

Multi-Analyte Plasma Risk Score Improves Sensitivity and Certainty for Early AD Detection in a Diverse Community-Based Cohort

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Background

Recent comparative plasma biomarker studies predominantly report p-Tau 217 or p-Tau 217/A β 42 ratio performance in pathology-rich cohorts with high tau-PET maturity. While these first-generation assays show high accuracy in advanced disease, they often underperform in real-world cohorts with less advanced pathology. Despite recognition that Alzheimer's is biologically multi-dimensional, current approaches remain bifurcated between single-marker or ratio assays and high-complexity proteomics that lack scalability. This leaves a diagnostic blind spot in real-world cohorts—the amyloid-positive but tau-negative (A+/T-) population—where p-Tau 217 signals frequently fall below clinical thresholds, expanding intermediate zones and reducing certainty. In a community-based cohort rich in A+/T- participants, we demonstrate that an ATN(I) approach integrating amyloid, tau, neurodegeneration, and neuroinflammation biomarkers significantly improves amyloid classification sensitivity and reduces diagnostic uncertainty relative to standalone p-Tau 217.

Methods

Bio-Hermes-002 Interim Analysis. Analyses were performed using interim plasma and PET imaging data from the ongoing Bio-Hermes-002 study (NCT06584357), a community-based, multi-center cohort designed to evaluate blood biomarkers across the Alzheimer's disease continuum in a real-world population. As the architectural successor to the original Bio-Hermes-001 study [1], this protocol leverages a global network of research sites specializing in Alzheimer's disease therapeutic development. Unlike pathology-enriched memory clinic cohorts, Bio-Hermes-002 intentionally captures earlier disease stages and includes substantial representation of amyloid-positive, tau-negative (A+/T-) individuals.

Methods. Using LucentAD Complete—which integrates p-Tau 217, A β 42/40, GFAP, and NFL—we mapped biomarker Z-score trajectories across a continuous scale of composite Risk Scores. To visualize individual biologies, we generated multi-dimensional radar plots for p-Tau 217-matched 'twins' using Z-score scaling relative to control baselines. This allowed for population-level trajectory mapping and case-level identification of differences in underlying biological activity despite similar p-Tau 217 or p-Tau 217/A β 42 levels.

Multi-Analyte Algorithm. LucentAD Complete is a 5-analyte plasma algorithm based on ATN(I) pathophysiological framework [2,3] representing four distinct biological disease axes (Figure 1). These include p-Tau 217 ("T": LucentAD p-Tau 217, a Janssen assay design [4]), amyloid β -42/40 ratio ("A": A β 42/40), neurofilament light chain ("N": NFL), and glial fibrillary acidic protein ("I": GFAP). The latter four biomarkers are quantified utilizing the multiplexed Simoa N4PE kit. The LucentAD Complete algorithm integrates these biomarkers via a logistic regression to generate a unified Amyloid Risk Score. Development and clinical validation of LucentAD p-Tau 217 and LucentAD Complete are described elsewhere [4, 5].

Figure 1. LucentAD Complete: Four-Axis "ATN(I)" Plasma Test

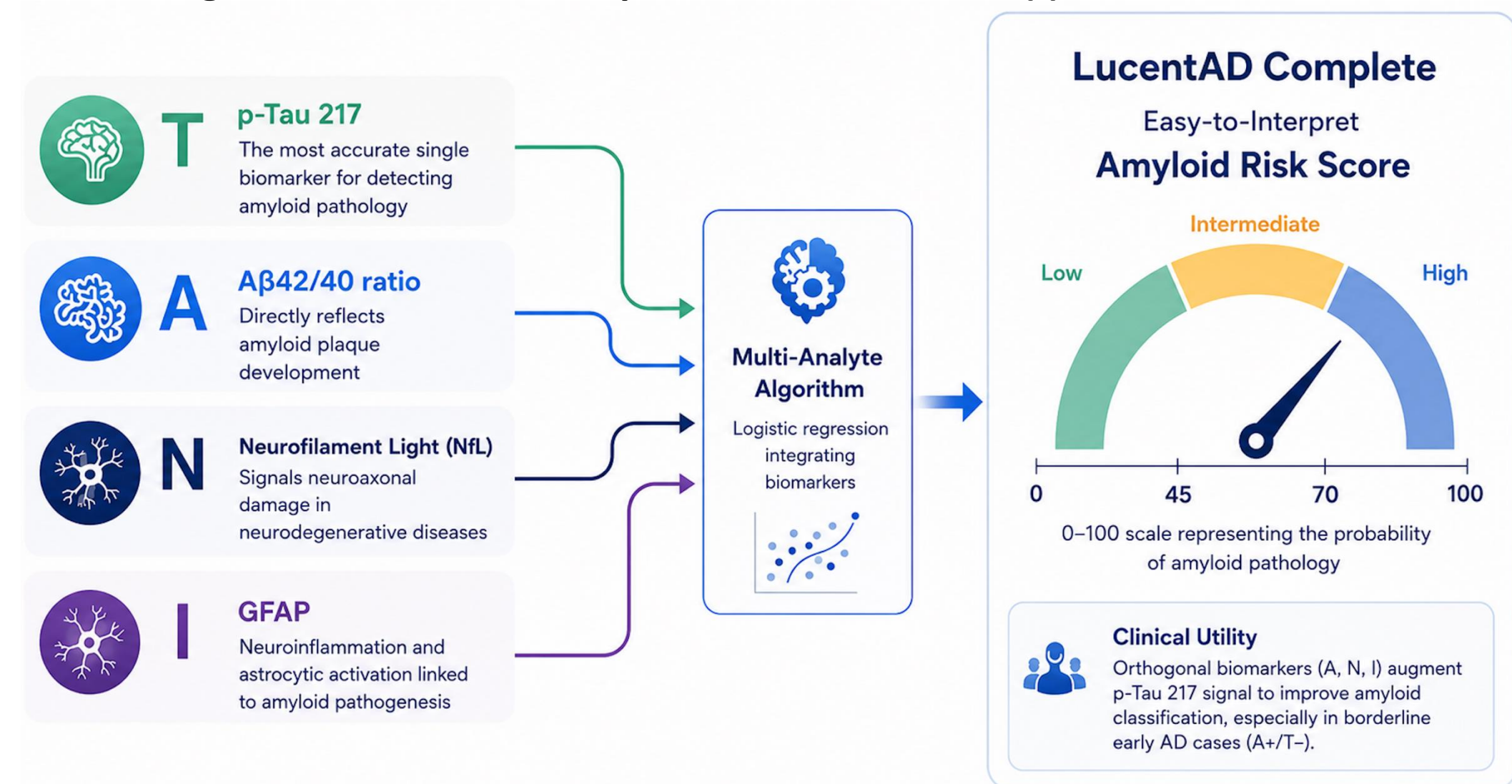


Figure 1. LucentAD Complete integrates four key Alzheimer's-relevant biomarkers representing the ATN(I) framework (Jack *et al*², Imbimbo *et al*³) into a composite Amyloid Risk Score. p-Tau 217 is the backbone of the test, and the orthogonal biomarkers A β 42/40 ratio, NFL, and GFAP augment the p-Tau 217 signal for amyloid classification in difficult borderline early AD cases (amyloid+, tau-, A+/T-). The LucentAD Complete test report includes the Amyloid Risk Score and the individual ATN(I) biomarkers values alongside interpretive normative ranges for additional potential clinical insights.

LucentAD Complete generally resolves ~2/3's of borderline cases that cannot be classified by p-Tau 217 alone. This additional resolution of borderline intermediate cases is illustrated in Figure 2.

Figure 2: LucentAD Complete - Resolution of Intermediate Borderline Cases

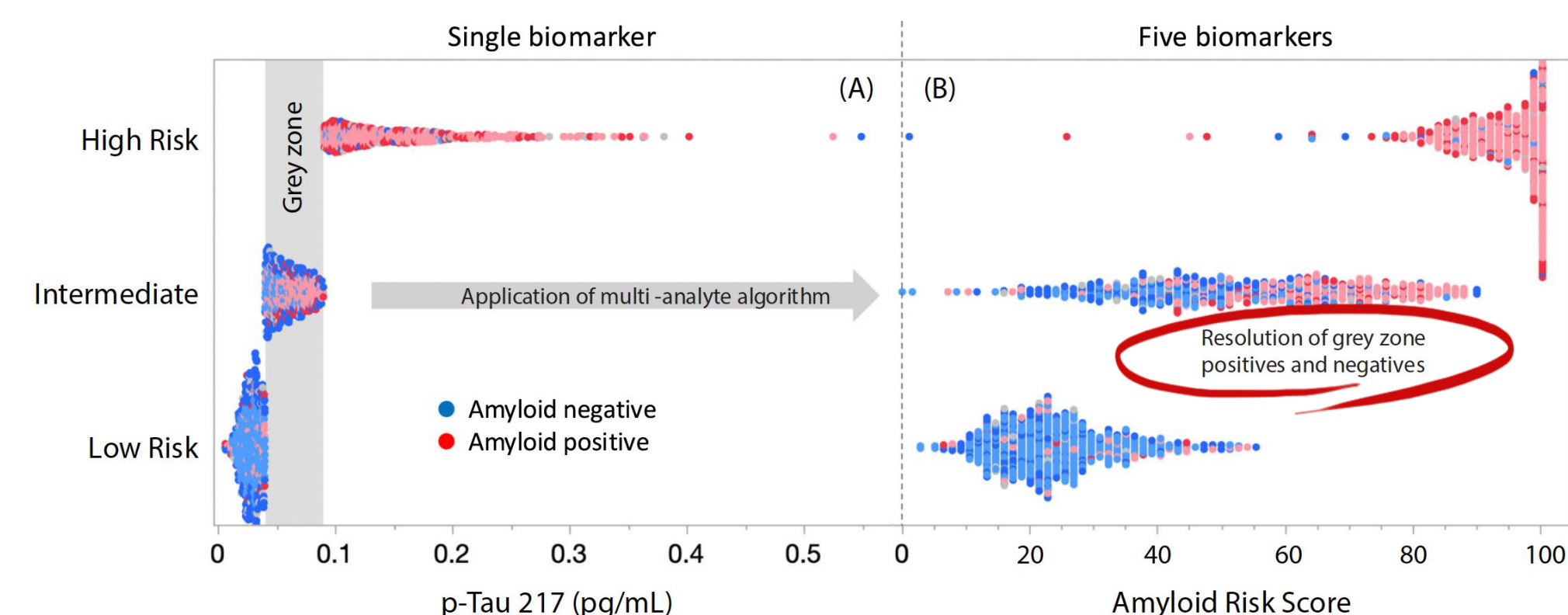


Figure 2. Multi-analyte interrogation of plasma samples for amyloid status. A. p-Tau 217 classifies samples with low and high amyloid burden, identifying intermediate risk cases. B. Multivariate analysis with all four of the ATN(I) biomarkers resolves majority of intermediate cases. All results are converted to an Amyloid Risk Score for final interpretation.

Results

Figure 3: Multi-Axis ATN(I) Integration Enhances Separation of Amyloid PET populations

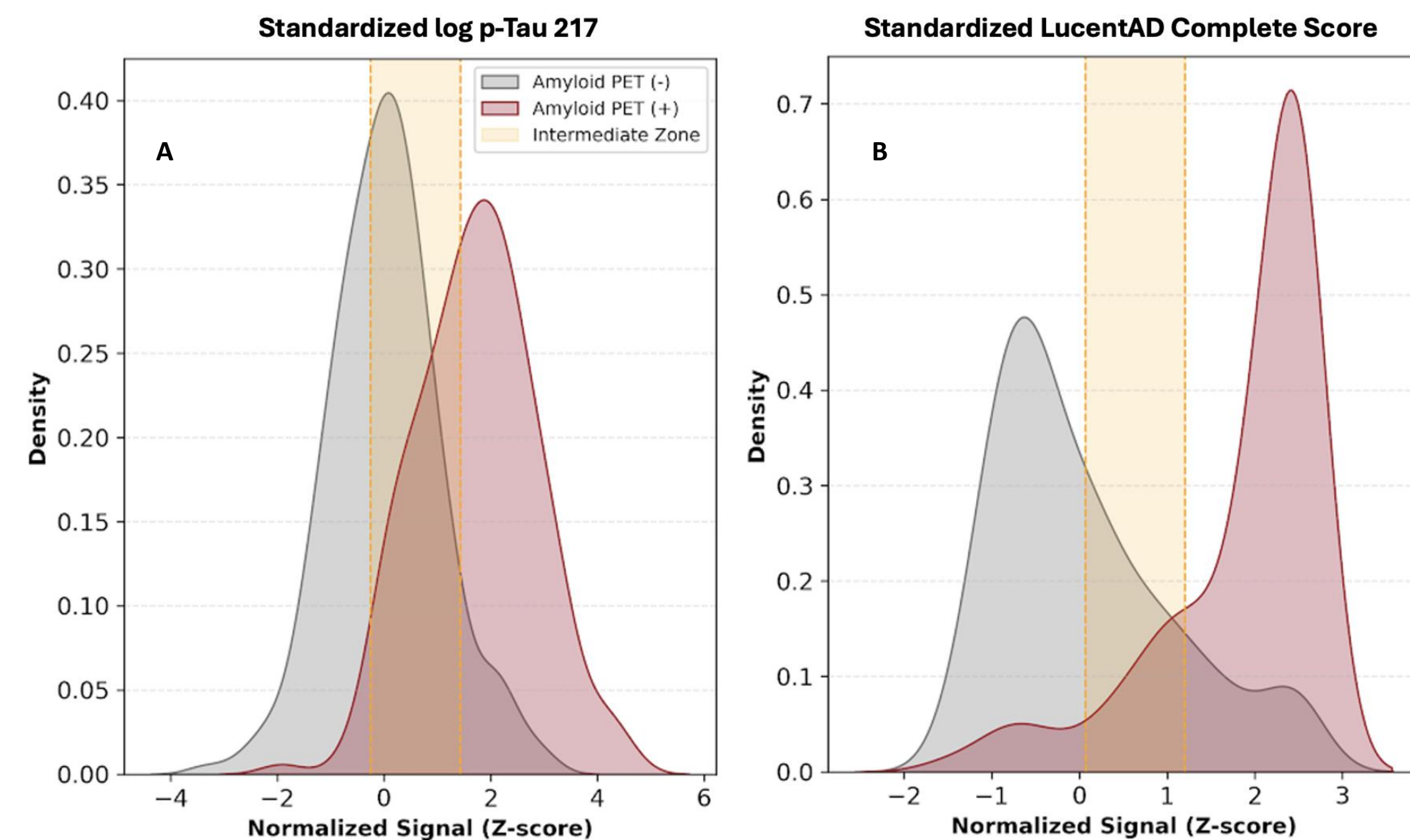


Figure 3. Continuous frequency distributions using Gaussian Kernel Density Estimation to map patient cohorts. Biomarker signals are standard-normalized into Z-scores to establish a uniform scale, where each unit corresponds to one standard deviation from the amyloid negative cohort mean. (A) Standalone log p-Tau 217 density plots demonstrate substantial population overlap between amyloid PET negative (grey) and amyloid PET positive (red) cohorts. Intermediate zone is depicted in orange shaded area, characterized by high clinical uncertainty. (B) In contrast, the LucentAD Complete Amyloid Risk Score produces a more definitive, bimodal separation between the amyloid PET negative and positive populations. By integrating orthogonal biological information across amyloid, tau, neurodegeneration, and neuroinflammation pathways, LucentAD Complete reduces intermediate ambiguity and increases classification certainty for more patients.

Table 1: Comparative Diagnostic Performance (AUC) for Amyloid and Tau PET Status

Target Pathology	Method	AUC, [95% CI]	AUC, [95% CI]
Amyloid PET (A+ vs. A-)	LucentAD Complete	0.918 [0.894 – 0.942]	Symptomatic Only (N=233) 0.903 [0.864 – 0.942]
	p-Tau 217	0.857 [0.824 – 0.890]	0.841 [0.794 – 0.888]
Tau PET (T+ vs. T-)	LucentAD Complete	0.902 [0.874 – 0.930]	Symptomatic Only N=184 0.914 [0.877 – 0.951]
	p-Tau 217	0.838 [0.803 – 0.873]	0.852 [0.805 – 0.899]

Table 1: Areas Under the Receiver Operator Curve, AUC, across the Bio-Hermes-002 interim cohort and symptomatic sub-populations. The 4-axis LucentAD Complete algorithm exhibited higher classification accuracy for both amyloid and tau pathology compared to p-Tau 217 alone. Note: The reduced sample size for Tau PET analysis reflects the subset of the interim cohort that had completed both plasma collection and [18F]flortaucipir PET imaging at the time of data cutoff.

Figure 4: Comparative Diagnostic Performance Across Imaging Sub-Cohorts

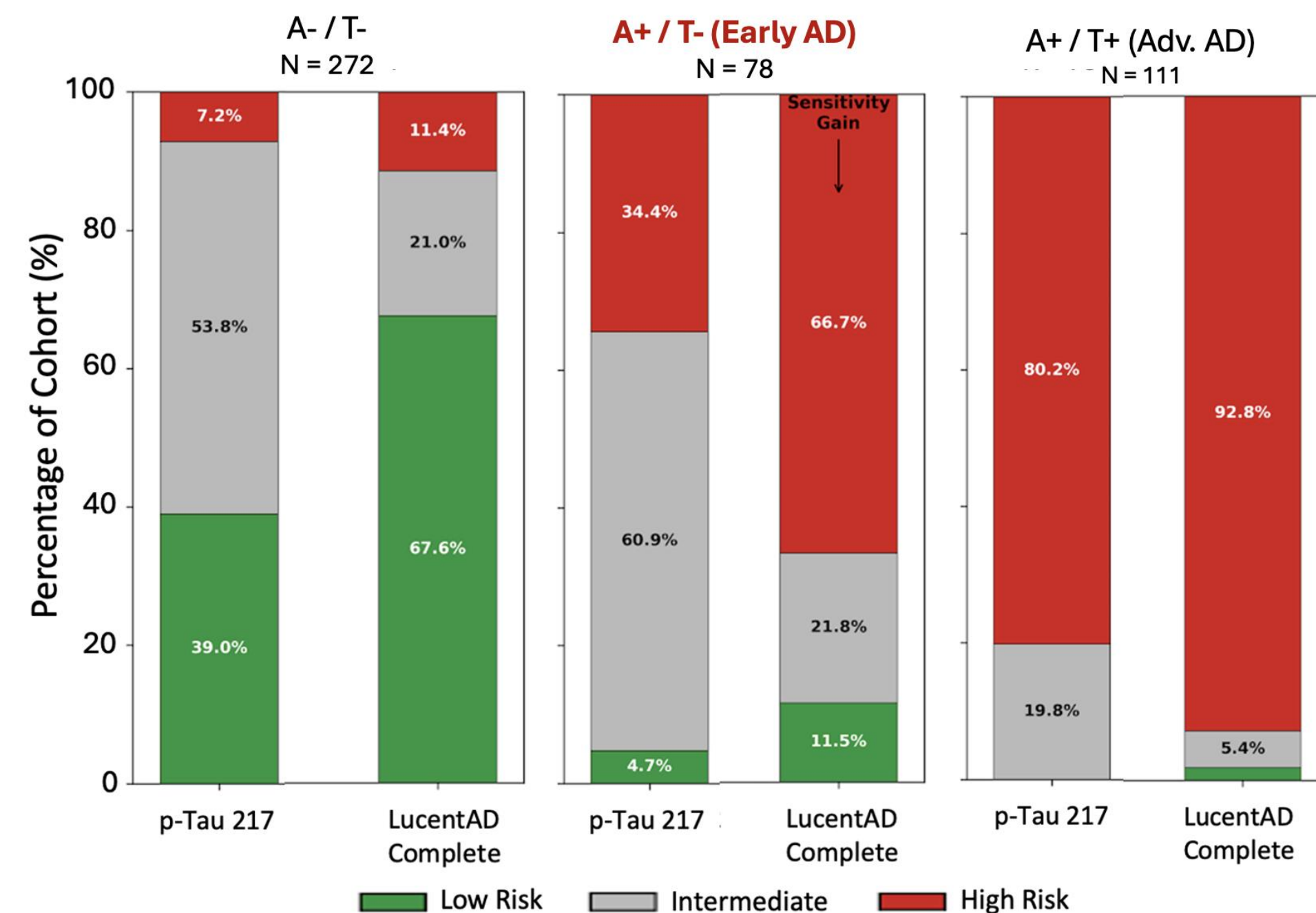


Figure 4. Distributions of Low (Green), Intermediate (Grey), and High Risk (Red) amyloid classifications. The A+/T- cohort (early Alzheimer's) represents the most challenging class of patients for plasma-based assays due to a weaker amyloid/p-Tau 217 signal vs. more advanced A+/T+ patients. In the A+/T- cohort, LucentAD Complete correctly classified 2X more patients with a 3X smaller intermediate zone than p-Tau 217 alone, correctly calling two-thirds of the patients in this difficult clinical category.

Results (cont.)

Figure 5: Minimizing Clinical Ambiguity and Assay Volatility Across the Clinical Spectrum

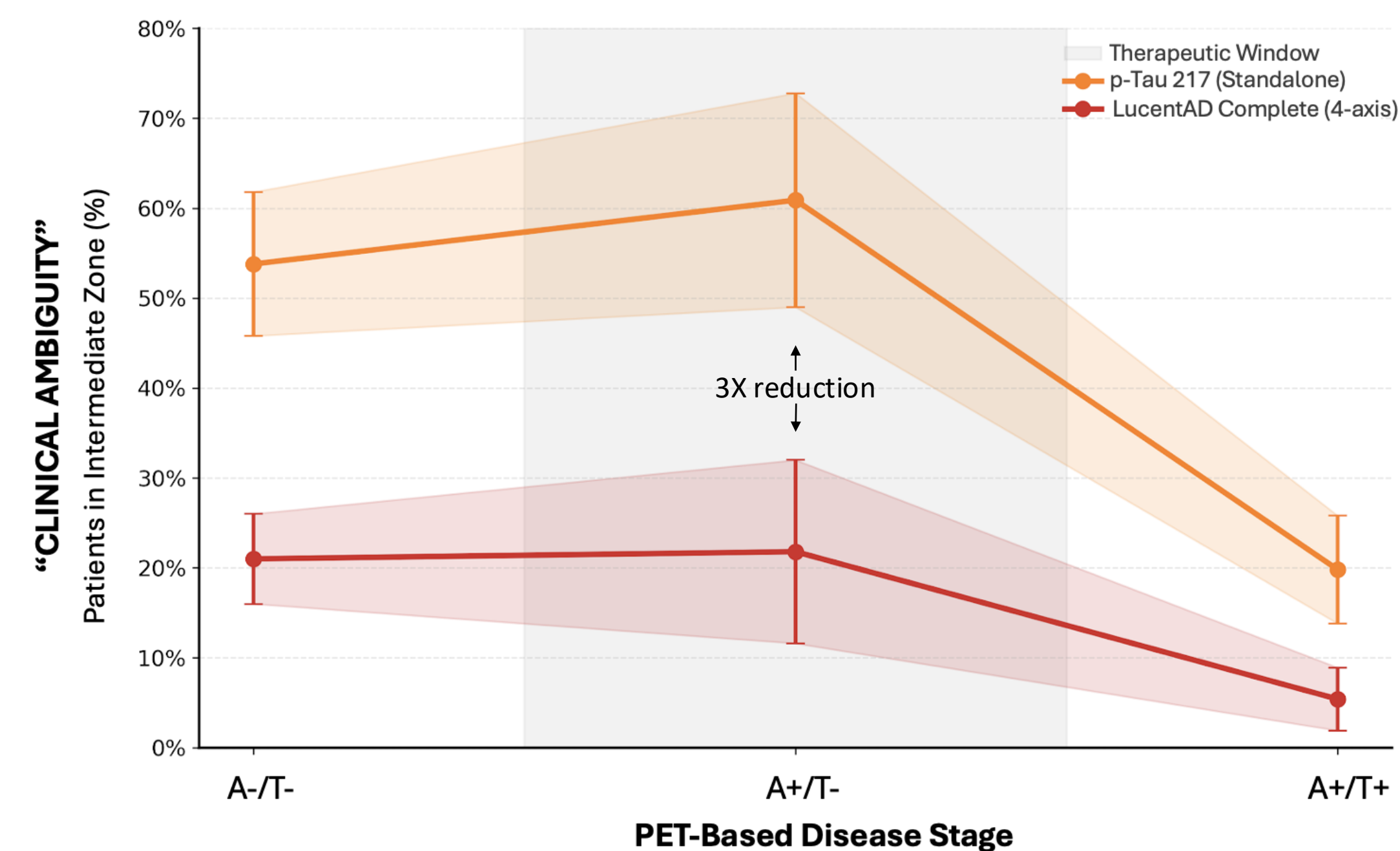


Figure 5. Comparison of the proportion of patients falling into the unclassified Intermediate Zone (%) between standalone p-Tau 217 (orange) and the multi-axis LucentAD Complete framework (red) across stages of pathological progression (corresponds to the gray bars in Figure 4). Shaded bands represent the 95% confidence intervals. The gray shaded region conceptually denotes the optimal therapeutic window for disease-modifying interventions, spanning the critical transition from early amyloid accumulation to the onset of downstream tau pathology. In addition to higher ambiguity, standalone p-Tau 217 exhibits higher volatility, with assay decisiveness highly dependent on disease severity. As has been described by others, p-Tau 217 (or p-Tau 217/A β 42 ratio) tests perform most cleanly only when a patient is already positive for both amyloid and tau (A+/T+) [6]. However, the critical window for therapeutic intervention targets the clinically challenging A+/T- stage. This comparison highlights the distinct therapeutic advantage of an integrated, four-axis ATN(I) approach, which delivers a lower-ambiguity profile across the disease continuum and effectively reduces the diagnostic decisiveness gap during early disease intervention.

Figure 6: Multi-Axis ATN(I) Integration Doubles Sensitivity and Minimizes Uncertainty

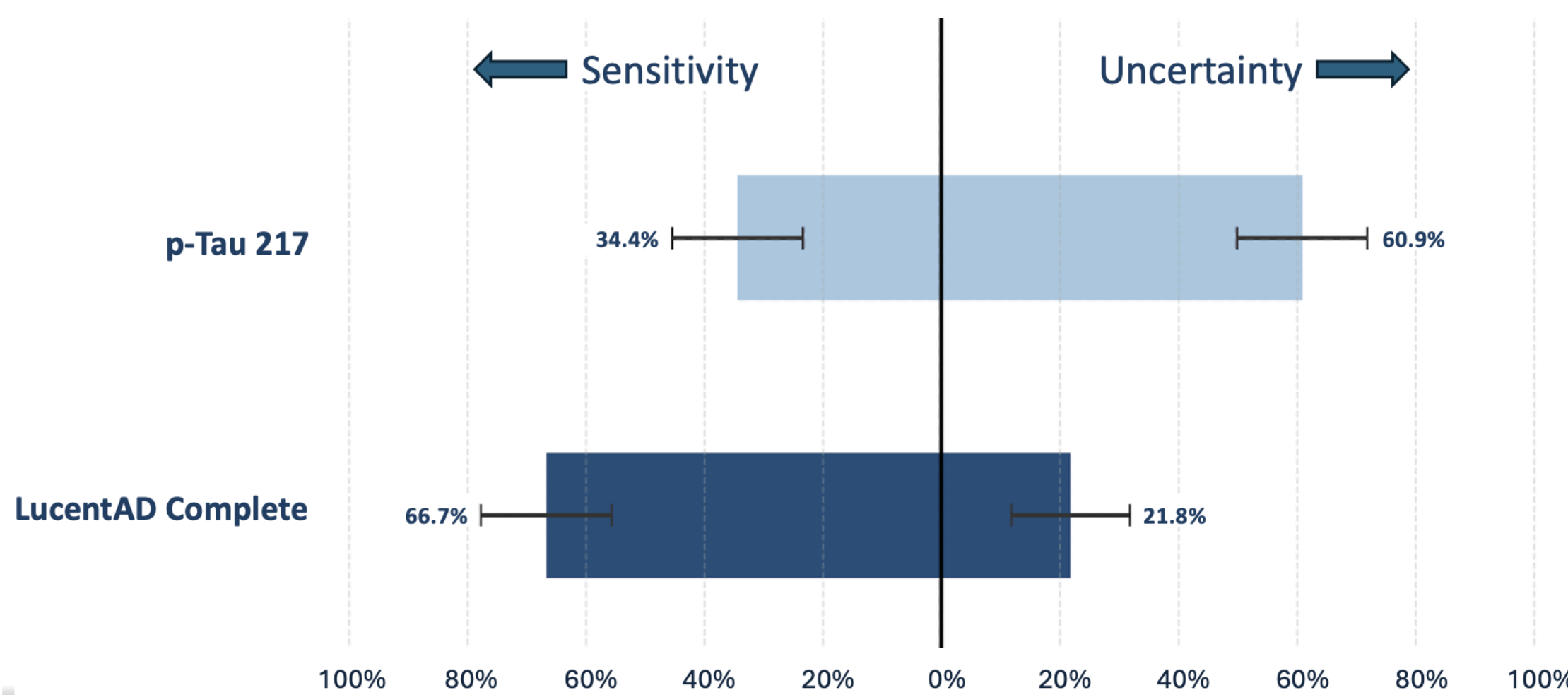


Figure 6. Diagnostic Sensitivity and Clinical Certainty in Early Pathology (A+/T- Cohort). A mirrored horizontal analysis demonstrates the diagnostic advantages of the multi-analyte composite framework (bottom) relative to standalone blood testing baseline metrics (top) within an early-stage, community-based cohort. Left Axis: Proportion of true amyloid-positive individuals correctly identified during the earliest phase of pathological accumulation. The multi-analyte algorithm nearly doubles diagnostic capture, increasing sensitivity to 66.7% compared to 34.4% for standalone p-Tau 217 (DeLong $p < 0.01$). Right Axis: Proportion of patients left in the intermediate zone. The composite risk score lowers clinical ambiguity almost three-fold from 60.9% down to 21.8% (Chi-squared $p < 0.001$). Error bars depict 95% CIs for each performance metric.

Conclusions

- LucentAD Complete demonstrated higher discrimination of both amyloid and tau pathology compared with standalone p-Tau217 in this real-world, community-based cohort enriched for early-stage disease.
- Multi-axis integration across the ATN(I) framework reduced diagnostic uncertainty and substantially narrowed the intermediate zone, providing more definitive patient classifications than tau biology alone.
- These findings suggest that Alzheimer's disease diagnostics may benefit from moving beyond single-marker paradigms toward biologically integrated, yet scalable, blood-based approaches.
- Reducing assay ambiguity in earlier pathological stages could improve identification of patients most likely to benefit from emerging disease-modifying therapies and clinical trial participation.

[1] Mohs RC, Beaugreard D, Dwyer J, et al. Bio-Hermes Collaborative Group. The Bio-Hermes Study: Biomarker database developed to investigate blood-based and digital biomarkers in community-based, diverse populations clinically screened for Alzheimer's disease. *Alzheimers Dement*. 2024 Apr;20(4):2752-2765.
[2] Jack CR Jr, Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimers Dement*. 2018 Apr;14(4):535-562. doi: 10.1016/j.jalz.2018.02.008.
[3] Imbimbo BP, Walling M, Imbimbo C, et al. Plasma ATN(I) classification and precision pharmacology in Alzheimer's disease. *Alzheimers Dement*. 2023 Oct;19(10):4729-4734. doi: 10.1002/alz.13084. Epub 2023 Apr 20. PMID: 37079778.
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[5] Wilson DH, Copeland K, Miller M, et al. Clinical performance of scalable automated p-tau 217 multi-analyte algorithm blood test with reduced intermediate zone using multiplexed digital immunoassay. *Alzheimers Dement (Amst)*. 2025 Nov;21(374):e70215. doi: 10.1002/dad2.70215.
[6] Karagami S, Rial AM, van Essen M, et al. Differential performance of plasma p-tau217 in detecting intermediate vs high Alzheimer's disease neuropathologic change. *Alzheimers Dement*. 2025 Dec;26(21):Suppl 2:e104257. doi: 10.1002/alz.70856_104257.