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VeraBIND Tau: a novel plasma assay reflecting Tau aggregation in Alzheimer's disease increases over time in individuals with positive Tau-PET signal

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Background

Blood-based biomarkers are critical for clinical trials, not only for confirming disease pathology, but also for screening, trial recruitment, early intervention, and monitoring drug efficacy. The concentration of tau hyperphosphorylated at specific epitopes (e.g., pTau217) is frequently elevated in the context of amyloid-β pathology (A+) but is poor at detecting early tau aggregation, especially in preclinical, cognitively unimpaired individuals.[1] Plasma assays associated with tau aggregation (T+), as observed using tau PET imaging, are still in development. Here, we present results of the innovative VeraBIND Tau™ assay which isolates pathologically active hyperphosphorylated tau (HP-tau) from plasma and tests its functional ability to aggregate with recombinant normal tau (nTau), moving beyond concentration-based detection to a mechanistically relevant "activity" biomarker. This detection of AD tau pathology in plasma, including the prion-like seeding of nTau to HP-tau, is a key clinical distinction of the VeraBIND Tau assay as compared to other blood-based biomarker tests which primarily quantify specific forms of phosphorylated tau.[2]

Methods

Two hundred sixty-eight EDTA plasma samples were collected from 145 participants in an ongoing prospective study at UCLouvain, Belgium over an average 1.7±0.9 years [min: 0.4, max: 3.9]. A+ status was determined using either CSF (Aβ42≤544 pg/mL) or amyloid-PET (Centiloid ≥ 20). F18MK6240 tau-PET status was determined visually as negative (Braak-like stage 0) or positive (Braak-like stages 1-6).[3] Plasma pTau217 was quantified using Lumipulse G pTau 217 Plasma (Fujirebio).[4] Pathologically active HP-tau was detected by the semi-quantitative VeraBIND Tau assay (Veravas). At the time of tau-PET, 79 participants were clinically normal (CU, 21A+) and 66 clinically impaired (MCI/AD, 52A+).

The VeraBIND Tau plasma assay is a semi-quantitative chemiluminescence test to detect pathologically active hyperphosphorylated tau (HP-tau) binding to normal tau (nTau) as a biomarker for AD tau pathology. The first step of the assay pre-analytically conditions samples to irreversibly inactivate endogenous phosphatases and cleans

samples to remove heterophilic and autoantibody interference. The second step of the assay involves the selective capture and purification of HP-tau with capture beads coated with anti-pTau217 and antipTau231 monoclonal antibodies (ADx Neurosciences, Gent, Belgium). In the third step, the capture beads are washed into a nTau binding buffer to facilitate the ionic and hydrophobic binding of recombinant nTau (with a recombinant tag) to HP-tau, akin to HP-tau-mediated nTau aggregation observed in the brain of AD patients. Lastly, after an overnight incubation, non-bound nTau is washed away, an anti-recombinant tag monoclonal antibody conjugated to Alkaline Phosphatase is added, non-bound conjugate is washed away, and a substrate is added to generate a relative chemiluminescence signal (RLU) that is directly proportional to the amount of recombinant nTau bound by the HP-tau. The test result Score for each sample is calculated by dividing the patient sample test result RLU by the assay cutoff RLU. A Score <1.000 is a negative test result and a Score >=1.000 is a positive test result – a single cut-off.

Patient Cohort and Results

Mean value *(SD)*	All N=145	CU N=79	CI N=66	Two-tail p-value
Age at Tau-PET (years)	70.5 *(8.5)*	69.4 *(7.6)*	71.9 *(9.3)*	0.07
Follow-up duration (years)	1.72 *(0.94)*	1.85 *(0.93)*	1.47 *(0.93)*	0.08
Male (%)	44.8%	39.2%	51.5%	0.14
Education (years)	16.3 *(3.5)*	16.9 *(2.9)*	15.5 *(4.0)*	**0.02**
E4 carriers (%)	54.6%	48.1%	62.5%	0.09
% High-Aβ individuals	50.3%	26.6%	78.8%	**<0.001**
MMSE (/30)	26.8 *(3.6)*	28.9 *(1.0)*	24.3 *(4.0)*	**<0.001**
Episodic memory z-score	-1.29 *(2.26)*	0.22 *(0.72)*	-3.29 *(2.02)*	**<0.001**
Entorhinal ^{F18}MK6240 Tau-SUVr	1.56 *(0.92)*	1.04 *(0.42)*	2.24 *(0.96)*	**<0.001**
Plasma $pTau_{217}$ (pg/ml)	0.37 *(0.41)*	0.19 *(0.22)*	0.59 *(0.48)*	**<0.001**
VeraBIND Tau Assay Score	1.02 *(0.21)*	0.94 *(0.17)*	1.11 *(0.21)*	**<0.001**

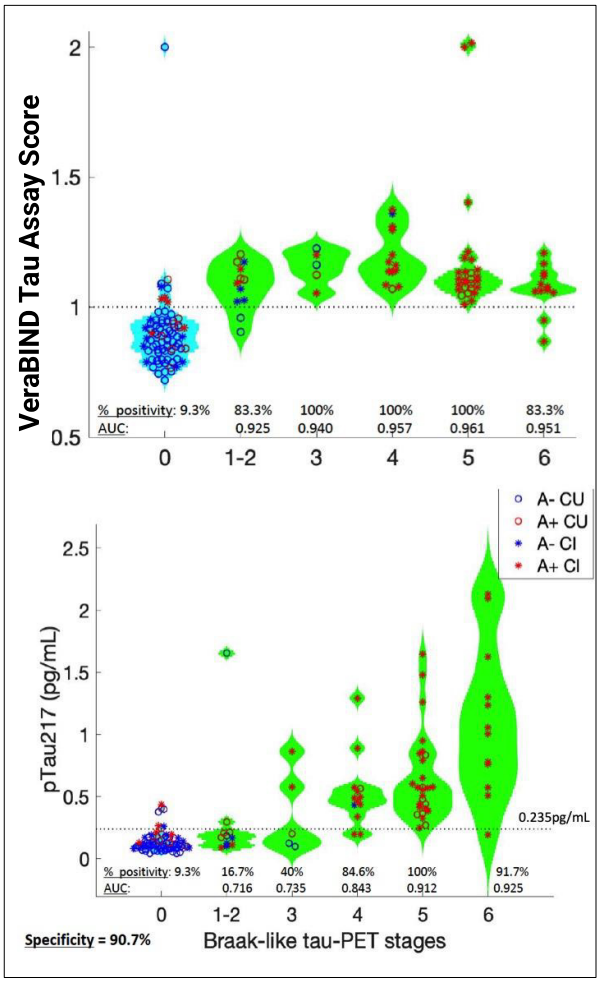
	VeraBIND Tau Score (≥ 1.0 for +)		Plasma pTau217 (≥ 0.185 pg/ml for +)		Plasma pTau217 (≥ 0.325 pg/ml for +)	
	Value	95% CI	Value	95% CI	Value	95% CI
Entire sample (n=145)						
Sensitivity	0.94	0.86 – 0.98	0.87	0.76 – 0.94	0.74	0.61 – 0.83
Specificity	0.96	0.89 – 0.99	0.84	0.74 – 0.91	0.95	0.87 – 0.99
Accuracy	0.95	0.90 – 0.98	0.85	0.78 – 0.91	0.85	0.78 – 0.90
Cognitively Unimpaired (n=79)						
Sensitivity	0.88	0.64 – 0.99	0.76	0.50 – 0.93	0.47	0.23 – 0.72
Specificity	0.98	0.91 – 1.00	0.92	0.82 – 0.97	0.95	0.86 – 0.99
Accuracy	0.96	0.89 – 0.99	0.88	0.79 – 0.95	0.85	0.75 – 0.92
PPV[A]	0.77	0.52 – 0.96	0.48	0.30 – 0.70	0.48	0.24 – 0.76
NPV[A]	0.98	0.96 – 0.99	0.97	0.94 – 0.99	0.94	0.92 – 0.97
Cognitively Impaired (n=66)						
Sensitivity	0.96	0.87 – 1.00	0.90	0.79 – 0.97	0.82	0.69 – 0.92
Specificity	0.86*	0.57 – 0.98	0.50	0.23 – 0.77	0.93	0.66 – 1.00
Accuracy	0.94	0.85 – 0.98	0.82	0.70 – 0.90	0.85	0.74 – 0.92
PPV[B]	0.80	0.64 – 0.94	0.58	0.47 – 0.72	0.84	0.65 – 0.97
NPV[B]	0.95	0.89 – 0.99	0.85	0.71 – 0.94	0.86	0.78 – 0.92

Note. [A] PPV and NPV were calculated using 10% prevalence of tau-PET positivity in CU individuals, [B] PPV and NPV were calculated using 43% prevalence of tau-PET positivity in CI individuals.[5] *This specificity is explained by two T- patients, including one A- patient with a cortico-basal degeneration diagnosis, and one A+ patient with Mild Cognitive Impairment (MCI) likely due to AD.

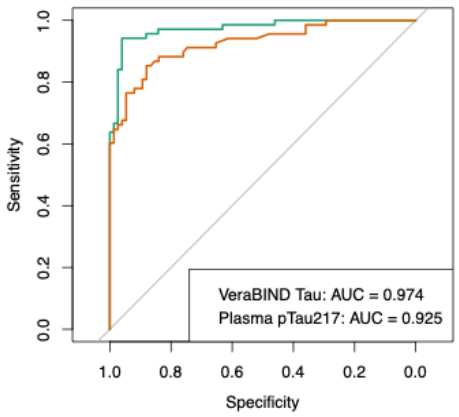
Braak-Like Stage Analysis

Using MK6240 tau-PET as ground truth for AD tau pathology in these 145 participants, VeraBIND Tau detected 58 of 60 A+T+ participants (**sensitivity=96%**) and excluded tauopathy in 59 of 62 A-T- participants (**specificity=95%**). Sensitivity was equivalent in

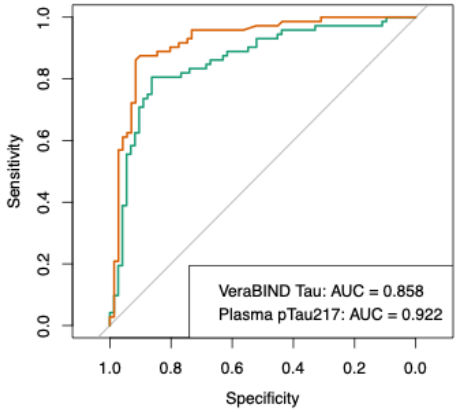
low (**Braak-like 1-3, 93%**) and high (**Braak-like 4-6, 95%**) tau-PET stages. In contrast, pTau217 sensitivity was lower in Braak-like 1-3 (48%) vs. Braak-like 4-6 (93%) tau-PET stages. VeraBIND Tau was more often positive in A-T+ (7/9) than in A+T- (4/13) individuals, indicating higher association with tau aggregates than with amyloid plaques. In contrast, pTau217 was more often positive in A+T- (7/13) than in A-T+ (2/9) individuals.



Prediction of tau-PET status



Prediction of amyloid-PET status

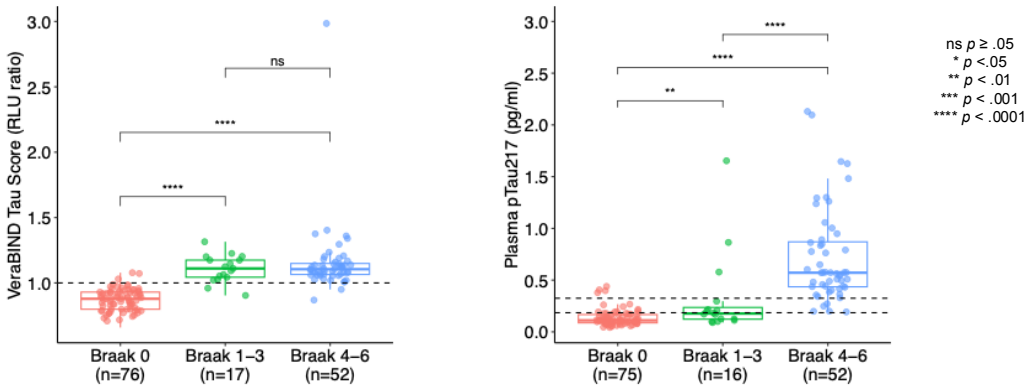


Box-Plot Analysis

Box-plot results demonstrate VeraBIND Tau is highly sensitive to early tau-PET positivity (**Braak-like stages 1-3; p<0.0001**) as well as late-stage tau-PET positivity (**Braak-like stages 4-6; p<0.0001**) with good signal-to-noise in test result Scores compared against tau-PET negative patients Braak-like stage 0. In comparison, while pTau217 does not demonstrate good separation in test results in Braak-like stages 1-3 as compared against Braak-like stage 0 (p=0.026), pTau217 does demonstrate very

good signal-to-noise and separation in test results in late-stage tau-PET Braak-like stages 4-6 (p<0.0001).

Simple group comparisons



With adjustment for age and sex

Sensitivity Comparison	VeraBIND Tau	pTau217
Braak-like 0 vs. Braak-like 1-3	**p < 0.0001**	p = 0.026
Braak-like 0 vs. Braak-like 4-6	**p < 0.0001**	**p < 0.0001**
Braak-like 1-3 vs. Braak-like 4-6	p = 0.233	**p < 0.0001**

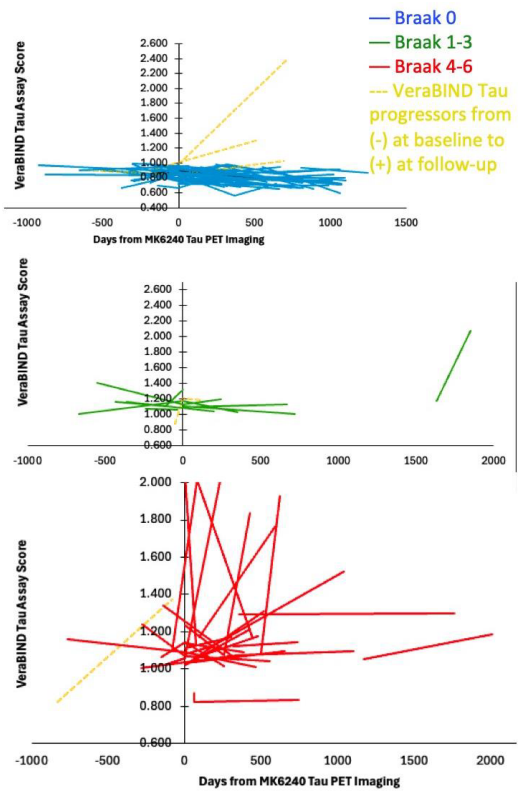
Cognitive Status Analysis

While VeraBIND Tau demonstrated **96.8% accuracy at detecting tau-PET positivity (T+) in cognitively unimpaired** (CU) patients and **97.2% accuracy at ruling-out tau-PET positivity (T-) in CU** patients, pTau217 demonstrated 88.9% accuracy at detecting tau-PET positivity (T+) in CU patients and 93.5% accuracy at ruling-out tau-PET positivity (T-) in CU patients using a two-cutoff approach with 12.7% (26/125) indeterminate results.

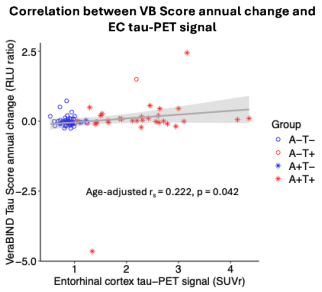
VeraBIND Tau vs MK6240 Tau PET						Lumipulse pTau217 (<=0.185, 1.86-0.324, >=0.325) vs MK6240 Tau PET					
Congtitive Status	MK6240 Tau PET	N	VB Tau+	VB Tau-	VB %Accuracy	Congtitive Status	MK6240 Tau PET	N	pTau217+	pTau217-	pTau217 %Accuracy
CU	T+	31	30	1	96.8%	CU	T+	18	16	2	88.9%
MCI	T+	31	27	4	87.1%	MCI	T+	29	25	4	86.2%
DEM	T+	19	19	0	100.0%	DEM	T+	19	17	2	89.5%
CU	T-	109	3	106	97.2%	CU	T-	107	7	100	93.5%
MCI	T-	17	0	17	100.0%	MCI	T-	6	0	6	100.0%
DEM	T-	-	-	-	-	DEM	T-	-	-	-	-

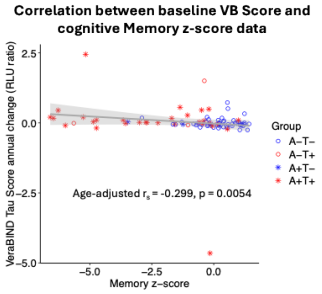
Longitudinal Analysis

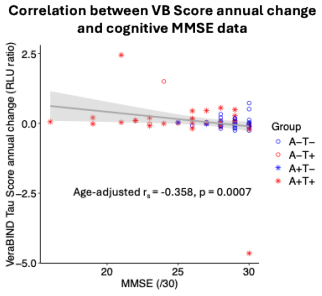
In longitudinal analyses of 207 EDTA plasma samples collected from 88 of these 145 participants at 2 to 5 different collection time points relative to their F18MK6240 tau-PET imaging dates (0.6±1.3 years; min: -2.5, max: 5.5), VeraBIND Tau demonstrated **93.8% sensitivity** (95CI, 85.6-97.7), **97.6% specificity** (95CI 92.7-99.4), and an **overall accuracy of 96.1% (ROC-AUC 0.956)** as compared against tau PET with accuracies of 97.2% (A-T-: N=106), 100% (AT+: N=6), 100% (A+T-: N=20), and 93.3% (A+T+: N=75) based on both amyloidosis and tau pathology status. The **annual change in VeraBIND Tau was associated with Braak stages** (age-adjusted Spearman's rho=0.32, p=0.002), **entorhinal tau-PET SUVr** (rho=0.222, **p=0.042**), **lower episodic memory zscores** (rho=-0.229, **p=0.0054**), and **lower MMSE scores** (rho=-0.358, **p=0.0007**), indicating that VeraBIND Tau measures (VeraBIND Tau Scores) increase with disease progression. Five individuals had initial negative VeraBIND Tau test while it became positive during follow-up. Of note, two had positive tau-PET with a retrospective negative sample; and three had negative tau-PET with a prospective positive sample. All positive VeraBIND tests retested positive after follow-up.



All VeraBIND Tau (+) at baseline remained (+) at follow-up







Conclusions

Whereas pTau217 is more closely associated with amyloid-β pathology (A+) than tau-PET positivity (T+), VeraBIND Tau is highly sensitive to early tau-PET positivity, indicating active tau aggregation, with or without amyloidosis. VeraBIND Tau is the first plasma biomarker to measure tau aggregation activity, not just a measure of the concentration of a single pTau species. It provides superior sensitivity for early tau pathology (Braak-like stages 1-3), opening the possibility of screening CU older adults. The mismatch between pTau217 and VeraBIND Tau results provides a plasma indication of discordant A/T PET status that would provide useful information in clinical trial recruitment.

The longitudinal analyses indicate >96% test-retest reliability and high correlation with disease progression, highlighting the potential of VeraBIND Tau for monitoring disease progression and drug efficacy.[6]

VeraBIND Tau addresses an unmet biomarker need by detecting tau aggregation activity early and reliably which is ideal for patient screening for clinical trials, and it is complementary to pTau217 as together they provide plasma-based A/T status staging enabling scalable early screening and stratification. VeraBIND Tau also offers the promise to monitor disease progression and therapeutic response since an increase in test result Scores strongly correlate with cognitive decline. While the strengths of this study include a longitudinal cohort, comprehensive comparison with second generation AD tau PET MK6240 tracer, high sensitivity and specificity, robust test-retest, and mechanistic innovation, the limitations are that the study size was small (N=145) and necessitates the testing of a larger sample size with a more diverse, multi-centered patient population.

References

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