Received: 14 August 2024 | Accepted: 14 August 2024

DOI: 10.1002/dad2.70003

Alzheimer's & Dementia
Diagnosis, Assessment & Disease Monitoring

RESEARCH ARTICLE

Performance of plasma p-tau217 and NfL in an unselected memory clinic setting

Rebecca Z. Rousset[1] | **Thomas Claessen**[1,2] | **Argonde C. van Harten**[2] | **Afina W. Lemstra**[2] | **Yolande A. L. Pijnenburg**[2] | **Wiesje M. van der Flier**[2] | **Anouk den Braber**[2,3] | **Andreas Jeromin**[4] | **Inge M. W. Verberk**[1] | **Charlotte E. Teunissen**[1]

[1]Neurochemistry Laboratory, Department of Laboratory Medicine, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam Neuroscience, De Boelelaan, Amsterdam, The Netherlands

[2]Alzheimer Center, Department of Neurology, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam Neuroscience, De Boelelaan, Amsterdam, The Netherlands

[3]Department of Biological Psychology, Vrije Universiteit Amsterdam, De Boelelaan, Amsterdam, The Netherlands

[4]ALZpath. Inc., Carlsbad, California, USA

Correspondence
Rebecca Z. Rousset, Neurochemistry Laboratory, Department of Laboratory Medicine, Amsterdam UMC, Vrije Universiteit Amsterdam, De Boelelaan 1117, 1081HV, Amsterdam Neuroscience, Amsterdam, The Netherlands.
Email: r.z.rousset@amsterdamumc.nl

Funding information
European Commission, Grant/Award Number: 860197; Innovative Medicines Initiative (IMI) 2 Joint Undertaking (JU), Grant/Award Numbers: 831434, 101034344; Joint Programme – Neurodegenerative Disease (JPND); National Multiple Sclerosis Society; Alzheimer's Drug Discovery Foundation; Alzheimer's Association; Health-Holland, Topsector Life Sciences & Health (PPP-allowance), Grant/Award Number: LSHM20106; Nederlandse Organisatie voor Wetenschappelijk Onderzoek; The Selfridges Group Foundation, Grant/Award Number: 1167260; Stichting Alzheimer Nederland; Stichting Steun Alzheimercentrum Amsterdam; Pasman Stichting; ZonMw, Grant/Award Numbers: #73305095007, 1051003212003

Abstract

INTRODUCTION: Plasma phosphorylated tau-217 (p-tau217) and neurofilament light (NfL) can differentiate between different dementias in selected cohorts. We aim to test the discrimination potential of these markers in a real-world cohort.

METHODS: We measured p-tau217 (ALZpath) and NfL (Quanterix) in 415 (unselected) consecutive memory clinic patients. Biomarker levels were dichotomized as low/high to create four biomarker profiles based on p-tau217 and NfL levels.

RESULTS: p-Tau217 levels were highest in patients with Alzheimer's disease (AD) dementia, whereas NfL levels were highest in patients with frontotemporal dementia (FTD). Low p-tau217/low NfL was associated mostly with non-neurological diagnoses (79%), and high p-tau217/low NfL indicated AD pathology at any stage (84%). Low p-tau217/high NfL indicated FTD (38%) and high p-tau217/high NfL indicated AD dementia (87%).

DISCUSSION: p-Tau217 can identify AD pathology at any disease stage. NfL can differentiate FTD from other diagnoses (e.g., AD dementia). Plasma p-tau217 and NfL can support clinical decision-making, and we suggest using them as complements to standard clinical assessment.

KEYWORDS
AD continuum, Alzheimer's disease, biomarker profiles, blood-based biomarkers, frontotemporal dementia, memory clinic, NfL, plasma biomarkers, psychiatry, p-tau217, real-world cohort

Rebecca Z. Rousset and Thomas Claessen contributed equally to this study.

Highlights

- Phosphorylated tau-2017 (p-tau217) can detect Alzheimer's disease (AD) across the clinical continuum.
- Neurofilament light (NfL) can differentiate frontotemporal dementia (FTD) from other diagnoses (AD dementia, dementia with Lewy bodies [DLB], and Psychiatry).
- p-Tau217 may detect AD co-pathology in other diseases or dementia types (e.g., DLB).
- p-Tau217 and NfL show potential for clinical implementation.

1 | BACKGROUND

Dementia has many causes, of which Alzheimer's disease (AD) is the most common.[1] Other common types of dementia include frontotemporal dementia (FTD) and dementia with Lewy bodies (DLB).[2] These dementia types may be difficult to differentiate from because of overlapping symptoms or an atypical presentation.[3–5] However, being able to give an accurate and timely diagnosis allows patients and health care professionals to make optimal decisions regarding (experimental) treatment and life and/or care planning.[6] Traditional diagnostic tools used in the diagnostic workup for cognitive decline in memory clinics include magnetic resonance imaging (MRI), positron emission tomography (PET),[7–9] and cerebrospinal fluid (CSF) biomarker analysis.[8,10] However, these tools are invasive, expensive, or require specialized personnel and equipment. Recently, plasma biomarkers have emerged as an innovative diagnostic tool for different types of dementia, in particular, AD dementia.[11,12]

Plasma biomarkers that have been researched for AD diagnosis include phosphorylated tau-217 (p-tau217) and neurofilament light (NfL).[12] p-Tau217 is highly specific to AD pathology[13–16] and can differentiate AD dementia from other dementia types, such as FTD.[14,17] Because p-tau217 is still a relatively new biomarker, different assays measuring p-tau217 are currently being tested in various cohorts. One such assay is the ALZpath p-tau217 assay, which has been shown to accurately detect AD pathology in a selected AD continuum cohort.[16] NfL is a cross-disease indicator of neurodegeneration elevated in most neurodegenerative conditions, including most dementias, with a disease-specific magnitude of increase.[18] Among dementias, NfL is most elevated in FTD when compared to AD dementia and DLB,[13,19–21] although these findings have not been consistent across all studies.[19,22]

Most studies assessing the diagnostic potential of NfL and p-tau217 have been conducted in highly selected cohorts using strict inclusion and exclusion criteria,[16,22,23] which makes these results not directly generalizable to the more diverse real-world clinical setting. Few real-world studies have been performed focusing on the clinical use of blood-based NfL for diagnosing AD and FTD.[23,24] One study found that NfL can discriminate FTD from other dementias in a heterogeneous memory clinic cohort.[25] Another study reported that serum NfL could confirm neurodegeneration.[24] To our knowledge, the diagnostic potential of p-tau217 has yet to be researched in an unselected memory clinic cohort. Because NfL and p-tau217 provide different types of diagnostic information, it would also be of interest to assess their combined potential to differentiate between dementia subtypes.

Our objective is to assess the discrimination potential of the novel ALZpath p-tau217 plasma assay in combination with plasma NfL for differentiating between different causes of cognitive complaints in an unselected real-world memory clinic cohort.

2 | METHODS

2.1 | Clinical samples

Our unselected real-world memory clinic cohort consisted of 415 consecutive patients who visited our tertiary memory clinic between December 2020 and December 2021. These patients consented to the use of their medical data and blood material for research as part of the Amsterdam Dementia Cohort (ADC).[26,27] All patients received the standard ADC test battery, as described elsewhere.[26] Diagnoses were determined during multidisciplinary experts meeting based on the current diagnostic criteria for AD dementia,[28] DLB,[29] FTD,[30] and others, as applicable. An in-depth description of the ADC cohort and procedures is available in Supplement Part A.

2.2 | Amyloid status assessment

CSF $A\beta_{1\text{-}42}$ and p-tau181 were measured using the Elecsys β-amyloid(1-42) CSF and Elecsys Phospho-Tau (181P) CSF electrochemiluminescence immunoassays (Roche Diagnostics International Ltd, Rotkreuz, Switzerland).[31,32] Patients were classified as amyloid positive if their p-tau181/$A\beta_{1\text{-}42}$ ratio was >0.020.[33,34] If a lumbar puncture could not be performed or CSF analysis was inconclusive, an amyloid PET scan was requested. This was the case for 36 patients. Amyloid PET scans were visually scored as normal or abnormal by an experienced nuclear radiologist. If CSF and PET analyses were in disagreement, the amyloid PET scan result was taken as the indicator of amyloid positivity.

2.3 | Plasma biomarker measurements

Ethylenediaminetetraacetic acid (EDTA)–plasma samples were stored in 0.3 mL aliquots at −80°C before use, as described elsewhere.[35] Samples were thawed at room temperature and centrifuged for 10 min at 10,000 × *g* before analysis. Both NfL (NF-light Advantage Kit, Quanterix)[36] and p-tau217 (ALZpath, ALZpath Inc.)[16] were measured on the Simoa HDx analyzer. NfL measurements were carried out in singulate and p-tau217 measurements in duplicate. NfL measurements were missing for 16 samples (3.8%), due to low sample volumes as p-tau217 measurements were prioritized. p-Tau217 measurements were missing for 43 samples (10.3%) due to Simoa measurement errors and low sample volumes. Measurement missingness occurred proportionally across diagnostic group. Run details are available in Supplement Part A.

2.4 | Case study selection

To evaluate if plasma p-tau217/NfL profiles could benefit clinical practice, we selected two cases from our cohort for whom the medical team could not decide on a conclusive diagnosis after the patient's first diagnostic screening visit, and for whom additional testing was requested. We drafted the case reports from the patient files and interpreted their plasma biomarker profiles according to the final diagnosis as agreed upon after additional ancillary investigations. The two cases were chosen based on biomarker availability and differential diagnostic considerations.

2.5 | Statistical analyses

Statistical analyses were conducted in R (version 4.0.3). Biomarker levels were log-transformed to achieve normal distributions for group comparison. Group differences were tested using a one-way analysis of variance (ANOVA) with Tukey's honestly significant difference (HSD) post hoc test. A p-value < 0.05 was considered statistically significant.

At the time of this writing, there were no externally validated cutoffs for the ALZpath p-tau217 assay. Therefore, a Youden's index cutoff value was derived from the cohort by comparing AD patients and amyloid beta (Aβ)− subjective cognitive decline (SCD) patients using the cutpointr package (version 1.1.2). In addition, p-tau217 was tested for its potential to differentiate between Aβ− and Aβ+ in the entire cohort using receiver-operating characteristic (ROC) analysis. The pROC package (version 1.18.4) was used to calculate area under the curve (AUCs), sensitivity and specificity, negative predictive values (NPVs) and positive predictive values (PPVs), and to plot ROC curves.

For NfL, we referred to an external reference range[37,38] using the age-adjusted value associated with the 90th percentile of normal as a cutoff (6.4–36.6 pg/mL across ages 20–82). In addition, we performed a sensitivity analysis for NfL using two alternative approaches (Supplement Part B).

RESEARCH IN CONTEXT

1. **Systematic review**: We identified literature from online databases. Plasma phosphorylated tau-2017 (p-tau217) is a well-performing novel biomarker able to detect Alzheimer's disease (AD) pathology, whereas neurofilament light (NfL) is a broad biomarker for neurodegeneration. The different p-tau217 assays have yet to be tested in real-world cohorts, which is most representative of clinical practice.
2. **Interpretation**: Based on analyzing p-tau217 and NfL in 415 consecutive tertiary memory clinic patients, these biomarkers show promise as aids in clinical decision-making. p-Tau217 is a good marker for AD pathology across the continuum and NfL differentiates between frontotemporal dementia (FTD) and other dementia in a real-world heterogeneous patient group. This supports previous results in more selective cohorts.
3. **Future directions**: We suggest further research in the form of (1) validation of this combination of markers in larger clinical cohorts, (2) assessment of its potential for detecting AD co-pathology in other dementia types, and (3) investigation of the real-world clinical utility of p-tau217 assays when used for clinical decision support.

Plasma biomarker levels were dichotomized based on the aforementioned p-tau217 and NfL cutoffs. Each patient was classified as having low/high NfL levels and low/high p-tau217 levels. Four patient groups were made: Low p-tau217/low NfL, high p-tau217/low NfL, low p-tau217/high NfL, and high p-tau217/high NfL. In addition, we assessed the discriminating potential of p-tau217 for AD dementia versus amyloid negative (Aβ−) SCD and Aβ− versus amyloid positive (Aβ+).

3 | RESULTS

3.1 | Cohort characteristics

Of the 415 patients assessed, 396 were given a diagnosis after their first assessment and 19 had to undergo additional ancillary investigations (e.g., genetic testing). The most common diagnosis was AD dementia (n = 138; AD = 134, logopenic primary progressive aphasia (PPA) = 4), followed by SCD (n = 104) and mild cognitive impairment (MCI; n = 50; due to AD = 37, other/unknown etiology = 13). SCD and MCI patients were further characterized as having underlying AD pathology (SCD+/MCI+) or not (SCD−/MCI−). Thirty-five patients were diagnosed with FTD (behavioral variant FTD = 25; non-fluent or semantic PPA = 10), and 17 patients with DLB. Eighteen patients were diagnosed with another type of dementia and nine were diagnosed with another neurological condition (Supplement Part A). The

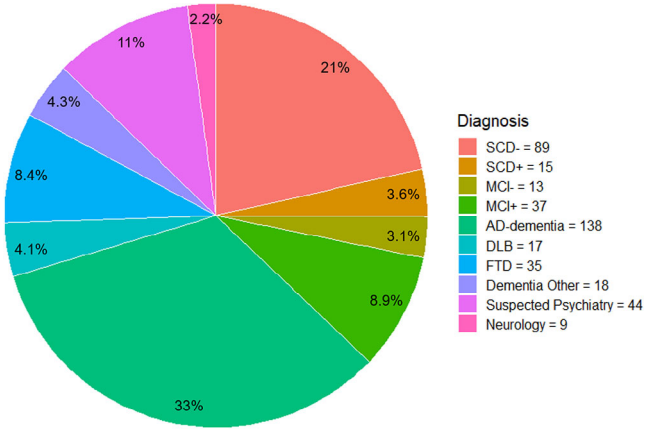

FIGURE 1 Proportion of patients per diagnostic group during prospective inclusion for the study. AD dementia, Alzheimer's disease dementia; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; MCI−, mild cognitive impairment without underlying AD pathology; MCI+, mild cognitive impairment with underlying AD pathology; SCD−, subjective cognitive decline without underlying AD pathology; SCD+, Subjective Cognitive Decline with underlying AD pathology.

remaining 44 patients were suspected to have an underlying psychiatric disease ("Suspected Psychiatry") (Figure 1).

Baseline characteristics per diagnostic group are summarized in Table 1. There were no significant differences in sex distribution between the diagnostic groups. Patients in the SCD− group were significantly younger than patients in the MCI+, AD−dementia, DLB, and Dementia Other groups. Patients in the Suspected Psychiatry group were significantly younger than those in the MCI+, AD dementia, and Dementia Other groups. Patients in the SCD, MCI, Neurology, and Suspected Psychiatry groups had the highest Mini-Mental State Examination (MMSE) scores. AD, DLB, FTD, and Dementia Other groups had low average MMSE scores.

3.2 | Biomarkers levels and cutoffs

3.2.1 | ALZpath p-tau217 diagnostic performance

The ALZpath p-tau217 assay showed good specificity and moderate sensitivity. This effect was driven by low sensitivity for low p-tau217 concentration measurements, as seen by high coefficients of variation (CVs), specifically for concentrations below 0.159 pg/mL (Figure S1). The Youden's index cutoff for differentiating between AD dementia and SCD− was 0.663 pg/mL. This cutoff was associated with a sensitivity of 0.70 and a specificity of 0.99 (Figure 2), and an AUC of 0.81 (95% confidence interval [CI]: 0.74–0.87). The AUC was 0.82 (95% CI: 0.75–0.88) when focusing only on AD patients with confirmed AD pathophysiology. An additional analysis was conducted to test the potential of p-tau217 for differentiating Aβ− patients from Aβ+ regardless of the main etiology, returning a cutoff of 0.61 pg/mL, an AUC of 0.78 (95% CI: 0.72–0.84), a sensitivity of 0.70, and a specificity of 0.91 (Figure 2). This cutoff was associated with an NPV of 0.84 and a PPV of 0.75.

3.2.2 | p-Tau217 distribution across diagnoses

Plasma p-tau217 levels were highest in the AD dementia (median = 1.04 pg/mL, interquartile range [IQR] = [0.43–1.52]) and MCI+ (median = 0.80 pg/mL, IQR = [0.42–1.16]) groups. The diagnostic groups with the lowest p-tau217 concentrations were SCD− (median = 0.23 pg/mL, IQR = [0.13–0.31]) and Neurology (median = 0.24 pg/mL, IQR = [0.12–0.29]) (Figure 3A). The p-tau217 levels of the AD dementia group were significantly elevated compared to the SCD−, Neurology, FTD, and Suspected Psychiatry groups (p-value < 0.01 for all), and were also significantly elevated in the MCI+ group compared to the SCD− and Neurology groups (p-value < 0.05 for both) (Table S1, Figure S2A). After dichotomizing the groups as low/high p-tau217, the groups with the highest proportion of patients with high p-tau217 were AD dementia (n = 84, 70% of AD dementia patients) and MCI+ (n = 25, 68% of MCI+ patients). The groups with the lowest proportion of patients with high p-tau217 were Neurology (n = 0, 0% of Neurology patients) and SCD− (n = 1, 1.2% of SCD− patients) (Figure S3).

3.2.3 | NfL distribution across diagnoses

Plasma NfL was most elevated in the Dementia Other (median = 35.4 pg/mL, IQR = [17.3–72.6]) and FTD (median = 32.0 pg/mL, IQR = [23.2–40.5]) groups, and lowest in the SCD− (median = 11.8 pg/mL, IQR = [9.1–18.6]) and Suspected Psychiatry (median = 14.0 pg/mL, IQR = [10.4–20.7]) groups (Figure 3B). NfL levels were significantly higher in the FTD and Dementia Other groups compared to the SCD−, SCD+, Suspected Psychiatry, AD-Dementia, and MCI+ groups (p-value < 0.001 for all), as well as the MCI− group (p-value < 0.01 for both) and DLB (p-value < 0.05 for both). NfL levels were also significantly higher in patients in the AD dementia, MCI+, and Neurology diagnostic groups compared to those with a SCD− diagnosis (p-value < 0.05 for all), and significantly higher in AD dementia patients compared to those in the Suspected Psychiatry group (p-value = 0.05) (Table S2, Figure S2B). After applying the age-adjusted NfL cutoffs, the groups with the highest proportion of patients with high NfL were FTD (n = 26, 79% of FTD patients), Neurology (n = 6, 67% of Neurology patients), and Dementia Other (n = 11, 65% of Dementia Other patients). The groups with the lowest proportion of patients with high NfL were SCD− (n = 23, 27% of SCD− patients) and MCI+ (n = 9, 24% of MCI+ patients) (Figure S3).

3.2.4 | Patient profiles based on p-tau217 and NfL

The most common profile was low p-tau217/low NfL (n = 137, 37%), followed by low p-tau217/high NfL (n = 99, 27%). The

TABLE 1 Clinical characteristics per diagnosis.***

	Female sex *n* (%)	Age, years median [IQR]	MMSE mean ± SD	Amyloid positivity *n* (%)	*APOE ε4* carriage *n* (%)	p-Tau217 concentration median [IQR]	NfL concentration median [IQR]
SCD− (*n* = 89)	49 (55)	59 [54–64]	28.2 ± 2.2	0 (0)	35 (39)	0.23 [0.13–0.23]	11.8 [9.1–18.6]
Assessed (*n*)	89	89	89	89	89	78	84
SCD+ (*n* = 15)	6 (40)	64 [62–70]	28.5 ± 1.5	15 (100)	9 (60)	0.62 [0.39–0.87]	17.5 [13.8–20.5]
Assessed (*n*)	15	15	15	15	15	13	14
MCI− (*n* = 13)	4 (31)	68 [62–70]	27.9 ± 2.1	0 (0)	5 (38)	0.30 [0.24–0.40]	17.2 [15.0–25.7]
Assessed (*n*)	13	13	13	13	13	12	12
MCI+ (*n* = 37)	16 (43)	67 [64–72]	27.2 ± 2.0	37 (100)	27 (73)	0.80 [0.42–1.16]	16.9 [14.1–25.1]
Assessed (*n*)	37	37	37	37	36	36	35
AD dementia (*n* = 138)	70 (51)	66 [60–71]	21.4 ± 4.7	106 (100)	99 (72)	1.04 [0.43–1.52]	20.5 [15.1–26.3]
Assessed (*n*)	138	138	133	106	137	120	133
DLB (*n* = 17)	3 (18)	66 [64–69]	23.2 ± 4.9	4 (33)	7 (41)	0.41 [0.15–0.68]	18.7 [12.9–27.9]
Assessed (*n*)	17	17	17	12	16	15	17
FTD (*n* = 35)	16 (46)	63 [59–69]	24.0 ± 4.6	1 (4.2)	6 (71)	0.33 [0.19–0.42]	32.0 [23.2–40.5]
Assessed (*n*)	35	35	35	24	35	33	35
Dementia Other (*n* = 18)	11 (61)	68 [63–71]	22.0 ± 5.0	0 (0)	4 (22)	0.28 [0.19–0.51]	35.4 [17.3–72.6]
Assessed (*n*)	18	18	18	13	18	16	17
Suspected Psychiatry (*n* = 44)	18 (41)	61 [52–65]	25.8 ± 3.0	0 (0)	13 (30)	0.31 [0.21–0.47]	14.0 [10.4–20.7]
Assessed (*n*)	44	44	44	28	28	40	43
Neurology (*n* = 9)	4 (44)	60 [52–65]	26.6 ± 2.1	0 (0)	2 (22)	0.24 [0.12–0.29]	18.9 [14.0–30.1]
Assessed (*n*)	9	9	9	5	9	9	9
Total (*n* = 415)	197 (47)	64 [58–69]	24.8 ± 4.7	159 (38)	208 (50)	0.40 [0.19–0.95]	18.3 [12.4–26.3]
Assessed (*n*)	415	415	410	342	396	372	399
p	0.16	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Abbreviations: AD dementia, Alzheimer's disease dementia; *APOE*, apolipoprotein E; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; MCI−, mild cognitive impairment without underlying AD pathology; MCI+, mild cognitive impairment with underlying AD pathology; MMSE, Mini-Mental State Examination; NfL, neurofilament light; p-tau217, phosphorylated tau-217; SCD−, subjective cognitive decline without underlying AD pathology; SCD+, subjective cognitive decline with underlying AD pathology.

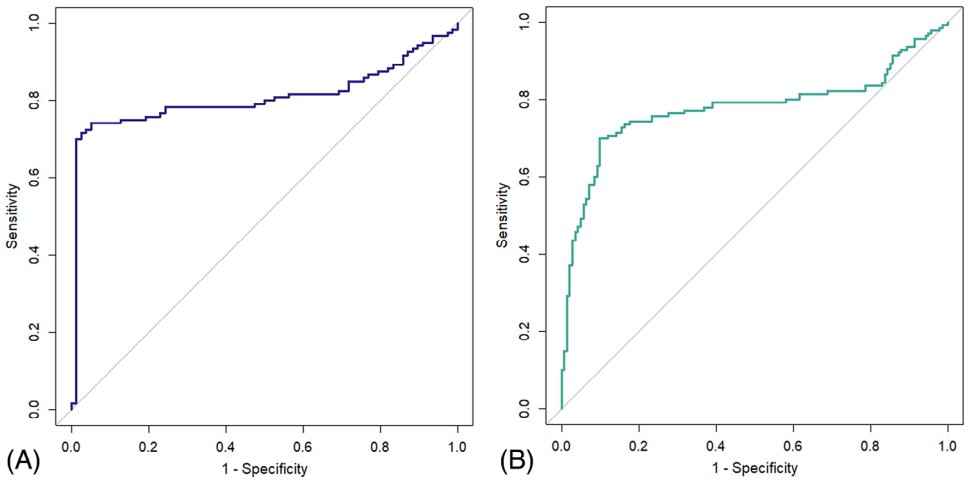

FIGURE 2 ROC curves. (A) ROC curve of SCD− vs AD from which the p-tau217 cutoff of 0.663 pg/mL was derived. AUC = 0.81 (95% CI: 0.74–0.87). (B) ROC curve of Aβ− vs Aβ+ with a cutoff of 0.61 pg/mL. AUC = 0.78 (95% CI: 0.72–0.84). Aβ, amyloid beta; AUC, area under the curve; CI, confidence interval; p-tau217, phosphorylated tau-217; ROC, receiver-operating characteristic.

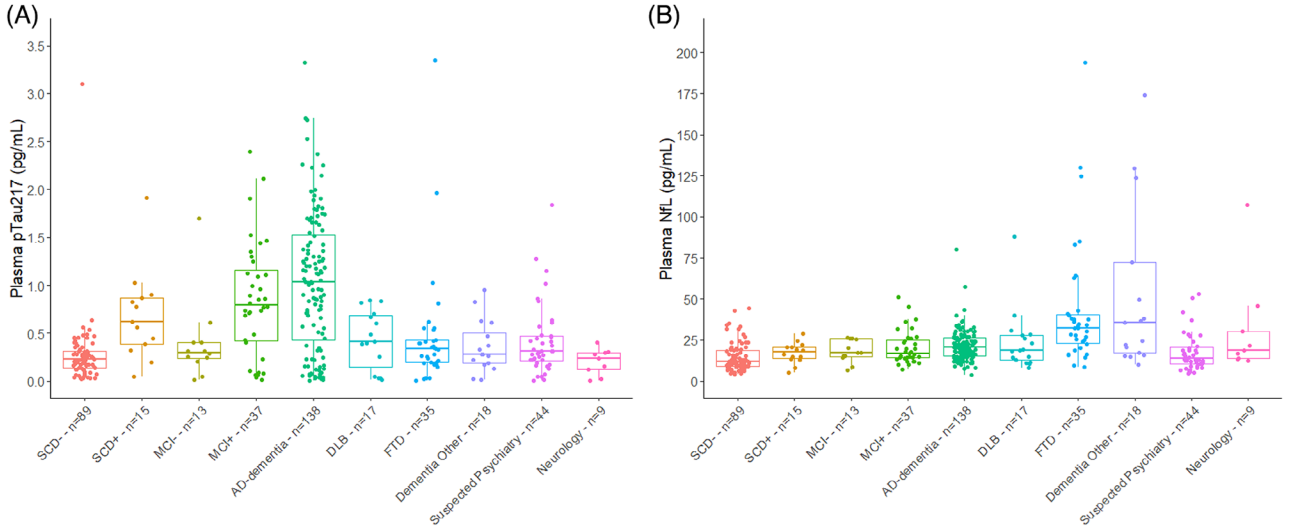

FIGURE 3 Biomarkers concentration within each diagnostic group. (A) p-Tau217 distribution; (B) NfL distribution. AD dementia, Alzheimer's disease dementia; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; MCI−, mild cognitive impairment without underlying AD pathology; MCI+, mild cognitive impairment with underlying AD pathology; SCD−, subjective cognitive decline without underlying AD pathology; SCD+, subjective cognitive decline with underlying AD pathology. For visibility, outliers are not pictured (one p-tau217; one NfL).

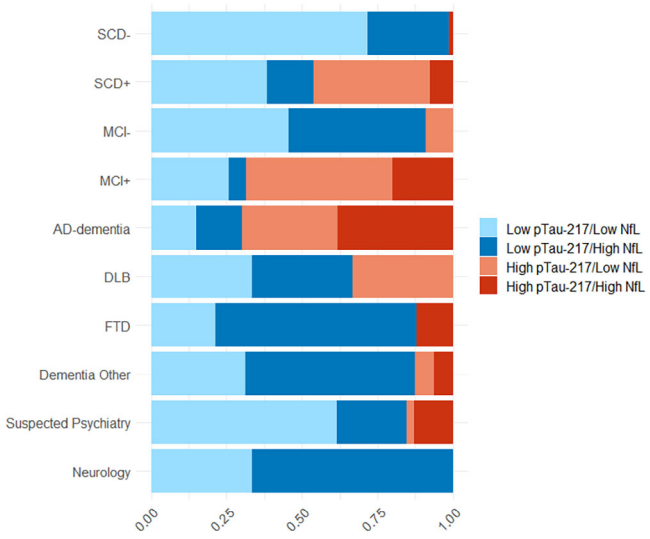

FIGURE 4 Proportion of patients in each of the four biomarker groups per diagnosis. Low/high plasma p-tau217 is based on Youden's index cutoff value of 0.66 pg/mL. Low/high plasma NfL is based on the value associated with the 90th percentile of normal based on each patient's age (mybiomarkers app). AD dementia, Alzheimer's disease dementia; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; MCI−, mild cognitive impairment without underlying AD pathology; MCI+, mild cognitive impairment with underlying AD pathology; SCD−, subjective cognitive decline without underlying AD pathology; SCD+, subjective cognitive decline with underlying AD pathology.

remaining patients were divided approximately evenly between high p-tau217/low NfL (n = 68, 18%) and high p-tau217/high NfL (n = 65, 18%) (Table S3). Figure 4 shows the distribution of these profiles over the different diagnoses. To determine which diagnosis was most prevalent per biomarker profile while also taking into account the large size difference between the different diagnostic groups, the raw count of patients per biomarker profile per diagnostic group was multiplied by the prevalence of that biomarker profile within that diagnostic group (Figure 5). Patients with a low p-tau217/low NfL profile were mostly SCD− patients (58%), followed by Suspected Psychiatry (21%). Patients with a high p-tau217/low NfL profile were most likely to be AD dementia patients (51%) or MCI+ patients (34%). Those with a high p-tau217/high NfL profile were most likely AD dementia patients (87%). Those with a low p-tau217/high NfL profile were most likely FTD patients (38%), followed by SCD− (15%) and Dementia Other (13%).

3.3 | Potential use of the p-tau217/NfL biomarker profiles in clinical practice

3.3.1 | AD versus frontotemporal lobar degeneration (FTLD) spectrum disease case

Mr. A, a 68-year-old man of North African origin, was referred for a second opinion. The patient had been diagnosed with a unipolar mood disorder in another hospital. His family disagreed with this diagnosis. During consultation, the patient and his family reported progressive problems in executive functioning, memory, and language. For example, he drove on the wrong side of the road, got lost multiple times, and could not speak, read, or write Dutch anymore while he previously could. The patient had a head-turning sign, bradyphrenia, apraxia, memory impairment, and word-finding difficulties. No other focal neurological deficits were found. His MMSE score was 18/30, his Montreal Cognitive Assessment (MoCA) score was 12/30, and his Geriatric Depression Scale score was 11/15. These scores suggested disorders in multiple domains and the presence of a mood disorder.

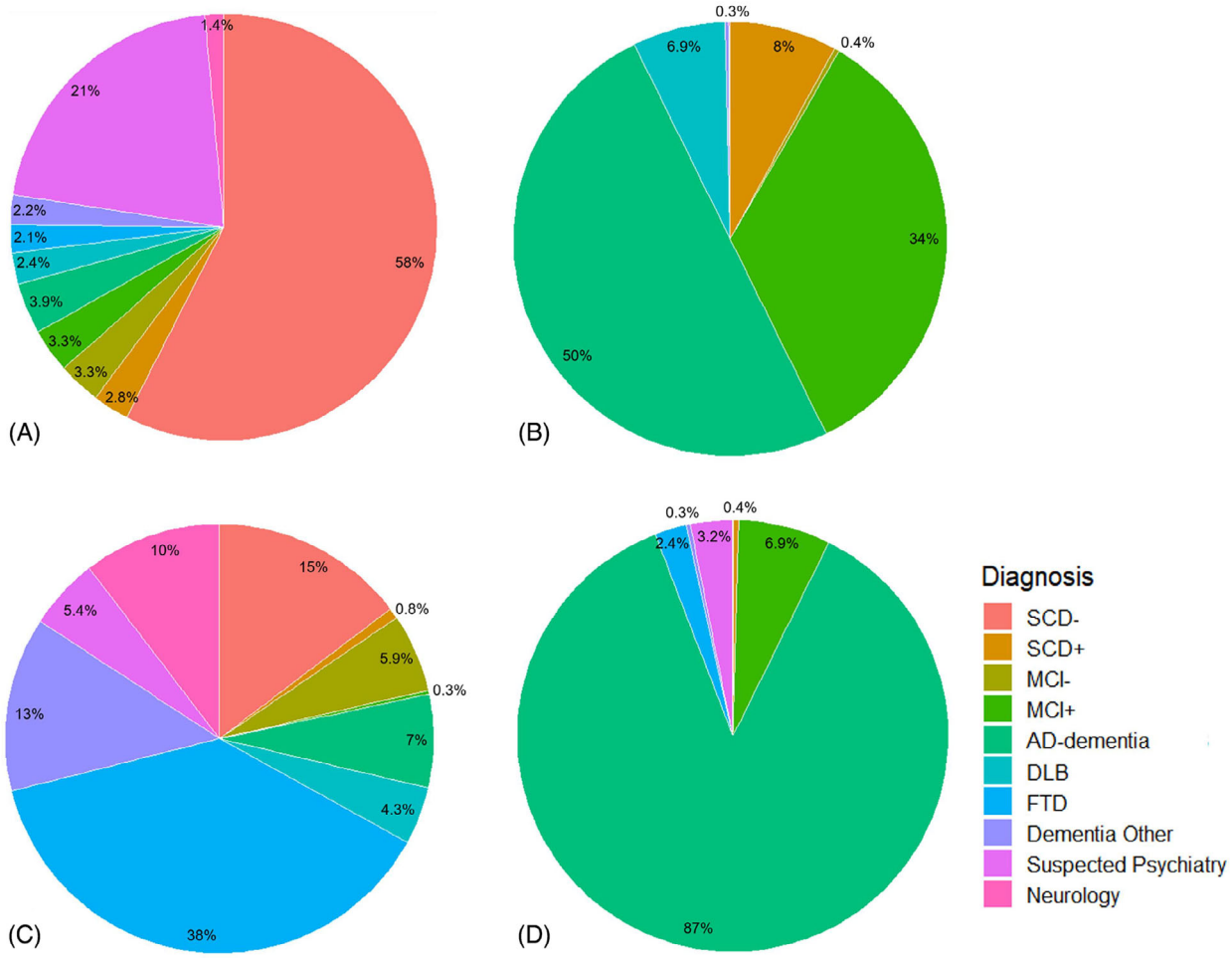

FIGURE 5 Count of patient diagnoses per biomarker profile, adjusted for prevalence within the diagnostic group. (A) Low p-tau217/low NfL; (B) high p-tau217/low NfL; (C) low p-tau217/high NfL; (D) high p-tau217/high NfL. AD dementia, Alzheimer's disease dementia; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; MCI−, mild cognitive impairment without underlying AD pathology; MCI+, mild cognitive impairment with underlying AD pathology; SCD−, subjective cognitive decline without underlying AD pathology; SCD+, subjective cognitive decline with underlying AD pathology.

Neuropsychological testing was complicated due to a language barrier but confirmed impaired executive functioning and language. Electroencephalography (EEG) revealed moderate bilateral abnormalities in the temporal lobes. Brain MRI showed neurodegenerative features with mild asymmetric cortical atrophy on the left parietal cortex which could be interpreted as suggestive for either underlying AD or frontotemporal lobar degeneration (FTLD) spectrum disorder. CSF biomarker values were abnormal for Aβ42 (753 pg/mL; cutoff value ≤1000 pg/mL), but normal for total tau ([t-tau] 150 pg/mL; cutoff value > 235 pg/mL), p-tau181 (9.7 pg/mL; cutoff value > 19 pg/mL), and the p-tau181/Aβ42 ratio (0.013; cutoff value > 0.020).

During the multidisciplinary meeting, a diagnosis of dementia was made. Due to persisting prominent parietal and memory clinical symptoms and the atrophy pattern on the MRI, AD was suspected to be the most likely etiology, whereas a FTLD spectrum disorder was considered to be less likely. However, CSF analyses showed an isolated low Aβ42 with a normal p-tau181/Aβ42 ratio, arguing against the AD diagnosis. Due to remaining clinical doubt, an amyloid PET scan was requested and found to be negative. Genetic testing revealed no underlying pathogeneous mutation. Over the next 2.5 years, the patient developed non-fluent speech, echolalia, and ultimately symmetric parkinsonism. These symptoms were clinically compatible with a corticobasal degeneration diagnosis.

Retrospective analyses of NfL and p-tau217 showed the following biomarker profile: a value of 85 pg/mL for NfL (cutoff: 22 pg/mL) and of 0.40 pg/mL for p-tau217 (cutoff: 0.66 pg/mL). This NfL measurement is particularly elevated, whereas the p-tau217 measurement is below this cohort's cutoff. This low p-tau217/high NfL biomarker profile supports the final FTLD spectrum disease diagnosis, as this profile occurs more frequently in the FTD and Dementia Other groups than in AD.

A second case (FTD vs Suspected Psychiatry) can be found in Supplement Part B.

4 | DISCUSSION

This study highlights the value of plasma p-tau217 and NfL in supporting diagnostic decision-making for dementia and non-dementia conditions in an unselected memory clinic cohort. The novel ALZpath p-tau217 plasma assay showed great specificity with modest sensitivity, suggesting a better use as a "rule-in" test for AD pathology (both at the MCI and dementia stage) rather than a "rule-out" in clinical settings. This was apparent when comparing p-tau217 levels between multiple diagnoses, where only a few group comparisons reached significance. Our results build o previous testing of the ALZpath assay in more selected cohorts, where it performed remarkably well in detecting Aβ and tau pathology across the AD continuum.[16,39] The lower assay sensitivity in our cohort compared to previous studies is likely due to the greater heterogeneity of diagnoses in an unselected cohort. Comorbidities or other confounding factors for which we did not control could also influence the sensitivity in a negative manner. However, our main aim was to study the prevalences of positive biomarker measures in a prospective, unselected clinical cohort, and not validation of the plasma biomarkers against a reference test.

The cutoff derived in this cohort is similar to the 95% specificity cutoff reported by Ashton et al.[16] Other assays currently available for plasma p-tau217 detection show good potential for discriminating between Aβ− and Aβ+ in AD-continuum cohorts, with AUCs ranging from 0.82 to 0.96 for the Janssen assay,[40–42] 0.71 to 0.94 for the Lilly assay,[40–42] and 0.92 to 0.97 for the Fujirebro assay.[15] For the ALZpath assay, our own AUC was 0.78, and Ashton and al. reported AUCs ranging from 0.92 to 0.96.[16] It is interesting to note that our AUC is significantly lower than the AUC reported by Ashton et al. Pre-analytical factors are not a likely cause, since p-tau and NfL are very resistant to major preclinical factors.[35] Analytical factors such as batch differences could be a cause. For optimizing diagnostic accuracy, a two cut-point approach might help.

The results of the current study support previous studies regarding the strong association between p-tau217 and AD pathology.[13,14,43–45] p-Tau217 levels were also elevated in about a third of patients in the DLB group in our study. This is unsurprising, as there is a high co-pathology rate between DLB and AD dementia.[46] DLB is largely diagnosed based on clinical assessment, whereas confirming AD co-pathology requires additional invasive testing.[29] Plasma p-tau217 may detect AD co-pathology in patients with DLB as a primary diagnosis, as reported before for p-tau217, p-tau181, and p-tau231.[47,48]

High NfL levels were strongly associated with dementia (AD dementia, FTD, and Dementia Other), whereas low levels were associated with SCD, MCI, and non-neurological conditions. NfL could differentiate FTD from other dementia types, particularly AD dementia. This is in agreement with previous studies.[13,19–21,49,50] The magnitude of the NfL elevation differed significantly between different disorders (Figure S2B), an effect not quite reflected by a low/high dichotomy. Adding a second NfL cutoff to differentiate between high NfL levels and drastically elevated NfL levels might improve the use of NfL for clinical support of diagnosis. In our own cohort, 12 patients with a variety of conditions were above this second cutoff, indicating that it could be useful for rare diseases.

Creating biomarker profiles based on low/high plasma NfL and p-tau217 levels allowed for further differentiation between SCD−/+, MCI−/+, Suspected Psychiatry, AD dementia, and FTD. Some of the diagnostic groups were too small (DLB) or too diverse (Neurology and Dementia Other) to draw firm conclusions. The potential clinical application of the biomarker profiles was also illustrated in the case reports. Plasma p-tau217 and NfL could have provided valuable information for the clinician to feel more secure in their decision. Furthermore, the information provided by the plasma biomarkers was in line with the information provided by the CSF analysis (ruling out AD pathology), suggesting that plasma analysis might suffice as an initial workup, making lumbar punctures an additional test performed in the case of uncertainty. Because these plasma biomarkers provide extra information this might reduce the need for additional ancillary investigations.

Before clinical implementation, we recommend further prospective validation of these biomarkers in larger cohorts from different centers, which will help define reference ranges for the ALZpath p-tau217 assay, as has already been done for NfL.[38] As no externally validated cutoff was available for this assay, our cutoff had to be derived from and applied back into the cohort. Nevertheless, our cutoff of 0.66 was very similar to the high-specificity cutoff (0.63 pg/mL) reported by Ashton et al.[16] Second, as mentioned above, we believe that the interpretation of NfL levels needs more nuance. Our sensitivity analysis showed that an alternative cutoff might, for example, allow for better differentiation between AD dementia and FTD (Table S4).

A strength of our study is the use of biomarker profiles based on low/high p-tau217 and NfL. These profiles differentiate disease etiology (AD vs FTD, FTD vs Suspected Psychiatry, MCI− vs MCI+) and stage (MCI+ vs. AD-dementia), both of which inform disease progression and treatment options. Another strength of our study is the use of a large unselected memory clinic cohort. Of note, our clinic is a specialized, tertiary memory clinic, which means that our findings need to be validated in other types of memory clinic cohorts. Including from our specialized tertiary clinic also leads to a limiation, which it that some diagnoses were underrepresented (vascular dementia, non-dementia neurological disorders), which makes it challenging to characterize the biomarker profiles of these conditions.

In conclusion, we showed that the combination of plasma p-tau217 and NfL can be used to differentiate between multiple diagnoses in a prospective unselected memory cohort. However, prospective validation of these biomarkers and assays is needed before implementation in clinical care. For now we envision the use of these biomarkers as a support tool for clinicians to be used with other forms of clinical assessment.

ACKNOWLEDGMENTS

Rebecca Z. Rousset participated in the laboratory measurements and performed the statistical analysis. Thomas Claessen provided clinical information and interpretation and selected the case studies. Rebecca

Z. Rousset and Thomas Claessen contributed equally to the writing of the manuscript. Argonde C. van Harten, Afina W. Lemstra, Yolande A. L. Pijnenburg, and Wiesje M. van der Flier are responsible for maintaining the Amsterdam Dementia Cohort data set and providing additional clinical input. Andreas Jeromin is an employee of ALZpath and provided the necessary reagents for the measurement of p-tau217. Andreas Jeromin, Inge M. W. Verberk, and Charlotte E. Teunissen designed the project. Anouk den Braber reviewed and provided input on the statistical plan. All authors reviewed and provided important feedback to the manuscript. Research of Charlotte E. Teunissen is supported by the European Commission (Marie Curie International Training Network, grant agreement No 860197 (Multi-omics Interdisciplinary Research Integration to Address DEmentia diagnosis)), Innovative Medicines Initiatives 3TR (Horizon 2020, grant no 831434), European Platform for Neurodegenerative Diseases (Innovative Medicines Initiative 2 Joint Undertaking (JU), grant No. 101034344) and Joint Programme - Neurodegenerative Disease (blood PRotein Identification to Discriminate dEmentias), National MS Society (Progressive MS alliance), Alzheimer's Drug Discovery Foundation, Alzheimer's Association, Health~Holland, Topsector Life Sciences & Health, the Dutch Research Council (Nederlandse Organisatie voor Wetenschappelijk Onderzoek), The Selfridges Group Foundation, Stichting Alzheimer Nederland. Research of Alzheimer's Center Amsterdam is part of the neurodegeneration research program of Amsterdam Neuroscience. Alzheimer Center Amsterdam is supported by Stichting Alzheimer Nederland and Stichting Steun Alzheimercentrum Amsterdam. The chair of Wiesje van der Flier is supported by Pasman Stichting. Wiesje M. van der Flier and Charlotte E. Teunissen are recipients of A Personalized Medicine Approach for Alzheimer's Disease (ABOARD), which is a public-private partnership receiving funding from ZonMW (#73305095007) and Health~Holland, Topsector Life Sciences & Health (PPP-allowance; #LSHM20106). More than 30 partners participate in ABOARD. ABOARD also receives funding from Edwin Bouw Fonds and Gieskes-Strijbisfonds. Charlotte E. Teunissen, Argonde C. van Harten, and Wiesje M. van der Flier are recipients of Timely, Accurate and Personalized (TAP)-dementia, receiving funding from ZonMW (#10510032120003) in the context of Onderzoeksprogramma Dementie, part of the Dutch National Dementia Strategy.

CONFLICT OF INTEREST STATEMENT

Andreas Jeromin is an employee of ALZpath, Inc. and has stock options. Charlotte E. Teunissen has research contracts with Acumen, ADx Neurosciences, AC-Immune, Alamar, ALZpath, Aribio, Axon Neurosciences, Beckman-Coulter, BioConnect, Bioorchestra, Brainstorm Therapeutics, Celgene, Cognition Therapeutics, EIP Pharma, Eisai, Eli Lilly, Fujirebio, Grifols, Instant Nano Biosensors, Merck, Novo Nordisk, Olink, PeopleBio, Quanterix, Roche, Toyama, and Vivoryon. She is editor in chief of *Alzheimer's Research and Therapy*, and serves on editorial boards of *Medidact Neurologie/Springer*, and *Neurology: Neuroimmunology & Neuroinflammation*. She had speaker contracts for Eli Lilly, Novo Nordisk, Olink and Roche. Research programs of Wiesje van der Flier have been funded by ZonMW, Dutch Research council (NWO), EU-Joint Programme - Neurodegenerative Disease Research, EU-Innovative Health Initiative, Alzheimer Nederland, Hersenstichting CardioVascular Onderzoek Nederland, Health~Holland, Topsector Life Sciences & Health, stichting Dioraphte, Gieskes-Strijbis fonds, stichting Equilibrio, Edwin Bouw fonds, Pasman stichting, stichting Alzheimer & Neuropsychiatrie Foundation, Philips, Biogen MA Inc., Novartis-NL, Life-MI, Advancement Via Individual Determination, Roche BV, Fujifilm, Eisai, and Combinostics. Wiesje M. van der Flier holds the Pasman chair. Wiesje M. van der Flier has been an invited speaker at Biogen MA Inc., Danone, Eisai, WebMD Neurology (Medscape), NovoNordisk, Springer Healthcare, European Brain Council. Wiesje M. van der Flier is consultant to Oxford Health Policy Forum CIC, Roche, Biogen MA Inc., and Eisai. Wiesje M. van der Flier is member of steering cie of NovoNordisk evoke/evoke+. Wiesje M. van der Flier participated in advisory boards of Biogen MA Inc., Roche, and Eli Lilly. Wiesje M. van der Flier is member of the steering committee of evoke/evoke+ (NovoNordisk) (NCT04777296/NCT04777409). All funding is paid to her institution. Wiesje M. van der Flier is member of the steering committee of Project Alzheimer's Value Europe and Think Brain Health. Wiesje M. van der Flier was associate editor of *Alzheimer, Research & Therapy* in 2020/2021. Wiesje M. van der Flier is associate editor at *Brain*. Rebecca Z. Rousset, Thomas Claessen, Argonde C. van Harten, Afina W. Lemstra, Yolande A. L. Pijnenburg, and Inge M. W. Verberk have no potential conflicts of interest to disclose. Author disclosures are available in the Supporting information.

CONSENT STATEMENT

All participants gave consent for their information to be used in Alzheimer's Disease research during their enrolment in the Amsterdam Dementia Cohort.

ORCID

Rebecca Z. Rousset https://orcid.org/0000-0001-9355-7286

REFERENCES

1. 2023 Alzheimer's disease facts and figures. Alzheimers Dement 2023;19:1598-1695.
2. Oh ES, Rabins PV. Dementia. *Ann Intern Med*. 2019;171(5):ITC33-ITC48.
3. Rizzo G, Arcuti S, Copetti M, et al. Accuracy of clinical diagnosis of dementia with Lewy bodies: a systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry*. 2018;89:358-366.
4. Bott NT, Radke A, Stephens M, Kramer JH. Frontotemporal dementia: diagnosis, deficits and management. *Neurodegener Dis Manag*. 2014;4(6):439-454.
5. Ducharme S, Price BH, Larvie M, Dougherty DD, Dickerson BC. Clinical approach to the differential diagnosis between behavioral variant frontotemporal dementia and primary psychiatric disorders. *Am J Psychiatry*. 2015;172(9):827-837.
6. Rasmussen J, Langerman H. Alzheimer's Disease—Why we need early diagnosis. *Degener Neurol Neuromuscul Dis*. 2019;9:123-130.
7. Oldan JD, Jewells VL, Pieper B, Wong TZ. Complete evaluation of dementia: PET and MRI correlation and diagnosis for the neuroradiologist. *Am J Neuroradiol*. 2021;42(6):998-1007.
8. Arvanitakis Z, Shah RC, Bennett DA. Diagnosis and management of dementia: a review. *JAMA*. 2019;322(16):1589-1599.

9. Chapleau M, Iaccarino L, Soleimani-Meigooni D, Rabinovici GD. The role of amyloid PET in imaging neurodegenerative disorders: a review. *J Nucl Med*. 2022;63(6):13S-19S.
10. Jr CRJ, Bennett DA, Blennow K, et al. NIA-AA research framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement*. 2018;14(4):535-562.
11. Swift IJ, Sogorb-Esteve A, Heller C, et al. Fluid biomarkers in frontotemporal dementia|: past, present and future. *J Neurol Neurosurg Psychiatry*. 2021;92:204-215.
12. Teunissen CE, Verberk IMW, Thijssen EH, et al. Blood-based biomarkers for Alzheimer's disease towards clinical implementation. *Lancet Neurol*. 2022;21(1):66-77.
13. Brickman AM, Manly JJ, Honig LS, et al. Plasma p-tau181, p-tau217, and other blood-based Alzheimer's disease biomarkers in a multiethnic, community study. *Alzheimers Dement*. 2021;17:1353-1364.
14. Palmqvist S, Janelidze S, Quiroz YT, et al. Discriminative accuracy of plasma phospho-tau217 for Alzheimer disease vs other neurodegenerative disorders. *JAMA*. 2020;324(8):772-781.
15. Arranz J, Zhu N, Rubio-Guerra S, et al. Diagnostic performance of plasma pTau 217, pTau 181, Aβ 1–42 and Aβ 1–40 in the LUMIPULSE automated platform for the detection of Alzheimer disease. *Alz Res Therapy*. 2024;16:139-153.
16. Ashton NJ, Brum WS, Molfetta GD, et al. Diagnostic accuracy of a plasma phosphorylated tau 217 immunoassay for Alzheimer disease pathology. *JAMA Neurol*. 2024:e235319.
17. Thijssen EH, Joie RL, Strom A, et al. Association of Plasma P-tau217 and P-tau181 with clinical phenotype, neuropathology, and imaging markers in Alzheimer's disease and frontotemporal lobar degeneration: a retrospective diagnostic performance study. *Lancet Neurol*. 2021;20(9):739-752.
18. Bridel C, Wieringen WNv, Zetterberg H, et al. Diagnostic value of cerebrospinal fluid neurofilament light protein in neurology: a systematic review and meta-analysis. *JAMA Neurol*. 2019;76(9):1035-1048.
19. Thijssen EH, Verberk IMW, Kindermans J, et al. Differential diagnostic performance of a panel of plasma biomarkers for different types of dementia. *Alzheimers Dement*. 2022;14:e12285.
20. Chouliaras L, Thomas A, Malpetti M, et al. Differential levels of plasma biomarkers of neurodegeneration in Lewy body dementia, Alzheimer's disease, frontotemporal dementia and progressive supranuclear palsy. *J Neurol Neurosurg Psychiatry*. 2022;93:651-658.
21. Gendron TF, Heckman MG, White LJ, et al. Comprehensive cross-sectional and longitudinal analyses of plasma neurofilament light across FTD spectrum disorders. *Cell Reports Medicine*. 2022;3(4):100607.
22. Illán-Gala I, Lleo A, Karydas A, et al. Plasma tau and neurofilament light in frontotemporal lobar degeneration and Alzheimer disease. *Am Acad Neurol*. 2021;96:e671-e683.
23. Khalil M, Teunissen CE, Otto M, et al. Neurofilaments as biomarkes in neurological disorders. *Nat Rev Neurol*. 2018;14:577-589.
24. Willemse EAJ, Scheltens P, Teunissen CE, Vijverberg E. A neurologist's perspective on serum neurofilament light in the memory clinic: a prospective implementation study. *Alzheimer's Res Ther*. 2021;13:101.
25. Sarto J, Ruiz-García R, Guillén N, et al. Diagnostic performance and clinical applicability of blood-based biomarkers in a prospective memory clinic cohort. *Neurology*. 2023;100(8):e860-e873.
26. Flier WMvd, Scheltens P. Amsterdam dementia cohort: performing research to optimize care. *J Alzheimers Dis*. 2018;62:1091-1111.
27. WMv Flier, d, Pijnenburg YAL, Prins N, et al. Optimizing patient care and research: the Amsterdam Dementia Cohort. *J Alzheimers Dis*. 2014;41(1):313-327.
28. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):263-269.
29. McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies. *Neurology*. 2017;89(1):88-100.
30. Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*. 2011;134(9):2456-2477.
31. Bittner T, Zetterberg H, Teunissen CE, et al. Technical performance of a novel, fully automated electrochemiluminescence immunoassay for the quantitation of β-amyloid (1-42) in human cerebrospinal fluid. *Alzheimers Dement*. 2016;12(5):517-526.
32. Lifke V, Kollmorgen G, Manuilova E, et al. Elecsys® Total-Tau and Phospho-Tau (181P) CSF assays: analytical performance of the novel, fully automated immunoassays for quantification of tau proteins in human cerebrospinal fluid. *Clin Biochem*. 2019;72:30-38.
33. Willemse EAJ, Tijms BM, Berckel BNMv, et al. Comparing CSF amyloid-beta biomarker ratios for two automated immunoassays, Elecsys and Lumipulse, with amyloid PET status. *Alzheimers Dement*. 2021;13(1):e12182.
34. Harten ACv, Wiste HJ, Weigand SD, et al. Detection of Alzheimer's disease amyloid beta 1-42, p-tau, and t-tau assays. *Alzheimers Dement*. 2022;18(4):635-644.
35. Verberk IMW, Misdorp EO, Koelewijn J, et al. Characterization of preanalytical sample handling effects on a panel of Alzheimer's disease–related blood-based biomarkers: results from the Standardization of Alzheimer's Blood Biomarkers (SABB) working group. *Alzheimers Dement*. 2022;18(8):1484-1497.
36. Hendricks R, Baker D, Brumm J, et al. Establishment of neurofilament light chain Simoa assay in cerebrospinal fluid and blood. *Bioanalysis*. 2019;11(15):1405-1418.
37. Neurochemistry lab of the Amsterdam University Medical Centers TN. NfL interface for physicians 2022. https://mybiomarkers.shinyapps.io/Neurofilament/
38. Vermunt L, Otte M, Verberk IMW, et al. Age- and disease-specific reference values for neurofilament light presented in an online interactive support interface. *Ann Clin Transl Neurol*. 2022;9(11):1832-1837.
39. Therriault J, Ashton NJ, Pola I, et al. Comparison of two plasma P-Tau217 assays to detect and monitor Alzheimer's pathology. *EBioMedicine*. 2024;102:105046.
40. Janelidze S, Bali D, Ashton NJ, et al. Head-to-head comparison of 10 plasma phospho-tau assays in prodromal Alzheimer's disease. *Brain*. 2023;146(4):1592-1601.
41. Groot C, Cicognola C, Bali D, et al. Diagnostic and prognostic performance to detect Alzheimer's disease and clinical progression of a novel assay for plasma p-tau217. *Alzheimer's Res Ther*. 2022;14(1):67.
42. Ashton NJ, Puig-Pijoan A, Milà-Alomà M, et al. Plasma and CSF biomarkers in a memory clinic: head-to-head comparison of phosphorylated tau immunoassays. *Alzheimers Dement*. 2022;19(5):1913-1924.
43. Mielke MM, Aakre JA, Algeciras-Schimnich A, et al. Comparison of CSF phosphorylated tau 181 and 217 for cognitive decline. *Alzheimers Dement*. 2022;18:602-611.
44. Mielke MM, Dage JL, Frank RD, et al. Performance of plasma phosphorylated tau 181 and 217 in the community. *Nat Med*. 2022;28(7):1398-1405.
45. Barthelemy NR, Horie K, Sato C, Bateman RJ. Blood plasma phosphorylated-tau isoforms track CNS change in Alzheimer's disease. *J Exp Med*. 2020;217(11):e20200861.
46. Coulthard EJ, Love S. A broader view of dementia: multiple copathologies are the norm. *Brain*. 2018;141(7):1894-1897.
47. Gonzalez MC, Ashton NJ, Gomes BF, et al. Association of plasma p-tau181 and p-tau231 concentrations with cognitive decline in patients

with probable dementia with Lewy bodies. *JAMA Neurol*. 2022;79(1):1-6.
48. Hall S, Janelidze S, Londos E, et al. Plasma phospho-tau identifies Alzheimer's co-pathology in patients with Lewy Body Disease. *Mov Disord*. 2020;36(3):767-771.
49. Janelidze S, Palmqvist S, Leuzy A, et al. Detecting amyloid positivity in early Alzheimer's disease using combinations of plasma Aβ42/Aβ40 and p-tau. *Alzheimers Dement*. 2022;18:283-293.
50. Baiardi S, Quadalti C, Mammana A, et al. Diagnostic value of plasma p-tau181, NfL, and GFAP in a clinical setting cohort of prevalent neurodegenerative dementias. *Alzheimer's Res Ther*. 2022;14:153-164.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Rousset RZ, Claessen T, van Harten AC, et al. Performance of plasma p-tau217 and NfL in an unselected memory clinic setting. *Alzheimer's Dement*. 2024;16:e70003. https://doi.org/10.1002/dad2.70003