

Background

- Alzheimer's disease (AD) is diagnosed histopathologically by the presence of both A β and tau pathologies.
- Plasma hyperphosphorylated tau (pTau)217** is among the most promising blood-based biomarkers to detect A β pathology associated with AD. A two-cutoff approach of the pTau217 assay may optimize its diagnostic performance compared to a single cutoff strategy¹.
→ Combining pTau217 with a plasma assay specifically targeting tau pathology may also streamline the detection of AD pathology.
- Tau seeding pathology involves the binding of pTau to normal tau.
- VeraBIND™ Tau plasma assay** (Veravas) is the first functional assay that detects pTau binding to recombinant normal tau using a tagged-tau chemiluminescent readout.
→ VeraBIND™ Tau was found to outperform plasma pTau217 test to detect tau positivity (T+), measured using positron emission tomography (PET)²
- Aim:** Assessing whether a two-cutoff pTau217 approach or a two-test approach combining low threshold pTau217 and VeraBIND Tau better identify T+ individuals in the presence of plasma amyloidosis

Methods

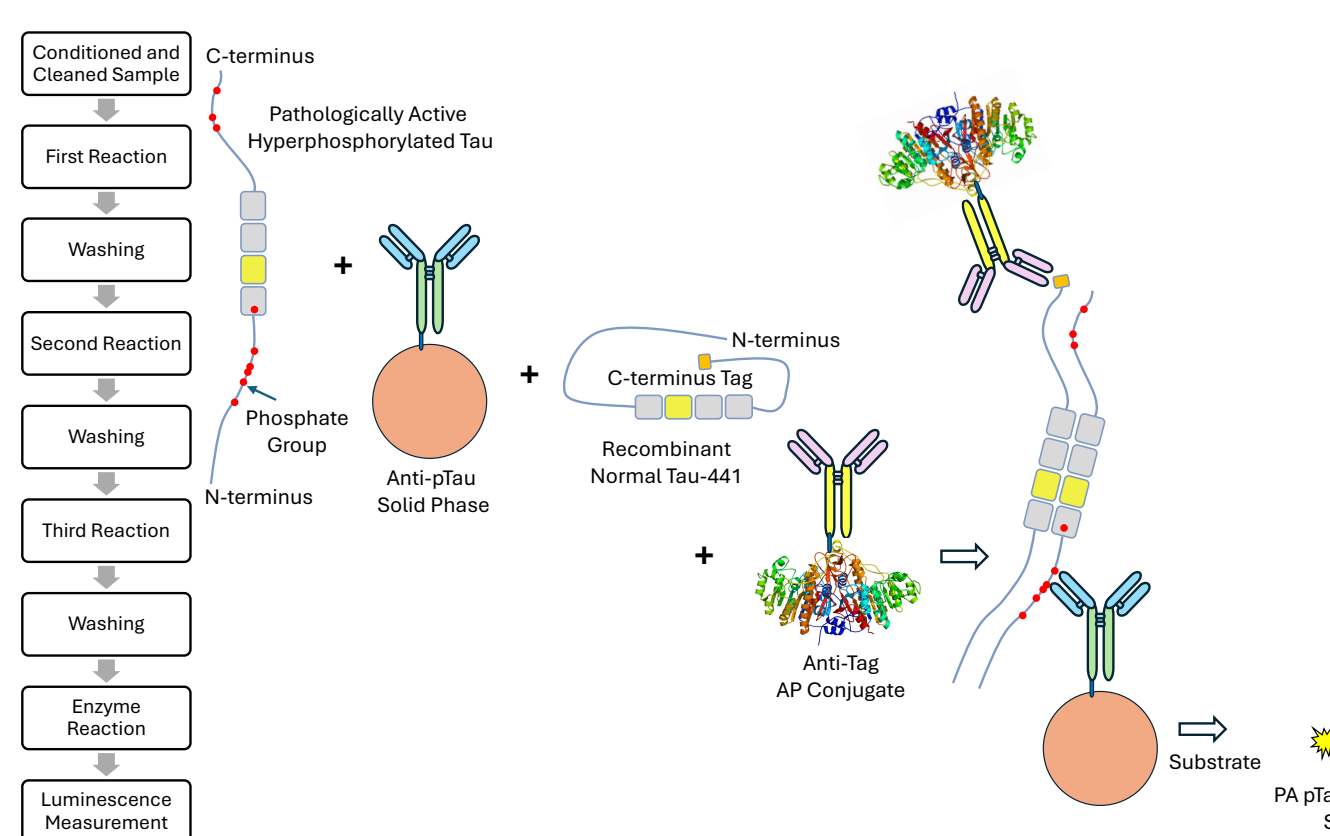
PARTICIPANTS

145 participants aged over 45 years old, from UCLouvain [¹⁸F]MK6240 study cohort in Brussels (UCL-2016-121), recruited between June 2019 and April 2025

PROCEDURE

Participants underwent :

- Standard cognitive assessment** evaluating memory, executive, language, visuo-spatial domains
→ Clinically unimpaired (CU): all cognitive composite scores > -1.5
→ Clinically impaired (CI): at least one cognitive composite scores ≤ -1.5
- 3T-MRI**
- [¹⁸F]MK6240 tau-PET**
→ Visual Braak-like staging : Tau-PET positive (T+) for Braak-like stages ≥ 1
- Amyloid status examination** : lumbar puncture or [¹⁸F]Flutemetamol or PiB amyloid-PET
→ Amyloid positive (A+) for CSF A β ₄₂ ≤ 544 pg/mL or Centiloid (CL) ≥ 20
- A blood test :**
 - Quantification of plasma pTau217 concentration (Lumipulse, Fujirebio)
 - VeraBIND™ Tau plasma assay :
 - Semi-quantitative Score < 1.0 = negative: pTau binding activity is not detected
 - Semi-quantitative Score ≥ 1.0 = positive: pTau binding activity is detected



BLOOD-BASED STRATEGIES

- Two-cut off pTau217 approach:
 - Low threshold : 0.142 pg/mL³
 - High threshold: 0.256 or 0.319 pg/mL³
- Two-test approach: 0.142 pg/mL as the single low threshold for pTau217 + VeraBIND Tau

Conclusion

A two-test strategy combining low threshold plasma pTau217 and a plasma assay targeting tau pathology appears more promising than a two-cutoff pTau217 approach to optimize the plasma detection of AD pathology.

Results

1. Participants' characteristics

	All N=145 Mean (SD)	CU N=79 Mean (SD)	CI N=66 Mean (SD)	p-value
Demographics and Genetics				
Age at tau-PET (years)	70.3 (8.4)	69.3 (7.8)	71.5 (9.0)	0.07
Male (N [%])	65 (44.8%)	31 (39.2%)	34 (51.5%)	0.19
Education (years)	16.3 (3.5)	16.9 (2.9)	15.5 (4.0)	0.02
APOE ε4 carriers (N [%])	78 (53.8%)	38 (48.1%)	40 (60.1%)	0.18
Aβ status and Tau-PET imaging				
A β positivity (A+; N [%])	73 (50.3%)	21 (26.6%)	52 (78.8%)	<0.001
Tau-PET positivity (T+; N [%])	69 (47.6%)	17 (21.5%)	52 (78.8%)	<0.001
AT classification				
A-T- (N [%])	63 (43.4%)	54 (68.3%)	9 (13.6%)	<0.001
A-T+ (N [%])	9 (6.2%)	4 (5.1%)	5 (7.6%)	0.77
A+T- (N [%])	13 (9.0%)	8 (10.1%)	5 (7.6%)	0.77
A+T+ (N [%])	60 (41.4%)	13 (16.5%)	47 (71.2%)	<0.001
Cognition				
MMSE (/30)	26.8 (3.6)	28.9 (1.0)	24.3 (4.0)	<0.001
Episodic memory z-score	-1.3 (2.3)	0.2 (0.7)	-3.3 (2.0)	<0.001
Plasma biomarkers				
Plasma pTau217 (pg/mL)	0.37 (0.41)	0.19 (0.22)	0.58 (0.48)	<0.001
VeraBIND Tau Assay (RLU)	1.00 (0.23)	0.92 (0.14)	1.10 (0.27)	<0.001

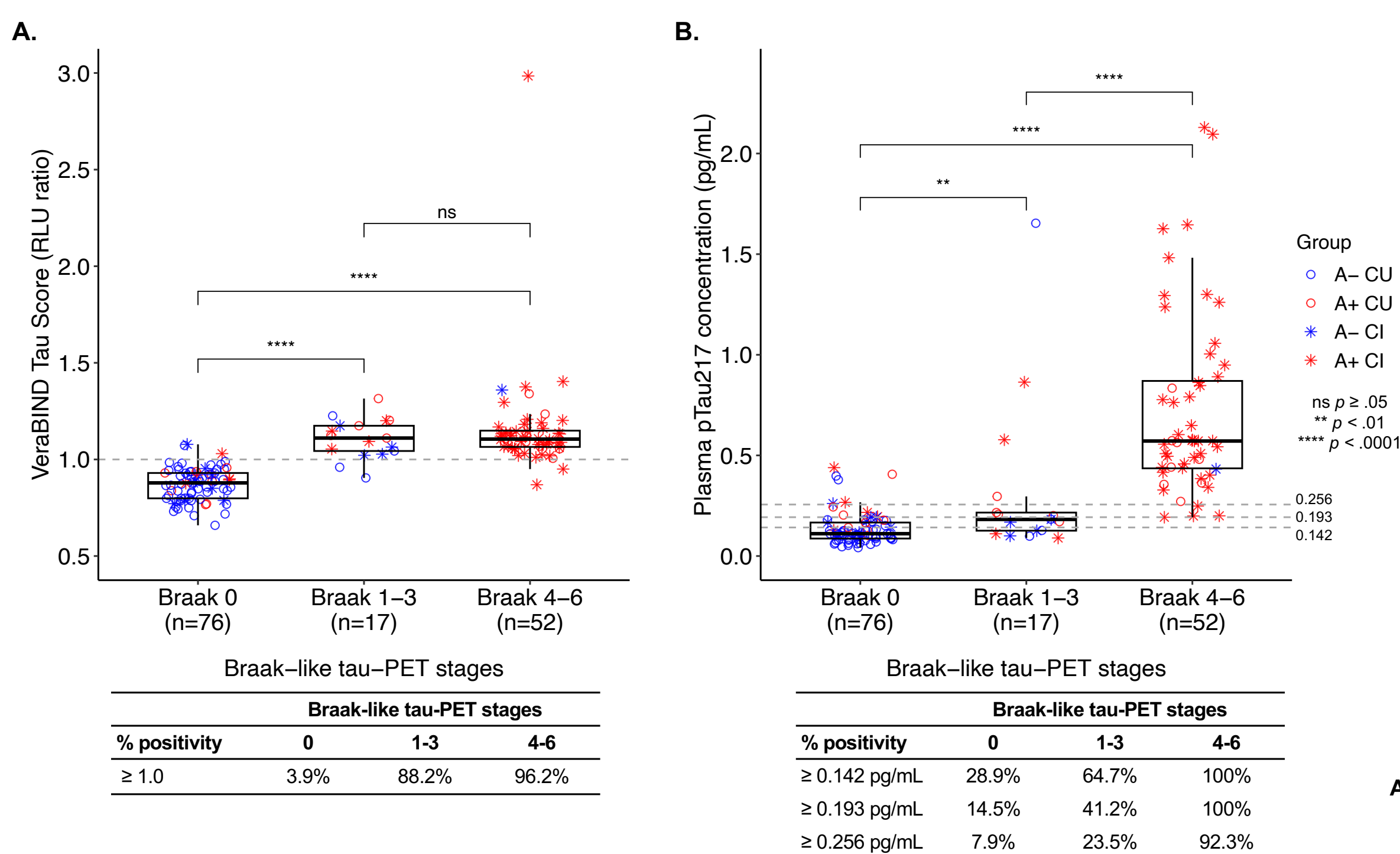
2. VeraBIND Tau outperforms plasma pTau217 to detect Tau-PET positivity, regardless of the threshold used for pTau217

	VeraBIND Tau + for ≥ 1.0		Plasma pTau217 + for ≥ 0.142 pg/mL		Plasma pTau217 + for ≥ 0.193 pg/mL		Plasma pTau217 + for ≥ 0.256 pg/mL	
	Value	95% CI	Value	95% CI	Value	95% CI	Value	95% CI
Entire sample (n=145)								
Sensitivity	94.2%	85.8 – 98.4	91.3%	82.0 – 96.7	85.5%	75.0 – 92.8	75.4%	63.5 – 85.0
Specificity	96.1%	88.9 – 99.2	71.1%	59.5 – 80.9	85.5%	75.6 – 92.6	92.1%	83.6 – 97.1
Accuracy	95.2%	90.3 – 98.0	80.7%	73.3 – 86.8	85.5%	78.7 – 90.8	84.1%	77.2 – 89.7
PPV ^a	95.6%	87.7 – 98.5	74.1%	66.7 – 80.4	84.3%	75.5 – 90.3	89.7%	79.9 – 95.0
NPV ^a	94.8%	87.6 – 97.9	90.0%	80.5 – 95.1	86.7%	78.4 – 92.1	80.5%	73.1 – 86.2
CU individuals (n=79)								
Sensitivity	88.2%	63.6 – 98.5	88.2%	63.6 – 98.5	76.5%	50.1 – 93.2	58.8%	32.9 – 81.6
Specificity	98.4%	91.3 – 100.0	80.7%	68.6 – 89.6	91.9%	82.2 – 97.3	95.2%	86.5 – 99.0
Accuracy	97.4%	91.0 – 99.7	81.4%	71.1 – 89.3	90.4%	81.7 – 95.9	91.5%	83.1 – 96.6
PPV ^b	85.9%	46.3 – 97.7	33.6%	22.8 – 46.4	51.3%	30.4 – 71.8	57.5%	29.5 – 81.4
NPV ^b	98.7%	95.3 – 99.6	98.4%	94.4 – 99.6	97.2%	93.7 – 98.8	91.5%	92.2 – 97.4
CI individuals (n=66)								
Sensitivity	96.2%	86.8 – 99.5	92.3%	81.5 – 97.9	88.5%	76.6 – 95.7	80.8%	67.5 – 90.4
Specificity	85.7%	57.2 – 98.2	28.6%	8.4 – 58.1	57.1%	28.9 – 82.3	78.6%	49.2 – 95.3
Accuracy	92.0%	82.6 – 97.2	66.8%	54.1 – 77.9	75.9%	63.8 – 85.6	79.9%	68.2 – 88.8
PPV ^b	91.0%	73.7 – 97.3	66.0%	58.0 – 73.2	75.6%	62.7 – 85.1	85.0%	67.3 – 94.0
NPV ^b	93.7%	79.0 – 98.3	71.2%	41.4 – 89.7	76.8%	57.8 – 88.8	73.2%	59.4 – 83.5

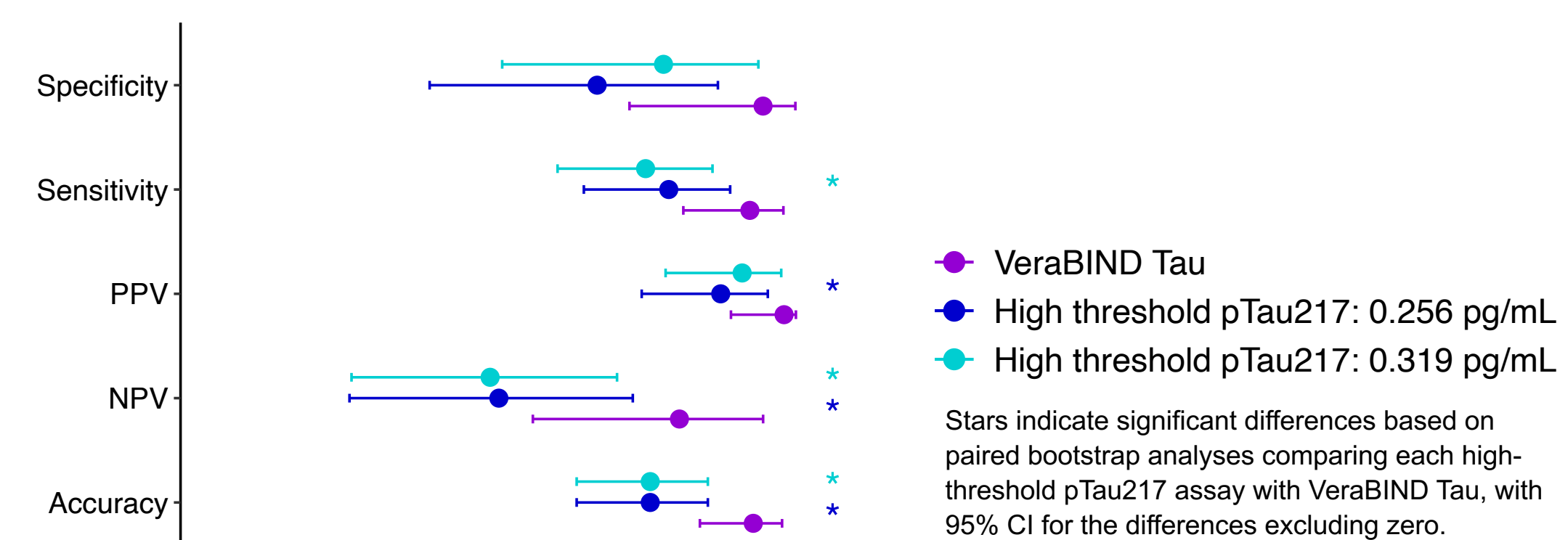
^a Positive Predictive Value (PPV) and Negative Predictive Value (NPV) calculated using the observed prevalence of tau-PET positivity in the entire sample

^b PPV and NPV calculated using the observed prevalence of tau-PET positivity in a large, recently published pooled cohort analysis including 6514 individuals, comprising CU individuals and patients with a clinical diagnosis of MCI, AD dementia or other neurodegenerative disorders (i.e., 60% prevalence in CI individuals, 10% prevalence in CU individuals)⁴

3. VeraBIND Tau outperforms plasma pTau217 to detect low Tau-PET stages



4. VeraBIND Tau outperforms high threshold pTau217 to detect Tau-PET positivity in individuals with plasma pTau217 levels ≥ 0.142 pg/mL



5. The two-test approach identified 100% A+T+ CU and 91.5% A+T+ CI individuals

