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Clinical performance and robustness of blood-based biomarkers for early detection of amyloid pathology associated with Alzheimer's disease

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Introduction

- Alzheimer's disease (AD) is characterized by the accumulation of amyloid-β (Aβ) plaques and neurofibrillary tangles within the brain.
- Amyloid positron emission tomography (PET) and cerebrospinal fluid (CSF) biomarker testing are routinely used to identify amyloid pathology and aid in the diagnosis of AD; however, these tests can be invasive, time-consuming, and expensive.
- An accurate and robust blood-based biomarker (BBBM) test is poised to address the increased demand for AD diagnosis.[1]
- There is an unmet need for BBBM tests to rule out amyloid pathology in people presenting with cognitive complaints or impairment.
  - Collection of plasma via venipuncture is minimally invasive, cost-effective, and widely accessible.
  - High clinical robustness means that the clinical performance of a given BBBM remains unaffected by small variations in the test conditions due to e.g., biological, pre-analytical, and analytical variability.
  - Robust BBBMs will enable timely and accurate triage of patients with low likelihood of amyloid pathology prior to referral for confirmatory PET or CSF biomarker testing.[2,3]
- Further evidence is required on the clinical performance and robustness of single BBBMs and combined BBBM models to aid accurate identification of patients with suspected amyloid pathology for enrollment in clinical trials and in routine practice.

Objectives

- **To evaluate the clinical performance and robustness of AD BBBMs for the detection of symptomatic patients with low likelihood of amyloid pathology.**
- **To determine suitability of global implementation of AD BBBMs as an in vitro diagnostics (IVD) solution for use in clinical routine.**

Methods

- Plasma samples were retrospectively analyzed at two sites using the fully automated Elecsys® prototype immunoassays for Aβ1–42 (Aβ42), Aβ1–40 (Aβ40), apolipoprotein E4 (ApoE4), phosphorylated-tau 181 (pTau181), glial fibrillary acidic protein (GFAP), and neurofilament light chain (NFL) on the cobas e 601 and cobas e 411 analyzers; (all Roche Diagnostics International Ltd, Rotkreuz, Switzerland).
- Samples were evaluated from three clinically distinct cohorts to resemble the intended use population:
  - **AIBL**: patients with mild cognitive impairment (MCI) and subjective cognitive decline (SCD).
  - **BioFINDER (NCT01208675)**: cognitively normal individuals (CN) and patients with MCI and SCD.
  - **CREAD (NCT02670083)**: patients with late mild cognitive impairment (LMCI).
- Amyloid PET visual read was used as the reference standard for defining amyloid status.
- Clinical performance of single BBBMs and combined BBBM models was evaluated using receiver operator characteristic-area under the curve (ROC–AUC) analysis.
  - The Aβ42/Aβ40 and pTau181/Aβ42 ratios were considered single BBBMs, and combined BBBM models were constructed using logistic regression.
  - ROC analysis was performed using R version 3.4.0, package pROC (The R Foundation, Indianapolis, IN, USA) and 95% confidence intervals (CIs) of AUC values calculated using the DeLong method.[4]
  - Negative percent agreement (NPA), negative and positive predictive values (NPV and PPV; adjusted for 30% disease prevalence), and screen-out rates were compared at an 85% positive percent agreement (PPA) cut-off.
- Robustness was defined as the change in clinical performance (Δ) with ±10% bias and ±10% coefficient of variation (CV) calculated at a cut-off of 85% PPA.

Results

Patient characteristics

- In total, 1,406 plasma samples were analyzed from the AIBL, BioFINDER, and CREAD cohorts. Selected baseline characteristics for all three cohorts are summarized in **Table 1**.

Table 1. Selected baseline patient characteristics from the AIBL, BioFINDER, and CREAD cohorts reflecting the intended use population of the BBBMs

	AIBL MCI + SCD	BioFINDER CN + MCI + SCD	CREAD LMCI
Total, N	543	425	438
Median age, years (min–max)	70.0 (59.0–90.0)	72.0 (59.0–85.0)	72.0 (50.0–85.0)
Male sex, n (%)	241 (44.38)	221 (52.0)	173 (39.5)
Negative amyloid PET status, n (%)	424 (78.08)	295 (69.41)	227 (51.83)

Max, maximum; Min, minimum.

Table 2. Summary of clinical performance and robustness of single BBBMs and combined BBBM models across the AIBL, BioFINDER, and CREAD cohorts

Single BBBM/ combined BBBM model	AUC, AIBL [BioFINDER; CREAD]	PPA (Δ), AIBL [BioFINDER; CREAD]	NPA (Δ), AIBL [BioFINDER; CREAD]	PPV, AIBL [BioFINDER; CREAD]	1-NPV, AIBL [BioFINDER; CREAD]	Screen-out rate (%), AIBL [BioFINDER; CREAD]
pTau181 + Aβ42	93.4 [87.9; 85.6]	85.9 (-40.4) [85.3 (-15.7); 85.6 (-25.0)]	89.5 (-11.9) [76.6 (-21.3); 75.7 (-8.74)]	77.8 [60.9; 60.2]	6.34 [7.61; 7.53]	66.9 [58.0; 57.3]
pTau181/Aβ42	93.2 [87.9; 85.5]	85.9 (-33.3) [85.3 (-15.7); 85.6 (-19.7)]	89.5 (-12.2) [76.6 (-21.0); 77.7 (-9.7)]	77.8 [60.9; 62.2]	6.34 [7.61; 7.36]	66.9 [58.0; 58.7]
pTau181 + ApoE4	91.8 [87.5; 83.7]	85.9 (-14.1) [85.3 (-3.92); 86.4 (-5.30)]	87.0 (-5.12) [73.6 (-5.02); 71.8 (-4.85)]	73.9 [58.1; 56.8]	6.51 [7.88; 7.52]	65.2 [56.0; 54.4]
pTau181 + Aβ40	90.2 [85.2; 84.8]	85.9 (-30.3) [85.3 (-14.7); 85.6 (-24.2)]	83.7 (-12.9) [69.0 (-25.1); 76.7 (-16.5)]	69.3 [54.1; 61.2]	6.75 [8.37; 7.44]	62.9 [52.7; 58.0]
pTau181 + GFAP	89.3 [83.6; 81.6]	85.9 (-9.09) [85.3 (-9.80); 85.6 (-11.4)]	78.6 (-7.14) [66.0 (-12.3); 68.9 (-7.77)]	63.2 [51.8; 54.1]	7.16 [8.72; 8.21]	59.2 [50.6; 52.6]
pTau181	89.3 [83.4; 81.6]	85.9 (-8.08) [85.3 (-8.82); 86.4 (-9.90)]	76.6 (-5.42) [64.4 (-13.4); 67.0 (-7.80)]	61.1 [50.7; 52.9]	7.33 [8.91; 8.02]	57.9 [49.5; 51.0]
Aβ42/Aβ40	85.8 [78.9; 78.6]	85.9 (-66.7) [85.6 (-77.0); 85.1 (-77.4)]	69.2 (-48.8) [61.2 (-56.7); 61.7 (-48.9)]	54.4 [48.6; 48.7]	8.06 [9.18; 9.40]	52.6 [47.1; 47.6]
GFAP	80.2 [76.1; 73.5]	85.9 (-4.04) [85.6 (-5.77); 85.1 (-7.20)]	54.4 (-8.84) [48.7 (-8.82); 49.6 (-6.00)]	44.7 [41.7; 42.0]	10.0 [11.3; 11.4]	42.3 [38.4; 39.2]
ApoE4*	73.5 [70.3; 69.0]	73.7 (-1.01) [70.2 (0); 74.7 (-0.59)]	73.4 (0) [73.6 (0); 66.7 (-0.76)]	54.3 [53.2; 49.0]	13.3 [14.8; 14.0]	59.2 [60.4; 54.3]
NFL	77.5 [63.7; 60.8]	85.9 (-8.08) [85.6 (-2.90); 85.8 (-7.40)]	51.9 (-11.3) [25.6 (2.50); 35.9 (-8.10)]	43.3 [33.0; 19.1]	10.5 [19.4; 6.53]	40.6 [22.3; 32.6]

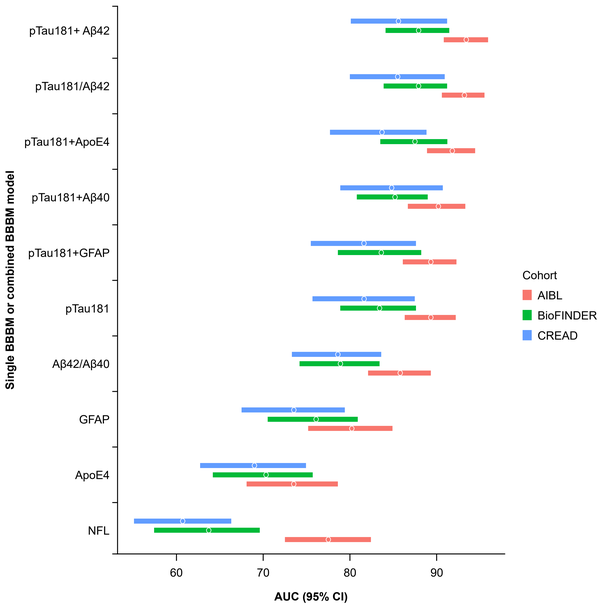
*Cut-off for ApoE4 was determined using Youden's index; cut-off was set at 85% PPA for all other BBBMs. The CREAD cohort included patients with amyloid screen failure.

Clinical performance

- Across cohorts, the best performing single BBBM was pTau181 (AUC: 81.6–89.3; **Table 2**).
- Combined BBBM models provided a small increase in clinical performance versus single BBBMs (**Figure 1**).
- The best performing combined BBBM models across cohorts were pTau181+Aβ42 (AUC: 85.6–93.4), pTau181+ApoE4 (AUC: 83.7–91.8), and pTau181+Aβ40 (AUC: 84.8–90.2; **Table 2**).
  - NPVs and PPVs were comparable for these combined BBBM models, providing high NPVs (>90%) and screen-out rates (>50%) across cohorts (**Table 2**).

Key message: pTau181 and combined BBBM models containing pTau181 had the highest clinical performance across cohorts (**Table 2; Figure 1**).

Figure 1. Clinical performance of single BBBMs and combined BBBM models across the AIBL, BioFINDER, and CREAD cohorts

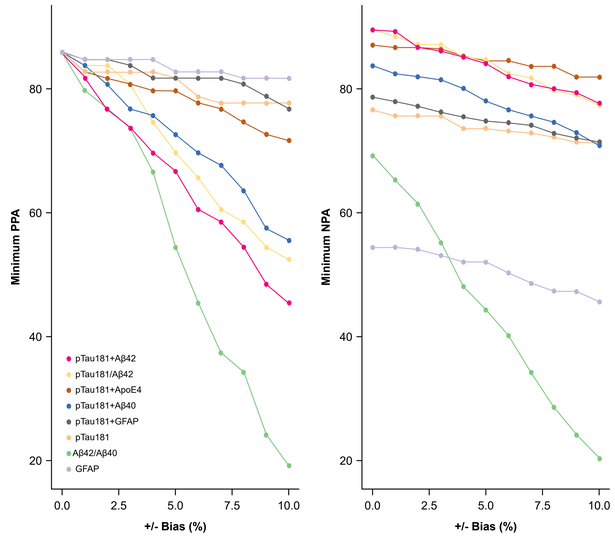


Clinical robustness

- Various single BBBMs and combined BBBM models had comparable clinical performance and were identified as possible biomarker candidates for further investigations for their clinical robustness.
- Across cohorts, the Aβ42/Aβ40 ratio was the least robust single BBBM measured with the highest PPAΔ and NPAΔ at a cut-off of 85% PPA (PPAΔ: -77.4, -66.7; NPAΔ: -56.7, -48.8; **Table 2**) compared with other single BBBMs.
  - Concurrently, the Aβ42/Aβ40 ratio and combined BBBM models containing either Aβ42 or Aβ40 had poor robustness when ±10% bias was introduced (**Figure 2**).
- pTau181 (PPAΔ: -9.90, -8.08; NPAΔ: -13.4, -5.42; **Table 2**) and GFAP (PPAΔ: -7.20, -4.04; NPAΔ: -8.84, -6.00; **Table 2**) and combinations containing pTau181, GFAP, or ApoE4 had the highest robustness (**Table 2** and **Figure 2**).

Key message: Aβ42/Aβ40 ratio and combined BBBM models containing either Aβ42 or Aβ40 had poor clinical robustness (**Figure 2**).

Figure 2. Change in clinical performance of top-performing single BBBMs and combined BBBM models when ±10% bias is introduced



The values presented are from the AIBL cohort only. For clarity, only bias is shown here as bias is the main contributing factor to clinical robustness.

Conclusions

- **Overall, pTau181+ApoE4 was the best performing combined BBBM model for detecting patients with low likelihood of amyloid pathology across cohorts.**
- **These findings support the suitability of these BBBMs to inform diagnostic assessments for patients with low likelihood of AD.**
- **Future large prospective studies will validate these results to confirm whether pTau181+ApoE4 is the most suitable IVD solution for a BBBM test for amyloid pathology.**

References

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Disclosures

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