

Introduction

Plasma p-tau217 and Aβ42 are well-established biomarkers of Alzheimer’s disease pathology and can be quantified using multiple assay platforms. Recently, the Lumipulse p-tau217/Aβ42 ratio received FDA approval as a diagnostic tool for detecting amyloid plaques, demonstrating positive predictive values of 92% and 97% using a two-cutpoint approach. However, it remains uncertain whether p-tau217 and Aβ42 measured on other platforms exhibit comparable clinical performance. In this study, we aimed to address this gap by comparing p-tau217/Aβ42 ratios derived from different platforms across multiple community-based preclinical cohorts.

Materials and Methods

- 276 plasma samples from three cohorts (HCP2 [n=93], PPG4 [n=134], and ALPS [n=49])
- P-tau217 measured:
 - NULISaseq CNS Disease Panel on Argo HT
 - Lumipulse on Fujirebio G1200
- Aβ42 measured:
 - Pitt IPMS
 - NULISaseq CNS Disease Panel on Argo HT
 - Lumipulse on Fujirebio G1200

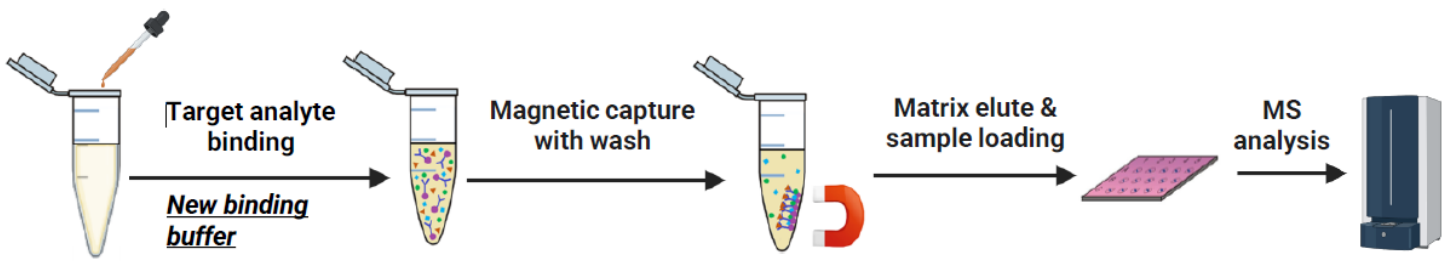


Figure 1. Pitt IPMS workflow.

- Amyloid positivity assessed with PiB PET
- Data analyzed with spearman correlations and ROC analyses comparing six p-tau217/Aβ42 ratios on different platform combinations

Table 1. Participant Characteristics.

Variable	N	Overall	By PiB Global			p-value ²
			A+ N = 41 ¹	A- N = 198 ¹	Not available N = 37 ¹	
Age	276	67.8 (62.0, 73.0)	71.1 (65.8, 76.9)	67.8 (62.0, 73.0)	64.0 (57.0, 73.0)	0.001
Race	276					0.3
AA		32 (11.6%)	4 (9.8%)	20 (10.1%)	8 (21.6%)	
Cauc		238 (86.2%)	37 (90.2%)	173 (87.4%)	28 (75.7%)	
Other		6 (2.2%)	0 (0.0%)	5 (2.5%)	1 (2.7%)	
Sex	276					0.005
Female		171 (62.0%)	17 (41.5%)	126 (63.6%)	28 (75.7%)	
Male		105 (38.0%)	24 (58.5%)	72 (36.4%)	9 (24.3%)	
Dx	143					0.4
Control		116 (81.1%)	18 (78.3%)	94 (82.5%)	4 (66.7%)	
MCI		24 (16.8%)	4 (17.4%)	18 (15.8%)	2 (33.3%)	
Other Dementia		3 (2.1%)	1 (4.3%)	2 (1.8%)	0 (0.0%)	
Study	276					<0.001
ALPS		49 (17.8%)	10 (24.4%)	38 (19.2%)	1 (2.7%)	
HCP2		93 (33.7%)	8 (19.5%)	53 (26.8%)	32 (86.5%)	
PPG4		134 (48.6%)	23 (56.1%)	107 (54.0%)	4 (10.8%)	
p-tau217 (Lumi)	260	0.1 (0.1, 0.2)	0.25 (0.2, 0.3)	0.11 (0.10, 0.14)	0.11 (0.08, 0.16)	<0.001
p-tau217 (NULISA)	236	2,594.8 (1,847.3, 3,234.5)	4,214.8 (2,914.6, 4,831.6)	2,567.7 (1,832.4, 3,027.8)	1,947.0 (1,600.7, 2,476.5)	<0.001
Aβ42 (Lumi)	260	25.5 (21.8, 29.0)	22.3 (20.5, 24.9)	26.3 (22.1, 29.8)	25.2 (20.6, 27.4)	<0.001
Aβ42 (MS)	260	0.54 (0.5, 0.6)	0.53 (0.4, 0.6)	0.54 (0.5, 0.6)	0.57 (0.5, 0.6)	0.088
Aβ42 (NULISA)	228	11,905.5 (9,815.3, 14,151.2)	9,909.6 (8,752.5, 11,851.1)	12,434.5 (10,176.5, 14,428.9)	11,359.6 (9,920.0, 13,610.5)	0.003

Results

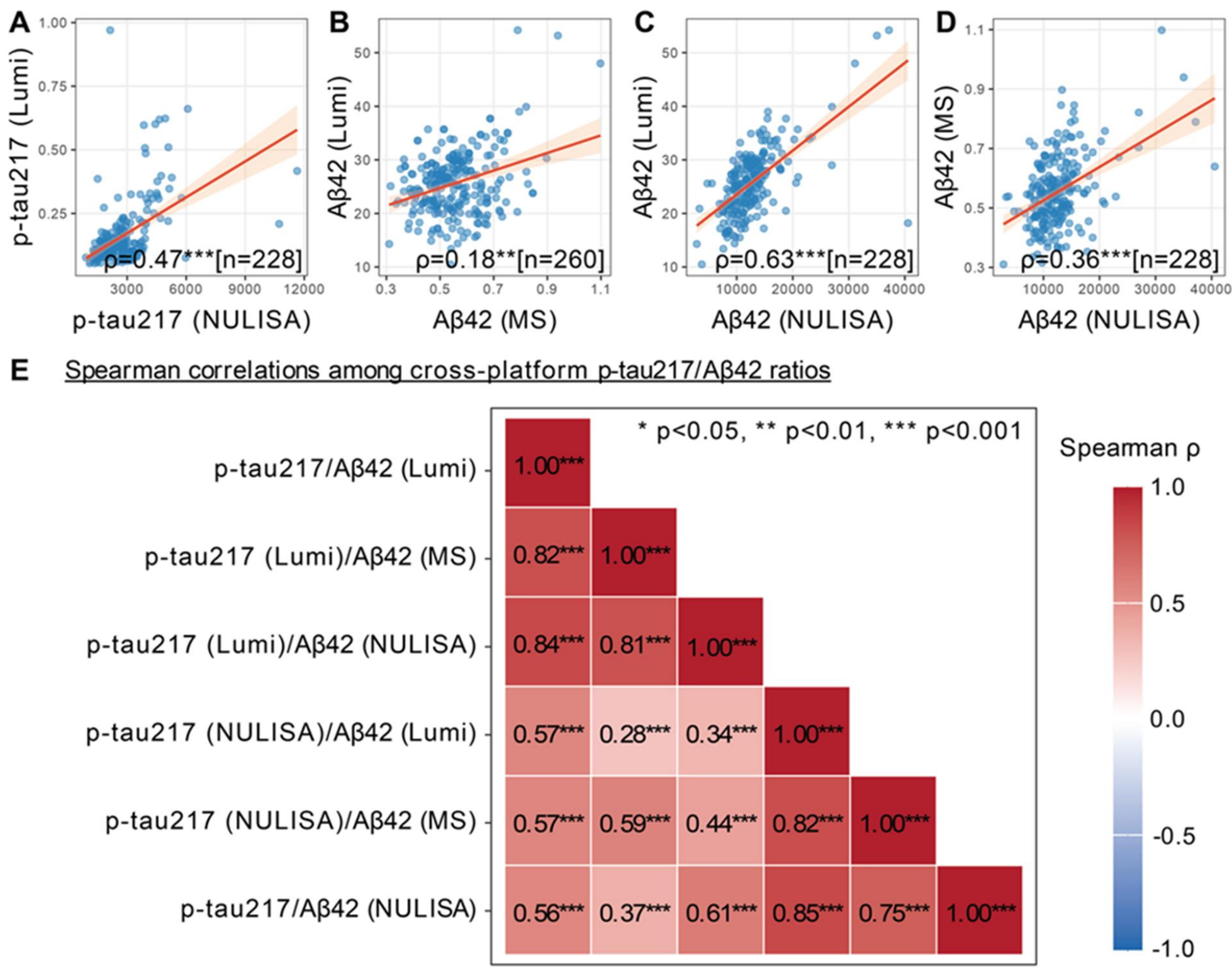


Figure 2. Cross-platform concordance of plasma p-tau217 and Aβ42 measures.

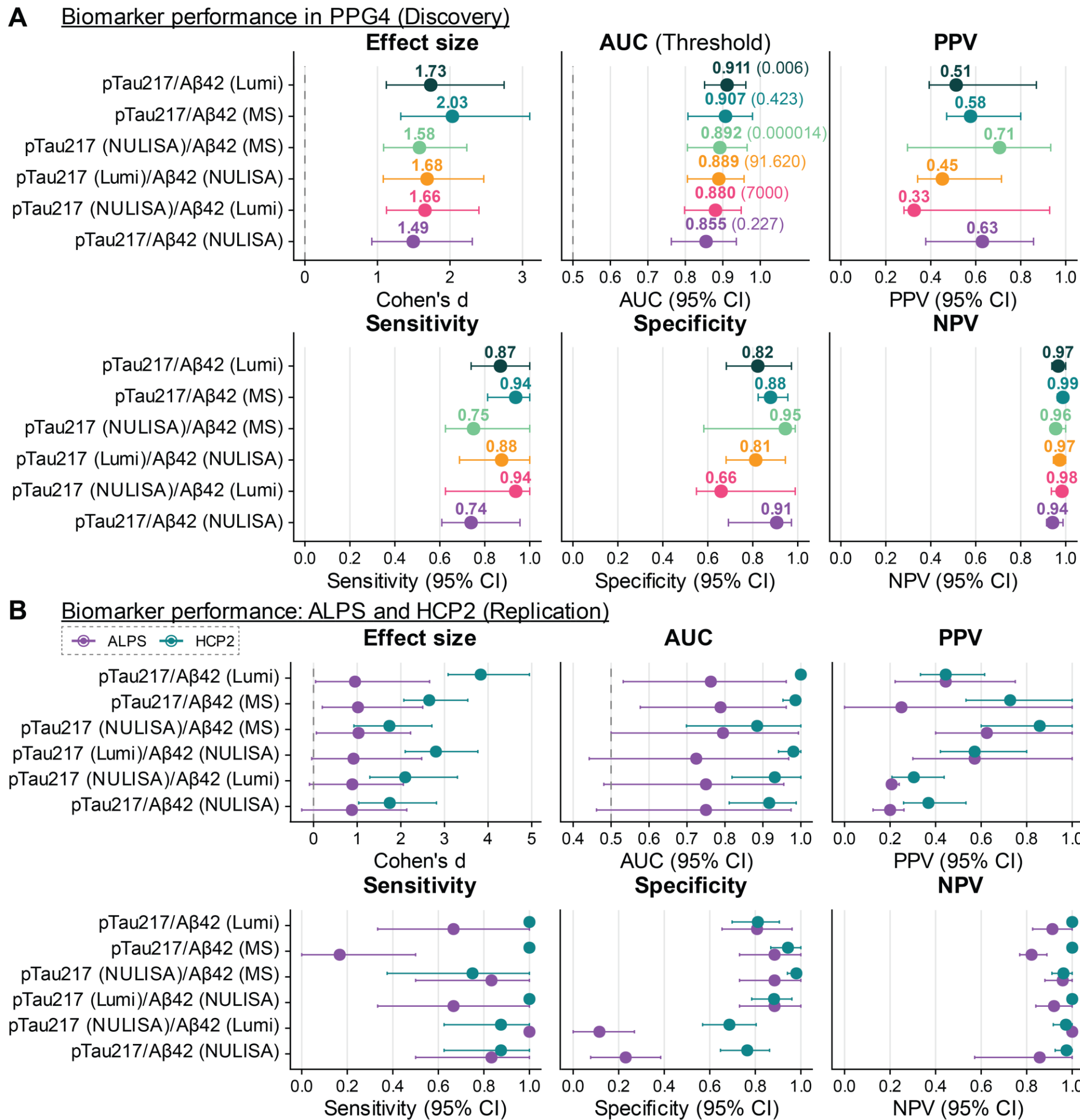


Figure 3. Diagnostic performance of plasma p-tau217/Aβ42 ratios for amyloid-PET classification.

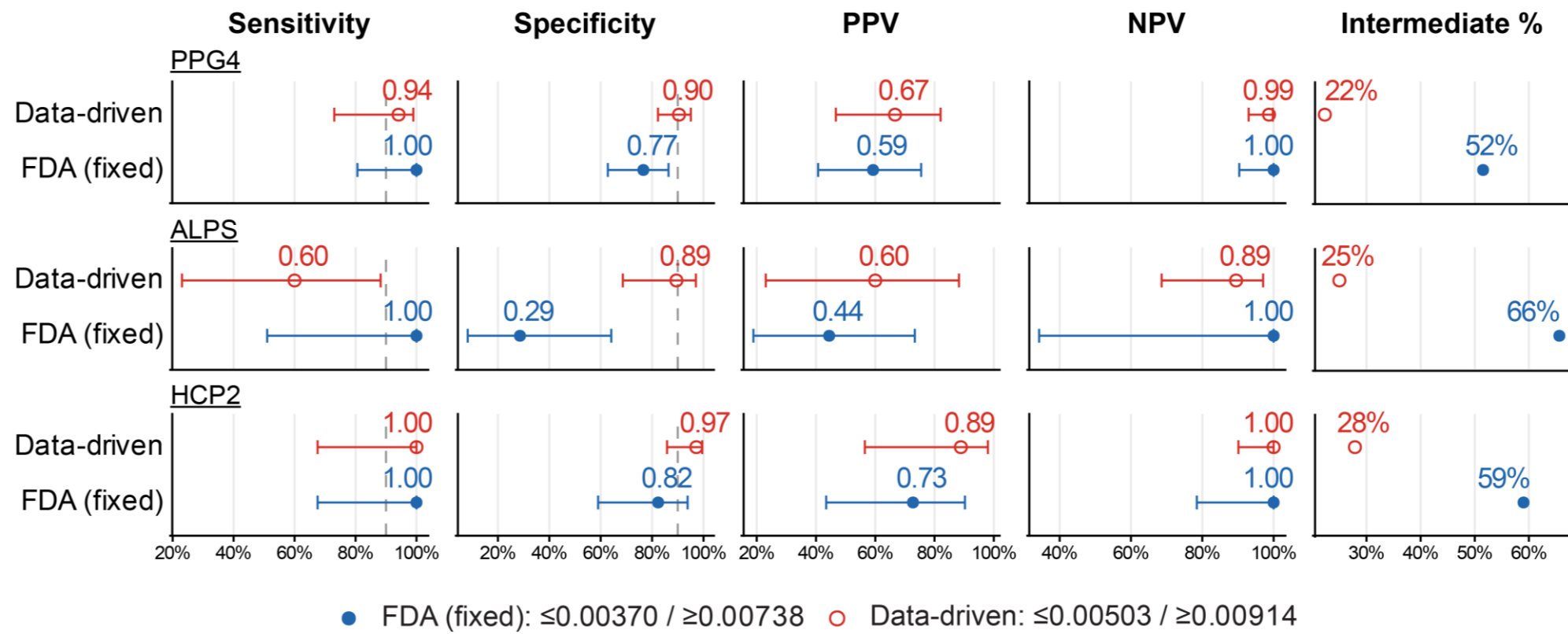


Figure 4. Performance metric comparison based on FDA-approved cutpoints vs. data-driven cutpoints. Data-driven cutpoints were derived using 90% sensitivity/90% specificity. Points indicate estimates with 95% CIs.

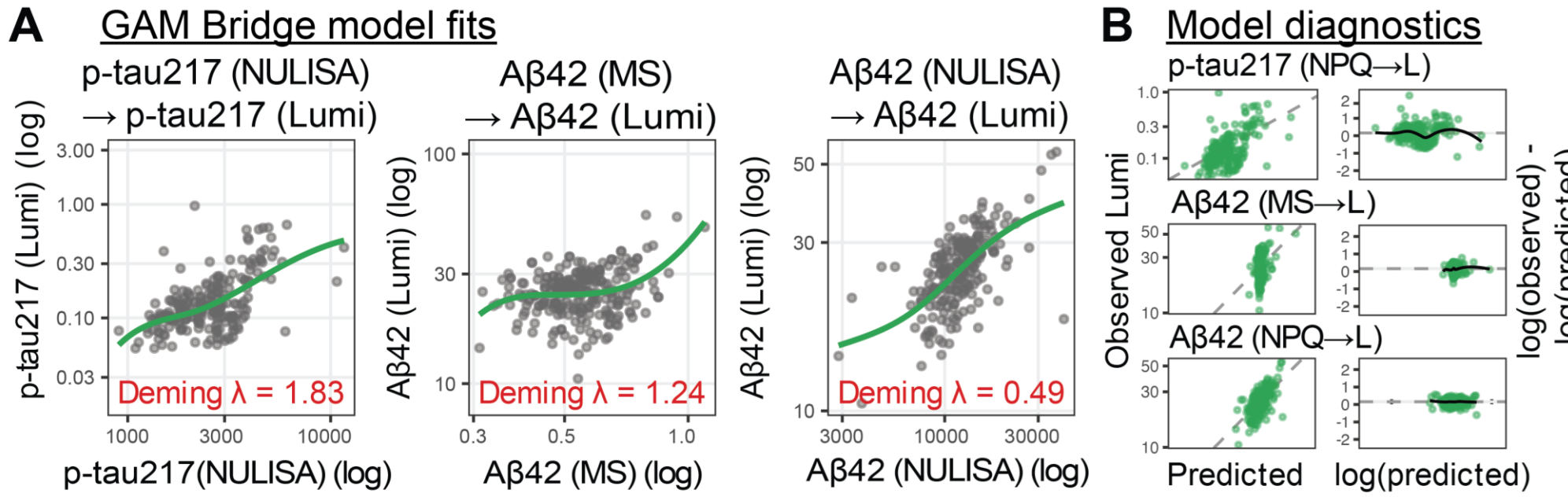


Figure 5. GAM-based transformation and performance of FDA-approved Lumipulse-scale ratios. A, Generalized additive models (GAMs) were fitted to transform NULISA and mass spectrometry measures to Lumipulse-scale values. Gray points show observed values and green lines show fitted curves. B, Model diagnostics of observed versus predicted values and log-scale residuals for each transformed marker. C, Heatmaps summarize sensitivity, specificity, PPV, NPV, and intermediate ranges for Lumipulse and transformed p-tau217/Aβ42 ratios using FDA-based cutpoints.

	Lumipulse p-tau217/Aβ42					
	SENS	SPEC	PPV	NPV	Int %	
p-tau217 (NPQ→L)/Aβ42 (L)	1.00	0.77	0.59	1.00	52%	PPG4
p-tau217 (L)/Aβ42 (MS→L)	1.00	0.86	0.71	1.00	64%	
p-tau217 (L)/Aβ42 (NPQ→L)	1.00	0.58	0.55	1.00	62%	
p-tau217 (NPQ→L)/Aβ42 (MS→L)	1.00	0.70	0.57	1.00	57%	
p-tau217 (NPQ→L)/Aβ42 (NPQ→L)	1.00	0.46	0.53	1.00	80%	
p-tau217 (NPQ→L)/Aβ42 (NPQ→L)	1.00	0.77	0.75	1.00	79%	ALPS
p-tau217 (NPQ→L)/Aβ42 (L)	1.00	0.29	0.44	1.00	66%	
p-tau217 (NPQ→L)/Aβ42 (L)	1.00	0.00	0.24	NA	34%	
p-tau217 (L)/Aβ42 (MS→L)	0.80	0.82	0.57	0.93	31%	
p-tau217 (L)/Aβ42 (NPQ→L)	0.80	0.81	0.57	0.93	34%	
p-tau217 (NPQ→L)/Aβ42 (MS→L)	1.00	0.00	0.44	NA	72%	HCP2
p-tau217 (NPQ→L)/Aβ42 (NPQ→L)	1.00	0.00	0.31	NA	59%	
p-tau217 (NPQ→L)/Aβ42 (L)	1.00	0.82	0.73	1.00	59%	
p-tau217 (NPQ→L)/Aβ42 (L)	1.00	0.80	0.75	1.00	73%	
p-tau217 (L)/Aβ42 (MS→L)	1.00	0.65	0.53	1.00	54%	
p-tau217 (L)/Aβ42 (NPQ→L)	1.00	0.71	0.57	1.00	51%	
p-tau217 (NPQ→L)/Aβ42 (MS→L)	1.00	0.71	0.75	1.00	78%	
p-tau217 (NPQ→L)/Aβ42 (NPQ→L)	1.00	0.88	0.86	1.00	76%	

Conclusion

- Lumipulse-based p-tau217/Aβ42 was among the top-performing ratios for Aβ-PET classification, with no significant pairwise AUC differences by DeLong test
- Compared with FDA-approved cut points, data-driven cut points reduced the proportion of participants in the intermediate zone and yielded higher thresholds, resulting in increased specificity and PPV at the expense of sensitivity and NPV.
- Generalized additive model (GAM) transformation produced Lumipulse-equivalent ratios with broadly comparable performance, supporting the feasibility of cross-platform harmonization while highlighting the need to consider cohort- and platform-specific variability.

Acknowledgement

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