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# Validity and Performance of Blood Biomarkers for Alzheimer Disease to Predict Dementia Risk in a Large Clinic-Based Cohort

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## Abstract

### Background and Objective

Blood biomarkers for Alzheimer disease (AD) have consistently proven to be associated with CSF or PET biomarkers and effectively discriminate AD from other neurodegenerative diseases. Our aim was to test their utility in clinical practice, from a multicentric unselected prospective cohort where patients presented with a large spectrum of cognitive deficits or complaints.

### Methods

The MEMENTO cohort enrolled 2,323 outpatients with subjective cognitive complaint (SCC) or mild cognitive impairment (MCI) consulting in 26 French memory clinics. Participants had neuropsychological assessments, MRI, and blood sampling at baseline. CSF sampling and amyloid PET were optional. Baseline blood A $\beta$ 42/40 ratio, total tau, p181-tau, and neurofilament light chain (NfL) were measured using a Simoa HD-X analyzer. An expert committee validated incident dementia cases during a 5-year follow-up period.

### Results

Overall, 2,277 individuals had at least 1 baseline blood biomarker available (n = 357 for CSF subsample, n = 649 for PET subsample), among whom 257 were diagnosed with clinical AD/mixed dementia during follow-up. All blood biomarkers but total tau were mildly correlated with their equivalence in the CSF (r = 0.33 to 0.46, p < 0.0001) and were associated with amyloid-PET status (p < 0.0001). Blood p181-tau was the best blood biomarker to identify amyloid-PET positivity (area under the curve = 0.74 [95% CI = 0.69; 0.79]). Higher blood and CSF p181-tau and NfL concentrations were associated with accelerated time to AD dementia onset with similar incidence rates, whereas blood A $\beta$ 42/40 was less

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## Glossary

**A $\beta$**  =  $\beta$ -amyloid peptide; **AD** = Alzheimer disease; **AUC** = area under the curve; **ApoE** = apolipoprotein E; **CDR** = Clinical Dementia Rating; **eGFR** = estimated glomerular filtration rate; **MCI** = mild cognitive impairment; **NfL** = neurofilament light chain; **ROC** = receiver operating characteristic; **SCC** = subjective cognitive complaint; **SUVr** = standard uptake value ratio; **TMT** = Trail Making Test.

efficient than CSF A $\beta$ 42/40. Blood p181-tau alone was the best blood predictor of 5-year AD/mixed dementia risk (c-index = 0.73 [95% CI = 0.69; 0.77]); its accuracy was higher in patients with clinical dementia rating (CDR) = 0 (c-index = 0.83 [95% CI = 0.69; 0.97]) than in patients with CDR = 0.5 (c-index = 0.70 [95% CI = 0.66; 0.74]). A “clinical” reference model (combining demographics and neuropsychological assessment) predicted AD/mixed dementia risk with a c-index = 0.88 [95% CI = 0.86–0.91] and performance increased to 0.90 [95% CI = 0.88; 0.92] when adding blood p181-tau + A $\beta$ 42/40. A “research” reference model (clinical model + apolipoprotein E genotype and AD signature on MRI) had a c-index = 0.91 [95% CI = 0.89–0.93] increasing to 0.92 [95% CI = 0.90; 0.93] when adding blood p181-tau + A $\beta$ 42/40. Chronic kidney disease and vascular comorbidities did not affect predictive performances.

## Discussion

In a clinic-based cohort of patients with SCC or MCI, blood biomarkers may be good hallmarks of underlying pathology but add little to 5-year dementia risk prediction models including traditional predictors.

During the past 2 decades, the possibility of highlighting the neuropathologic features of Alzheimer disease (AD) during a person’s lifetime significantly affected clinical practice and dementia research. The emergence of AD biomarkers has allowed clinicians and researchers to go beyond “probable” or “possible” diagnoses of AD by identifying people at risk of developing AD dementia with the concepts of “prodromal AD” and “preclinical AD.”<sup>1–3</sup> These biomarkers have also been used to stratify patients for enrollment in clinical trials based on both neuropsychological and neuropathologic profiles. Recently, reducing the burden of some of these biomarkers has been recognized by the US Food and Drug Administration as a valid surrogate end point for AD clinical trials, although this decision has been debated.<sup>4</sup>

In vivo AD biomarkers first relied on amyloid-PET imaging and/or the measure of A $\beta$  peptides, tau, and phosphorylated-tau concentrations within the CSF.<sup>5</sup> More recently, tau-PET became available.<sup>6</sup> These techniques showed satisfactory accuracy in identifying AD neuropathologic features (and the topographical progression of lesions in the case of tau-PET). Unfortunately, they are invasive and/or expensive and/or restricted to tertiary centers and can only be proposed to a few participants, mainly in a research context. However, the potential emergence of immunotherapies specifically targeting prodromal AD raises the question of the technical, logistical, and economic capacities to identify in routine care participants with such hallmarks of AD.

In this prospect, blood biomarkers of AD have recently been developed, first using mass spectrometry techniques<sup>7</sup> and then immunoassays.<sup>8</sup> Despite the use of different antibodies and detection techniques, and the targeting of different epitopes on the same peptide, these blood biomarkers were consistently correlated with CSF or PET biomarkers across studies.<sup>8–11</sup> Moreover, blood phosphorylated tau proved to be effective in discriminating AD cases from controls and patients with

other neurodegenerative diseases, compared either with clinical diagnoses or with neuropathologic features as gold standards.<sup>12–18</sup>

In addition, first longitudinal studies showed that these biomarkers could predict AD dementia risk in participants with mild cognitive impairment (MCI) or subjective cognitive complaint (SCC).<sup>14,19</sup> Blood biomarkers were also associated with progressive cognitive decline and gray matter loss, alone or in combination with other factors.<sup>20–22</sup> However, these longitudinal findings were mainly based on BioFINDER (n < 400 SCC/MCI) and ADNI (n < 600 MCI) for the largest cohorts and with many overlaps between research articles. Furthermore, these cohorts had strict inclusion criteria, preventing conclusions about “real-life” patient populations (for instance, ADNI was initially designed as a simulated randomized controlled trial).<sup>23</sup> Thus, to reach clinical practice, these biomarkers still need to be studied and validated in very large multicentric prospective cohorts with heterogeneous and unselected populations, implemented in natural settings. It also requires participants with a lower pretest probability of having AD pathology, reflecting the practice of memory clinics at first visit.<sup>24</sup>

The objectives of our study in the MEMENTO cohort was (1) to compare AD (A $\beta$  peptides, total tau, p181-tau) and neurodegeneration (neurofilament light chain; NfL) blood biomarkers with their equivalence in the CSF and with amyloid-PET status and (2) to assess their performance to predict clinical dementia over 5-year follow-up in a large (n = 2,323) unselected cohort of outpatients, recruited from 26 French memory clinics, with either MCI or SCC at enrollment.

## Methods

### Participants

The MEMENTO cohort enrolled outpatients consulting in 26 French memory clinics.<sup>25,26</sup> The main inclusion criteria in

the MEMENTO cohort were a Clinical Dementia Rating (CDR) scale score  $\leq 0.5$ , a very mild to mild cognitive impairment ( $< 1$  SD below the age, sex, and education-level thresholds in one or more cognitive test(s)), or isolated SCC (for people older than 60 years). Cognitive complaints were assessed using visual analog scales. Exclusion criteria included history of head trauma with persistent neurologic deficits, stroke in the last 3 months or with persistent neurologic deficits, brain tumor, epilepsy, schizophrenia, known mutation in familial AD genes, and illiteracy.

### Standard Protocol Approvals, Registrations, and Patient Consents

All participants provided informed consent. The study protocol was approved by the ethics committee “CPP Sud-Ouest et OutreMer III” and registered at ClinicalTrials.gov (NCT01926249).

### Clinical Follow-up

During a 5-year follow-up period, patients underwent a clinical and neurologic evaluation at least yearly. The Mini-Mental State Examination and the CDR were also systematically performed. At baseline and during annual follow-up visits, Free and Cued Selective Reminding Test, Delayed Matching-to-Sample 48, Letter and 2 minutes semantic fluencies (2 minutes task for letter P and animals), image naming, praxis assessment, and Trail Making Test (TMT) A and B were administered. Training sessions were organized to optimize standardization across centers for quoting of CDR and neuropsychological tests. All incident cases of dementia were reviewed by an expert committee, blinded to genetic and biological biomarkers using the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV criteria). The etiologic diagnosis of dementia was made according to the international criteria (National Institute on Aging - Alzheimer's Association criteria for AD,<sup>2</sup> DLB consortium for dementia with Lewy bodies,<sup>27</sup> and Rascovsky criteria for frontotemporal lobar degeneration<sup>28</sup>).

### MRI, Amyloid-PET Acquisition, and ApoE Genotyping

Participants underwent brain scanning on 1.5 or 3 T MRI machines. The morphological protocol consisted of 1-mm isotropic 3D T1-weighted and 2D T2-weighted FLAIR images, acquired after a standardization of the imaging parameters by a dedicated team of neuroimaging specialists (Centre pour l'Acquisition et le Traitement des Images, Paris, France).<sup>29</sup> All scans were centralized, quality-controlled, and postprocessed to obtain standardized measurements for each participant. Intracranial volumes were extracted with Statistical Parametric Mapping; hippocampal volumes were estimated with the SACHA software and cortical thickness with FreeSurfer 5.3 in each region of interest of the Desikan atlas.<sup>26</sup> The MRI AD signature was calculated based on regionally specific cortical thinning in a list of Desikan's cortical areas (entorhinal, inferior temporal, middle temporal, inferior parietal, fusiform, and precuneus) corresponding to Dickerson's signature of AD.<sup>30</sup>

Some participants were proposed to participate in an amyloid-PET ancillary study at baseline (Insight-PreAD) or during follow-up (AMYGING, NCT02164643, 2 years on average after inclusion in MEMENTO). Radioligands were <sup>18</sup>F-florbetapir (<sup>18</sup>F-AV45) in some centers or <sup>18</sup>F-flutemetamol (Vizamyl) in the others. Amyloid positivity was defined for each radioligand according to a previously described procedure (thresholds: florbetapir  $> 0.88$ , flutemetamol  $> 1.063$ ).<sup>31</sup>

Apolipoprotein E (ApoE) genotype was determined by KBiosciences (UK).<sup>25</sup>

### CSF and Blood Biomarkers Measures

Lumbar puncture was optional and was performed in a subsample of participants, as previously described.<sup>25</sup> We restricted the analysis on CSF markers to participants who had their lumbar puncture within 1 year of blood biomarkers measurements. Amyloid- $\beta$  42 peptide ( $A\beta_{42}$ ),  $A\beta_{40}$ , total tau, and phosphorylated-tau (p181-tau) levels were measured using the standardized commercially available INNOTEST (Fujirebio, Belgium). CSF NfL were measured using single molecular array ultra-sensitive immunoassay method (Simoa) with commercial kits on a Quanterix HD-X analyzer (Quanterix, MA).

Blood samples were collected in each memory clinic participating in MEMENTO. Standard biological measurements (including estimated glomerular filtration rate [eGFR]) were performed at local biochemistry departments. Study-specific blood samples were collected at baseline by venipuncture into gel-separator tubes for serum and EDTA tubes for plasma. They were left at room temperature for 30 minutes to coagulate, before centrifugation at 1,500g for 15 minutes at 4°C. Once separated, small volumes of serum and plasma were aliquoted to avoid thawing cycles (250  $\mu$ L in 2 mL Sarstedt cryotubes) and stored at  $-80^{\circ}\text{C}$ . Consequently, the analyses were performed after only 1 freeze/thaw cycle. Blood biomarkers were measured using Simoa technology with commercial kits on a Quanterix HD-X analyzer: plasma  $A\beta_{42}$ ,  $A\beta_{40}$ , total tau using Neurology 3-Plex A Advantage Kit (item No. 101995), serum p181-tau using p181-tau Advantage V2 Kit (item No. 103714), and serum NfL using NF-light Advantage Kit (item No. 103186). Sensitivity cutoffs (functional lower limit of quantification) were (pg/mL) 0.69 for NfL, 0.33 for p181-tau, 0.25 for total tau, 2.7 for  $A\beta_{40}$ , and 0.56 for  $A\beta_{42}$ . All the datasheets and validation reports containing the technical characteristics of the immunoassays (calibration curves, coefficients of variation, reproducibility precision, etc) are available on the manufacturer's website ([quanterix.com/simooa-assay-kits/](http://quanterix.com/simooa-assay-kits/)). Measures were performed in Bordeaux University Hospital research platform in the centralized biobank (Bordeaux Biothèques Santé, Centre de Ressources Biologiques), blinded of any other data.

### Statistical Analyses

Descriptive data are presented as percentages for qualitative variables and as the median, 1st and 3rd quartiles for quantitative variables. Correlations between CSF and blood biomarkers concentrations were estimated with Spearman rank correlation coefficients. Associations between amyloid-PET

status and blood biomarkers concentrations were tested with nonparametric Wilcoxon rank tests, and the performance of blood biomarkers to discriminate amyloid positivity on PET was determined with receiver operating characteristic (ROC) curve analyses.

We ran survival analysis to predict AD dementia risk and modeled time to dementia for incident cases, time to death, or time to end of follow-up, whichever occurred first. Individuals who developed either clinically defined AD or mixed AD dementia<sup>2</sup> were considered “AD dementia converters.” Participants who did not develop dementia during follow-up or who developed dementia of another etiology were classified as “non-AD dementia converters” and censored at time of dementia diagnosis. Kaplan-Meier survival curves were performed to model tertiles of blood and CSF biomarkers in relation to dementia risk. Tertiles were used because no “pathologic” cutoffs of blood biomarkers are available to date.

For multivariable analysis, we performed Cox proportional hazard models (with continuous measures of blood biomarkers). Blood biomarker concentrations were log-transformed. We defined a “clinical” reference prediction model based on data collected in usual clinical practice: age, sex, educational level, memory (total recalls of the Free and Cued Selective Reminding Test), and executive (TMT-B) performance. We also defined a “research” reference model including less accessible measures on top of the “clinical” prediction model: ApoE genotype and MRI cortical thickness in AD-signature regions. The predictive value of blood biomarkers were modeled alone or in combination with the “clinical” or “research” reference models. To reduce optimism in estimations, we computed 5-fold cross-validation probabilities. Subsequent indicators were based on these cross-validated probabilities. For each model, we calculated a c-index for discrimination capacities (from 0 to 1, the higher the better), a Brier score for prediction errors (the lower the better), and c-index difference between a model of interest and a reference one (0 indicates no difference, positive differences are in favor of the model of interest). Brier scores and c-index difference 95% confidence intervals (95% CI) were estimated using bootstrapping. As sensitivity analyses, we ran the same Cox proportional hazard models on subgroups of patients based on their baseline CDR (0 or 0.5) or based on the nature of MCI (amnesic or nonamnesic). As another sensitivity analysis, we also adjusted the Cox models on comorbidities known to affect blood biomarkers concentrations<sup>32,33</sup>: eGFR and history of vascular event (stroke or myocardial infarction).

Analyses were performed with SAS 9.4, and programs were derived from Nancy Cook and colleagues’ SAS macros ([ncook.bwh.harvard.edu/sas-macros.html](http://ncook.bwh.harvard.edu/sas-macros.html)).

## Data Availability

Anonymized data will be shared by request from any qualified investigator for the sole purpose of replicating procedures and results presented in the article and as long as data transfer is in

agreement with EU legislation on the general data protection regulation.

## Results

### Characteristics of the MEMENTO Cohort and Subsamples

From 2011 to 2014, 2,323 nondemented outpatients from 26 French memory clinics were consecutively enrolled in the MEMENTO study.<sup>25</sup> Among them, 2,277 (98.0%) had at least 1 AD or neurodegeneration blood biomarker measured. Among them, 357 (15.7%) had a lumbar puncture within 1 year of blood sampling. Amyloid-PET was available for 649 individuals (150 [23.1%] were amyloid-positive). The demographic, clinical, neuropsychological, biological, and MRI characteristics at baseline of the main analytical sample and of the CSF subsample are presented in Table 1. Data on sex differences in CSF and blood biomarkers measures are provided in eTable 1 ([links.lww.com/WNL/C445](https://links.lww.com/WNL/C445)).

The follow-up rates for the whole sample were 91.4% at 1 year, 85.3% at 2 years, 78.6% at 3 years, 73.0% at 4 years, and 64.3% at 5 years. Over the 5-year follow-up period, 257 incident cases of clinically defined AD (or mixed) dementia were diagnosed, amounting to an incidence rate of 2.84 per 100 person-years (PY) (95% CI = 2.50; 3.20). In the CSF subsample, the incidence of AD dementia was 4.40 per 100 PY [95% CI = 3.39; 5.62] (n = 64). Characteristics of “AD converters” and “non-converters” are presented in Table 1 for both samples. In the AD “nonconverters” group, 63 patients developed dementia of another etiology in the whole cohort, of whom 13 patients were in the CSF subsample.

### Comparisons of Blood Biomarkers With Amyloid-PET and CSF Biomarkers

Blood A $\beta$ 42/40 ratio and concentrations of p181-tau and NfL were associated with amyloid-PET status (Figure 1A), with the highest effect size for p181-tau: Mean concentration (SD) was 0.88 (0.55) pg/mL in patient with negative amyloid-PET vs 1.44 (0.85) in patients with positive amyloid-PET (+63%, Cohen’s d = 0.82). Mean A $\beta$ 42/40 ratio was 6.12 (2.13) vs 5.13 (1.28) (–16%, d = 0.49), and mean NfL concentration was 19 (8.2) vs 24 (15) pg/mL (+26%, d = 0.48). Total tau concentrations did not differ according to amyloid-PET status.

ROC analyses of blood biomarkers to identify amyloid-PET positivity are shown in Figure 1B. Blood p181-tau was the best discriminator with an area under the curve (AUC) of 0.74 (95% CI = 0.69; 0.79).

CSF and plasma biomarkers were mainly intercorrelated. Except for total tau, blood biomarkers were correlated with their equivalence in the CSF (Table 2).

Tertiles of blood and CSF AD and neurodegeneration biomarkers were modeled in relation to AD dementia risk over

**Table 1** Demographic, Clinical, and Biological Features of the Analytical Samples at Baseline: Whole MEMENTO Cohort (n = 2,277) and CSF Subsample (n = 357)

	Analytical Sample						CSF Subsample						CSF Subsample vs Analytical Sample
	Global (n = 2,277)		AD dementia converters (n = 257)		Nonconverters (n = 2020)		Global (n = 357)		AD dementia converters (n = 64)		Nonconverters (n = 293)		p Value
<b>Demographic variables</b>													
Age, y	71.6	(65.5; 77.1)	76.2	(69.9; 80.7)	71.2	(65.1; 76.7)	68.9	(63.5; 74.6)	70.6	(66.3; 75.7)	68	(62.6; 74.3)	<10 <sup>-4</sup>
Female, n (%)	1,406	(61.7)	138	(53.7)	1,268	(62.8)	186	(52.1)	34	(53.1)	152	(51.9)	<10 <sup>-4</sup>
High education level, n (%)	1,251	(55.0)	122	(47.5)	1,129	(55.9)	203	(56.9)	34	(53.1)	169	(57.7)	0.44
ApoE (ε4 ± or +/+), n (%)	657	(30.1)	135	(54.9)	522	(26.9)	135	(39.2)	42	(68.9)	93	(32.9)	<10 <sup>-4</sup>
<b>Baseline CDR</b>												0.024	
CDR = 0, n (%)	922	(40.7)	26	(10.1)	896	(44.6)	126	(35.3)	5	(7.8)	121	(41.3)	
CDR = 0.5, n (%)	1,344	(59.3)	231	(89.9)	1,113	(55.4)	231	(64.7)	59	(92.2)	172	(58.7)	
Other incident dementia, n (%)	63	(2.8)	—	—	63	(3.1)	13	(3.6)	—	—	13	(4.4)	<10 <sup>-4</sup>
<b>Comorbidities</b>													
eGFR <sup>3</sup>												0.0008	
<60 (mL/minute/1.73 m <sup>2</sup> ), n (%)	214	(9.4)	34	(13.2)	180	(8.9)	20	(5.6)	6	(9.4)	14	(4.8)	
60–90 (mL/minute/1.73 m <sup>2</sup> ), n (%)	1,445	(63.5)	175	(68.1)	1,270	(62.9)	216	(60.5)	40	(62.5)	176	(60.1)	
>90 (mL/minute/1.73 m <sup>2</sup> ), n (%)	618	(27.1)	48	(18.7)	570	(28.2)	121	(33.9)	18	(28.1)	103	(35.2)	
History of myocardial infarction, n (%)	69	(3.0)	10	(3.9)	59	(2.9)	6	(1.7)	1	(1.6)	5	(1.7)	0.105
History of stroke, n (%)	91	(4.0)	12	(4.7)	79	(3.9)	17	(4.8)	0	(0)	17	(5.8)	0.42
<b>Neuropsychological tests</b>													
MMSE	28	(27; 29)	26	(25; 28)	29	(27; 29)	28	(27; 29)	26	(24; 28)	28	(27; 29)	0.017
FCSRT free recall	27	(21; 32)	14	(9; 20)	28	(23; 33)	26	(19; 31)	13	(8; 19)	27	(21; 32)	0.0007
FCSRT total recall	46	(43; 47)	37	(28; 43)	46	(44; 48)	45	(41; 47)	34.5	(25; 43)	46	(43; 47)	0.0012
DMS-48 delayed recall	46	(43; 47)	42	(37; 46)	46	(44; 47)	46	(43; 47)	43	(37; 46)	46	(44; 47)	0.87
Semantic fluency	28	(22; 34)	22	(18; 27)	29	(23; 35)	27	(21; 35)	23	(18; 28)	28	(22; 35)	0.22
Literal fluency	20	(15; 25)	18	(13; 23)	20	(15; 25)	20	(15; 25)	19	(15; 23)	20	(15; 25)	0.64
TMT-A, sec/correct move	1.9	(1.5; 2.4)	2.3	(1.8; 3.1)	1.8	(1.5; 2.3)	1.8	(1.4; 2.3)	2.2	(1.7; 2.7)	1.8	(1.4; 2.3)	0.032
TMT-B, sec/correct move	4	(3.0; 5.8)	5.8	(4.2; 9.0)	3.9	(2.9; 5.5)	3.9	(3.1; 5.3)	4.9	(4.0; 7.7)	3.8	(2.9; 5.0)	0.40
<b>Biological biomarkers</b>													
CSF NfL, pg/mL	—	—	—	—	—	—	1,230	(901; 1920)	1960	(1,460; 2,880)	1,120	(858; 1,680)	
CSF AB42/40 ratio (×100)	—	—	—	—	—	—	8.2	(5.4; 10.9)	4.9	(3.4; 6.1)	9.1	(6.7; 11.4)	
CSF total tau, pg/mL	—	—	—	—	—	—	295	(215; 442)	647	(433; 818)	265	(196; 374)	
CSF p181-tau, pg/mL	—	—	—	—	—	—	55.3	(44.0; 73.5)	91.1	(67.1; 108.4)	52.1	(42.2; 65.3)	
Blood NfL, pg/mL	18.2	(13.4; 25.0)	24.1	(17.3; 29.7)	17.7	(13.0; 24.2)	16.8	(12.4; 23.3)	22	(16.3; 28.9)	16	(11.9; 21.8)	0.0010
Blood AB42/40 ratio, (×100)	5.6	(4.8; 6.5)	5.1	(4.3; 5.7)	5.7	(4.9; 6.6)	5.6	(4.8; 6.6)	5	(4.3; 5.8)	5.7	(4.9; 6.7)	0.99
Blood total tau, pg/mL	1.9	(1.4; 2.6)	2.0	(1.5; 2.9)	1.9	(1.4; 2.6)	1.8	(1.4; 2.5)	1.9	(1.5; 2.7)	1.8	(1.4; 2.4)	0.135
Blood p181-tau, pg/mL	0.9	(0.6; 1.4)	1.5	(1.0; 2.1)	0.9	(0.6; 1.2)	0.9	(0.6; 1.4)	1.4	(1.0; 1.8)	0.8	(0.6; 1.2)	0.70

Continued

**Table 1** Demographic, Clinical, and Biological Features of the Analytical Samples at Baseline: Whole MEMENTO Cohort (n = 2,277) and CSF Subsample (n = 357) (continued)

	Analytical Sample						CSF Subsample						CSF Subsample vs Analytical Sample p Value
	Global (n = 2,277)		AD dementia converters (n = 257)		Nonconverters (n = 2020)		Global (n = 357)		AD dementia converters (n = 64)		Nonconverters (n = 293)		
<b>MRI biomarkers</b>													
Normalized hippocampal volume (×1,000)	4.0	(3.6; 4.3)	3.5	(3.0; 3.8)	4.0	(3.7; 4.4)	4.0	(3.6; 4.3)	3.7	(3.1; 4.0)	4.0	(3.7; 4.3)	0.92
AD signature cortical thickness, mm	2.6	(2.5; 2.7)	2.5	(2.4; 2.6)	2.6	(2.5; 2.7)	2.6	(2.5; 2.7)	2.5	(2.5; 2.6)	2.6	(2.6; 2.7)	0.67

Abbreviations: Aβ = amyloid beta; AD = Alzheimer disease; ApoE = apolipoprotein E; CDR = Clinical Dementia Rating scale; DMS-48 = Delayed Matching-to-Sample Task 48 items; FCSRT = Free and Cued Selective Reminding Test; MMSE = Mini-Mental State Examination; NfL = neurofilaments light chain; TMT = Trail Making Test.

All quantitative variables are represented with median and 1st and 3rd interquartiles (Q1–Q3).

<sup>a</sup> Estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.

5-year follow-up using Kaplan-Meier survival analyses (Figure 2 and eTable 2 [links.lww.com/WNL/C445] for incidence rates). Blood and CSF p181-tau, NfL, and Aβ42/40 ratio were associated with incident AD dementia risk following a dose-response pattern ( $p < 0.0001$ ,  $p < 0.0001$ , and  $p = 0.0033$ , respectively, on log-rank tests). For p181-tau and NfL, blood or CSF tertile concentrations led to similar incidence rates. Blood Aβ42/40 ratio was less efficient than CSF Aβ42/40 ratio. CSF t-tau was associated with incident AD dementia ( $p < 0.0001$ ) but not blood t-tau ( $p = 0.43$ ).

### Prediction of Future AD Dementia With Blood Biomarkers and Other Metrics

Table 3 shows accuracy of blood biomarkers alone or in combination to predict AD dementia. Baseline blood p181-tau was the best blood biomarker alone to predict AD dementia (c-index = 0.731 [95% CI = 0.694; 0.768]). The model prediction performance was improved to 0.757 (95% CI = 0.726; 0.789) for the combination of NfL + p181-tau + Aβ42/40 ratio (difference in c-index difference = 0.027 [95% CI = 0.010; 0.043]). The “clinical” reference model (age, sex, education level, memory and executive performance) predicted AD dementia risk with a c-index = 0.884 (95% CI = 0.862; 0.905). Model prediction performance rose to 0.899 (95% CI = 0.882; 0.917) when adding blood p181-tau and Aβ42/40 ratio (difference in c-index 0.016 [95% CI = 0.006; 0.026]). The “research” reference model (clinical data + ApoE genotype and MRI cortical thickness in AD-signature regions) predicted AD dementia with a c-index = 0.907 (95% CI = 0.888–0.926). Performance increased to 0.917 (95% CI = 0.901; 0.933) when adding blood p181-tau and Aβ42/40 ratio (difference in c-index 0.009 [95% CI = 0.001; 0.018]).

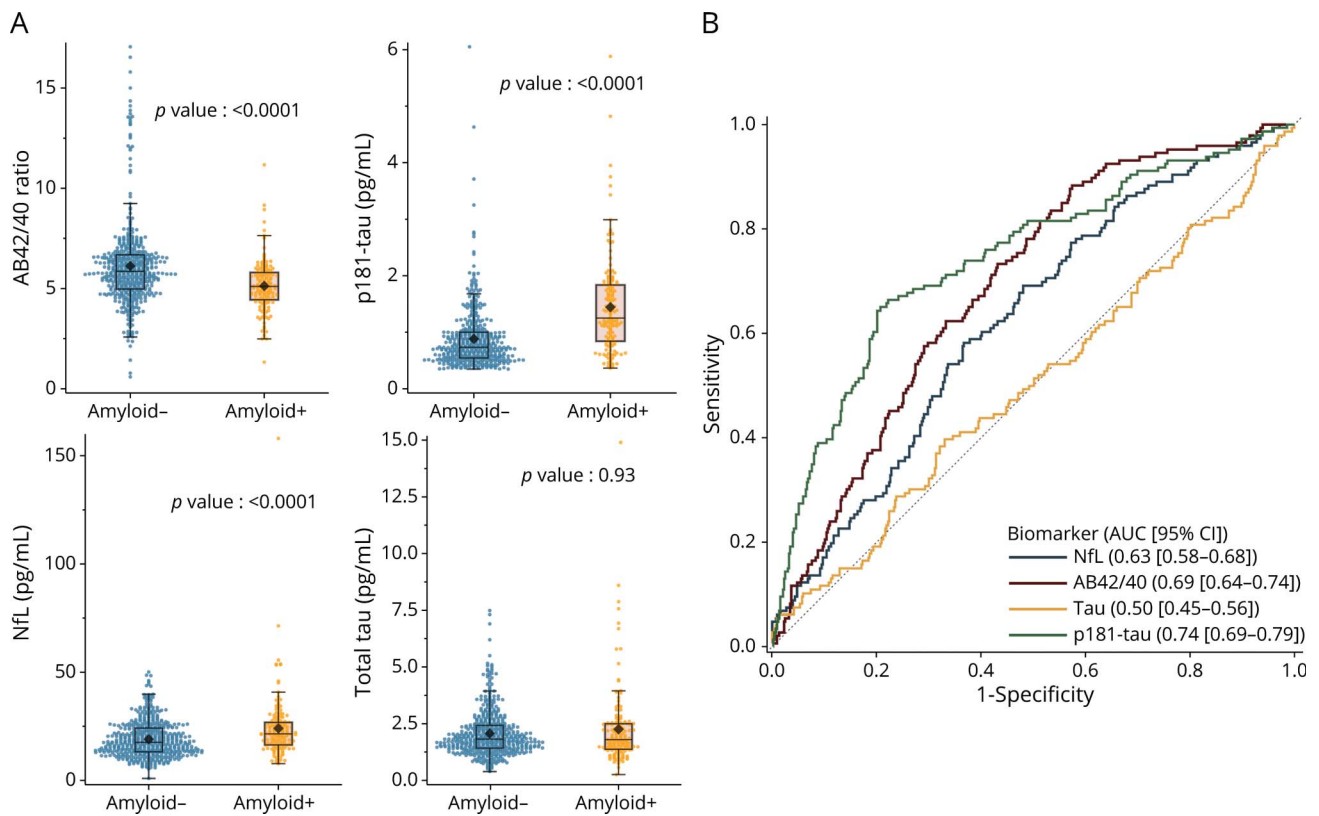
Most of the memory care centers do not have access to quantitative volumetric analyses but uses visual read of atrophy such as the Scheltens scale.<sup>34</sup> Thus, we added this grading of hippocampal atrophy to the “clinical” reference model

(eTable 3, links.lww.com/WNL/C445). Interestingly, predictive performances were similar to the “research” reference model, suggesting that brain MRI assessment methods (quantitative measure of cortical thickness in AD-signature regions or hippocampal grading) are equivalent to predict AD dementia risk in this large clinic-based cohort.

Because it can be argued that clinical status at baseline (SCC or MCI) and the nature of MCI can influence the predictive value of biomarkers, we performed a first sensitivity analysis where we split the analytical sample in 2 subgroups according to baseline CDR (CDR = 0 or CDR = 0.5) and another where we divided the MCI group in 2 subgroups (amnesic or non-amnesic). The accuracy of blood p181-tau to predict AD dementia was higher in patients with CDR = 0 (c-index = 0.830 [95% CI = 0.694; 0.967]) than in patients with CDR = 0.5 (c-index = 0.697 [95% CI = 0.658; 0.737]). However, in both subgroups (as in the whole cohort), blood biomarkers added little to 5-year dementia risk prediction models including traditional predictors (eTable 4, links.lww.com/WNL/C445). Regarding the nature of MCI, blood biomarkers were equivalent to predict dementia risk in nonamnesic MCI and in amnesic MCI, but clinical and research models were slightly more performant in amnesic MCI (eTable 5, links.lww.com/WNL/C445).

To test whether comorbidities known to affect blood biomarkers concentration may change our findings, we performed the same statistical analyses after the exclusion of patients with chronic kidney diseases (eGFR < 60 mL/min/1.73 m<sup>2</sup>) and we found the same results (eTable 6, links.lww.com/WNL/C445). We also added in the “clinical” and “research” models the eGFR and the history of cardiovascular event. We found no substantial change in the predictive performances of the models (eTable 7, links.lww.com/WNL/C445).

**Figure 1** Dot-Plots Distributions of Blood Biomarkers According to Amyloid-PET Status and ROC Curve Analysis



(A) Boxplots indicate median, 1st and 3rd quartiles; the black diamonds indicate the mean. *p*-values are for nonparametric Wilcoxon rank tests. (B) ROC curve analyses showing the performance of the 4 blood biomarkers to discriminate amyloid positivity on PET. A $\beta$  = amyloid beta; AUC = area under the curve; NfL = neurofilaments light chain; ROC = receiver operating characteristic.

Finally, we ran the same Cox proportional hazard models in the CSF subsample. The “clinical” reference model predicted AD dementia risk with a c-index = 0.831 [95% CI = 0.769; 0.893]. Performance reached 0.856 [95% CI = 0.807; 0.905] after addition of all CSF biomarkers and 0.856 [95% CI = 0.801; 0.911] for the best blood biomarker combination (p181-tau + A $\beta$ 42/40 ratio + NfL). The “research” reference models had c-index of 0.858 [95% CI = 0.811–0.904], 0.870 [95% CI = 0.836; 0.904] with addition of CSF biomarkers, and 0.862 [95% CI = 0.818; 0.907] with addition of blood p181-tau + A $\beta$ 42/40

ratio + NfL). The addition of either CSF or blood biomarkers to the “research” reference model did not significantly improve its performance (c-index differences 0.011 [95% CI = -0.018; 0.040] and 0.005 [95% CI = -0.015; 0.025], respectively).

## Discussion

In this study, we reported the biological and clinical relevance of blood AD biomarkers for the first time in the MEMENTO cohort. In models that included both CSF and blood biomarkers (CSF subsample), we have shown that blood and CSF concentrations of p181-tau and NfL had equivalent abilities to predict AD dementia risk over a 5-year follow-up. This suggests that, at first visit in memory clinics and without any other knowledge regarding patients’ health or socio-demographic condition, blood and CSF p181-tau and NfL may be interchangeable to stratify patients according to their risk of conversion to AD dementia in the next 5 years. In this context, the moderate correlation between blood and CSF p181-tau would not reflect distinct biological information<sup>35</sup> but would instead be explained by variability in preanalytical handling,<sup>36</sup> differential analytical performance between CSF and blood, peripheral clearance of these peptides, and/or the patients’ comorbidities.<sup>32,33,37</sup> Blood A $\beta$ 42/40 ratio was less

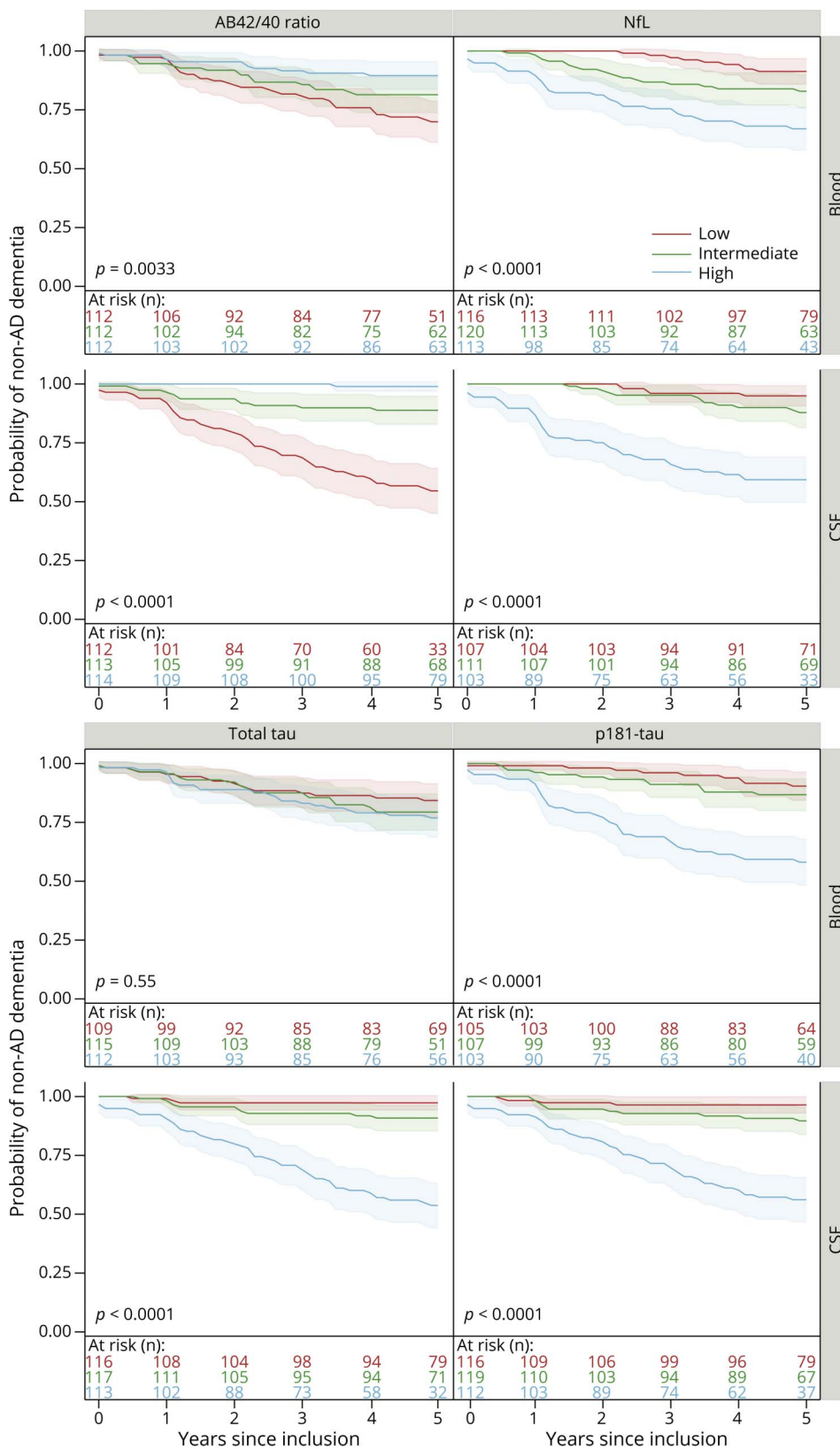
**Table 2** Correlations Between CSF and Blood Biomarkers Concentrations in the CSF Subsample (n = 357)

CSF Biomarkers	Blood Biomarkers			
	NfL	A $\beta$ 42/40 ratio	p181-tau	Total tau
NfL	0.47 ***	-0.04	0.24 ***	-0.14 *
A $\beta$ 42/40 ratio	-0.32 ***	0.34 ***	-0.40 ***	-0.06
p181-tau	0.26 ***	-0.23 ***	0.32 ***	0.08
Total tau	0.32 ***	-0.25 ***	0.33 ***	0.08

Abbreviations: A $\beta$  = amyloid beta; NfL = neurofilaments light chain. Spearman correlation coefficients, \*\*\**p* < 0.001, \*\**p* < 0.01, \**p* < 0.05.



**Figure 2** Kaplan-Meier Survival Curves Representing the Association Between Incident AD Dementia and Baseline Blood (Top Panel) or CSF Biomarkers (Bottom Panel) Concentrations During a 5-Year Follow-up Period (CSF Subsample)



Each biomarker was divided in 3 tertiles of distribution (low in red, intermediate in green, high in blue).  $p$ -values are for log-rank tests among the tertiles. A $\beta$  = amyloid beta; AD = Alzheimer disease; NFL = neurofilaments light chain.

**Table 3** Performance for Predicting AD Dementia During a 5-Year Follow-up in the Whole Analytical MEMENTO Cohort, Cox Models (n = 2,277)

	c-Index [95% CI]	Brier score [95% CI]	c-Index difference [95% CI]
<b>Blood biomarkers alone</b>			
NfL	0.659 [0.621; 0.698]	0.107 [0.106; 0.107]	-0.098 [-0.132; -0.063]
Aβ42/40 ratio	0.635 [0.598; 0.671]	0.105 [0.105; 0.106]	-0.122 [-0.158; -0.085]
pTau181	0.731 [0.694; 0.768]	0.099 [0.099; 0.099]	-0.027 [-0.043; -0.010]
Total tau	0.527 [0.487; 0.567]	0.107 [0.107; 0.108]	-0.228 [-0.273; -0.183]
<b>Best combination: NfL + p181-tau + Aβ42/40 ratio</b>	0.757 [0.726; 0.789]	0.097 [0.097; 0.098]	Ref
<b>Clinical setting</b>			
<b>Reference model: age, sex, education, memory, executive functions</b>	0.884 [0.862; 0.905]	0.076 [0.075; 0.076]	Ref
<b>Ref model + NfL</b>	0.884 [0.863; 0.905]	0.076 [0.075; 0.076]	0.001 [-0.001; 0.002]
<b>Ref model + Aβ42/40 ratio</b>	0.888 [0.868; 0.909]	0.074 [0.074; 0.075]	0.005 [-0.002; 0.012]
<b>Ref model + p181-tau</b>	0.896 [0.878; 0.914]	0.072 [0.071; 0.072]	0.013 [0.005; 0.020]
<b>Ref model + total tau</b>	0.884 [0.863; 0.905]	0.076 [0.075; 0.076]	0.000 [-0.001; 0.002]
<b>Ref model + best combination (p181-tau + Aβ42/40 ratio)</b>	0.899 [0.882; 0.917]	0.071 [0.070; 0.071]	0.016 [0.006; 0.026]
<b>Research setting</b>			
<b>Reference model: age, sex, education, memory, executive functions, ApoE genotype, quantitative MRI</b>	0.907 [0.888; 0.926]	0.067 [0.067; 0.067]	Ref
<b>Ref model + NfL</b>	0.907 [0.888; 0.926]	0.067 [0.067; 0.067]	0.000 [-0.001; 0.001]
<b>Ref model + Aβ42/40 ratio</b>	0.912 [0.894; 0.930]	0.066 [0.066; 0.066]	0.005 [-0.001; 0.011]
<b>Ref model + p181-tau</b>	0.912 [0.896; 0.929]	0.065 [0.064; 0.065]	0.005 [-0.000; 0.011]
<b>Ref model + total tau</b>	0.906 [0.887; 0.925]	0.067 [0.066; 0.067]	0.000 [-0.003; 0.002]
<b>Ref model + Best combination (p181-tau + Aβ42/40 ratio)</b>	0.917 [0.901; 0.933]	0.064 [0.064; 0.064]	0.009 [0.001; 0.018]

Abbreviations: MRI = cortical thickness in AD-signature regions. Memory = total recall on the free and cued selective reminding test. Executive functions = Trail Making Test B performance. Blood biomarkers were log-transformed to reach Gaussian distributions. Aβ = amyloid-β; ApoE = apolipoprotein E; NfL = neurofilaments light chain.

efficient than CSF Aβ42/40 ratio to predict dementia conversion risk, suggesting that peripheral Aβ production (in platelets or skeletal muscles)<sup>38</sup> still prevents accurate measurement of what happens in the brain using blood samples.<sup>39</sup> Blood total tau was not correlated with CSF total tau, nor associated with incident dementia in our study. It is in accordance with previous findings,<sup>21,40</sup> except 1 report in the Framingham cohort.<sup>41</sup> This lack of correlation between CSF and blood total tau concentrations may be explained by the peripheral expression of tau, particularly in the kidney, skeletal muscle, and breast (proteintlas.org). At the same time, phosphorylated tau may be specific of brain pathology.

Recent community-based studies have shown the impact of chronic kidney disease and cardiovascular comorbidities on the concentration of AD blood biomarkers.<sup>32,33,37</sup> While they could modify the thresholds to be adopted to determine diagnostic cutoffs in the future, our study interestingly shown

that these comorbidities do not affect prediction of AD dementia, probably because these comorbidities are not in themselves strong predictors of cognitive decline.

In multivariate models that included only blood biomarkers, NfL, p181-tau, and Aβ42/40 ratio were significantly associated with incident AD dementia. The best predictive biomarker was p181-tau (c-index = 0.731 in the whole analytical sample and c-index = 0.830 in patients with CDR = 0 at baseline). The authors of a study performed similar analyses in the BioFINDER (with blood p217-tau) and ADNI (p181-tau) cohorts and found predictive performance of p-tau alone close to what we found in patients with CDR = 0 (AUC = 0.83 and 0.78, respectively). It suggests that BioFINDER and ADNI patients have characteristics closer to the CDR = 0 patients included in MEMENTO and that the accuracy of blood p-tau to predict dementia may be “stage-specific.” We can also state that patients with CDR = 0 at baseline but

developing AD dementia within 5 years are rapid progressors, whereas patients with CDR = 0.5 have a more “usual” evolution from MCI to AD dementia. It is therefore likely that their biological characteristics are different and that high blood p181-tau concentration may be a marker of a more aggressive course of AD because it was previously described for the highest CSF t-tau concentrations.<sup>42</sup> In turn, the performance of blood p181-tau to predict the risk of AD dementia in MEMENTO is better in patients with CDR = 0.

In MEMENTO, the accuracy of blood biomarkers to predict 5-year AD/mixed dementia risk strongly increased when it was associated with demographics, cognitive performance, ApoE genotype, and brain MRI (c-index = 0.92). The authors of a study<sup>19</sup> found very similar performance of an equivalent “research” model combined with p-tau to predict AD dementia risk over 4-year follow-up (AUC = 0.92 and 0.91 according to the cohort). These findings were also replicated in a smaller clinical trial cohort of MCI with a 3-year follow-up.<sup>43</sup> In these previous works, the authors did not report the performance of their model without blood p-tau. However, in our study, “clinical” and “research” models (without p181-tau) already had a high accuracy in predicting dementia (c-index = 0.88 and c-index = 0.91, respectively). It suggests that blood AD biomarkers might have a very slight interest in addition to the factors already known to predict cognitive decline and dementia in both clinical and research settings. In MEMENTO, as in BioFINDER and ADNI, no significant differences were observed in predictive accuracy when using CSF biomarkers instead of blood biomarkers in the same subsample.<sup>19</sup>

Regarding the external validation of our biological findings, when cerebral A $\beta$  pathology was defined using amyloid-PET, the blood A $\beta$ 42/40 ratio decreased by 16% in A $\beta$ + participants, according to previous findings (10%–20% decreased).<sup>7,8,44</sup> Among blood biomarkers, the strongest association with cerebral amyloidosis was found with p181-tau (mean increase of 63% in A $\beta$ + participants vs A $\beta$ -), which is also in accordance with previous findings.<sup>12,45</sup> However, in our cohort and others, blood p181-tau concentrations overlap between A $\beta$ + and A $\beta$ - individuals with SCC or MCI, unlike the comparison between patients with AD dementia and cognitively unimpaired participants.<sup>12</sup> Furthermore, correlations between blood and CSF NfL, p181-tau, and A $\beta$ 42/40 were moderate in MEMENTO (0.32 < r < 0.47). These results are consistent but in the lower range of what has been previously reported,<sup>35,46,47</sup> correlations coefficient being able to reach up to 0.6 for NfL<sup>48</sup> and 0.7 for p181-tau.<sup>14</sup> However, correlations were mainly driven by A $\beta$  pathology<sup>14</sup> or dementia status<sup>48</sup> in these studies. Taken together, these biological results further suggest that the performance of AD blood biomarkers is “stage-specific” and therefore dependent on the selection criteria of the cohort.

Beyond many strengths, our study has limitations. While the same immunoassay was used to measure NfL in blood and CSF, we must acknowledge that different techniques were used for dosing A $\beta$  peptides, p181-tau, and total tau in blood and

CSF, which may lead to weakened correlations. Furthermore, the commercial Simoa-Quanterix assay measured A $\beta$ <sub>x-42</sub> and A $\beta$ <sub>x-40</sub> in blood, whereas the Innotech-Fujirebio assay measured full-length A $\beta$ <sub>1-42</sub> and A $\beta$ <sub>1-40</sub> in CSF, known to be more specific for brain amyloidosis.<sup>49</sup> One could also argue that we did not use p217-tau, which may have slightly better diagnosis accuracy than p181-tau.<sup>17</sup> Still, recent head-to-head comparisons of these biomarkers, also comparing different assays and antibodies, did not show clinically significant difference.<sup>9,11</sup> Another limitation concern the use of tertile distribution or of continuous measures of blood biomarkers concentrations in this study, instead of defining cutoffs more applicable to clinical practice. Future studies will need to establish cut points relevant for the different contexts of use.<sup>50</sup> We also acknowledge that social determinants of health were not investigated in this study, although they may affect diagnostic and predictive performances of biological biomarkers.

These results bring an essential step forward for implementing blood biomarkers in memory clinics.<sup>24</sup> Indeed, our findings reinforce the idea that blood biomarkers are as sensitive as CSF markers to detect early AD pathology, but may not be very accurate in predicting dementia risk if they are measured alone, in unselected participants consulting in memory clinics (such as CSF biomarkers). However, prediction accuracy strongly increases in selected patients with memory and executive impairments ( $\pm$  ApoE4 genotype and AD signature on brain MRI). These findings echo recent IWG recommendations regarding the clinical diagnosis of AD<sup>3</sup>: Only patients with suggestive clinical and radiologic AD prodromal phenotypes should be considered for fluid biomarkers testing, to give reliable advice in clinical practice.

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## Disclosure

F. Blanc was the French national coordinator for the Eisai Delphia (E2027) and Axovant Headway-DLB therapeutic trials; he is currently the French national coordinator of the Roche Graduate therapeutic trial; he had received

honoraria from Roche, Eisai, and Biogen for oral presentations. O. Godefroy has served on scientific advisory boards and as a speaker for Novartis, CSL-Behring, Biogen, Genzyme, Lilly, Bristol-Myers Squibb, Boehringer-Ingelheim, Covidien, Teva Santé, and Astra Zeneca. The other authors declare that they have no competing interests related to the present work. Go to [Neurology.org/N](https://www.neurology.org/N) for full disclosures.

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<b>Vincent Bouteloup, PhD</b>	Bordeaux University, France	Major role in the acquisition of the data; conducted the statistical analyses; revised the manuscript for intellectual content
<b>Isabelle Pellegrin, MD, PhD</b>	Bordeaux University, France	Major role in the acquisition of the data; revised the manuscript for intellectual content
<b>Jean-François Mangin, PhD</b>	Paris-Saclay University, France	Major role in the acquisition of the data; revised the manuscript for intellectual content
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## Appendix (continued)

Name	Location	Contribution
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<b>Isabelle Jalenques, MD, PhD</b>	Clermont-Ferrand University, France	Major role in the acquisition of the data; revised the manuscript for intellectual content
<b>Geneviève Chêne, MD, PhD</b>	Bordeaux University, France	Designed and conceptualized study; obtained funding
<b>Carole Dufouil, PhD</b>	Bordeaux University, France	Designed and conceptualized study; obtained funding; revised the manuscript for intellectual content; supervision

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