# Utility of Clinically Scalable Biomarkers for Prescreening in Preclinical Alzheimer's Disease: Insights from RETAIN

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## Introduction

### Challenges

- Identifying asymptomatic individuals with underlying Alzheimer's disease (AD) pathology for clinical trial enrollment remains a critical bottleneck, driving high screen-failure rates and substantial operational burden.
- Clinical workups, neuropsychological evaluations, and PET imaging are costly and logistically prohibitive at scale.

### Objectives

Evaluate models that use scalable, lower-burden tools to predict three outcomes for preclinical AD trial (pre-)screening:

- **Elevated plasma pTau-217**, using demographics and speech-derived measures.
- **Cognitive impairment (MMSE based)**, using demographics, speech-based digital cognitive assessment (SB-C) scores, and plasma pTau-217 values in pTau-217 positive individuals.
- **Elevated Tau PET**, using demographics, speech-derived measures, plasma pTau-217 values, and MRI measures on pTau-217 positive, cognitively unimpaired individuals.

## The RETAIN study

RETAIN (NCT06544616) is a Phase 2 trial evaluating the efficacy, safety, and immunogenicity of the phosphorylated tau–targeted immunotherapy JNJ-64042056, developed with AC Immune SA (Lausanne, Switzerland), in individuals with preclinical Alzheimer's disease (AD).

RETAIN prescreened participants using a plasma pTau-217 assay (Simoa platform, LucentAD[1]), followed by screening with cognitive and functional assessments and neuroimaging. An exploratory speech-based digital, phone-administered cognitive assessment (SB-C, ki:elements GmbH[2]) was acquired at prescreening.

The RETAIN study offers a unique opportunity to evaluate the potential benefit of a staged, multimodal prescreening strategy, combining self-administered speech-based biomarkers of cognition (SB-C), plasma pTau-217, and MRI biomarkers, as clinically scalable trial enrichment tools in preclinical AD (Figure 1).

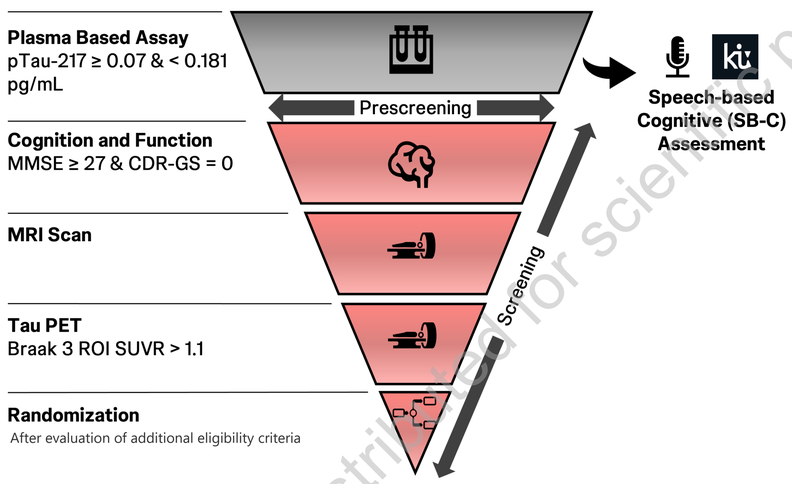



**Figure 1.** RETAIN (pre-)screening funnel.

## Methods

- **Speech-derived metrics:** the speech-based cognitive assessment performed during prescreening included repeated Rey Auditory Verbal Learning Task (RAVLT) and Semantic Verbal Fluency (SVF) tasks, yielding 114 low-level speech-derived metrics (from Raw Speech) and 4 SB-C scores (3 sub-domain scores for memory, processing speed, and executive function and an overall cognition composite score).
- **Demographics**: age, years of education, and gender.
- **Cognitive assessment**: participants with AD-related pathology, defined as pTau-217 ≥ 0.07 pg/mL, underwent cognitive and functional assessment by CDR and MMSE.
- **Neuroimaging data**: T1 MRI[3] and 18F-MK6240 tau PET data were collected for eligible pTau-217-positive, cognitively unimpaired participants (CDR-GS=0; education-adjusted MMSE ≥ 27). Tau PET positivity was defined as Braak 3 ROI SUVR > 1.1, and MRI measures, including cortical thickness and volume, were derived.
- **ML models**: for each of the 3 prediction tasks, data modalities collected at previous steps of the (pre-)screening funnel (Table 1) were used to train ML models, using the approach shown in Figure 2. Performance for all models was evaluated on 100 held-out test sets using ROC AUCs.

**Table 1.** Considered data modalities and target labels for each classification task (modalities collected in the prescreening phase in dark grey and during the screening phase in pink).

| Detection of | | Elevated plasma pTau-217 | Cognitive impairment | Elevated Tau burden |
|---|---|---|---|---|
| Population | | Global | Global | US, English only |
| # Participants | | N=17,248 | N=832 | N=203 |
| Data modality (# of available features) | SB-C (4) | ✓ | ✓ | ✓ |
| | Raw speech (114) | ✓ | | ✓ |
| | Demographics (3) | ✓ | ✓ | ✓ |
| | pTau-217 (1) | | ✓ | ✓ |
| | MRI (223) | | | ✓ |
| Target Label (Positive Class) | | pTau-217 ≥ 0.07 pg/mL | MMSE ≥ $\gamma$ a) $\gamma$ = 27 b) $\gamma$ = 24 | Braak3 ROI SUVR > 1.1 |

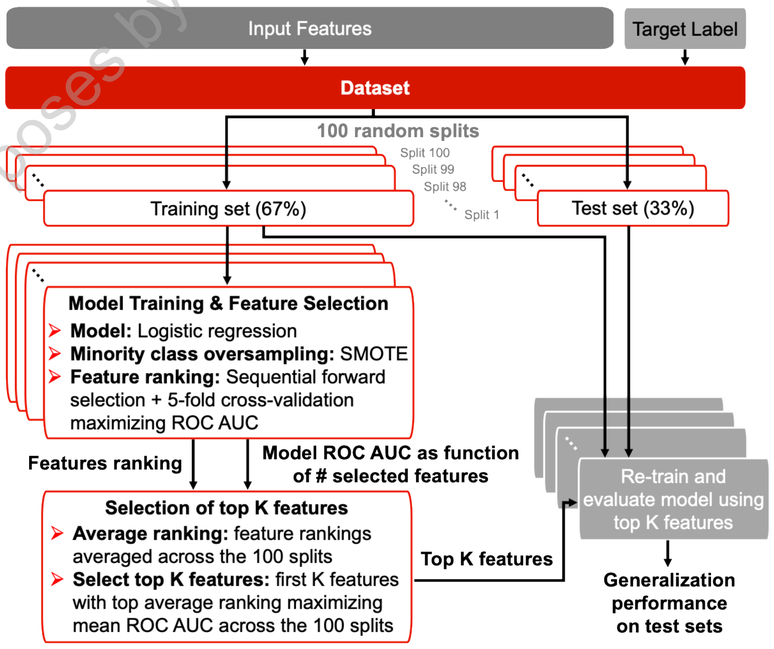



**Figure 2.** Model training and evaluation pipeline.

## Results

The results of the monomodal and multimodal models assessed on the three targeted tasks are compiled in the tables below and plotted in Figure 3.

**Red values** indicate the best-performing model with the lowest feature count.

**Elevated plasma pTau-217** – ROC curves in Figure 3C

| Feature Modality | | | | | | | |
|---|---|---|---|---|---|---|---|
| | SB-C | ✓ | | | | ✓ | ✓ |
| | Raw speech | | ✓ | | ✓ | | ✓ |
| | Demographics | | | ✓ | ✓ | ✓ | ✓ |
| # Top K Features | | 1 | 11 | 3 | 14 | 4 | 15 |
| Mean ROC AUC (%) | | 55.7 | 56.5 | 63.5 | **64.0** | 63.9 | 64.0 |

- Demographics (age, in particular) were a better predictor of pTau-217 positivity than speech-derived metrics.

**Cognitive impairment** – ROC curves in Figures 3A and 3B

| Feature Modality | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | SB-C | ✓ | | | ✓ | ✓ | | ✓ |
| | Demographics | | ✓ | | ✓ | | ✓ | ✓ |
| | pTau-217 | | | ✓ | | ✓ | ✓ | ✓ |
| MMSE ≥ 27 vs. < 27 – ROC curves in Figure 3A | | | | | | | | |
| # Top K Features | | 1 | 3 | 1 | 4 | 2 | 4 | 5 |
| Mean ROC AUC (%) | | 73.1 | 68.4 | 51.6 | **75.2** | 73.1 | 68.5 | 75.2 |
| MMSE ≥ 24 vs. < 24 – ROC curves in Figure 3B | | | | | | | | |
| # Top K Features | | 1 | 3 | 1 | 4 | 2 | 4 | 5 |
| Mean ROC AUC (%) | | 80.5 | 70.6 | 54.7 | **80.6** | 80.5 | 70.7 | 80.6 |

- SB-C composite scores meaningfully predicted cognitive impairments within pTau-217 positive participants.

**Elevated Tau burden** – ROC curves in Figure 3D

| Feature Modality | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | SB-C | ✓ | | | | | | |
| | Raw speech | | ✓ | | | ✓ | | ✓ |
| | Demographics | | | ✓ | | | | |
| | pTau-217 | | | | ✓ | | ✓ | ✓ | ✓ |
| | MRI | | | | | ✓ | | ✓ | ✓ |
| # Top K Features | | 1 | 6 | 2 | 1 | 10 | 7 | 11 | 17 |
| Mean ROC AUC (%) | | 52.8 | 63.5 | 48.8 | 60.9 | 76.1 | 65.6 | 78.5 | **82.5** |

- Integrating speech with pTau-217 yielded a small but statistically significant improvement over pTau-217 alone.
- Combining speech and pTau-217 with MRI yielded a statistically significant and meaningful gain when compared to the model using only MRI and pTau-217.

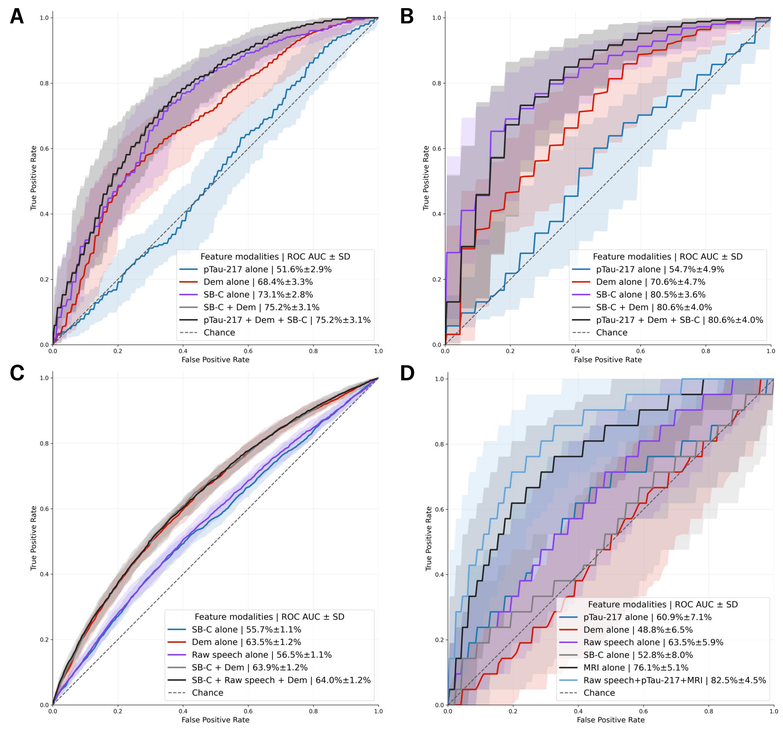



**Figure 3.** ROC curves (mean ± standard deviation - SD) of different modality combinations for the considered classification tasks: cognitive impairment with (A) MMSE ≥ 27, and (B) MMSE ≥ 24; (C) elevated plasma pTau-217; (D) elevated Tau burden.

## Conclusions

### Speech as a Scalable Screening Modality

Low-burden, remote speech-derived cognitive measures demonstrated sensitivity to early cognitive impairment in pTau-217 positive, cognitively unimpaired individuals and contributed meaningfully to prediction of Tau PET.

### Feasibility and Operational Scalability

Speech-based cognitive assessment demonstrated high feasibility in the RETAIN preclinical AD cohort, with >18,000 completed administrations and 98% data completeness, supporting deployment at clinical-trial scale.

### Clinical Trial Recruitment

Integration of digital cognitive assessments with plasma biomarkers and neuroimaging may support more targeted use of later-stage screening procedures, reduce screen-failure rates, and optimize recruitment costs in preclinical AD trials.

References

1. Wilson, David, et al. "A Blood Test for p-Tau 217 to Aid in the Diagnostic Evaluation for Alzheimer's Disease." (2023).
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3. Wong, Janice, et al. "Tau positron emission tomography analysis methods for the quantification of tau spread in preclinical and early Alzheimer's disease." Alzheimer's & Dementia 22.6 (2026): e71573.

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