prior diagnosis of a cognitive disorder, family history of dementia, relevant medications, prior Alzheimer's-related genetic testing, willingness to undergo serial venipuncture, ability to access a collection site, and protocol-specific inclusion and exclusion items. Only minimum-necessary responses are recorded.

Coordinators are prohibited from ordering any test or kit, interpreting symptoms, providing medical advice, discussing APOE genotype or p-tau217 result interpretation, or creating a study account on an individual's behalf.

16.3.2 Waiver of documentation of consent

A waiver of documentation of consent is requested for Stage 1 under 45 CFR 46.117(c). The interaction presents no more than minimal risk; it involves no procedure for which written consent is normally required outside the research context; and the principal record linking the individual to the research would be the consent document itself. The substance of informed consent is obtained and documented in the Pre-Screening Log.

16.3.3 Records and retention

The Pre-Screening Log records verbal agreement, date and time, coordinator identity, eligibility responses, pre-screen outcome, and any do-not-contact request. For individuals who decline, are unreachable, or do not pre-screen eligible, identifiable pre-screening records are destroyed within [30] days. Do-not-contact requests are processed within one business day and the minimum information necessary to honor the request is retained.

Voicemail messages contain no study details beyond the Sponsor's name and a callback request. No more than [3] voicemail attempts are made, separated by at least [2] business days.

16.3.4 Escalation during pre-screening

If an individual reports significant emotional distress, hopelessness, or any indication of self-harm, the coordinator discontinues eligibility questioning, provides the 988 Suicide and Crisis Lifeline, remains on the line if the individual wishes, notifies the Principal Investigator the same day, and completes an escalation note per the escalation standard operating procedure.

16.4 Stage 2: Screening consent and screening procedures

16.4.1 Screening consent

Individuals who pre-screen eligible are directed to the study website, Saturn-test.com, where they review and electronically sign the Screening Consent and HIPAA Authorization. The consent is available for unlimited review time; the coordinator's direct contact information is provided for questions; and no time pressure is applied.

The Screening Consent documents the individual's independent elections regarding return of individual results as specified in Section 16.6.

The electronic consent process provides identity verification at account creation, presentation of the complete consent with the ability to pause and resume, a comprehension check, capture of an electronic signature attributable to the signer with date and time stamp, recording of the exact consent version presented, an immutable audit trail, and automatic delivery of a copy of the signed consent to the participant. The system is maintained in accordance with FDA and OHRP guidance on electronic informed consent and with 21 CFR Part 11 requirements for electronic records and signatures. A system description and validation summary are maintained in the study file.

Screening consent does not obligate the individual to enroll in the main study.

16.4.2 Screening procedures

The following are performed only after the Screening Consent is signed:

1.**Study account creation** on https://app.headsup.health/link/provider?group_code=ILG5D75P, with collection of contact and baseline demographic information.

2.Brief Cognitive Assessment performed at SaturnTest.com and results report code shared the study

3.**APOE genotyping and polygenic risk scoring** on a saliva sample processed by Nucleus CLIA approved laboratories . APOE genotype is to be returned to the participant by a laboratory holding CLIA certification or exempt status under a CMS-approved state licensure program, as specified in Section 16.6.3. (ie. Nucleus Genomics)

4.**Plasma p-tau217 measurement** on a 5 mL venous blood sample collected at a LabCorp patient service center or at a location accessible to the participant, with processing per the approved laboratory manual. (use of intermediary providers such as Care Access will be acceptable)

5.**Eligibility determination** by the Principal Investigator or designee, integrating genotype, p-tau217 status, and pre-screening information against the criteria in Section 3.3 and 3.4.

16.4.3 Screen failure

Individuals who do not meet eligibility criteria are notified of the outcome. Notification states the objective criterion not met and explicitly states that the determination is not a clinical diagnosis. Individuals are advised to direct health concerns to their own clinician.

Biospecimens and identifiable data from individuals who do not enroll are retained for future research on cognitive disorders in de-identified form only where the individual has separately opted in. Screen-failure disposition is documented.

16.5 Stage 3: Main study enrollment

Individuals meeting all eligibility criteria complete the Main Study Informed Consent before any main-study procedure. The main consent addresses the longitudinal visit and biospecimen schedule, the full analytical panel including research-use-only assays, the return-of-results and genetic counseling provisions in Section 16.6, and the associated safety monitoring burden.

16.6 Return of individual results

16.6.1 Scope and elections

Participants may elect to receive their individual Saturn Cogntive Test Score, APOE genotype, plasma p-tau217 status. Each election is independent and separately documented. A participant may enroll in and complete the study while declining all disclosure. Elections are recorded at screening consent, re-confirmed at the pre-disclosure education session, and may be changed or withdrawn at any time before disclosure without effect on study participation.

Because the cohort is APOE4-enriched, a participant may be able to draw inferences about their own genotype from the fact of eligibility. This inferential risk is disclosed in the consent documents.

16.6.2 Non-returnable results

Results from research-use-only assays, including the NULISA CNS220 panel, circRNA measures, and methylomic measures, are not returned to participants or to their clinicians under any election. This limitation is stated explicitly in the consent documents.

16.6.3 Laboratory certification requirement

Individual results are returned only from laboratories holding CLIA certification, or exempt status under a CMS-approved state licensure program. Where a required assay is performed on a research-use-only basis, either the result is not returned, or confirmatory testing is performed at a qualifying laboratory before disclosure. Laboratory certification documentation is maintained in the study file.

16.6.4 Pre-disclosure readiness assessment

Before any disclosure session, participants complete the 15-item Geriatric Depression Scale (GDS-15), the six-item short form of the State-Trait Anxiety Inventory (STAI-6), and the electronic Columbia Suicide Severity Rating Scale (eC-SSRS).

Instrument	Result	Action
GDS-15	< 6	Proceed to disclosure
GDS-15	6–10 inclusive	Proceed only on documented investigator judgment, with specific attention to items 3, 6, 12, and 14
GDS-15	> 10	Defer disclosure; offer clinical referral
STAI-6	< 17	Proceed to disclosure
STAI-6	17–19 inclusive	Proceed only on documented investigator judgment
STAI-6	> 19	Defer disclosure; offer clinical referral
eC-SSRS	Active suicidal ideation with any intent to act within the past 6 months, or suicidal behavior excluding non-suicidal self-injury within 2 years	Disclosure not performed; immediate referral per Section [X].7

Failure to meet readiness criteria results in **deferral of disclosure, not exclusion from the study**. Deferred participants remain enrolled, continue all other study procedures, and may be reassessed at a subsequent visit. This is stated in the consent documents.

16.6.5 Pre-disclosure education session

Participants who elect disclosure and meet readiness criteria attend an education session with an ABGC-certified genetic counselor, delivered by video visit or telephone according to

participant preference, of approximately 45 minutes' duration, scheduled at least [7] days before the disclosure session. Written educational materials are provided in advance.
Session content includes: Alzheimer's disease epidemiology and the distinction between risk and diagnosis; APOE genetics and allele dose; explicit statement that APOE ε4 is neither necessary nor sufficient to cause Alzheimer's disease; the meaning and limitations of plasma p-tau217, including that an elevated result is not a diagnosis and cannot predict whether or when symptoms will occur; cumulative and modifiable risk factors, with explicit statement that risk-reducing behaviors are not proven to prevent or alter disease progression; family history discussion and pedigree construction; insurance and employment implications, including that the Genetic Information Nondiscrimination Act does not extend to life, disability, or long-term care insurance; anticipatory discussion of the participant's expected reaction to each possible result; re-confirmation of disclosure elections; and a comprehension check. The session is repeated if comprehension is inadequate.

16.6.6 Disclosure session

Disclosure is performed by an ABGC-certified genetic counselor, or by a physician-investigator trained on the counselor-developed disclosure script, in a synchronous video or telephone session of approximately 30 minutes with no fixed maximum duration.
Results are never delivered by electronic mail, portal message, postal letter, or voicemail, and are never disclosed to a third party in the participant's absence.
The session comprises: confirmation of identity and of the participant's current wish to receive results; brief re-orientation to test meaning and limitations; plain disclosure of the result followed by a pause; presentation of risk using age- and sex-specific absolute lifetime and remaining-lifetime estimates from a cited published source, alongside population-average comparison, and not relative risk alone; response to the participant's emotional reaction before proceeding; discussion of implications for relatives and of relative testing as a separate decision for discussion with the relative's own clinician; discussion of modifiable risk factors with the caveat stated in Section 16.6.5; provision of a written summary including the result, the risk estimates presented, and contact information; and an offer of a follow-up counseling session at no cost. Participants may be accompanied by a support person at any session. A companion is **required** for participants reporting subjective cognitive decline and for participants whose readiness scores fall in an intermediate band.

16.6.7 Post-disclosure safety monitoring

Timepoint	Modality	Assessments
3 days post-disclosure	Telephone or secure electronic	GDS-15, STAI-6, Impact of Event Scale, test-specific distress items
6 weeks post-disclosure	Secure electronic, telephone if not completed	GDS-15, STAI-6, Impact of Event Scale, perceived Alzheimer's disease risk
6 months post-disclosure	Secure electronic, telephone if not completed	GDS-15, STAI-6, Impact of Event Scale, perceived risk, health-behavior change

Each subsequent study visit	In-visit	GDS-15, STAI-6

Any of the following triggers contact by the genetic counselor or physician-investigator within one business day: GDS-15 greater than 10 or an increase of at least 5 points from pre-disclosure baseline; STAI-6 greater than 19 or an increase of at least 6 points from baseline; any affirmative response on eC-SSRS suicidal ideation items; any Impact of Event Scale score in the clinically significant range; any spontaneous participant report of significant distress; or non-response to two consecutive scheduled follow-up assessments.

16.7 Adverse events of special interest and referral pathway

Psychological distress following disclosure of individual results is a protocol-defined adverse event of special interest. Such events are recorded, summarized in continuing review reports to the IRB, and, where seriousness criteria are met, submitted to WCG IRB as promptly reportable information.

A written referral pathway is established before the first disclosure session and comprises: named local mental health clinicians accepting research referrals; a named licensed telehealth mental health provider for participants outside the local catchment; the 988 Suicide and Crisis Lifeline, provided in all participant materials; and a standing agreement with a licensed psychiatrist or clinical psychologist for urgent same-day consultation. Acute suicidality triggers immediate activation of emergency services per the escalation standard operating procedure, followed by promptly reportable information submission to the IRB.

Responsibility for the cost of referral care is born by the participant.

16.8 Privacy and HIPAA authorization

Participants sign a HIPAA authorization as part of the Screening Consent, specifying the information subject to use and disclosure, the recipients, the duration, and the right and method of revocation.

A partial waiver of HIPAA authorization under 45 CFR 164.512(i)(2)(ii) is requested in the alternative, applicable only where a covered entity discloses limited identifiable information to the Sponsor for recruitment purposes before authorization is signed. The supporting determinations are: the use or disclosure involves no more than minimal privacy risk given the limited data elements and the protections specified; an adequate plan exists to protect identifiers from improper use and disclosure, comprising access limited to named study staff, storage in the validated study system with audit trail, and prohibition of secondary use; an adequate plan exists to destroy identifiers at the earliest opportunity, with pre-screening records for non-proceeding individuals destroyed within [30] days; written assurance is provided that protected health information will not be reused or disclosed except as required by law or for oversight of the research; the research could not practicably be conducted without the waiver, because genotype- and biomarker-defined eligibility cannot be established without first identifying and contacting candidates; and the research could not practicably be conducted without access to and use of the protected health information.

16.9 Personnel and training

Role	Requirement

Genetic counselor	ABGC certification; licensure in each state from which participants are enrolled, where required; documented protocol training
Physician-investigator	Documented training on the counselor-developed disclosure script; available for escalation
Mental health consultant	Licensed psychiatrist or clinical psychologist under written agreement
Research coordinators	Documented training on the pre-screening script and demonstrated script competency; training on readiness instruments and escalation triggers; prohibited from disclosing individual results

Telehealth licensure coverage is verified for every state of participant residence before enrollment from that state.

16.10 Documentation

The following are retained for each individual as applicable: Pre-Screening Log entry with verbal agreement and outcome; signed Screening Consent and HIPAA Authorization with audit trail; disclosure elections and any subsequent changes; readiness instrument scores and any investigator-judgment rationale; pre-disclosure education session note and comprehension check; disclosure session note including the specific risk estimates presented; the written summary provided to the participant; all post-disclosure monitoring scores; and any escalation or referral action with outcome.

IRB APPROVED
Aug 19, 2026

RESEARCH PARTICIPANT CONSENT FORM
SCREENING CONSENT AND HIPAA AUTHORIZATION

Version 1.0 / 8-10-2026

TITLE: Assessing Tools that Predict and Stage Mild Cognitive Impairment

PROTOCOL NO.: PRC-PREDICT-001, Version 2.0
WCG IRB Protocol #20260518

SPONSOR: Prevention Research Consortium Corp

INVESTIGATOR: Foster Carr, MD
2534 State Street 305
San Diego, California 92103
United States

STUDY-RELATED PHONE NUMBER(S): 877-271-6078

RESEARCH CONSENT SUMMARY

You are asked to be in a research study. A person who takes part in a research study is called a research participant. This document will explain what you need to know before you decide. You can ask questions at any time.

This form covers **only the screening part** of the PREDICT study. Screening means we do some tests to find out whether you can join the main study. Signing this form does **not** commit you to the main study. If your screening results show you are eligible, you will be given a separate, longer consent form for the main study, and you can decide then whether to continue.

★ **Your rights — read these first**
- Your participation is **completely voluntary.**
- You may decide not to participate or you may leave the study at any time.
- Your decision will not result in any penalty or loss of benefits to which you are otherwise entitled.
- If you have questions, concerns, or complaints, or think this research has hurt you, talk to the research team at the phone number(s) listed in this document.

How long will I be in this research?

Screening is expected to take about 4 to 6 weeks from start to finish. If you are found eligible and decide to continue, the main study is described in a separate consent form.

Why is this research being done?

PREDICT is an observational research study. That means we observe and measure — we do not give you any drug or treatment. We are studying whether genetic information and proteins measured in blood can predict who is more likely to develop memory and thinking problems in the future.

To find out if you can join, we need to know two things: certain features of your genes, and the level of a protein called **p-tau217** in your blood. Neither of these tests is part of your regular medical care. We are doing them only to see whether you can join this study.

About 100 people will take part in the screening phase of this research at this site. Other sites are also taking part.

What happens to me if I agree to take part?

If you want to be in this study, you will:

- Create an account on the study website, https://app.headsup.health/link/provider?group_code=ILG5D75P, and enter your contact information and some basic health and demographic information.
- Provide a saliva sample at home using a kit we mail to you. You will mail the kit back to a laboratory called Nucleus for genetic testing. This test looks at your **APOE** gene and calculates a combined genetic risk score.
- Have a blood draw at a LabCorp patient service center or through CareAccess, to measure the protein p-tau217.
- Wait for the study team to review your results and tell you whether you can join the main study.

You will also choose whether or not you want to be told your own APOE and p-tau217 results. That choice is yours, and it does not affect whether you can take part.

Could being in this research hurt me?

The most important risks of taking part in this study are:

- **Blood draw.** Pain, bruising, bleeding, or light-headedness at the needle site. Infection is uncommon.
- **Learning information about your own risk.** If you choose to be told your APOE gene result or your p-tau217 result, some people find this information upsetting or worrying.
- **Loss of privacy.** Any time health information is collected there is a risk it could be seen by someone who should not see it.
- **Insurance.** A federal law called the Genetic Information Nondiscrimination Act (GINA) generally stops health insurers and employers from using your genetic information against you. GINA does **not** apply to life insurance, disability insurance, or long-term care insurance.

Will being in this research benefit me?

Taking part in screening will not help you personally. You will not receive medical care or a diagnosis as part of screening. Possible benefits to others include helping scientists better understand and predict memory disorders in the future.

What other choices do I have?

This research is not designed to diagnose, treat, or prevent any disease. Your alternative is not to take part.

What else should I know?

Because this study enrolls extra people who carry the APOE ε4 gene, you may be able to guess something about your own genes simply from the fact that you were found eligible. We want you to know this in advance, even if you choose not to be told your results.

Your name and other details may be removed from your health data and from your samples (saliva and blood). They may then be kept and used for future research on memory disorders without asking for your consent again. You can say no to this and still be screened. You will make this choice later in this form.

✓ **Check Your Understanding**
Before moving on, your study staff may ask you these questions to make sure the information is clear. There are no wrong answers — this is just to help.

- **Q:** If you chose to join the study and then changed your mind, what would you do?
- **Q:** Is there anything about the tests or the results that concerns you?

DETAILED RESEARCH CONSENT

Why is this research being done?

The purpose of this research is to find out whether genetic information and proteins measured in blood can predict who is more likely to develop memory and thinking problems later in life. PREDICT is an observational study: we observe and measure, and we do not give you any drug or treatment.

Before anyone can join the main PREDICT study, we must run two tests that are not part of routine medical care:

- A **genetic test** that looks at your **APOE** gene, which affects the risk of Alzheimer's disease, and calculates a combined genetic risk score.
- A **blood test** for a protein called **p-tau217**, which is linked to changes in the brain.

This form asks your permission for those screening tests only.

About 100 participants will take part in the screening phase of this research at this site. Other sites are also taking part in this study.

How long will I be in this research?

If you join, screening will take about 4 to 6 weeks from start to finish. If you choose to receive your own results, there are follow-up contacts at 3 days, 6 weeks, and 6 months after you are told your results. If you are found eligible and you choose to continue, you will sign a separate consent form for the main study.

✓ **Check Your Understanding**
Before moving on, your study staff will ask you these questions to make sure the information is clear. There are no wrong answers — this is just to help.

- **Q:** Can you tell me in your own words what this study is trying to find out?
- **Q:** About how long would screening take?

What happens to me if I take part in this research?

If you want to be in this study, you will:

1. **Set up a study account.** You will create an account on our study website, Saturn-test.com. You will enter contact information and some basic health and demographic information. This takes about 15 minutes and can be done from home.
2. **Have genetic testing.** We will mail a saliva collection kit to your home. You will spit into a small tube, seal it, and mail it back in the prepaid envelope we provide. This takes about 10 minutes and there is no needle. The kit goes to a laboratory called **Nucleus**, which holds a CLIA certificate. This test looks at your **APOE** gene and calculates a combined genetic risk score.
3. **Have a blood test for p-tau217.** You will have a blood draw at a **LabCorp** patient service center or through **CareAccess** at a location convenient to you. We will draw about 1 teaspoon of blood (5 mL). The sample is used to measure p-tau217 and to confirm sample quality.
4. **Have your eligibility reviewed.** The study team reviews your genetic results, your p-tau217 result, and your screening information to decide whether you can join the main study. We will tell you the outcome either way.

Is any product, device, or procedure in this study investigational?

This study does not give you any drug, device, or treatment. Some of the laboratory tests used in this research are **research-only** tests. This means they have not been approved by the U.S. Food and Drug Administration (FDA) for use in your medical care, and their results cannot be used to diagnose or treat you.

Screening schedule

Step	When	Where	About how long
Study account and screening questions	Day 1	Online (Saturn-test.com)	About 15 minutes
Saliva sample for genetic testing (Nucleus)	Within 1 week	At home, mail-in kit	About 10 minutes
Blood draw for p-tau217	Within 2 weeks	LabCorp or CareAccess site	About 20 minutes
Eligibility review and result letter	Within 4 to 6 weeks	By phone or online	No visit needed
Optional: education session with a genetic counselor	About 1 week before results	Video call or telephone	About 45 minutes
Optional: results session	After eligibility review	Video call or telephone	About 30 minutes
Optional: check-in contacts	3 days, 6 weeks, and 6 months after results	By telephone	About 10 minutes each

Can I find out my own results?

Yes, if you want to. This is your choice, and you make it separately for each type of result. You can change your mind at any time before you are told. Choosing not to receive results will **not** affect your ability to take part in screening or in the main study.

Please check one box in each row:

Result	I want to be told	I do not want to be told
My APOE gene result — which version of the APOE gene you have	[ ]	[ ]
My p-tau217 blood result — reported as not elevated, intermediate, or elevated	[ ]	[ ]
My genetic risk score — a combined score based on many genes	[ ]	[ ]

How results are given to you

If you ask for results, here is what happens:

1. **A questionnaire first.** Before you are told anything, we will ask you some short questions about your mood and how you have been feeling. This is a normal safety step. If your answers suggest that this is a difficult time for you, we may suggest waiting until later, and we can offer you help finding support. Waiting does **not** mean you are out of the study, and you can be asked again at a later visit.
2. **An education session.** About a week before you get your results, a **certified genetic counselor** will meet with you by video call or telephone for about 45 minutes. You will be sent written material in advance. The counselor will explain what the tests do and do not mean, discuss your family history, and answer your questions. We will also ask again whether you still want your results. It is completely fine to change your mind.
3. **The results session.** A certified genetic counselor, or a study doctor working with the counselor, will tell you your results in a video call or telephone call lasting about 30 minutes. We will explain what your result means for your risk compared with other people your age and sex, and give you a written summary to keep. We will never send your results by email, letter, or voicemail, and we will never leave them with someone else.
4. **Check-ins afterward.** We will contact you 3 days, 6 weeks, and 6 months after you receive your results to ask how you are doing. This is to make sure you are supported. If you tell us you are struggling, a member of the study team will contact you within one business day, and we can help you find counseling or mental health care. The study does not pay for this care. You or your health insurance would be responsible for the cost of any counseling or mental health care you receive outside the study. You will also be given the number for the 988 Suicide and Crisis Lifeline.

You may bring a family member or friend to any of these sessions. If you have noticed changes in your own memory or thinking, or if your questionnaire answers suggest you would benefit from extra support, we will ask you to bring someone with you.

A follow-up session with the genetic counselor is available at no cost to you, at any point, if you have more questions later.

Important limits on what results can tell you

- Having an APOE ε4 gene does **not** mean you will get Alzheimer's disease. Not having it does not mean you are safe. The gene is neither necessary nor sufficient to cause the disease.
- An elevated p-tau217 result is **not** a diagnosis of Alzheimer's disease. It cannot tell you whether or when you will develop symptoms.
- We can only give you results from laboratories that are certified to report results to patients. Several tests in this study are **research-only** tests, including the broader protein panel, circRNA, and methylation tests. Those results **cannot** be given to you, no matter what you choose above, and they will not be given to your doctor.
- Because this study enrolls extra people who carry the APOE ε4 gene, you may be able to guess something about your own genes simply from the fact that you were found eligible.

What are my responsibilities if I take part in this research?

If you join, you should:

- Give complete and accurate information when you answer the screening questions.
- Complete the sample collection steps as explained to you.
- Attend the scheduled blood draw appointment, or tell us if you need to reschedule.
- Tell the study team if your contact information changes.
- Tell the study team if you become distressed at any point, especially after receiving results.

Could being in this research hurt me?

There may be risks in the study. Sometimes things happen that are not expected. If you get hurt or feel unwell because of a study procedure, call the study team right away. The risks of screening include:

Physical risks

Blood draw. Drawing blood may cause pain, bruising, bleeding, or light-headedness at the needle site. These effects are common, usually mild, and usually go away within a few days without treatment. Fainting and infection at the needle site are uncommon. For every 100 people who have blood drawn, fewer than 1 develops an infection at the site.

Saliva sample. There are no physical risks from giving a saliva sample at home. No needle is used.

Psychological risks

Learning information about your own risk. This study measures the **APOE** gene, which affects the risk of Alzheimer's disease, and the protein **p-tau217** in your blood. If you choose to, you can be told your own results. Some people find this information upsetting or worrying. Studies of people who received their APOE results have not found lasting increases in anxiety or depression, but some people do feel distress about the result, especially at first.

You do not have to receive any of your results. If you do choose to receive them, the education session, the questionnaire, and the check-in contacts described above are all there to support you. You will also be given the number for the 988 Suicide and Crisis Lifeline.

Answering questions about your memory, thinking, and mood may also feel uncomfortable. You may skip any question you do not want to answer.

Privacy risks
Any time health information is collected there is a risk it could be seen by someone who should not see it. Genetic information is personal and could reveal information about your blood relatives as well as about you. The steps we take to protect your information are described in the section "What happens to the information collected for this research?"

Social, economic, and insurance risks
A federal law called the Genetic Information Nondiscrimination Act (GINA) generally prevents health insurers and employers from using your genetic information against you. GINA does **not** apply to life insurance, disability insurance, or long-term care insurance. Companies that sell those kinds of insurance could ask you whether you have had genetic testing, and could use your answer when deciding whether to sell you a policy or what to charge.

Some people also worry about how family members will react to genetic information, or feel differently about themselves after learning a result. The genetic counselor can help you think through who you want to tell, and when.

✓ Check Your Understanding
Before moving on, your study staff may ask you these questions to make sure the information is clear. There are no wrong answers — this is just to help.

- **Q:** Can you tell me in your own words about the most important risk we just discussed?
- **Q:** Does an APOE ε4 result mean you will definitely get Alzheimer's disease?
- **Q:** What number would you call if you felt very upset after getting your results?

Will it cost me money to take part in this research?
There is no charge to you for any screening test. Neither you nor your insurance will be billed for the saliva kit, the genetic test, the blood draw, or the p-tau217 test.

You will not be paid back for travel to the LabCorp or CareAccess site, or for parking, mileage, or time away from work. These costs are yours.

If you choose to receive your results and you later want counseling or mental health care, the study does not pay for that care. You or your health insurance would be responsible for the cost.

Will being in this research benefit me?
There is no direct medical benefit to you from screening. You will not receive medical care or a diagnosis as part of screening, and the study is not designed to treat any condition. We cannot promise any benefits to others from your taking part in this research. However, possible benefits to others include helping scientists understand and predict memory disorders, which may in the future help doctors identify people at risk earlier.

If you choose to receive your APOE or p-tau217 results, some people value knowing this information for personal planning. This is not a medical benefit, and knowing your result will not change your medical care as part of this study.

What other choices do I have besides taking part in this research?

This research is not designed to diagnose, treat, or prevent any disease. Your alternative is not to take part. If you want information about your risk of memory problems outside of research, you can talk to your own doctor about clinical testing and evaluation.

What if I am not eligible?

If your screening results show you cannot join the main study, we will let you know and your participation ends at that point. Being screened out is common and does not mean anything is wrong with your health.

What happens to your information and samples if you screen out. Your saliva and blood samples, and your screening data with your name and other identifying details removed, will be kept and used for future research on memory disorders. This is true whether or not you join the main study.

You can say no to this and still be screened. Please check one box below:

[ ]	**Yes.** My samples and de-identified screening data may be kept and used for future research on memory disorders.
[ ]	**No.** My samples must be destroyed and my identifiable screening information deleted within 90 days after screening ends. I understand I can still be screened.

What happens to the information collected for this research?

Your information is stored in a secure, access-controlled study system. Only trained study staff have access. Samples and data sent to laboratories are labeled with a code, not your name. Study results are reported in groups, never in a way that identifies you.

The study doctor and staff will see your personal and health records. Your information may also be shared with:

- The research sponsor, Prevention Research Consortium Corp, and people who work with the sponsor
- Nucleus, the genetic testing laboratory
- LabCorp and CareAccess, for blood collection and processing
- Heads up Health the participant secure communication system
- Veeva the study data system
- Banner Alzheimer’s Institute and the Alzheimer’s Prevention Registry, if that registry told you about this study. The registry may share your contact information with us. At this time we do **not** send any of your study information back to the registry.
- Government agencies, such as the Food and Drug Administration (FDA)
- WCG IRB, the Institutional Review Board (IRB) that reviewed this research

Your name will not be used in reports or talks about the study. We may share your information if the law requires it or in an emergency.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Who else can answer my questions about this research?

If you have questions about the study, or if you feel you have been harmed, contact Foster Carr, MD at 877 271 6078 or drcarr@telemedical.com, available 9 am – 5 pm PST M-F.

You may also contact the sponsor, Prevention Research Consortium Corp, at drcarr@prevention-research.org.

This research is being overseen by WCG IRB. An IRB is a group of people who perform independent review of research studies. You may contact them at 855-818-2289 or clientcare@wcgclinical.com if:

- You have questions, concerns, or complaints that are not being answered by the research team.
- You are not getting answers from or cannot reach the research team.
- You have questions about your rights as a research participant.

What if I am injured because of taking part in this research?

If you get hurt or sick because of this study, call the study team right away. The study team will help you get the right care. Your insurance may be billed for this care. Prevention Research Consortium Corp, the company paying for the study, will pay for costs related to a research injury that your insurance does not cover. No other payment is offered. You do not give up any of your legal rights by signing this form.

If you become very distressed after learning your results, the study team will help you find counseling or mental health care. The study does not pay for that care. You or your health insurance would be responsible for the cost.

Can I be removed from this research without my approval?

The study doctor may remove you from screening for safety or other reasons, such as:

- Your screening results show you are not eligible for the main study
- A sample cannot be collected or the laboratory cannot produce a usable result
- It is in your best interest, for example if receiving results would not be safe for you at this time
- You are unable to complete the screening steps or keep your scheduled appointments
- The research is canceled by the sponsor or an oversight agency

We will tell you about anything new that may affect your health, welfare, or choice to stay in this research.

What happens if I agree to be in this research, but I change my mind later?

Taking part is entirely voluntary. You may refuse, or stop at any point during screening, for any reason. This will not affect your medical care, your relationship with your doctor, or any benefits you are entitled to. If you were told about this study by a registry, declining will not affect your standing with that registry.

There are no medical risks to you from leaving screening early. Please call the study team so we can stop any tests that have not yet been run and tell you what will happen to any sample already collected.

We will keep you informed. If we learn something new during screening that might change your decision to stay, we will tell you right away.

Will I be paid?

You will not be paid for taking part in screening. You will also not be paid back for travel, parking, or other costs of taking part.

Your samples or data (even with your name removed) may be used to make a profit. You will not receive financial benefit or profit from the products or tests developed from your samples or data.

✓ **Final Check Before Signing**

Before you sign, please make sure you can answer these questions. Ask the study team if anything is unclear.

- **What is the main purpose of this screening?**
- **What are the most important risks you heard about?**
- **Have you decided which results, if any, you want to be told?**
- **What can you do if you want to leave the study?**
- **Who do you call if something feels wrong?**

Statement of Consent

I have read this form, or it has been read to me. I have had the chance to ask questions and my questions have been answered. I voluntarily agree to take part in screening for this study, and I authorize the use and sharing of my health information as described in this form. I will be given a copy of this signed form.

Your signature documents your consent to take part in this research.

Printed name of participant

Signature of participant	Date and time

Printed name of person obtaining consent

Signature of person obtaining consent	Date and time

Electronic signature
When this form is signed electronically on https://patients.myveeva.com/login, the system records the signer's identity, the date and time stamp, the exact consent version presented, and an audit trail, and automatically delivers a copy of the signed form to the participant. This follows FDA and OHRP guidance on the use of electronic informed consent in clinical investigations and 21 CFR Part 11 requirements for electronic records and electronic signatures.

HIPAA AUTHORIZATION FOR RESEARCH

What is this form?

This form asks for your permission to use and share your health information for this research study. Your health information is called Protected Health Information. You do not have to sign this form, but if you do not, you cannot be in the study. Your care and benefits will not change if you do not sign.

What information will be used?

The study may use:

- Your name and contact details
- Your date of birth, sex, race, and ethnicity
- The health and cognitive information you report during screening
- Your medical history, medicines, and treatments
- Your saliva sample and your genetic test results, including your APOE result and genetic risk score
- Your p-tau217 result and other laboratory results generated during screening

Only information needed for this study will be used.

Who may use or share my information?

- The study team at Prevention Research Consortium Corp
- Nucleus, the genetic testing laboratory
- LabCorp and CareAccess, for blood collection and processing
- Saturn-test.com, the study data system
- Your doctors and clinic staff, if they provide records for this study

Who may receive my information?

- The research team and the study sponsor, Prevention Research Consortium Corp
- Banner Alzheimer’s Institute and the Alzheimer’s Prevention Registry, if that registry referred you. The study does not send your information back to the registry at this time.
- Government groups that oversee research, including the Food and Drug Administration (FDA)
- WCG IRB

Why is my information being used?
Your information will be used to:

- Decide whether you can join the main study
- Do the research study
- Follow study and legal rules
- Check safety and study quality
- Report results without using your name

How long does this permission last?
There is no end to your permission. If required by law, your permission will end 50 years after you sign this authorization. Research records must be kept for a long time so that results can be checked.

Can I change my mind?
Yes. You may cancel this permission at any time by writing to Foster Carr, MD 2534 State St 305, San Diego CA 92101 and drcarr@telemedical.com. If you cancel, we will stop collecting new information about you. Information already collected can still be used, because removing it would make the research results unreliable, and it may still be needed to follow up on a research injury.

Privacy risks
Once shared, your information may no longer be protected by the federal privacy rule (HIPAA) and could be shared again without your permission. Some organizations that receive your information may not be covered by HIPAA, and in that case that law would not protect the information they hold. The study team will work to protect your privacy as required by law.

Will this affect my care?
No. Your medical care and benefits will not change if you do not sign this form. However, you cannot take part in screening or in the main study without signing, because this is the only way we can obtain the information needed to determine whether you are eligible.

Copy of this form
You will receive a copy of this signed form.

Agreement and signature

I have read this form or had it read to me. I agree to the use and sharing of my health information as described.

Printed name of participant

Signature of participant	Date and time

Informed Consent Form

TITLE:	Assessing Tools that Predict and Stage Mild Cognitive Impairment
PROTOCOL NO.:	PRC-PREDICT-001, Version 2.0 WCG IRB Protocol #20260518
SPONSOR:	Prevention Research Consortium Corporation
INVESTIGATOR:	Foster Carr, MD 2534 State Street 305 San Diego, California 92103 United States
STUDY-RELATED PHONE NUMBER(S):	877-271-6078 (24 hours)

Your participation in this research study is voluntary. You may decide not to participate or you may leave the study at any time. Your decision will not result in any penalty or loss of benefits to which you are otherwise entitled.

If you have questions, concerns, or complaints, or think this research has hurt you, talk to the research team at the phone number(s) listed in this document.
You may not receive any direct medical benefit from this research.

RESEARCH CONSENT SUMMARY

How long will I be in this research?

We expect that your taking part in this research will last about 24 months (2 years), with in-person visits about every 6 months and continuous or frequent digital monitoring during this time.

Why is this research being done?

The purpose of this research is to test whether a pre-specified proteogenomic 'Progression and Risk' (P&R) model—combining blood-based biomarkers (including pTau217 and related Alzheimer's proteins), genetic risk scores, and digital monitoring—can help predict which

cognitively normal or very mildly impaired adults with an ApoE4 gene are most likely to develop early memory and thinking problems (mild cognitive impairment related to Alzheimer's disease) over about 2 years. This is a first-in-human observational study to validate this prediction model.

What happens to me if I agree to take part in this

Before you reach this form, you will already have completed a separate Screening Consent and screening tests. During screening you had a genetic test for the APOE gene, a blood test for a protein called p-tau217, and a review of your health and memory. You signed a separate consent form before any of those tests were done.

This form is about the main study, which is what happens next if the screening showed you are eligible. Screening does not commit you to the main study, and you are free to stop here.

If you meet the criteria for participation and decide to take part, you will have 5 in-person visits over about 2 years for blood draws, memory and thinking tests, and digital cognitive assessments. You will use digital tools (such as an Oura Ring and smartphone apps with platforms like Punto Health) that collect information about your activity, sleep, speech features, and other behaviors on a continuous or frequent basis. Some participants may have data collected and used for this research if you agree from standard of care procedures such as EEG or retinal imaging, and clinically indicated imaging or spinal fluid collection that are performed as part of your standard of care outside of this research.

Could being in this research hurt me?

The most important risks or discomforts that you may expect from taking part in this research include:

- Blood draws: Pain, bruising, bleeding, swelling, feeling faint, or rarely infection at the needle or fingerstick site
- Cognitive testing: Tiredness, frustration, or anxiety about performance
- Genetic and biomarker results: Anxiety, sadness, or worry about Alzheimer's risk; small risk of information misuse if confidentiality breached
- Continuous digital monitoring: Privacy concerns; risk of unauthorized data access despite encryption; some may find monitoring intrusive
- Triggered assessments: Psychological impact of being contacted when data suggest possible cognitive changes
- Loss of confidentiality
- Unknown risks: There may be risks not yet known

Will being in this research benefit me?

The most important benefits that you may expect from taking part in this research include:

Direct clinical benefit is not guaranteed. However, you may gain early insights into your cognitive status and risk factors through closer monitoring of memory and thinking over time, and you may have access to some clinically validated biomarker or genetic results if your site returns them (per institutional policy). This study is not designed to provide treatment or change your routine medical care.

Possible benefits to others include:

This study may help improve tools for early detection and staging of Alzheimer's disease, enable better risk-prediction models, develop more scalable biomarker strategies, and help design future prevention or treatment studies. The main benefit is to future patients and society rather than individual participants.

What other choices do I have besides taking part in this research?

Instead of being in this research, your choices may include:

You may choose not to be in any research study, or you may seek standard evaluation or care for memory concerns from your usual healthcare providers or memory clinic, or join other research studies for which you are eligible. Your decision will not affect your regular medical care.

What else should I know about this research?

There is a possibility that your de-identified information or biospecimens may be used for future research studies. Any future use of your coded samples and data will be reviewed by an ethics board when required and will follow applicable privacy laws. You will be asked separately whether you agree to future research use; declining does not affect your participation in this main study.

DETAILED RESEARCH INFORMATION

1. Why is this study being done?

This study is being done to learn whether a combination of blood-based biomarkers, genetic risk scores, and continuous digital monitoring (such as measures of activity, sleep, speech

patterns, and smell) can help predict who is likely to develop very early memory and thinking problems related to Alzheimer's disease.

This is a first-in-human observational study designed primarily as a prospective validation of a pre-specified proteogenomic Progression and Risk (P&R) model for predicting conversion from cognitively normal (CN) or very mildly impaired status to pTau217-positive mild cognitive impairment (MCI Stage I) over 24 months in ApoE4-positive adults.

The P&R model combines:

- A polygenic risk score (PRS) based on your existing whole-genome sequencing or genotyping array data
- APOE genotype status (you already carry at least one ApoE4 allele)
- Plasma biomarkers including pTau217, Aβ42/40, GFAP, NfL, and additional proteomic markers
- DNA methylation measures in some participants
- Whole blood Circular RNA measures in some participants.
- Standardized cognitive and functional tests (such as Clinical Dementia Rating and digital cognitive assessments)
- Digital and wearable data such as Oura Ring sleep and activity metrics, smartphone-based cognitive tasks, and speech features

Please feel free to ask the study staff any questions you may have about this model.

We are especially interested in adults who carry the ApoE4 gene, which is associated with a higher chance of developing late-onset Alzheimer's disease. We will follow participants for about 2 years to see who remains cognitively normal and who develops mild changes in memory or thinking (mild cognitive impairment, or MCI), and how this relates to the biomarkers and monitoring data.

Up to about 1000 people will take part in this study at this and/or other sites.

2. Why am I being asked to take part?

You are being asked to participate because:

- You are 55 years of age or older.

- You carry at least one copy of the APOE ε4 gene. This was established in one of two ways: either you already had genetic testing showing this before you joined, or the study performed genetic testing for you during screening.
- If you did not already have genetic test results, the study arranged an APOE genetic test and a genetic risk score for you as part of screening. This testing is done for

research purposes. You signed a separate Screening Consent before that testing was done, and that form explained your choices about whether to be told your own results.
- If you already had genetic test results, you agreed to share your existing genomic data (for example, whole-genome sequencing or genotyping array files from prior clinical testing, research studies, or direct-to-consumer services) so that a genetic risk score could be calculated.
- You are cognitively normal or very mildly impaired at baseline (the study focuses on participants who do not yet meet criteria for established MCI with positive Alzheimer's biomarkers; if you develop pTau217-positive MCI during the study, you will be referred to a neurologist and your active study participation will end).
- You are willing to undergo blood collection, cognitive testing, and continuous digital monitoring (for example through a smartphone and wearable devices).
- You are willing to use wearable devices such as an Oura Ring and smartphone apps, and to allow the study to access certain medical record information needed for risk scoring, as permitted by you and by privacy regulations.

You do not have to be in this study. You may choose not to participate.

3. What will happen if I take part?

Overview

If you join this study, you will be followed for about 2 years. You will:

- Attend 5 in-person visits at the study site at the beginning (baseline) and at 6, 12, 18, and 24 months (±2 months).
- Have blood collected up to 5 times over 2 years during the main study. This is in addition to the one blood sample that was collected during screening, before you signed this form.
- Complete memory and thinking tests and questionnaires at each in-person visit.

  Use digital tools including an Oura Ring or an Apple Watch (for continuous sleep, activity, and heart rate monitoring) and smartphone-based cognitive and speech assessments through platforms such as Punto Health and Food for the Brain Cognitive Online Test that measure activity, sleep, brief cognitive tasks, speech features (not content), and other behaviors continuously or frequently.

  Data may also be collected from your medical records if additional procedures (for example, spinal fluid collection or brain scan if clinically indicated and ordered by your treating doctor regardless of this research). If there is leftover spinal fluid after the clinically indicated procedure, you might be asked if the leftover sample can be

used for testing in this research for biomarkers known to be associated with Alzheimer's Disease and cognitive decline.

Sub-Cohort of participants may be asked to have non-invasive retinal imaging or EEG procedures performed as part of this research.

The total time for each in-person visit will usually be approximately 1 hour.

Screening

Screening happened before this form. Screening for this study is covered by a separate document, the Screening Consent and HIPAA Authorization, which you read and signed before any screening test was performed. Nothing in this section happens after you sign the form you are reading now. It is described here so that the full study is in one place.

During screening, the following took place:

- You were asked about your medical history, medications, and any neurological or psychiatric conditions.
- You were asked about your memory and daily functioning, and you may have been given brief memory tests.
- Your APOE gene was tested. If you already had APOE results from prior testing, those were verified instead. A genetic risk score was calculated, either from testing done for this study or from genomic data you already had.
- A blood sample was collected at a LabCorp location or by CareAccess to measure a protein called p-tau217.
- If you already had genomic data from prior testing, you were asked to sign a release allowing the study to obtain those files.
- If you have an Oura Ring or an Apple Watch, you were asked whether the study may access that data. This was optional.

If screening showed that you are eligible and you still want to take part, you are now being asked to read and sign this form before the baseline visit. **Signing the Screening Consent did not commit you to the main study.** You may decide not to continue, and that decision will not affect your medical care.

Baseline visit (Month 0)

At the baseline visit, you will:

1. Review and sign this consent form (if not already signed).
2. Medical and neurological evaluation
    - Vital signs (blood pressure, pulse, weight, height).
    - Brief physical and neurological examination.

3. Memory and thinking tests
    - A structured interview and rating scale about your memory and function (such as the Clinical Dementia Rating, or CDR) using a no-informant version when an informant is not available.
    - A set of paper-and-pencil or computerized tests of memory, attention, language, and thinking.
    - Digital cognitive tests using an app or tablet (for example, through a platform such as Punto Health) and brief speech-based measures.
4. Blood collection
    - Blood will be drawn from a vein in your arm and/or by fingerstick.
    - Blood will be used to measure Alzheimer's disease biomarkers (for example, a protein called pTau217 and related markers including pTau181, Aβ42/40, GFAP, and NfL), and to perform proteomic, genomic, and methylation analyses in some participants.
    - If needed, some blood may be used for routine safety lab tests or obtained from your primary care provider's records.
5. Genomic data access and PRS calculation

    Your APOE genotype and genetic risk score were established during screening. Depending on your situation, this was done in one of two ways.

    If you did not have prior genetic testing, the study arranged APOE genotyping and genetic risk scoring for you. This was performed for research purposes by the study's genetics laboratory. Where your individual APOE result is to be given back to you, the test is performed or confirmed by a laboratory that is certified to report results to patients.

    If you already had genetic testing, you were asked to authorize release of your prior whole-genome sequencing or genotyping array data from the laboratory or service where it was originally performed. Those existing data were used to calculate your genetic risk score and confirm your APOE genotype.

    This study does not perform new whole-genome sequencing.

6. Additional data collection from standard of care procedures that were performed outside of this research if available (not required for participation; performed only when clinically indicated)
    - Spinal fluid collection (lumbar puncture): Only if clinically indicated as part of your routine care outside the study, a sample of leftover fluid from your lower back may be used to measure Alzheimer's-related proteins. This protocol does not require any research-mandated lumbar punctures.
    - Retinal imaging (sub-cohort): Imaging of the back of your eye (retina) using a camera that may detect changes related to brain health using hyperspectral imaging.
    - EEG (electroencephalogram) (sub-cohort): A test that uses small sensors on your scalp to measure electrical activity in your brain at rest and during simple tasks (such as memory or attention tasks).

- Brain scans (such as amyloid PET): Only if medically indicated and clinically available as part of your standard-of-care, your treating doctor may order such scans and we may use the results in our research with your permission. MRI or PET scans are not required by this study.

7. Digital monitoring setup
    - If you already have an Oura Ring or an Apple Watch, you may choose to let the study access data from those devices. If you agree, we will help you install an app that connects your device to the study.
    - These tools may collect information about your:
        - Physical activity and step counts.
        - Sleep patterns (including sleep stages, heart rate variability, and other cardiovascular metrics from the Oura Ring).
        - Location patterns (for example, how often you leave home and where you go, but not the content of what you do).
        - Speech characteristics (for example, pace and tone of your voice, not your actual spoken content) collected during brief app-based tasks.
        - Periodic cognitive assessments and, if available, smell tests, to measure cognitive function and sense of smell.

    We will help you set up these devices and show you how to use them.

8. Optional Sub-Cohort procedures (not all participants will be asked to have these additional procedures performed).
    - Retinal imaging (sub-cohort): Imaging of the back of your eye (retina) using a camera that may detect changes related to brain health using hyperspectral imaging.
    - EEG (electroencephalogram) (sub-cohort): A test that uses small sensors on your scalp to measure electrical activity in your brain at rest and during simple tasks (such as memory or attention tasks).

Follow-up visits (Months 6, 12, 18, and 24)

At each follow-up visit, you will:

- Update your medical history and medications.
- Have vital signs measured.
- Repeat memory and thinking tests similar to the baseline visit.
- Repeat digital cognitive tasks and brief speech-based measures.
- Have blood drawn again (venipuncture or fingerstick) for biomarker and other tests including pTau217 and related biomarkers, with extended proteomic and methylomic panels performed in some participants as budget permits.
- Discuss any problems or questions about the digital devices and review your Oura Ring or Apple IPhone/Watch and app adherence.

Some procedures (such as EEG or retinal imaging) may be repeated at selected visits (for example, at 24 months) depending on feasibility and your willingness and are limited to sub-cohorts.

Continuous digital monitoring

During the 2-year study:

- You will be asked to use a smartphone app and/or wearable sensors most days including continuous or frequent Oura Ring wear and periodic completion of app-based cognitive and speech tasks.
- The devices will passively measure some aspects of your behavior (activity, sleep, location patterns) and sometimes ask you to complete brief tasks or questions.
- The study team may contact you if the data suggest notable changes in your functioning, or if you are not using the devices regularly, to see if you are having any difficulties.

If you have any questions or concerns using the Oura Ring or the iPhone App, please contact the study team for assistance.

Additional "triggered" assessments

If there are concerns about new memory or thinking problems---for example, because of changes in your test scores, digital data, or your own report---we may invite you for an extra visit. At that visit, you may repeat some of the cognitive tests and blood tests, and if criteria for pTau217-positive MCI are met, you will be referred to a neurologist and your active participation in the study will end, though samples and data already collected may continue to be used for research.

4. How long will I be in the study?

Your participation in this study will last about 24 months (2 years) from your baseline visit. At the end of the 2 years, your active participation in this study will stop. If you develop pTau217-positive MCI during the study and are referred to a neurologist, your active participation may end earlier. In all cases, your samples and data may continue to be used for research as described below if you provide separate permission for future use.

You may choose to leave the study earlier at any time.

5. What are the risks and discomforts?

Taking part in this study may involve the following risks or discomforts:

Blood draws (venipuncture or fingerstick)

- Pain, bruising, bleeding, or swelling at the needle or fingerstick site.
- Feeling light-headed or faint.
- Very rarely, infection or inflammation at the puncture site.

EEG (sub-cohort procedure)

- Mild discomfort from wearing a cap and having electrodes on your scalp.
- Possible skin irritation from the gel or adhesive.
- Fatigue from sitting still.

Retinal imaging (sub-cohort procedure)

- Bright lights may be uncomfortable and could cause temporary blurry vision or sensitivity to light.
- Eye drops (if used) may temporarily blur your vision.

Cognitive testing

- Some people feel tired, frustrated, or anxious during or after memory and thinking tests.
- You may worry about your performance or what it means.

Genetic testing and biomarker results

- Learning that you carry APOE ε4, or that you have biomarker changes associated with Alzheimer's disease, may cause anxiety, sadness, or worry about the future. This may be true whether the information is new to you or something you already knew.
- **If the study performed your genetic test, you may be learning this about yourself for the first time.** Studies of people who were told their APOE results have not found lasting increases in anxiety or depression. Some people do feel distress about the specific result, particularly in the first weeks. Because of this, you are never simply handed a result: a certified genetic counselor works with you before and after, and we check in with you afterward. This is described in Section 10.
- You do not have to be told any of your results. You made this choice on the Screening Consent, you may change it at any time, and choosing not to be told will not affect your participation in this study.
- There is a small risk of misuse or misunderstanding of genetic or biomarker information by others if confidentiality is breached, although we take steps to protect your information.
- **Insurance and employment.** A federal law called the Genetic Information Nondiscrimination Act, or GINA, generally prevents health insurance companies and

employers from using your genetic information against you. GINA **does not** apply to life insurance, disability insurance, or long-term care insurance. If you are considering buying or changing any of those policies, you may want to think about that timing, and the genetic counselor can discuss it with you.
- Because this study enrolls a higher-than-usual number of people who carry APOE ε4, you may be able to guess something about your own genes simply from the fact that you were found eligible. We want you to know this even if you choose not to be told your results.

We will explain which results, if any, will be shared with you and under what circumstances. You can choose not to learn certain results if allowed by law and IRB policy.

Digital monitoring (there is a risk of loss of privacy and confidentiality)

- Your activity, location patterns, sleep, speech features (not content), and other sensor-based signals including Oura Ring cardiovascular and sleep metrics will be collected electronically.
- Although we use encryption and secure systems, there is a risk of unauthorized access or data breach.
- You may find some aspects of continuous monitoring intrusive or bothersome.
- Being contacted for a triggered assessment when digital data suggest possible cognitive changes may cause psychological distress or worry.

You may choose to disable or pause some monitoring temporarily; however, this may limit how much data we can use for the study. You may choose not to take part in specific optional procedures (EEG, retinal imaging, or certain digital features) and still remain in other parts of the study, when feasible and allowed by the protocol.

The following procedures would only be performed as part of your standard of care treatment and regardless of this research. These risks are outside of this research context.

Lumbar puncture (if clinically indicated and ordered by your treating physician as standard of care)

- This procedure will be only performed when clinically indicated as part of your routine care and regardless of this research.
- Headache after the procedure.
- Back discomfort.
- Rarely, bleeding, infection, or nerve injury.

Brain imaging (if clinically indicated and ordered by your treating physician as standard of care)

- These scans are only performed when ordered by your treating physician as part of routine care and regardless of this research.
- MRI: discomfort from lying still, noise, or claustrophobia; in very rare cases, contrast agents can cause allergic reactions or kidney problems.
- PET: exposure to low levels of radiation, similar to or less than many diagnostic imaging procedures; rare allergic reactions to the tracer.

Other risks

- There may be risks that are unknown or unexpected at this time.
- If we learn of new risks or important new information that might affect your willingness to continue, we will tell you.

6. Are there benefits to taking part?

You may or may not receive any direct benefit from being in this study.

Possible personal benefits may include:

- Learning more about your memory and thinking over time.
- Having access to some biomarker or genetic information that might not otherwise be available, if your site's policy is to share such results.
- Being more closely monitored for early changes in memory and function, which you can discuss with your healthcare providers.

However, this study is not designed to provide treatment and may not improve or change your health. You may gain early insights into your cognitive status and risk factors through closer monitoring, though this study is not designed to provide treatment or change your routine medical care.

The information learned from this study may help researchers better understand how to detect Alzheimer's disease at its earliest stages and may help design future prevention or treatment studies. The main benefit is to future patients and society via better risk-prediction models, more scalable biomarker strategies, and improved early detection tools.

7. What other choices do I have besides taking part in this research?

You may choose not to be in any research study, or you may seek standard evaluation or care for memory concerns from your usual healthcare providers or memory clinic, or you can

join other research studies for which you are eligible. Your decision will not affect your regular medical care.

8. What about privacy and confidentiality?

We will do our best to protect your privacy and the confidentiality of your information.

- You will be assigned a unique study number. Your samples and most data will be labeled with this number instead of your name whenever possible.
- A master list that links your name to your study number will be kept in a secure, limited-access file.
- Electronic data (including digital monitoring data) will be stored on secure systems with password protection, encryption, and access limited to authorized study staff.
- Paper records will be kept in locked cabinets or offices.

For digital data such as Oura Ring or Apple IPhone/Watch metrics or app-based cognitive tests, data will be transmitted over encrypted connections to secure servers and stored under coded identifiers. Any sharing with collaborators or sponsors will use de-identified or limited datasets under data-use agreements that prohibit re-identification.

People who may see your study records include:

- The research team and staff at the study site.
- Institutional review boards (IRBs) and other institutional committees that oversee research.
- Regulatory agencies (for example, the U.S. Food and Drug Administration) if required by law.
- Study sponsors or collaborators, in de-identified or limited data form, under data-sharing agreements designed to protect your privacy. This includes academic research collaborators and commercial partners involved in model development and biomarker analysis.

When we publish or present study results, we will not use your name or any information that could easily identify you.

9. Will my information or samples be used for future research?

As part of this study, we will collect blood (and possibly spinal fluid) and detailed digital and clinical data. These may be stored for future research.

- Future research may be related to Alzheimer's disease, other brain or aging conditions, or to the development of new tests or models. Future studies may be conducted with or without Alzheimer's disease as the primary focus, as long as they are IRB-approved.
- Any future use of your samples or data will follow applicable laws and will be reviewed by a research ethics board when required.

You will be asked to indicate whether you agree to allow your samples and data (with your identifying information removed or coded) to be stored and used for future research. You may:

- Agree to future use, or
- Decline future use (in which case, your samples will be destroyed at the end of this study or as per institutional policy).

Your decision about future use will not affect your participation in this main study.

10. Will any results be returned to me?

Yes, if you want them. This study offers to give you your own results, and it is entirely your choice whether to receive them.

What you can choose to receive
You made these choices on the Screening Consent. You may change any of them at any time before you are told, by telling the study team. Each choice is separate:

- Your **APOE gene result** — which version of the APOE gene you carry.
- Your **p-tau217 blood result** — reported as not elevated, intermediate, or elevated.

- Your **genetic risk score**, if this test is available from a laboratory certified to report results to patients.

Choosing not to receive any result will not affect your participation in this study in any way.
What cannot be given to you
Some tests in this study are research-only tests. These include the broader protein panel, circRNA measures, and DNA methylation measures. Research-only tests have not been set up to give reliable results for individual people, so those results **cannot** be given to you or to your doctor, no matter what you choose. We can only return results from laboratories that are certified to report results to patients.
How results are given to you
If you asked for results, this is what happens:
1. A short questionnaire first. Before you are told anything, we ask you some questions about your mood and how you have been feeling. This is a routine safety step. If your answers suggest this is a hard time for you, we may suggest waiting, and we can help you

find support. **Waiting does not mean you are out of the study.** You stay enrolled, you continue everything else, and we can ask again at a later visit.
2. An education session. About a week before you get your results, a certified genetic counselor meets with you by video call or telephone for about 45 minutes. You receive written material in advance. The counselor explains what the tests do and do not mean, goes through your family history, discusses insurance questions, and answers anything you want to ask. At the end, we ask again whether you still want your results. Changing your mind is completely fine.
3. The results session. A certified genetic counselor, or a study doctor working with the counselor, gives you your results in a video call or telephone call of about 30 minutes. We explain what your result means for your risk compared with other people your age and sex, and give you a written summary to keep. We will never send your results by email, letter, or voicemail, and we will never leave them with someone else.
You may bring a family member or friend to any session. If you have noticed changes in your own memory or thinking, or if your questionnaire answers suggest you would benefit from extra support, we will ask you to bring someone with you.
4. Check-ins afterward. We contact you 3 days, 6 weeks, and 6 months after you receive your results, and briefly at each later study visit, to ask how you are doing. If you tell us you are struggling, a member of the study team contacts you within one business day and can help you find counseling or mental health care. [State whether the study pays for this care.] You are given the number for the 988 Suicide and Crisis Lifeline, which you can call or text at any time.
A follow-up session with the genetic counselor is available at no cost to you, at any point, if questions come up later.
What these results cannot tell you

- Carrying an APOE ε4 gene does **not** mean you will develop Alzheimer's disease. Not carrying it does not mean you are safe. This gene is one factor among many, and it is neither necessary nor sufficient to cause the disease.
- An elevated p-tau217 result is **not** a diagnosis of Alzheimer's disease. It cannot tell you whether or when you will develop symptoms.

- Nothing in this study is a substitute for evaluation by your own doctor. If you have concerns about your memory, please talk to them.

11. What happens if I am injured?

This is mainly an observational study with procedures similar to those used in standard medical care. Injury from study procedures is unlikely but possible (for example, from blood draws).

If you are injured as a direct result of study procedures, medical care will be available. Your site will explain whether financial compensation or coverage for such injury is available under institutional policy. If you are injured as a result of this study, you do not give up your right to pursue a claim through the legal system.

12. Do I have to be in this study? What if I change my mind?

Participation is voluntary.

- You may choose not to be in the study.
- If you decide to be in the study, you may leave at any time, for any reason, without penalty.
- Your decision will not affect your legal rights or your regular medical care.

If you leave the study, we may continue to use information and samples already collected unless you
specifically withdraw permission for this use, as allowed by law and institutional policy.

The study doctor may also decide to stop your participation without your consent if:

- You are unable to follow study instructions.
- You develop a medical condition that makes continued participation unsafe.
- The study is stopped by the sponsor, the institution, or the IRB.

13. Who can answer my questions?

If you have questions, concerns, or complaints, or think this research has hurt you, talk to the research team at the phone number(s) listed in this document.

This research is being overseen by WCG IRB. An IRB is a group of people who perform independent review of research studies. You may talk to them at 855-818-2289 or clientcare@wcgclinical.com if:

- You have questions, concerns, or complaints that are not being answered by the research team.
- You are not getting answers from the research team.
- You cannot reach the research team.
- You want to talk to someone else about the research.
- You have questions about your rights as a research subject.

14. Will I be paid to participate?

You will not be paid for being in this study.

15. Consent and Authorization

By signing below, you:

- Confirm that you have read this form (or had it read to you).
- State that all your questions have been answered.
- Understand that your participation is voluntary.
- Agree to take part in this research study.

You will receive a copy of this signed and dated form, as well as signed and dated copy of the Experimental Subject's Bill of Rights.

Participant Name (print): _____

Participant Signature: _____ Date: _____

Person Obtaining Consent (print): _____

Signature of Person Obtaining Consent: _____ Date: _____

15.1 Optional: Permission for Future Use of Samples and Data

Please initial one option:

_____ YES, I agree that my coded samples and data may be stored and used for future research related to brain health, aging, or related conditions, as approved by an ethics board.

_____ NO, I do not agree to future research use of my samples and data beyond this study. I understand that my participation in the main study is still allowed.

Participant Signature (for this section): _____ Date: _____

15.2 Optional: Permission to Access Oura Ring Data

Please initial one option:

_____ YES, I agree that deidentified Oura Ring Data may be stored and used for future research related to brain health, aging, or related conditions, as approved by an ethics board.

_____ NO, I do not agree to future research use of my Oura ring data beyond this study. I understand that my participation in the main study is still allowed.

Participant Signature (for this section): _____ Date: _____

15.3 Optional: Permission for Retrieval and Use of Apple Health Data

Please initial one option:

_____ YES, I agree that my Apple Health Data may be used by this study, as approved by an ethics board.

_____ NO, I do not agree that my Apple Health Data may be used by this study I understand that my participation in the main study is still allowed.

Participant Signature (for this section): _____ Date: _____

15.4 Optional: Permission to Retrieval of Data from Standard of Care Imaging or Lumbar Puncture Procedures or to use leftover Spinal Fluid from a Lumbar Puncture Procedure.

Please initial one option:

_____ YES, I agree that my data from the above referenced procedures may be used by this study, as approved by an ethics board.

_____ NO, I do not agree that my data from standard of care imaging or lumbar puncture procedures and leftover spinal fluid sample may be used by this study I understand that my participation in the main study is still allowed.

Participant Signature (for this section): _____ Date: _____

15.5 Optional: Permission for Retrieval of Data Obtained from Optional Retinal Imaging or EEG Procedures

Please initial one option:

_____ YES, I agree that my data from the optional retinal imaging or EEG procedures may be used by this study, as approved by an ethics board.

_____ NO, I do not agree that my data from the optional retinal imaging or EEG procedures may be used by this study I understand that my participation in the main study is still allowed.

Participant Signature (for this section): _____ Date: _____

15.6 Your choices about receiving your own results

You made these choices when you signed the Screening Consent. Please confirm them here, or change any of them. You may change your mind again at any time before you are told, just by telling the study team. These choices do not affect your participation in the study.

Result	**I want to be told**	**I do not want to be told**
My APOE gene result	[ ]	[ ]
My p-tau217 blood result	[ ]	[ ]
My genetic risk score [include only if available from a certified clinical laboratory]	[ ]	[ ]

Participant Signature (for this section): _____ Date: _____

AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

What information may be used and given to others?
The study doctor will get your personal and medical information. For example:

- Past and present medical records
- Research records
- Records about phone calls made as part of this research
- Records about your study visits.

Who may use and give out information about you?
The study doctor and the study staff. They may also share the research information with an agent for the study doctor, if applicable.

Who might get this information?
The sponsor of this research. "Sponsor" means any persons or companies that are:

- working for or with the sponsor, or
- owned by the sponsor.

Your information may be given to:

- The U.S. Food and Drug Administration (FDA),
- Department of Health and Human Services (DHHS) agencies,
- Governmental agencies in other countries,
- The institution where the research is being done,
- Governmental agencies to whom certain diseases (reportable diseases) must be reported, and
- Institutional Review Board (IRB)

Why will this information be used and/or given to others?

- to do the research,

- to study the results, and
- to make sure that the research was done right.

If the results of this study are made public, information that identifies you will not be used.

What if I decide not to give permission to use and give out my health information?
Then you will not be able to be in this research study.

May I review or copy my information?
Yes, but only after the research is over.

May I withdraw or revoke (cancel) my permission?
This permission will be good until December 31, 2070.

You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the study doctor. If you withdraw your permission, you will not be able to stay in this study.

When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others.

Is my health information protected after it has been given to others?
There is a risk that your information will be given to others without your permission.

Authorization:

I have been given the information about the use and disclosure of my health information for this research study. My questions have been answered.

I authorize the use and disclosure of my health information to the parties listed in the authorization section of this consent for the purposes described above.

AUTHORIZATION SIGNATURE:

_____ _____

Signature of Participant Date

August 19, 2026

Dear Study Team:

SUBJECT: PARTIAL WAIVER OF AUTHORIZATION FOR SCREENING SUBJECTS
Sponsor: Prevention Research Consortium Corporation
Sponsor Pr. No.: None
IRB Pr. No.: 20260518 IRB Study No.: 1405909
Protocol Title: Assessing Tools that Predict and Stage Mild Cognitive Impairment

On August 19, 2026, WCG IRB approved a request for a partial waiver of authorization for use and disclosure of protected health information (PHI). This review was conducted at a convened meeting. Please note that this letter is supplemental to the WCG IRB Certificate of Action for this study.

WCG IRB determined that documentation received from you satisfies the three requirements for a partial waiver of authorization under 45 CFR 164.512. These requirements are:

1. The use or disclosure of the PHI involves no more than minimal risk to the individuals, based on the following elements:

    a. An adequate plan to protect identifiers from improper use and disclosure;
    b. An adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research (unless there is a health or research justification for retaining the identifiers, or such retention is otherwise required by law); and,
    c. Adequate written assurances that the PHI will not be reused or redisclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of PHI would be permitted by HIPAA.

2. The research could not be practicably conducted without access to and use of the PHI; and,

3. The research could not practicably be conducted without the waiver.

The Board determined that a waiver of authorization for the following protected health information and uses is needed and approved for this research:

> Information about potential subjects' past and present health, as well as demographic and contact information used to determine potential eligibility and to contact subjects to determine if they are willing to participate in this research study.

You may address the Board in person or in writing regarding its action. If you wish to address the Board in person or if you have questions, please contact Amber Whaley, BA, CIP, at 360-570-1299, or e-mail RegulatoryAffairs@wcgclinical.com.

Sincerely,



Kelly FitzGerald, PhD
IRB Executive Chair and
Vice President IBC Affairs