

Plasma P-tau217 Performance In Preclinical Alzheimer's Disease: Reliability over sensitivity

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INTRODUCTION

- Amyloid and tau pathology begin decades before symptoms in AD, highlighting the need for reliable blood-based biomarkers for early Alzheimer's disease detection.
- Detecting AD pathology during the preclinical stage may enable earlier intervention, improve clinical trial recruitment, and support future disease-modifying treatment strategies.
- Plasma p-tau217 is a promising blood-based biomarker, and fully automated assays have recently transitioned into routine clinical practice.
- However, whether these automated assays retain the analytical performance needed to reliably detect the earliest stages of AD in cognitively unimpaired individuals and maintain consistency across platforms remains uncertain.

OBJECTIVES

- Evaluate plasma p-tau217 as a biomarker of Alzheimer's pathology in cognitively unimpaired individuals.
- Compare p-tau217 performance between
 - Roche Cobas e801
 - Quanterix HD-X Simoa platform
- Assess cross-platform consistency in relation to amyloid-PET burden, cognitive status, and longitudinal outcomes.

METHODS

Cohort: Wisconsin Registry for Alzheimer's Prevention (WRAP), a longitudinal cohort enriched for preclinical Alzheimer's disease, with participants contributing plasma samples across multiple visits.

Sample: This interim analysis included 670 participants with available amyloid-PET imaging.

Biomarker Measurement: Plasma p-tau217 concentrations were measured using both the Quanterix HD-X Simoa ultrasensitive research platform and the Roche cobas e801 fully automated clinical analyzer.

Amyloid Assessment: Amyloid burden was quantified using amyloid-PET Centiloid (CL) values. Participants were classified using thresholds of >12.1, >18.1, and >24.1 CL.

Statistical Analyses: We evaluated the performance of plasma p-tau217 for detecting amyloid-PET positivity, assessed agreement between measurement platforms, and modeled longitudinal changes in p-tau217 in relation to amyloid burden and cognitive status.

RESULTS

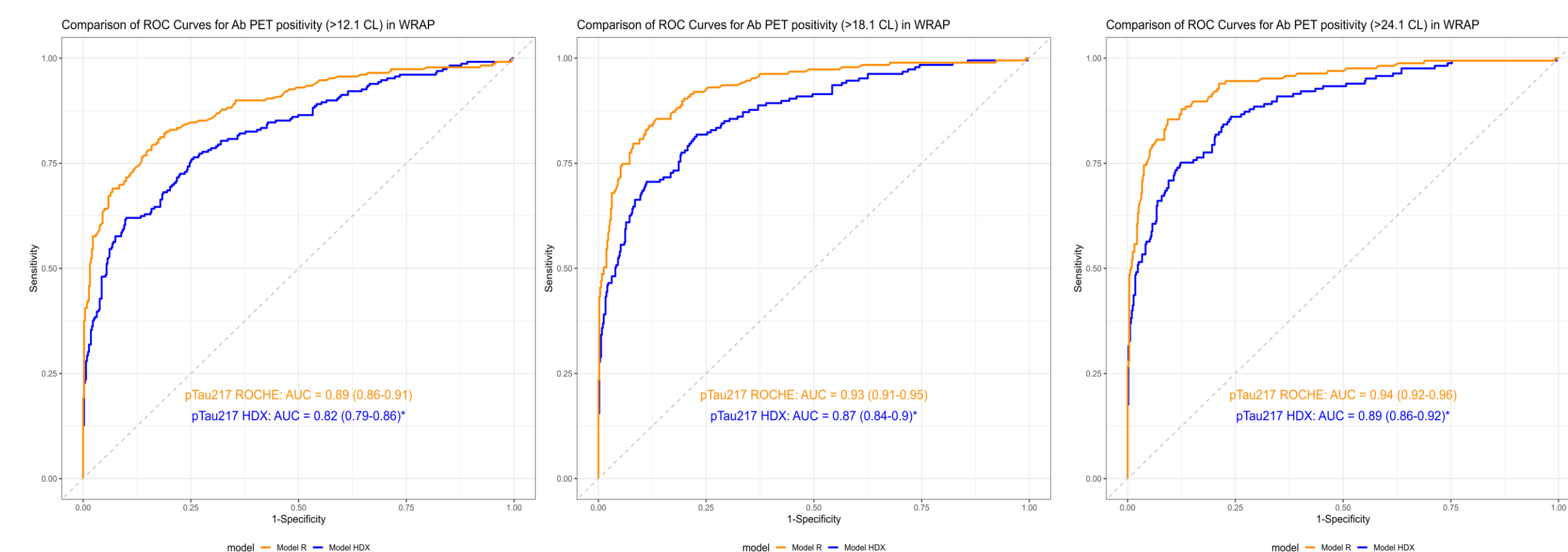


Figure 1. ROC curve analysis comparing Roche and HDX across clinical thresholds. At cutoffs of >12.1 CL, >18.1 CL, and >24.1 CL, Roche demonstrated AUCs of 0.89 (95% CI: 0.86-0.91), 0.93 (0.91-0.95), and 0.94 (0.92-0.96), respectively, compared with HDX AUCs of 0.82 (0.79-0.86), 0.87 (0.84-0.90), and 0.89 (0.86-0.92). Across all thresholds, Roche outperformed HDX based on AUC values.

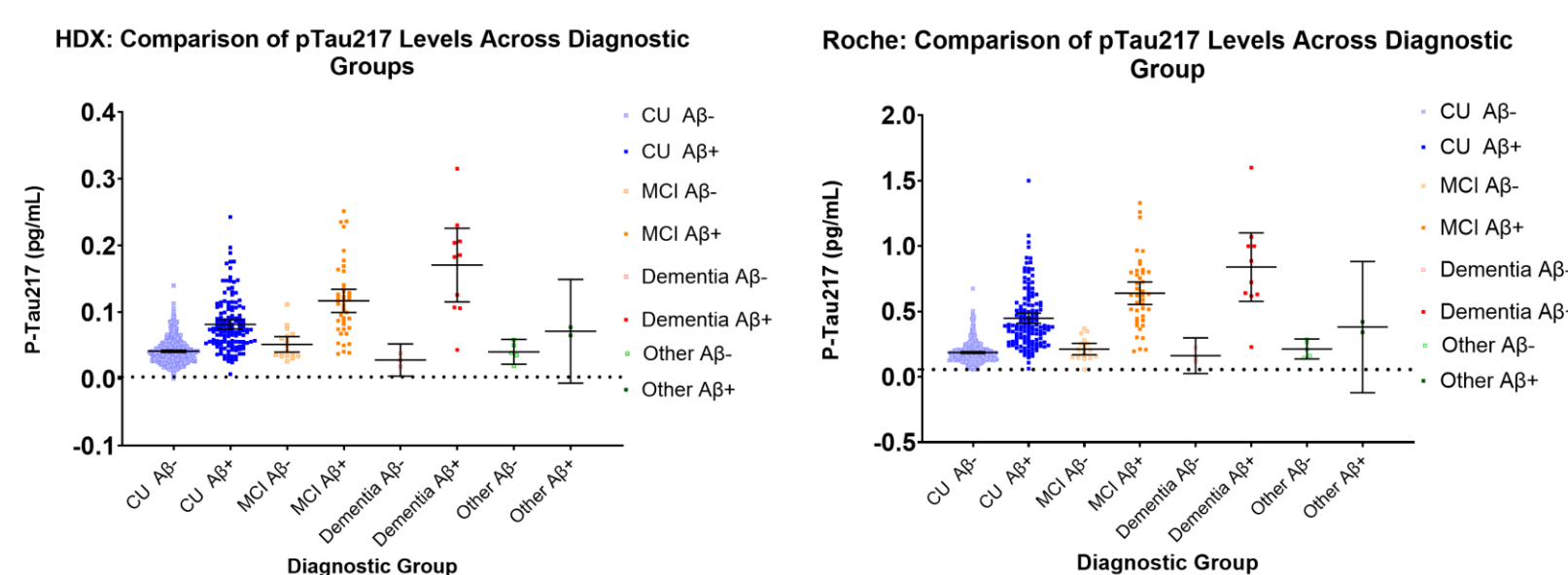


Figure 3. Baseline plasma pTau217 concentrations by diagnostic group and amyloid-β (Aβ) status, measured using HDX and Roche assays. Groups (CU, MCI, dementia, other) were stratified by Aβ-/Aβ+. Each point represents a baseline sample; group means ± error bars are shown. Baseline was defined by PET data and limited to these time points.

Correlation Plot: HD-X vs Roche

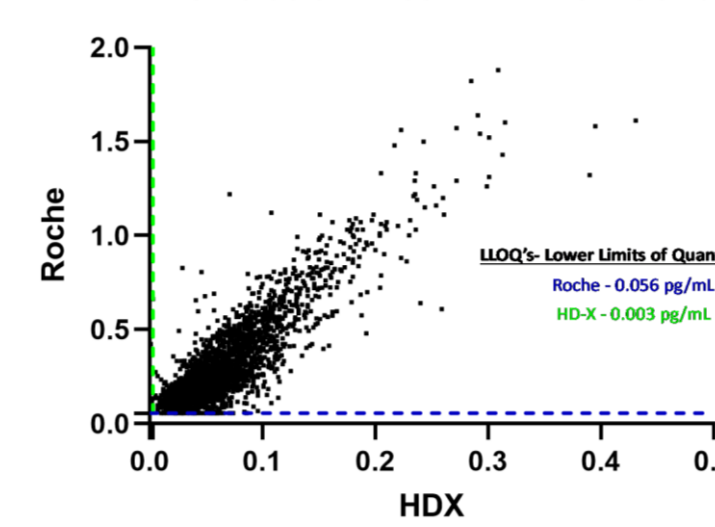


Figure 4. Correlation of plasma p-tau217 concentrations measured on Roche Cobas e801 and Quanterix HD-X Simoa platforms. Each point represents an individual sample. Strong correlation was observed between platforms, though values are not directly interchangeable.

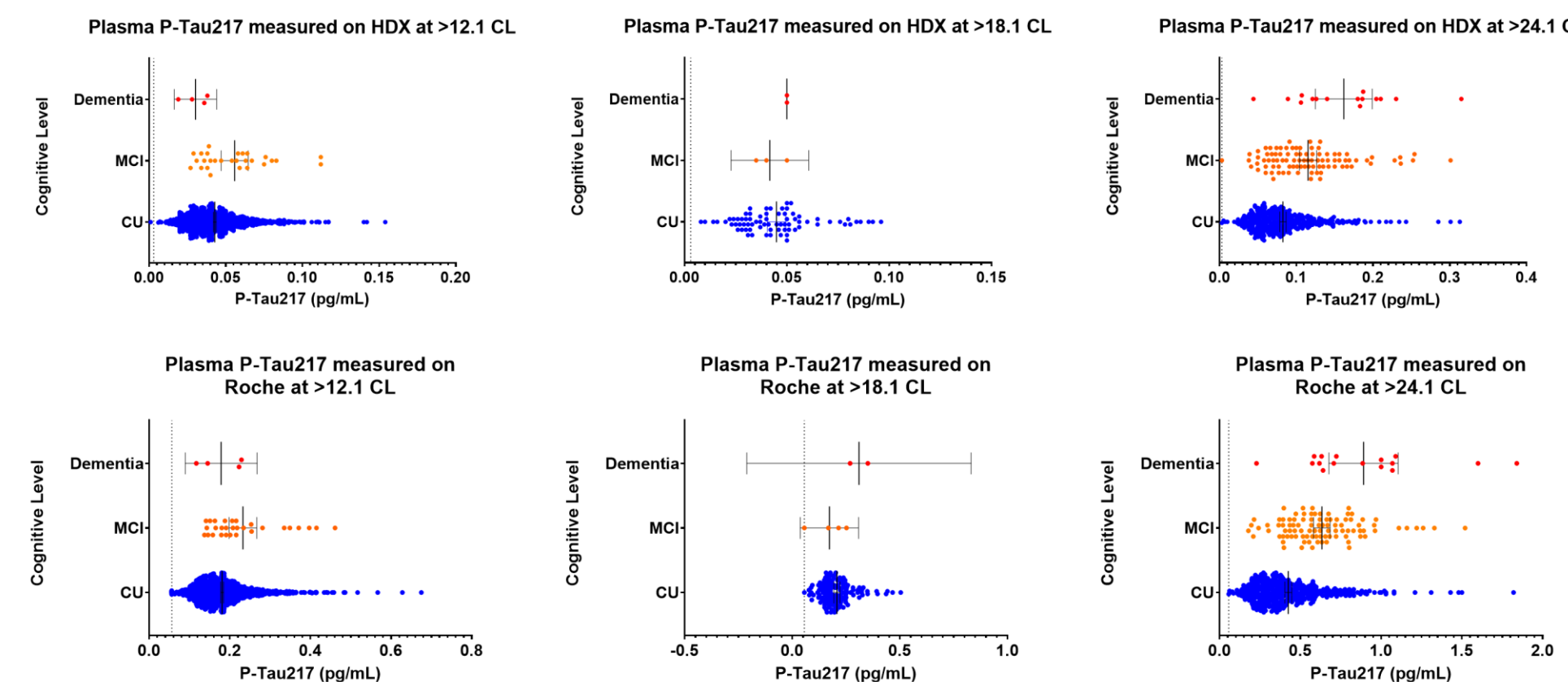


Figure 2. Concentrations (pg/mL) by cognitive status (CU, MCI, dementia) across CL cutoffs (>12.1, >18.1, and >24.1) and assay (HDX, Roche). Points represent individual samples; error bars indicate mean ± error. Vertical dotted lines mark assay-specific LLOQs (HDX: 0.003 pg/mL; Roche: 0.056 pg/mL). All available longitudinal samples were included.

- ✓ ROC analysis showed consistently stronger discriminative performance for the Roche assay compared with HDX at all evaluated clinical thresholds, with higher AUC values observed at >12.1 CL, >18.1 CL, and >24.1 CL, indicating improved classification accuracy across cut points (Figure 1).
- ✓ HD-X and Roche measurements showed a significant mean difference of 0.194 (SD = 0.155; $p < 0.0001$), indicating Roche values were consistently higher.
- ✓ The estimated difference was highly precise with a 95% CI of 0.190-0.198 and SEM = 0.00218, supporting reliability of the result.
- ✓ HD-X and Roche measurements were strongly correlated ($r = 0.88$, $p < 0.0001$; Figure 4), but the large effect size indicates substantial platform differences, suggesting the methods are not interchangeable.

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ACKNOWLEDGMENTS

We sincerely thank the participants and their families for their invaluable contributions to this study. Their involvement is part of the foundation of all progress in Alzheimer's disease research. We also gratefully acknowledge our donors and funding organizations, whose generous support made this work possible and helps advance meaningful breakthroughs. Research reported in this publication was supported by the National Institute on Aging of the National Institutes of Health under award number R01AG058468.

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Characteristics	
WRAP cohort (N=670)	
Age, mean (SD)	68.9 (7.6)
Female, N (%)	457 (68.2)
Male, N (%)	213 (31.8)
APOE e4 carriers, N (%)	251 (37.5)
Diagnosis	
Normal, N (%)	590 (88.1)
MCI, N (%)	61 (9.1)
Dementia, N (%)	13 (1.9)
Impaired - other, N (%)	6 (0.9)

Across-study CV by PQC Level and Instrument			
	Roche CV (%)	HD-X CV (%)	Lower CV
Low PQC	6.77	15.11	Roche
Mid PQC	4.37	10.2	Roche
High PQC	3.9	11.85	Roche



≈1500
samples in an
8hr workday



≈156 samples in 3-4
hours

CONCLUSION

- ✓ Roche demonstrated stronger, more consistent analytical performance than HD-X across all centiloid thresholds, with higher AUC values indicating greater reliability in assessing p-tau217 relative to amyloid burden.
- ✓ While HD-X and Roche measurements were strongly correlated, a significant mean difference between platforms indicates they are not interchangeable and require platform-specific interpretation.
- ✓ Roche supports substantially higher sample throughput and superior ROC performance, making it well suited for high-volume, automated workflows that enhance scalability without compromising assay quality.
- ✓ HD-X remains valuable for research applications, offering ultra sensitivity and flexibility for biomarker discovery, exploratory analyses, and custom assay development.