Certificate of Action

Investigator Name: Foster Carr, MD	**Board Action Date:** 03/27/2026
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: 1-1939855-1	
Protocol Title: Assessing Tools that Predict and Stage Mild Cognitive Impairment	

THE FOLLOWING ITEMS ARE APPROVED:
Investigator
Food for the Brain Cognitive Test (Screenshots) #45775000.0-As Submitted (source: FoodfortheBrain Cognitive Screen (2).pdf)
Protocol (03-05-2026) (source: protocol1.1b)
PUNTOTEST #45774127.0-As Submitted (source: Copy of PuntoTest_User_Guide_EN)
Revised Protocol (03-24-2026) (source: IRB Protocol-01.1c)
Consent Form [Cal0-0]
Financial Disclosure Form (03-23-2026) Foster Carr

Please note the following information:
The Board requires that all adult participants must be able to consent for themselves to be enrolled in this study. This means that you cannot enroll incapable adult participants who require enrollment by consent of a legally authorized representative.

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 subjects involved in the research.
- Personally conduct or supervise the research.
- Conduct the research in accordance with the relevant current protocol approved by the IRB.
- 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 subjects.
- For research subject to continuing review, submit continuing review reports when requested by the IRB.
- Submit a closure form to close research (end the IRB's oversight) when:
    - The protocol is permanently closed to enrollment
    - All subjects have completed all protocol related interventions and interactions
    - For research subject to federal oversight other than FDA:

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    - No additional identifiable private information about the subjects is being obtained
    - Analysis of private identifiable information is completed
- For research subject to continuing review, if research approval expires, stop all research activities and immediately contact the IRB.
- 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 subjects ("finder's fees.")
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- 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.
- Please note that any advertisements or subject material that contain both English and translated content must be submitted through the translations process in addition to standard review to have the translated content approved.

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- 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 human subject research subjects 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 report that directly and materially affects subject safety or their willingness to continue participation. Such reports will be provided to the IRB within 5 days.
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For Investigator's Brochures, an approval action indicates that the IRB has the document on file for the research.

When the Board approves subject 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.
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.

If 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, the HIPAA Privacy Rule requires you to obtain written authorization from each research subject 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 subject sign a separate authorization agreement.

If this study includes 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.

For research subject to continuing review, you will receive Continuing Review Report forms from WCG IRB when the expiration date is approaching.

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: 3/24/2026

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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. I,

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.

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

Informed Consent Form

TITLE:	Assessing Tools that Predict and Stage Mild Cognitive Impairment
PROTOCOL NO.:	None 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.
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

To determine if you meet criteria for enrollment, you will be evaluated in what is called a Screening period where the following will occur:

- your current medications will be reviewed as well as your medical record;
- your neurologic or psychiatric history will be reviewed;
- prior ApoE genotyping results will be verified as well as your whole genome sequencing (WGS) if available;
- you may be verbally tested for memory and asked about your ability to carry out daily tasks.

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

2. 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
- 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.

3. Why am I being asked to take part?

You are being asked to participate because:

- You are 55 years of age or older.
  You already have results from prior genetic testing showing at least one ApoE4 gene copy, and you are willing 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 polygenic risk score can be calculated. This protocol does not perform new ApoE genotyping or whole-genome sequencing for research purposes.
  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.

4. 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.
- 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 form 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

Before you are enrolled, we will:

- Ask you about your medical history, medications, and any neurological or psychiatric conditions.
  Verify that you have prior ApoE genotype results showing at least one ApoE4 allele (documentation from prior clinical or research testing required).
  Verify that you have prior whole-genome sequencing (WGS) data or equivalent high-density genotyping array data suitable for polygenic risk score (PRS) calculation.
  Ask you to sign a data release authorization allowing the study to obtain WGS/genomic data files from your prior testing laboratory, research biobank, or direct-to-consumer service (if applicable).
  If you have an Oura Ring or an Apple Watch, ask for optional approval to access past and/or future Oura Ring data.

- Ask about your memory and daily functioning.
- Possibly administer brief memory tests to make sure the study is appropriate for you.

If you are eligible and still want to participate, you will be asked to sign this consent document and proceed to the baseline visit.

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

    If your existing genomic data are not yet available to the study, we will ask you to authorize release of prior whole-genome sequencing or genotyping array data from the laboratory or service where they were originally performed. This protocol does not require new whole-genome sequencing or new ApoE testing for research purposes. Your existing data will be used to calculate a polygenic risk score (PRS) and confirm APOE genotype.
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 and Apple then you may opt in to allowing continuous digital access to these devices for this study. Connectivity with your approval through an installed app that allows connection to the Oura Ring or Apple iPhone/Watch Web Site.
    - 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.

5. 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.

6. 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 (or knowing) that you carry ApoE4 or have biomarker changes associated with Alzheimer's disease may cause anxiety, sadness, or worry about the future.
- 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.

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.

7. 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.

8. 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.

9. 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.

10. 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.

12. Will any results be returned to me?

Whether and how individual results are returned to you (for example, ApoE status, pTau217 levels, imaging findings) depends on institutional policies, laboratory certification, and IRB guidance.

In general:

- If results are clinically validated, clearly interpretable, and considered potentially important to your health, we may offer to share them with you and, with your permission, with your healthcare provider.
- Some research-only tests may not be suitable for clinical decision-making and may not be returned.
- We will tell you, during the consent discussion, which types of results may be returned and how.

Any decision to share individual genetic or biomarker results (such as ApoE status, polygenic risk scores, or pTau217 levels) will follow institutional policies, laboratory certification requirements, and IRB guidance, and will be discussed with you, including options to decline certain results when allowed by law.

You may choose not to receive certain kinds of results if allowed by law.

13. 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.

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14. 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.

15. 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.

16. Will I be paid to participate?

You will not be paid for being in this study.

17. 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: _____

17.1 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: _____

17.2 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: _____

17.3 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: _____

17.4 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: _____

17.5 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: _____

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 <u>may</u> 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