

Comparing Brain-Derived and Total Plasma pTau217 in the Alzheimer's Disease Neuroimaging Initiative

Valentina Ghisays^{1,2}, Marisa N. Denkinger^{1,2}, Alpana Singh^{1,2}, Tainá M. Marqués^{1,2}, Michael Malek-Ahmadi^{1,2}, Kendall Van-Keuren Jensen³, Hillary D. Protas², Javad Sohankar², Dhruman D. Goradia², Vivek Devadas², Yi Su², Michael W. Weiner⁴, Eric M. Reiman², Nicholas J. Ashton^{1,2,5}, for the Alzheimer's Disease Neuroimaging Initiative

¹Banner Sun Health Research Institute, Sun City, AZ, USA | ²Banner Alzheimer's Institute, Phoenix, AZ, USA | ³Translational Genomics Research Institute, Phoenix, AZ, USA | ⁴University of California San Francisco, San Francisco, CA, USA | ⁵Department of Psychiatry and Neurochemistry, Institute of Neuroscience & Physiology, Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden

INTRODUCTION

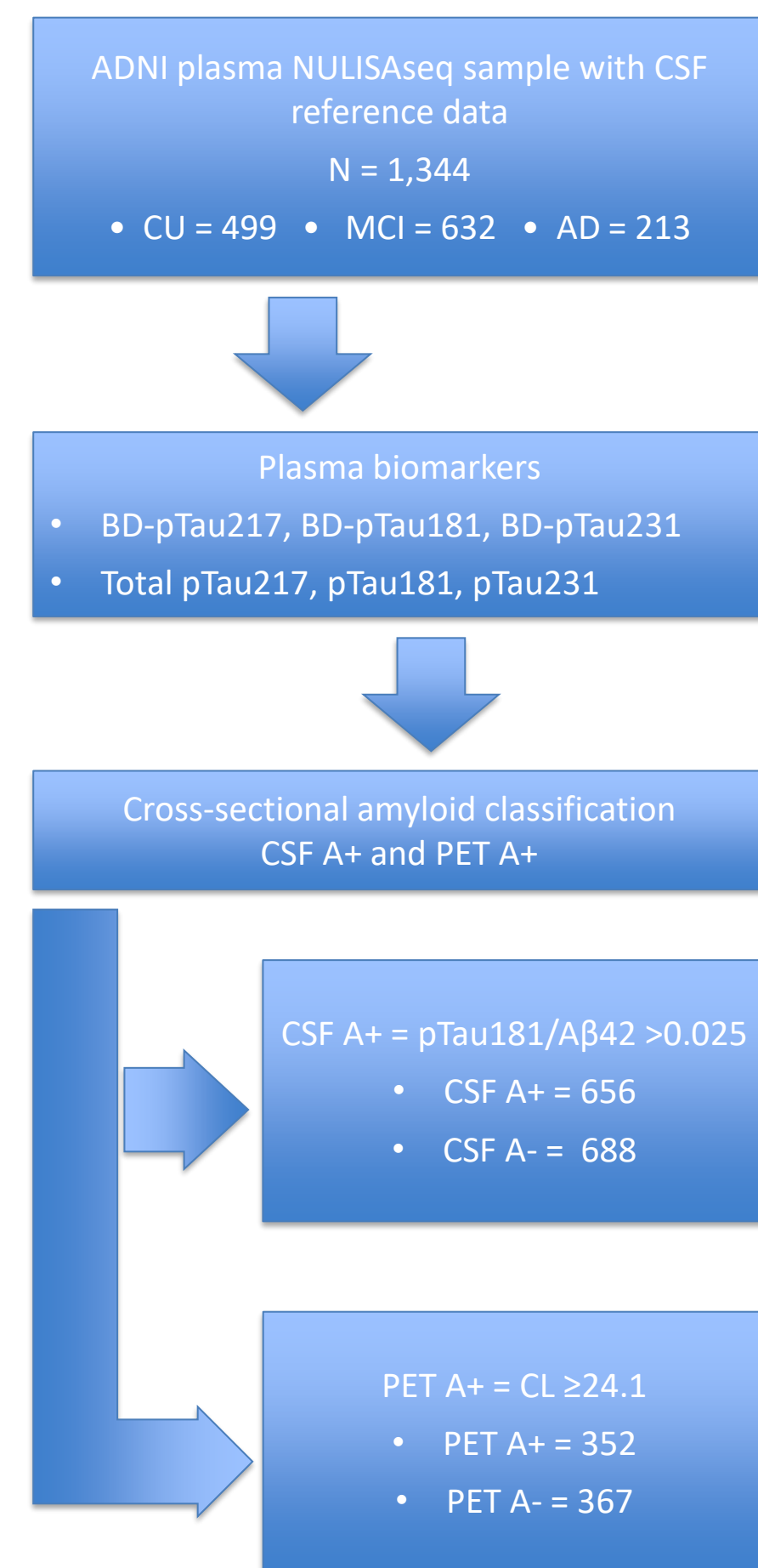
Background

- Plasma phosphorylated tau biomarkers are promising tools for detecting Alzheimer's disease pathology and supporting clinical trial screening.^{1,2}
- Conventional plasma pTau assays measure total circulating pTau, while newer assays can selectively quantify brain-derived pTau species.^{3,4}
- It remains unclear whether brain-derived pTau biomarkers improve amyloid classification compared with total plasma pTau measures in large AD cohorts.^{2,4}

Study aims

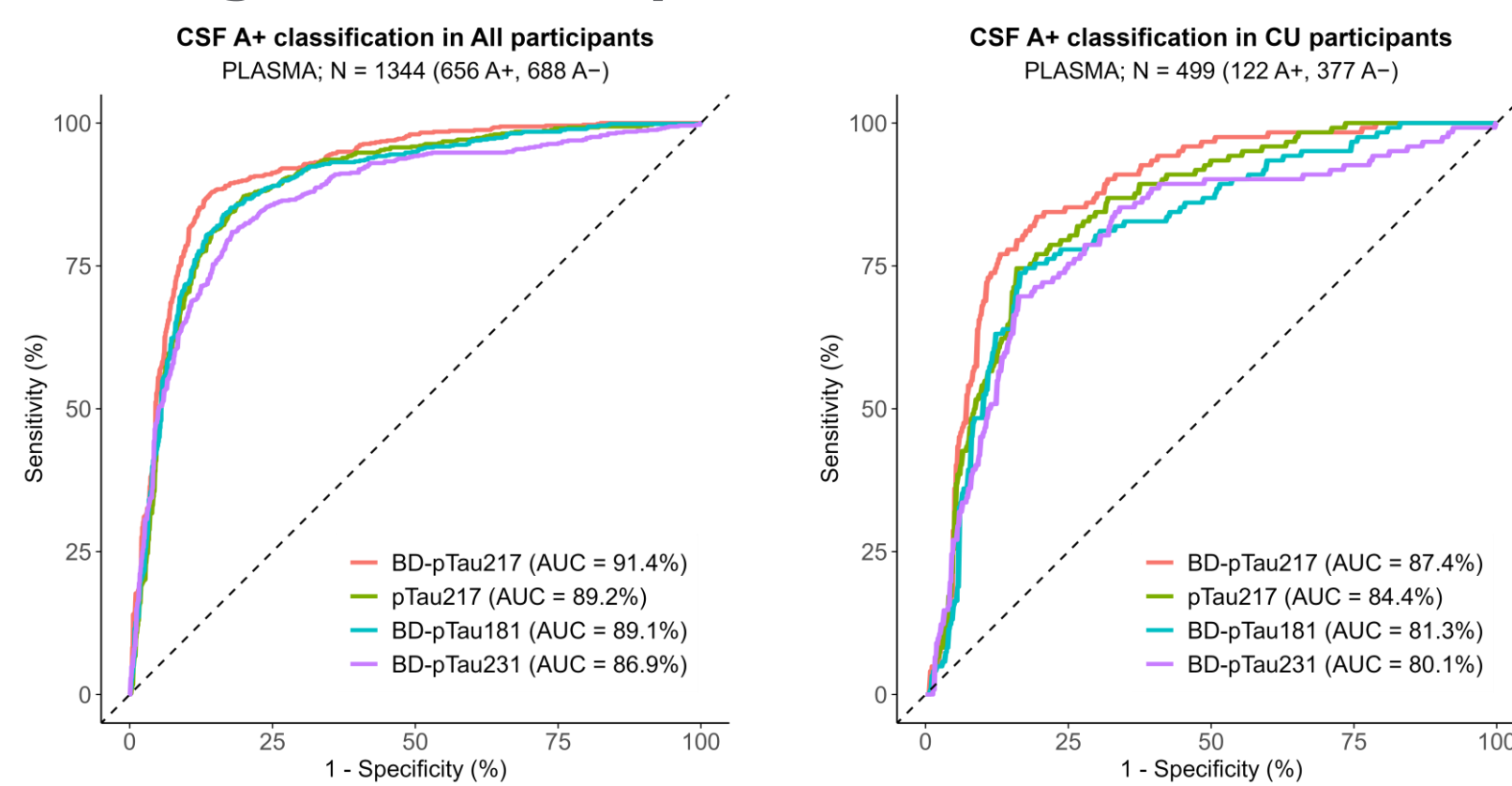
- Compare brain-derived and total plasma pTau217, pTau181, and pTau231 for amyloid classification in ADNI.
- Determine whether BD-pTau217 ranks highest among plasma pTau markers for CSF- and PET-defined amyloid positivity.
- Assess whether brain-derived pTau181 and pTau231 show higher classification performance than their total pTau counterparts.

Figure 1. Study overview



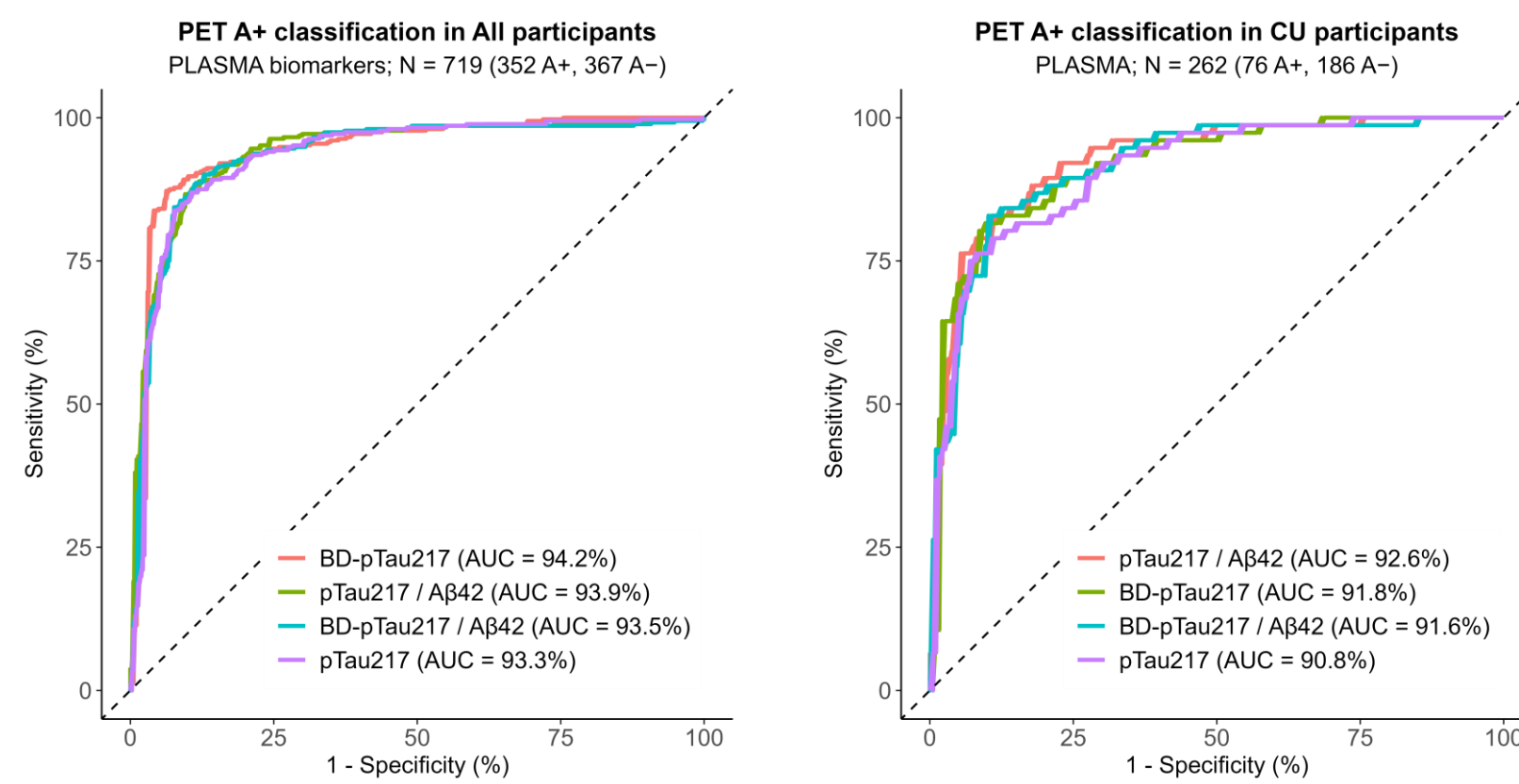
RESULTS

Figure 2. CSF amyloid classification AUCs



- BD-pTau217 ranked highest for CSF-defined amyloid positivity; BD-pTau181 and BD-pTau231 also showed higher AUCs than their total pTau counterparts.

Figure 3. PET amyloid classification AUCs



- PET-defined amyloid positivity was classified with high accuracy by pTau17-based markers, with no sig. difference between BD and total pTau217 after FDR correction.

Figure 4. pTau217 performance by amyloid reference standard

Reference standard	Group	Best marker	AUC	Key comparison
CSF A+	All	BD-pTau217	0.914	BD-pTau217 vs pTau217: ΔAUC = 0.023; FDR p = 1.35 × 10 ⁻⁸
CSF A+	CU	BD-pTau217	0.874	BD-pTau217 vs pTau217: ΔAUC = 0.030; FDR p = 0.001
PET A+	All	BD-pTau217	0.942	BD-pTau217 vs pTau217: ΔAUC = 0.010; FDR p = 0.060
PET A+	CU	pTau217 / Aβ42	0.926	Similar to BD-pTau217; FDR p = 0.688
Additional epitope comparisons				
CSF A+, All participants:			PET A+, All participants:	
• BD-pTau181 AUC = 0.891 vs pTau181 AUC = 0.802			• BD-pTau181 AUC = 0.920 vs pTau181 AUC = 0.827	
• BD-pTau231 AUC = 0.869 vs pTau231 AUC = 0.839			• BD-pTau231 AUC = 0.914 vs pTau231 AUC = 0.877	
CSF A+, CU participants:			PET A+, CU participants:	
• BD-pTau181 AUC = 0.813 vs pTau181 AUC = 0.713			• BD-pTau181 AUC = 0.873 vs pTau181 AUC = 0.756	
• BD-pTau231 AUC = 0.801 vs pTau231 AUC = 0.762			• BD-pTau231 AUC = 0.863 vs pTau231 AUC = 0.825	

- BD-pTau217 significantly outperformed total pTau217 for CSF-defined amyloid positivity, while PET-defined amyloid classification was similarly high for BD-pTau217 and total pTau217.
- In CSF analyses, brain-derived pTau181 and pTau231 also showed higher AUCs than their corresponding total pTau measures.
- Across CSF and PET reference standards, BD-pTau181 and BD-pTau231 showed higher AUCs than their corresponding total pTau measures.

METHODS

Study Design

- Cross-sectional biomarker comparison in ADNI participants with plasma NULISaseq measurements.

Participants / Samples

- ADNI1/GO/2/3 participants with plasma NULISaseq CNS panel data.
- Total sample: N = 1,344.
- Cognitively unimpaired subset: N = 499.
- Participants included CU, MCI, and AD dementia diagnostic groups.

Measurements

- Plasma biomarkers: BD-pTau217, BD-pTau181, BD-pTau231, and total pTau217, pTau181, pTau231.
- CSF amyloid positivity: CSF pTau181/Aβ42 > 0.025.⁵
- Amyloid PET positivity: Centiloid ≥ 24.1.^{6,7}

Statistical Analysis

- Cross-sectional amyloid classification was evaluated using ROC AUC.
- AUCs were compared using paired DeLong tests with FDR correction.
- Exploratory longitudinal analyses were conducted separately and are presented in a companion late-breaking poster.

CONCLUSION / DISCUSSION

Conclusions

- In one of the first large-scale ADNI comparisons of brain-derived and total plasma pTau markers, BD-pTau217 was the top-performing plasma marker for CSF-defined amyloid positivity and significantly outperformed total pTau217.
- For PET-defined amyloid positivity, BD-pTau217 and total pTau217 showed similarly high classification performance after FDR correction.
- BD-pTau181 and BD-pTau231 ranked above their corresponding total pTau measures, suggesting that brain-derived measurement may improve classification across additional pTau epitopes.

Implications

- Brain-derived pTau biomarkers may improve interpretation of blood-based AD biomarker profiles.
- pTau217 remains the most accurate plasma pTau epitope overall.
- These findings may inform blood-based screening and enrichment strategies for AD clinical trials.

Take-home message

- Brain-derived p-tau biomarkers provide significant value for detecting CSF-defined amyloid pathology and markedly improved performance of pTau231 and pTau181, while pTau217 remains the most accurate plasma marker overall. These findings inform interpretation and potential clinical trial utility of next-generation blood-based tau biomarkers.

REFERENCES

- Schindler et al. (2024). Acceptable performance of blood biomarker tests of amyloid pathology - recommendations from the Global CEO Initiative on Alzheimer's Disease. *Nat Rev Neurol*, 20(7):426-439. doi:10.1038/s41582-024-00977-5
- Warmenhoven et al. (2025). A comprehensive head-to-head comparison of key plasma phosphorylated tau 217 biomarker tests. *Brain*, 148(2):416-431. doi:10.1093/brain/awae346
- Janelidze et al. (2025). A comparison of p-tau assays for the specificity to detect tau changes in Alzheimer's disease. *Alzheimers Dement*, 21(4):e70208. doi:10.1002/alz.70208
- Jiang et al. (2026). Head-to-head comparison of brain-derived pTau217 and total pTau217 for brain amyloid and tau pathology classification. *Proc Natl Acad Sci U S A*, 123(10):e2536792123. doi:10.1073/pnas.2536792123
- Shaw et al. (2023). An Overview of the Roche Elecsys ADNI CSF Batch Analyses run in ADNI3. Alzheimer's Disease Neuroimaging Initiative. UPENN CSF Biomarkers Elecsys Methods (Batch 9-13) [ADNI1, GO, 2, 3].
- Lu et al. (2025). Posttreatment Amyloid Levels and Clinical Outcomes Following Donanemab for Early Symptomatic Alzheimer Disease: A Secondary Analysis of the TRAILBLAZER-ALZ 2 Randomized Clinical Trial. *JAMA Neurol*, 82(12):1251-1256. doi:10.1001/jamaneurol.2025.3869
- Iaccarino et al. (2025). A practical overview of the use of amyloid-PET Centiloid values in clinical trials and research. *Neuroimage Clin*, 46:103765. doi:10.1016/j.nicl.2025.103765

ACKNOWLEDGMENTS

Data used in this study were obtained from the Alzheimer's Disease Neuroimaging Initiative. We thank the ADNI participants, study partners, investigators, and study staff. ADNI (NIA grant U19AG024904). We also acknowledge the Alamar Biosciences team for NULISaseq assay generation and technical support. Attendance at this conference was supported by an AAIC 2026 Conference Fellowship.

Email for more info

Valentina.ghisays@bannerhealth.com