Speech-Based Biomarkers for Assessing Cognitive Status in Preclinical Alzheimer's Disease: Insights from the REtAIN Study

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Background

RETAIN (NCT06544616) is a Phase 2b trial assessing the efficacy of a phosphorylated tau-targeted immunotherapy (JNJ-64042056), developed with AC Immune SA (Lausanne, Switzerland), in individuals with preclinical/asymptomatic Alzheimer's disease (AD). The study employs an innovative prescreening strategy that includes an exploratory speech-based digital cognitive (SB-C) assessment[1] (ki:elements GmbH) and a blood-based p217+tau assay (Johnson & Johnson; Quanterix platform, LucentAD)[2] to test for AD related pathology. During screening, individuals positive for pTau217 complete in-clinic cognitive assessments, including MMSE and CDR, which are used to assess cognitive impairment status.

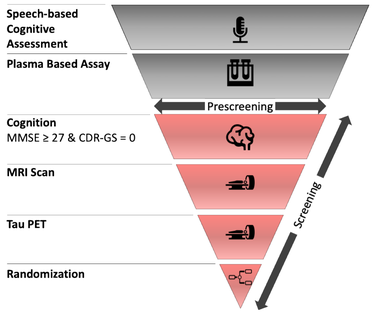

Figure 1. RETAIN (pre-)screening funnel. Speech-based cognitive assessment was exploratory and not used as eligibility criteria.

Objective

To examine whether the SB-C assessment score can distinguish cognitively unimpaired vs. impaired individuals across multiple countries and languages and to explore its potential as a scalable, standardized prescreening biomarker.

Methods

- Remote phone-based assessment through the ki:elements' Mili platform (Figure 2):
  - four repetitions of the Rey auditory verbal learning test;
  - a single semantic categorical fluency test.
- Audio recordings analyzed to generate cognitive domain-specific (processing speed, executive function, and learning & memory) SB-C scores.
- Domain-specific SB-C scores combined to create a single SB-C composite score for each participant (lower scores indicating overall greater cognitive impairment).
- Participants' cognitive status was defined as:
  - **Cognitively unimpaired**: Clinical Dementia Rating (CDR)-Global Score = 0 and Mini-Mental State Examination (MMSE) score ≥ 27 after education adjustment;
  - **Cognitively impaired**: CDR-Global Score > 0 and/or MMSE score < 27 after education adjustment.
- Discriminative performance of the SB-C composite score for distinguishing pTau217 positive cognitively unimpaired vs. impaired individuals was assessed using ROC AUC, Precision-Recall (PR) AUC, balanced accuracy, sensitivity, specificity, precision, and F1 score at the SB-C threshold maximizing balanced accuracy (Youden cut-off) for each country.

Results

- As of September 2025, data from a total of 665 participants who completed the SB-C assessment and advanced to screening were analyzed: 540 from the USA (English), 39 from the UK (English), and 86 from Japan (Japanese) (Table 1).
- Classification performance for distinguishing pTau217 positive cognitively unimpaired vs. impaired individuals (Table 2) yielded ROC AUCs of 72.2%, 75.0%, and 67.5% for participants from the USA, UK, and Japan cohorts, respectively (Figure 3).

Table 1. Participant characteristics.

Characteristic	Country		
	USA (English), N = 540	UK (English), N = 39	Japan (Japanese), N = 86
Female	325 (60.2%)	20 (51.3%)	36 (41.9%)
Age (Mean ± SD)	67.4 ± 5.4	66.0 ± 5.3	67.6 ± 5.0
Education (Mean ± SD)	14.8 ± 2.8	16.2 ± 2.8	14.6 ± 2.2
MMSE ≥ 27 & CDR-Global Score = 0	318 (58.9%)	31 (79.5%)	74 (86.1%)

Table 2. Performance metrics per country using SB-C thresholds that maximizes balanced accuracy (Youden cut-off).

Country	SB-C Threshold (Youden cut-off)	ROC AUC	PR AUC	Balanced Accuracy	Sensitivity	Specificity	Precision	F1 Score
USA (English)	0.39	72.2%	74.4%	67.9%	73.6%	62.2%	73.6%	73.6%
UK (English)	0.48	75.0%	91.4%	74.6%	74.2%	75.0%	92.0%	82.1%
Japan (Japanese)	0.34	67.5%	91.4%	71.2%	75.7%	66.7%	93.3%	83.6%

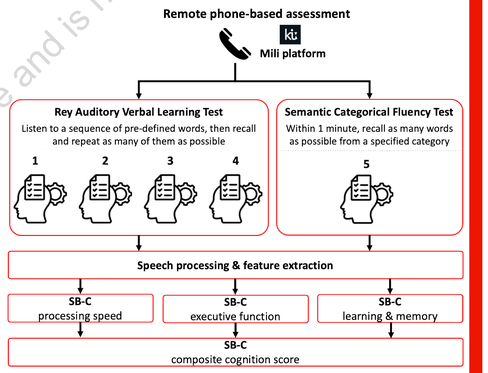

Figure 2. Remote phone-based assessment followed by the extraction of SB-C composite score.

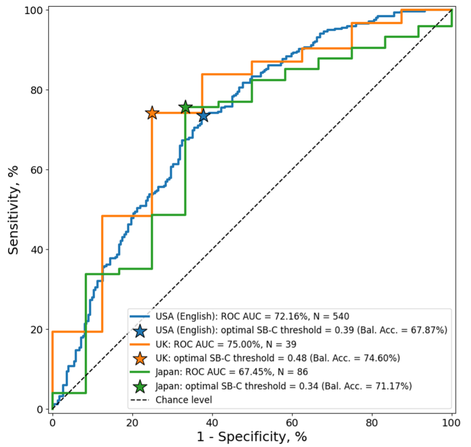

Figure 3. ROC AUCs for differentiating cognitively unimpaired vs. impaired individuals across countries. Stars indicate ROC AUC points corresponding to thresholds that maximize balanced accuracy (Youden cut-off) for each country.

Conclusions

Cognition predictive value:
The SB-C composite score can differentiate between cognitively unimpaired and impaired individuals who are pTau217 positive.

Generalizability:
Classification was good with average AUC of 71.6% across geographies.

Performance optimization:
SB-C score thresholds can be calibrated for each geography separately to optimize performance criteria (e.g., balanced accuracy, cost reduction, diagnostic accuracy, etc.).

Limitations:
Further validation and additional data are needed for robustly assessing performance across geographies due to small sample size and class imbalance in the UK and Japan datasets.

Utility:
Our findings support the use of SB-C scores as a non-invasive, scalable prescreening tool to improve recruitment efficiency and reduce trial costs.

References
1. Tröger, J., Schwed, L.,. (2022). Validation of the Remote Automated ki:e Speech Biomarker for Cognition in Mild Cognitive Impairment: Verification and Validation following DiME V3 Framework. Digital Biomarkers, 6(3), 107–116.
2. Wilson, D., Copeland, K (2025). Alzheimer's Pathology Detection Made Simple: A Blood Test for p-Tau 217 to Aid in the Diagnostic Evaluation for Alzheimer's Disease. Lucent Diagnostics, 1-5.