

Background and Purpose

- Biomarker thresholds are used for Alzheimer's disease diagnosis and clinical trial enrolment
- But many individuals fall into an intermediate "gray zone" where classification is uncertain, causing a real-world implementation challenge.

Amyloid Negative (<12 Centiloids) High Misclassification Risk Amyloid Positive (>30 Centiloids)

Diagnostic Gray Zone

- Plasma p-tau217, a promising blood-based biomarker, strongly correlates with amyloid and tau pathology, but its value in resolving diagnostic uncertainty remains problematic.

Methods

- Data analysed from 565 participants in the ADNI
- Linear mixed-effects models estimated individual plasma p-tau217 slopes, which were compared against amyloid PET SUVR for predicting clinical conversion, tau PET positivity, and MMSE decline.
- Gray zones were defined as ranges around centiloid cut-offs (± 10 to ± 25) where classification uncertainty is highest.
- Logistic and Cox regression models were used to evaluate predictive performance.

Results

- Across the full cohort, amyloid PET showed slightly higher accuracy than p-tau217 for clinical conversion (AUC = 0.79 vs. 0.75).
- However, within gray-zone subgroups, p-tau217 trajectories showed relatively higher predictive performance in some analyses, particularly for clinical conversion (0.77 vs. 0.75) and tau PET positivity (0.75 vs. 0.62).

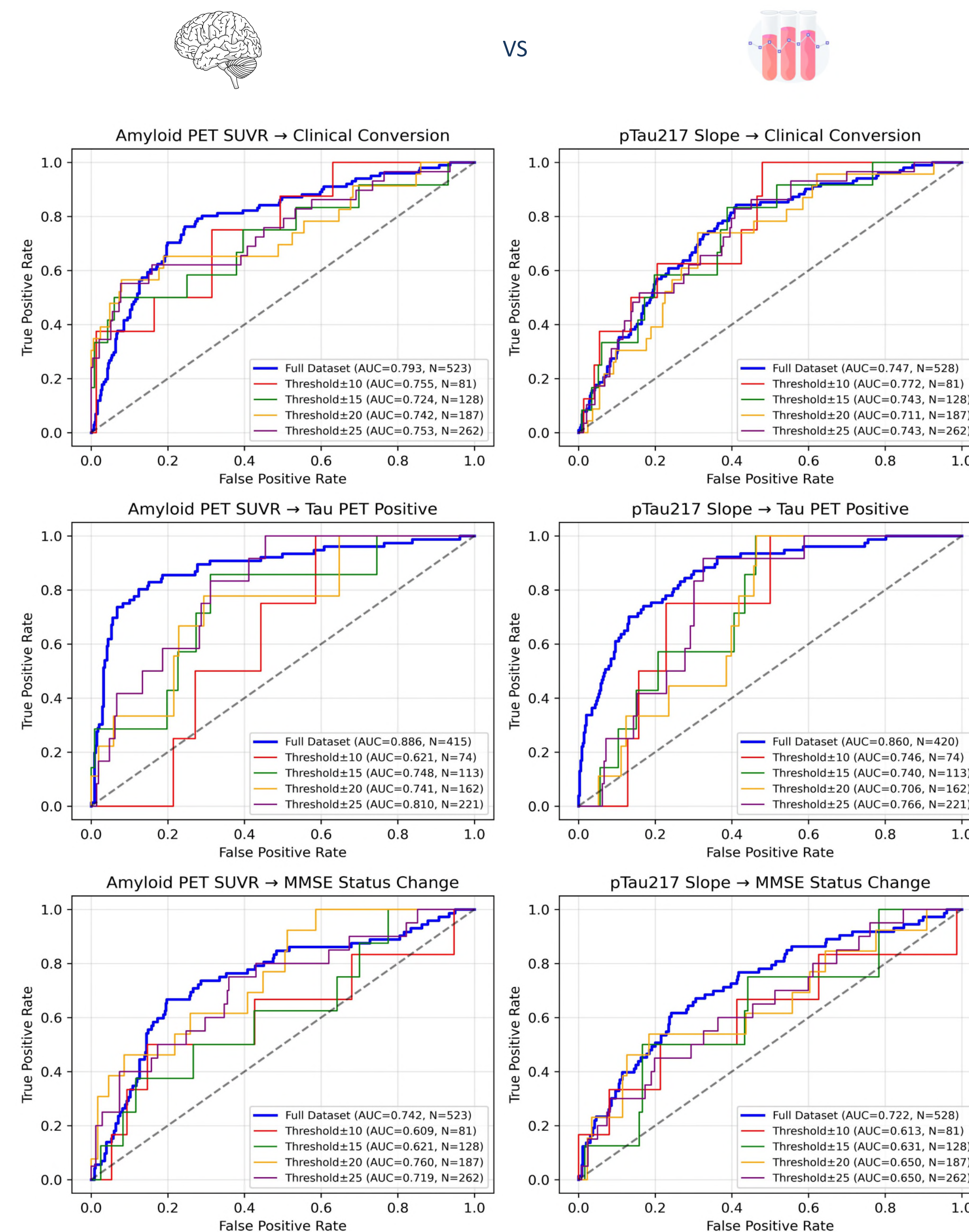


Fig 1. Receiver Operating Characteristic (ROC) Curves Showing Biomarker Performance within Gray Zone Centiloid Ranges

Discussion and Conclusion

- Longitudinal plasma p-tau217 trajectories provide added diagnostic value in borderline biomarker cases, where misclassification risk is highest.
- By addressing gray zones as a practical implementation issue, our findings support a diagnostic workflow that uses longitudinal plasma tests when uncertainty remains (Figure 3).
- Sensitivity analyses across assay platforms (Lumipulse, C2N) yielded consistent results.

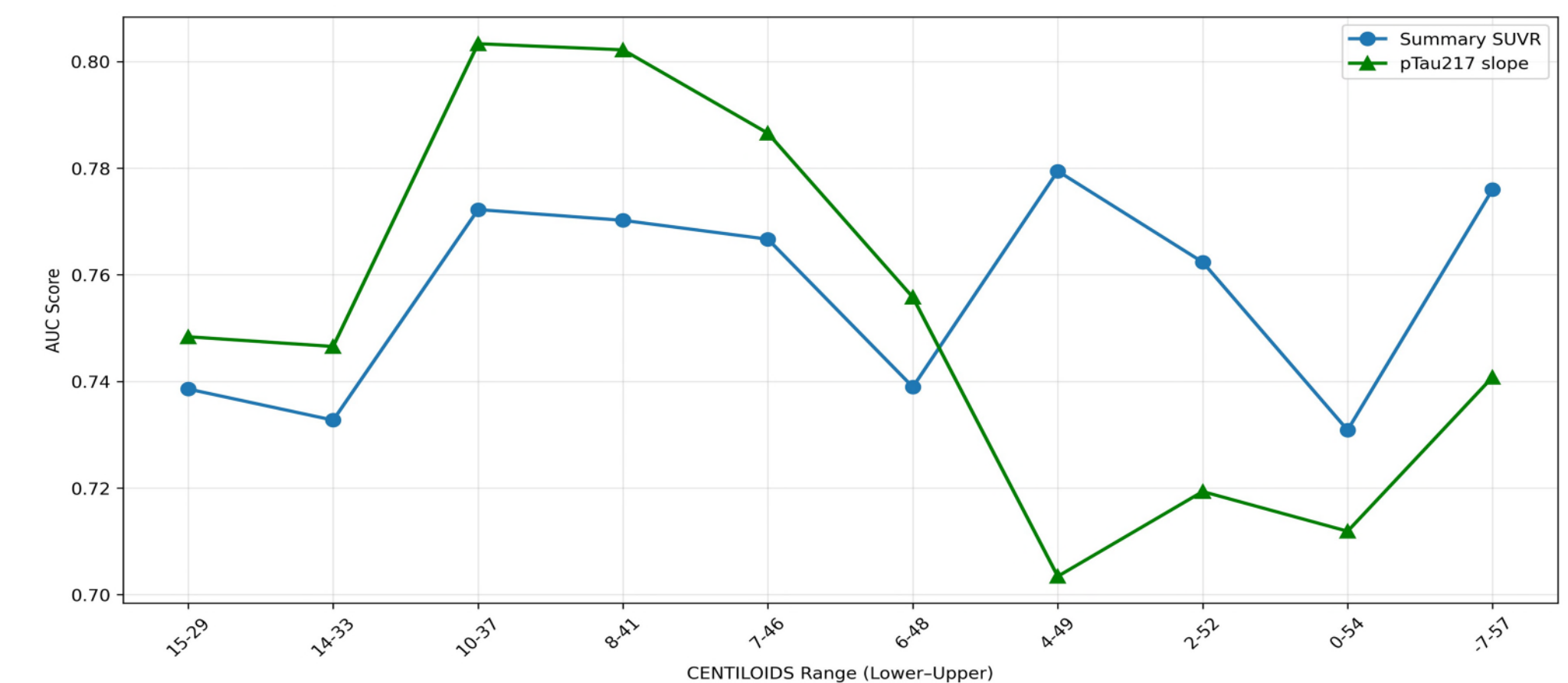


Fig 2. Comparison of AUC Between Summary SUVR and pTau217 Slope Across Centiloid Ranges

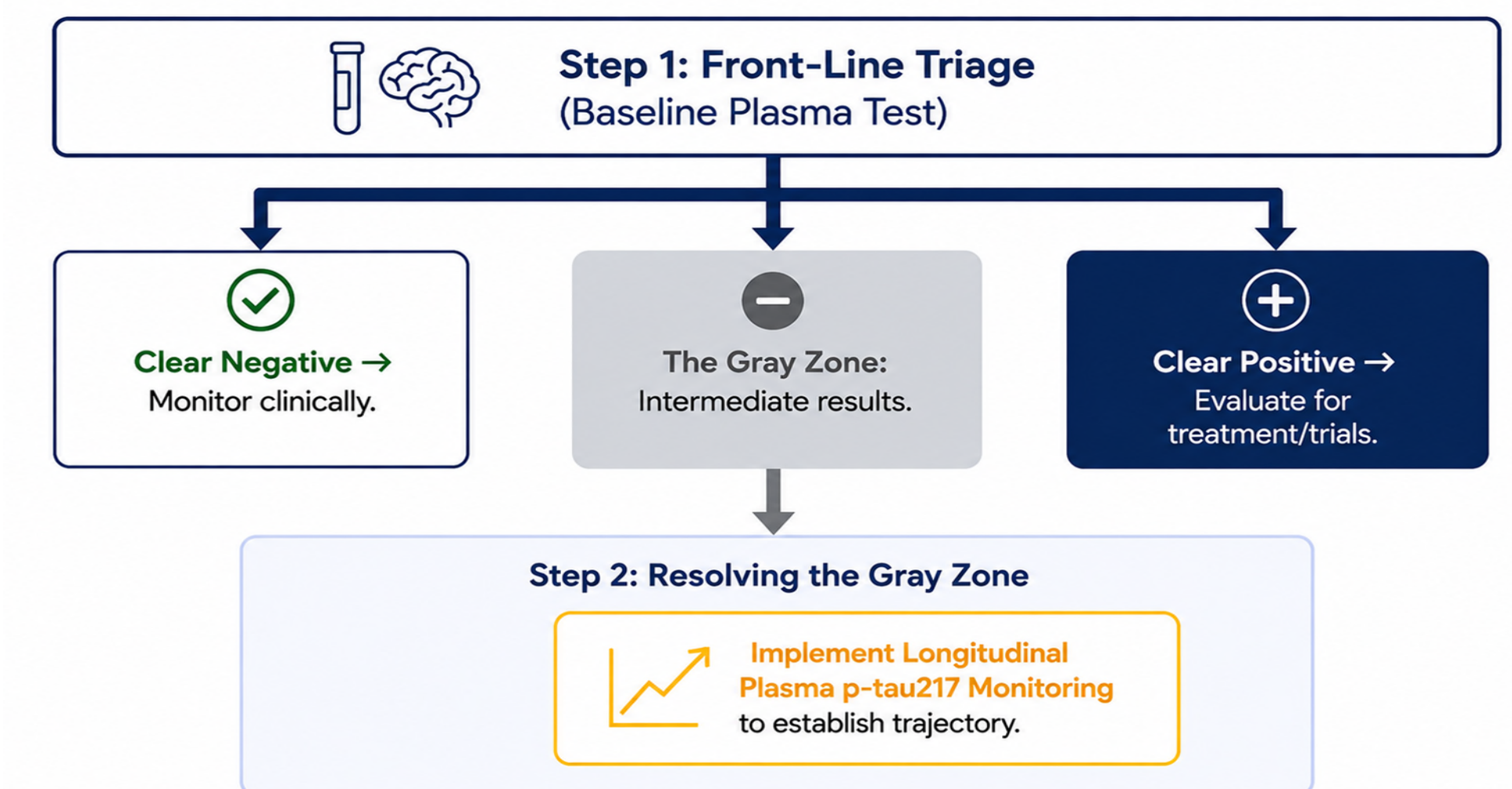


Fig 3. Clinical diagnostic pathway with longitudinal plasma

References

- Hazan J, Liu KY, Isaacs JD, Howard R. Cut-points and gray zones: The challenges of integrating Alzheimer's disease plasma biomarkers into clinical practice. *Alzheimer's & Dementia* 2025; 21(3): e70113.
- Brum WS, Cullen NC, Janelidze S, Ashton NJ, Zimmer ER, Theriault J et al. A two-step workflow based on plasma p-tau217 to screen for amyloid β positivity with further confirmatory testing only in uncertain cases. *Nature Aging* 2023; 3(9): 1079-1090.