Received: 18 June 2024 | Revised: 26 September 2024 | Accepted: 27 September 2024

DOI: 10.1002/dad2.70031

Alzheimer's & Dementia
Diagnosis, Assessment & Disease Monitoring

RESEARCH ARTICLE

Aβ status assessment in a hypothetical scenario prior to treatment with disease-modifying therapies: Evidence from 10-year real-world experience at university memory clinics

Matthias Brendel[1,2,3] | **Tandis Parvizi**[1,4,5] | **Johannes Gnörich**[1] | **Christof Elias Topfstedt**[6] | **Katharina Buerger**[2,6] | **Daniel Janowitz**[6] | **Boris-Stephan Rauchmann**[7] | **Robert Perneczky**[2,3,5,8,9] | **Carolin Kurz**[7] | **Dirk Mehrens**[10] | **Wolfgang G. Kunz**[10] | **Julia Kusche-Palenga**[1] | **Agnes Bernadette Kling**[1] | **Antonia Buchal**[10] | **Elizabet Nestorova**[7] | **Sara Silvaieh**[4,5] | **Raphael Wurm**[4,5] | **Tatjana Traub-Weidinger**[11,12] | **Sigrid Klotz**[5,13] | **Günther Regelsberger**[5,13] | **Axel Rominger**[14] | **Alexander Drzezga**[15,16,17] | **Johannes Levin**[2,3,18] | **Elisabeth Stögmann**[4,5] | **Nicolai Franzmeier**[3,6,19] | **Günter U. Höglinger**[2,3,18]

[1]Department of Nuclear Medicine, LMU University Hospital, LMU Munich, Munich, Germany

[2]German Center for Neurodegenerative Diseases (DZNE) Munich, Munich, Germany

[3]Munich Cluster for Systems Neurology (SyNergy), Munich, Germany

[4]Department of Neurology, Medical University of Vienna, Vienna, Austria

[5]Comprehensive Center for Clinical Neurosciences and Mental Health, Medical University of Vienna, Vienna, Austria

[6]Institute for Stroke and Dementia Research (ISD), LMU University Hospital, LMU Munich, Munich, Germany

[7]Department of Psychiatry and Psychotherapy, LMU University Hospital, LMU Munich, Munich, Germany

[8]Ageing Epidemiology (AGE) Research Unit, School of Public Health, Imperial College London, London, UK

[9]Sheffield Institute for Translational Neuroscience (SITraN), University of Sheffield, Sheffield, UK

[10]Department of Radiology, LMU University Hospital, LMU Munich, Munich, Germany

[11]Division of Nuclear Medicine, Department of Biomedical Imaging and Image-Guided Therapy, Medical University of Vienna, Vienna, Austria

[12]Department of Diagnostic and Therapeutic Nuclear Medicine, Klinik Donaustadt, Vienna, Austria

[13]Division of Neuropathology and Neurochemistry, Department of Neurology, Medical University of Vienna, Vienna, Austria

[14]Department of Nuclear Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

[15]Department of Nuclear Medicine, Faculty of Medicine and University Hospital Cologne, Cologne, Germany

[16]German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany

[17]Institute of Neuroscience and Medicine (INM-2), Molecular Organization of the Brain, Forschungszentrum Jülich, Jülich, Germany

[18]Department of Neurology, LMU University Hospital, LMU Munich, Munich, Germany

[19]The Sahlgrenska Academy, Institute of Neuroscience and Physiology, Department of Psychiatry and Neurochemistry, Mölndal and Gothenburg, University of Gothenburg, Mölndal, Sweden

Matthias Brendel, Tandis Parvizi, and Johannes Gnörich contributed equally as first authors.

Elisabeth Stögmann, Nicolai Franzmeier, and Günter U. Höglinger contributed equally as last authors.

Correspondence
Matthias Brendel, Department of Nuclear Medicine, LMU University Hospital, LMU Munich, Marchioninistrasse 15, 81377 Munich, Germany.
Email: matthias.brendel@med.uni-muenchen.de

Funding information
Bright Focus Foundation, Grant/Award Number: A2021026S; Alzheimer's Association, Grant/Award Number: AARG-22-973496; Alzheimer Forschung Initiative, and the Hertie Network of Excellence in Neuroscience; German Center for Neurodegenerative Disorders; Hirnliga e.V.; Deutsche Forschungsgemeinschaft; Germany's Excellence Strategy within the Munich Cluster for Systems Neurology, Grant/Award Number: 390857198; Davos Alzheimer's Collaborative; VERUM Foundation; Robert-Vogel-Foundation; National Institute for Health and Care Research (NIHR) Sheffield Biomedical Research Centre, Grant/Award Number: NIHR203321; University of Cambridge–Ludwig Maximilian University Munich Strategic Partnership; German Excellence Initiative and Excellence Strategy and the European Commission under the Innovative Health Initiative program, Grant/Award Number: 101132356

Abstract

INTRODUCTION: With the advent of disease-modifying therapies, accurate assessment of biomarkers indicating the presence of disease-associated amyloid beta (Aβ) pathology becomes crucial in patients with clinically suspected Alzheimer's disease (AD). We evaluated Aβ levels in cerebrospinal fluid (Aβ CSF) and Aβ levels in positron emission tomography (Aβ PET) biomarkers in a real-world memory-clinic setting to develop an efficient algorithm for clinical use.

METHODS: Patients were evaluated for AD-related Aβ pathology from two independent cohorts (Ludwig Maximilian University [LMU], $n = 402$, and Medical University of Vienna [MUV], $n = 144$). Optimal thresholds of CSF biomarkers were deduced from receiver operating characteristic curves and validated against Aβ PET positivity.

RESULTS: In both cohorts, a CSF Aβ42/40 ratio ≥ 7.1% was associated with a low risk of a positive Aβ PET scan (negative predictive value: 94.3%). Implementing two cutoffs revealed 14% to 16% of patients with intermediate results (CSF Aβ42/40 ratio: 5.5%–7.1%), which had a strong benefit from Aβ PET imaging (44%–52% Aβ PET positivity).

DISCUSSION: A two-cutoff approach for CSF Aβ42/40 including Aβ PET imaging at intermediate results provides an effective assessment of Aβ pathology in real-world settings.

KEYWORDS
Alzheimer's disease, biomarkers, cerebrospinal fluid, dementia, positron emission tomography, real world

Highlights

- We evaluated cerebrospinal fluid (CSF) and positron emission tomography (PET) amyloid beta (Aβ) biomarkers for Alzheimer's disease in real-world cohorts.
- A CSF Aβ 42/40 ratio between 5.5% and 7.1% defines patients at borderline levels.
- Patients at borderline levels strongly benefit from additional Aβ PET imaging.
- Two-cutoff CSF Aβ 42/40 and PET will allow effective treatment stratification.

1 | INTRODUCTION

With the possible approval of anti-amyloid therapies for Alzheimer's disease (AD) in Europe on the horizon, assessing the patient's extracellular amyloid beta (Aβ) status before initiating drug treatment is of utmost importance. According to currently approved tests, the Aβ status can either be determined by Aβ levels in cerebrospinal fluid (CSF) or by positron emission tomography (PET) with Aβ radiotracers.[1] Costs, accessibility, and side effects of both assessments need to be considered together with the costs of Aβ-lowering therapies to ensure proper access to current health-care systems. In this regard, it is also crucial to develop diagnostic algorithms that provide optimized accuracy at minimal cost. Several studies have compared diagnostic accuracies of CSF and PET assessments and found considerable agreement.[2–5] However, regarding the determination of amyloid positivity, a discordance rate of 10% to 20% between these two modalities has been reported especially in earlier stages of the disease,[6–9] thus creating uncertainty in clinical practice when only one investigation is performed at the individual patient level. The implementation of blood-based biomarkers may streamline the prognostic and diagnostic work-up of AD and further reduce the number of invasive or cost-intensive examinations in the future.

Real-world scenarios that allow conclusions of Aβ status assessment at the individual patient level on an on-demand basis are still rare. Thus, we aimed to investigate 10-year real-world data of memory clinics at tertiary centers comprising two independent German and Austrian cohorts with the goal to set up an efficient algorithm for Aβ status assessment. We used CSF Aβ and Aβ PET as currently approved tests as a timely scenario due to the imminent approval of anti-amyloid antibodies in Europe, but we note that integration of blood-based biomarkers into the proposed two-cutoff approach will be straightforward upon approval.

2 | METHODS

2.1 | Study design and patient cohort

This retrospective, cross-sectional, bicentric study included participants from two independent cohorts: patients recruited through three specialized outpatient clinics at the Ludwig Maximilian University (LMU) hospital (Department of Psychiatry and Psychotherapy, Department of Neurology, Institute of Stroke and Dementia Research), $n = 402$, and the memory clinic of the Department of Neurology, Medical University of Vienna (MUV), $n = 144$. The German cohort included cognitively unimpaired individuals (either no objective cognitive concerns or subjective cognitive decline [SCD]) and cognitively impaired patients (categorized as having mild cognitive impairment [MCI], probable AD dementia, or other neurodegenerative disorders). Diagnoses of MCI and probable AD dementia were based on core clinical criteria according to the recommendations of the National Institute on Aging and Alzheimer's Association (NIA-AA).[10,11] Patients with subjective cognitive complaints who did not fulfill criteria for MCI were classified as SCD. Patients with non-AD neurodegenerative disorders fulfilled clinical criteria for frontotemporal dementia,[12] non-fluent or semantic primary progressive aphasia,[13] corticobasal syndromes,[14] progressive supranuclear palsy,[15] and vascular dementia.[16] The Austrian cohort consisted of cognitively impaired patients with a clinical diagnosis of MCI due to AD and probable AD dementia, based on core clinical criteria according to the NIA-AA recommendations.[10,11]

In the German cohort, subgroup analyses were performed in all patients with cognitive impairment (AD and non-AD neurodegenerative disorders, $n = 351$) and patients with a clinical diagnosis along the AD continuum (i.e., MCI due to AD and probable AD dementia, $n = 303$). In a next step, we combined patients with MCI and mild dementia (Mini-Mental State Examination [MMSE] > 20, functional impact mainly on instrumental activities of daily life),[17] as this group of patients with early symptomatic cognitive decline would be potential candidates for anti-amyloid therapies.

In addition to a thorough standardized diagnostic examination including neurological evaluation, neuropsychological testing, magnetic resonance imaging (MRI), and basic laboratory testing, all patients underwent Aβ PET imaging and CSF analyses of established AD biomarkers (Aβ42, Aβ40, total tau [t-tau], and phosphorylated tau 181 [p-tau181]). On this basis, the amyloid ratio (Aβ42/40) was determined.

2.2 | Neuropsychological examination

Assessment of cognitive function and analysis of different domains were conducted using the Neuropsychological Test Battery Vienna (NTBV) and the Vienna Visuo-Constructional Test 3.0 (VVT 3.0)[18–20] at the Department of Neurology, MUV. Adequate normative data from cognitively unimpaired individuals were available, and z scores for each variable were calculated and corrected for age, education, and sex. Depressive symptoms were assessed using the Beck Depression Inventory (BDI-II).[21] Similar assessments were performed at the Department of Psychiatry and Psychotherapy, LMU.

At the Institute for Stroke and Dementia Research, LMU, and the Department of Neurology, LMU, cognitive assessments were conducted using the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-NP) Plus battery, consisting of a standardized set of neuropsychological tests including MMSE, word list learning test, Trail Making Test Parts A and B, and word fluency test.[22,23]

The clinical distinction between MCI and dementia was determined by the results of neuropsychological testing, as well as the assessment of the individual's ability to perform activities of daily living.

2.3 | CSF AD biomarkers

CSF was obtained by lumbar puncture and handled based on current international recommendations.[24] Concentrations of Aβ42, Aβ40, p-tau181, and t-tau in CSF were measured using commercially available enzyme-linked immunosorbent assays (ELISA; Innotest beta-amyloid 1-42, Innotest beta-amyloid 1-40, Innotest phosphoTAU 181p, and Innotest hTAU Ag, Fujirebio Europe).[25,26]

RESEARCH IN CONTEXT

1. **Systematic Review**: The authors systematically reviewed the literature using PubMed. In light of the imminent approval of disease-modifying therapies in Europe, accurate and timely identification of patients who would benefit from these treatments is of great importance. Although growing evidence shows consistent results between currently approved biomarkers in cerebrospinal fluid (CSF) and positron emission tomography (PET) imaging in up to 90%, the widespread use of these biomarkers is still limited, and algorithms on an individual patient level are scarce.
2. **Interpretation**: We show that the implementation of a two-cutoff approach would substantially reduce the amount of additional biomarker testing. In both cohorts, a CSF amyloid beta (Aβ)42/40 ratio ≥ 7.1% was associated with a low risk of Aβ PET positivity, thus excluding an underlying amyloid pathology with a high negative predictive value. Patients exhibiting intermediate CSF Aβ42/40 results would benefit from additional PET imaging.
3. **Future Directions**: Follow-up studies regarding patients with intermediate and discordant results will be necessary, for example, with quantification tools for PET imaging or ultrasensitive immunoassays in CSF and blood, to better determine the diagnostic and prognostic value of these findings in a real-world setting before administration of anti-amyloid therapies.

2.4 | Aβ PET imaging

Aβ PET imaging was performed at the Department of Nuclear Medicine, LMU, and the Division of Nuclear Medicine, MUV. [^{18}F]flutemetamol Aβ PET scans (LMU and MUV; average dose: 182 ± 11 MBq), [^{18}F]florbetaben Aβ PET (LMU; average dose: 288 ± 14 MBq) or [^{11}C]Pittsburgh compound-B (PiB, MUV; average dose 400 MBq) were performed 90 to 110 minutes ([^{18}F]flutemetamol and [^{18}F]florbetaben) or 40 to 60 minutes (PiB) after injection on a Siemens Biograph 64 PET. Low-dose computed tomography (CT) was acquired for attenuation correction. Scans were evaluated daily by a visual read (resident with validation by an attending as an expert reader with > 500 evaluated Aβ PET scans) as positive or negative for the presence of cortical Aβ pathology. In the majority of the cases, attendings evaluated the scan blinded to the resident's opinion. Both resident and attending physicians received certified reader training for the interpretation of [^{18}F]flutemetamol (Vizamyl) and [^{18}F]florbetaben (Neuraceq) scans, following the guidelines and recommendations provided in the summary of product characteristics. PET images of [^{18}F]flutemetamol and PiB were analyzed using a rainbow color scale, while [^{18}F]florbetaben images were analyzed using a grayscale. The readers manually adjusted the threshold window using the pontine/cerebellar white/gray matter contrast as a reference. All readers had access to clinical information and morphology (i.e., MRI in ≈ 80%, CT in ≈ 20%). All images were systematically evaluated, starting at the level of the pons/cerebellum and moving upward through the frontal lobes, anterior cingulate, posterior cingulate, precuneus, temporoparietal regions (including the insula and lateral temporal lobes), including the striatal region for [^{18}F]flutemetamol and PiB scans. The interpretation was performed visually by comparing the tracer uptake in cortical gray matter to that in adjacent cortical white matter. If any of these regions showed clear positive (abnormal) activity, the image was classified as positive; otherwise, it was classified as negative. Semiquantitative Aβ PET data were additionally available for [^{18}F]flutemetamol and [^{18}F]florbetaben as supporting information to the readers, expressed as *z* scores in Aβ PET target regions (frontal, parietal, temporal, posterior cingulate cortex) and their composite. The pons was used as reference tissue for [^{18}F]flutemetamol and the cerebellar cortex was used as reference tissue for [^{18}F]florbetaben. In discrepant cases, the visual interpretation of the attending was decisive (< 15%). The attending regularly consulted a second attending before final decision making in discrepant cases.

2.5 | Statistical analysis

Diagnostic accuracy of CSF biomarkers for predicting the dichotomous Aβ PET result were assessed using receiver operating characteristic (ROC) curves. In this study, Aβ PET positivity determined by visual read was considered the standard of truth for Aβ status because agreement of Aβ PET with autopsy validation was 95% to 96% in phase 3 studies.[27,28] The predefined thresholds were successfully validated with Aβ PET positivity as the standard of truth for the investigated cohorts. Determination of optimal cutoffs was deduced from ROC analyses. A *P* value of < 0.05 was interpreted as statistically significant. All calculations were performed in SPSS (version 29.0.1.0, IBM).

3 | RESULTS

3.1 | Classification of Aβ PET status and predictive value of CSF biomarkers in the German cohort

Detailed characteristics of both cohorts are summarized in Table 1.

Considered alone, CSF Aβ42 levels (changing cutoff during the 10-year period: 375/450 pg/mL) demonstrated very low sensitivity (14.6%) and high specificity (94.7%) in detecting positivity in Aβ PET at the individual patient level in the German cohort. The CSF Aβ42/40 ratio (cutoff: 5.5%) showed superior performance, with 86.7% sensitivity and 87% specificity. CSF p-tau181 (cutoff: 61 pg/mL) showed a sensitivity of 74.1% in detecting positivity in Aβ PET, with a specificity of 67.1%. Additionally, the optimal cutoff values for the CSF biomarkers in this cohort were determined. These were calculated as 5.5% for the CSF Aβ42/40 ratio (area under the curve [AUC] = 0.92, 95% confidence interval [CI] = 0.89–0.95, $P < 0.001$), 689 pg/mL for CSF Aβ42 (AUC = 0.85, 95% CI = 0.81–0.89, $P < 0.001$), and 63.4 pg/mL for CSF p-tau181 (AUC = 0.78, 95% CI = 0.74–0.83, $P < 0.001$).

Next, we focused on patients with discrepant classification between Aβ PET and CSF to determine an optimized algorithm for the determination of the individual Aβ status. Considering the Aβ42/40 ratio the CSF test with the best performance (negative predictive value [NPV] 82.6%, positive predictive value [PPV] 90.2%), 31 of 178 (17.4%) patients did not show evidence of AD-related Aβ pathology in the CSF Aβ42/40 ratio based on a 5.5% threshold but a positive Aβ PET scan. Furthermore, 22 of 224 patients (9.8%) with diagnostic CSF Aβ42/40 ratio (i.e., a ratio ≤ 5.5%) exhibited a negative Aβ PET scan.

Within the subgroup of CSF Aβ42/40 ratio non-diagnostic cases (CSF Aβ42/40 ratio > 5.5%), a data-driven cutoff of 7.1% discriminated best between Aβ PET positive and negative cases ($n = 178$, AUC = 0.85, 95% CI = 0.77–0.93, $P < 0.001$, Figure 1). Patients with a CSF Aβ42/40 ratio between 5.5% and 7.1% ($n = 55$, 13.7%) revealed Aβ PET positivity in 43.6%, meaning that only 2.3 patients of this subpopulation had to be scanned to identify an additional case with Aβ positivity. To the contrary, patients with a CSF Aβ42/40 ratio ≥ 7.1% ($n = 123$, 30.6%) showed only 5.7% cases with Aβ PET positivity, indicating that 17.5 patients of this subpopulation would need to be scanned to detect an additional case with Aβ positivity (Figure 1). Subgroup analyses in patients with all-cause cognitive impairment ($n = 351$) and a clinical diagnosis of AD (MCI due to AD and probable AD dementia, $n = 303$) confirmed the value of a two-cutoff approach (Figures S1 and S2 in supporting information).

In contrast, within the subgroup of CSF Aβ42/40 ratio–positive patients ($n = 224$), no suitable cutoff value was identified to detect discrepant cases (9.8%) with negative Aβ PET (AUC = 0.61, 95% CI = 0.47–0.76, $P = 0.129$; Figure 1). The application of two cutoffs resulted in a higher NPV (94.3%), while the PPV remained unchanged (90.2%).

TABLE 1 Patient characteristics of the German and Austrian cohort.

	German cohort *n* = 402	Austrian cohort *n* = 144
Age	70.9 (64.2–76.1)	66.4 (59.3–75.1)
Sex (*f*)	189 (47%)	70 (48.6%)
MMSE	26 (23-28)	26 (22–28)
Amyloid PET tracer		
[^{18}F]florbetaben	86 (21.4%)	–
[^{18}F]flutemetamol	316 (78.6%)	67 (45.6%)
[^{11}C]Pittsburgh compound B	–	77 (53.5%)
Diagnoses		
CU/SCD	51 (12.7%)	–
MCI/AD dementia (mild)	267 (66.4%)	124 (86.1%)
AD dementia (moderate-severe)	36 (9.0%)	20 (13.9%)
Non-AD neurodegenerative disorders*	48 (11.9%)	–

Note: Data are presented as median and interquartile range (25th to 75th percentile) or *n* (%).
Abbreviations: AD, Alzheimer's disease; CU, cognitively unimpaired; f, female; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; PET, positron emission tomography; SCD, subjective cognitive decline.
*Non-AD neurodegenerative disorders included patients with frontotemporal dementia, primary progressive aphasia, corticobasal syndrome, progressive supranuclear palsy and vascular dementia. Patients were categorized either as MCI /mild dementia (*n* = 41) or moderate to severe dementia (*n* = 7).

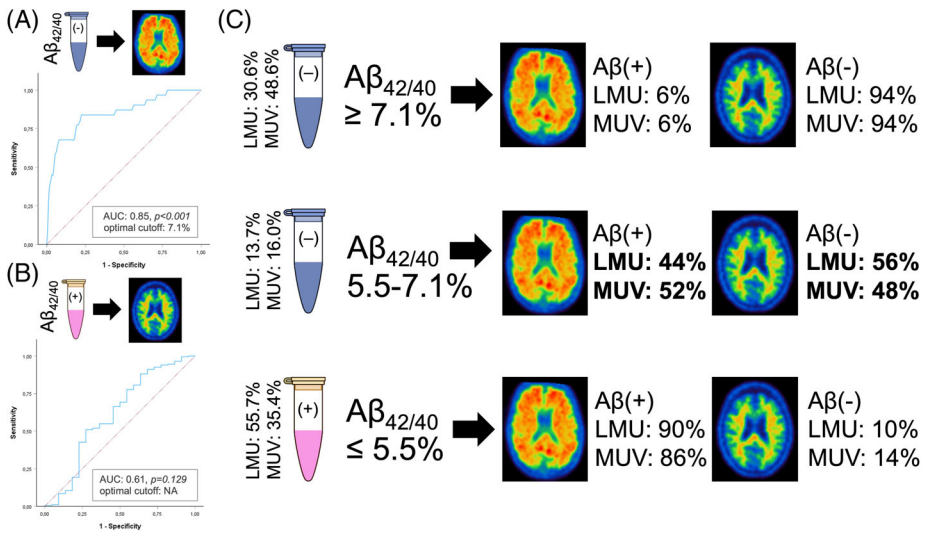

FIGURE 1 Data-driven cutoff for the CSF Aβ42/40 ratio regarding Aβ PET positivity and evaluation of a two-cutoff approach in the German (LMU) and Austrian (MUV) cohort. ROC curves were constructed to determine the optimal cutoff for the CSF Aβ42/40 ratio in predicting Aβ PET positivity in the CSF Aβ42/40 negative cohort (> 5.5%, A) and positive cohort (≤ 5.5%, B). These data-driven thresholds were further used to implement two cutoffs, which categorized patients as at low, intermediate, and high risk of harboring a positive Aβ PET scan (C). AUC, area under the curve; Aβ, amyloid beta; CSF, cerebrospinal fluid; LMU, Ludwig Maximilian University; MUV, Medical University of Vienna; PET, positron emission tomography; ROC, receiver operating characteristic

3.2 | Performance of CSF biomarkers regarding cerebral Aβ PET status in the Austrian validation cohort

In the Austrian cohort, both CSF Aβ42 (cutoff 500 pg/mL) and CSF Aβ42/40 (cutoff 7.0%) demonstrated higher sensitivity (80% and 93.3%, respectively) but lower specificity (65.5% and 79.8%, respectively) in detecting cerebral amyloidosis on Aβ PET imaging compared to the German cohort. CSF p-tau181 (cutoff 61 pg/mL) showed a sensitivity of 81.7% and specificity of 85.7% to detect positivity in Aβ PET.

Similar to the German cohort, CSF Aβ42/40 showed the best performance (NPV 94.4%, PPV 76.7%) regarding the prediction of

positivity in Aβ PET imaging. By applying the predefined threshold of 7.0%, 21 out of 144 patients (28.9%) yielded discordant results (Aβ42/40 > 7.0% and positive Aβ PET scan 5.6%, Aβ42/40 ≤ 7.0% and negative Aβ PET scan 23.3%). Using the predefined threshold of the German cohort (cutoff ≤ 5.5%), 23 of 144 patients (30.9%) yielded discordant results (Aβ42/40 > 5.5% and positive Aβ PET scan 17.2%, Aβ42/40 ≤ 5.5% and negative Aβ PET scan 13.7%), resulting in an NPV of 82.8% and PPV of 86.3%.

When the optimized two-cutoff approach of the German cohort was applied (≤ 5.5% and ≥ 7.1%), 16% of the patients were classified in the intermediate range, again with a high frequency of a positive Aβ PET scan in 52.2% of these cases. Notably, in patients with a CSF Aβ42/40 ratio ≥ 7.1%, only 5.7% of the patients showed positive Aβ PET scans, which is consistent with the findings of the German cohort. Comparing the two-cutoff approach with the threshold of the Austrian cohort (7.0%), the NPV remained high (94.3%), while the PPV was improved (86.3%).

3.3 | Diagnostic accuracy of CSF Aβ42/40 in predicting Aβ PET status in early symptomatic cognitive decline

In the next step, we focused on patients with MCI and mild dementia in the German cohort (n = 308). By applying a threshold of 5.5% for the CSF Aβ42/40 ratio, 28 of 122 patients (23%) showed discordant results, with positive Aβ PET scans and a ratio > 5.5%. Furthermore, 18 of 186 patients (9.7%) exhibited a ratio ≤ 5.5% with no evidence of cerebral amyloidosis in Aβ PET imaging.

In this cohort, the optimal cutoff value for the CSF Aβ42/40 ratio was 5.4% (AUC = 0.90, 95% CI = 0.86–0.94, P < 0.001), resulting in a sensitivity of 84.7%, specificity of 85.7%, NPV of 76.2%, and PPV of 91.2%. Additionally, in the subgroup of patients with a negative CSF ratio (i.e., > 5.5%, n = 122), a cutoff value of 7.2% differentiated best between Aβ PET positive and negative cases (AUC = 0.85, 95% CI = 0.76–0.94, P < 0.001).

Using both data-driven cutoffs, 15.6% of the patients (n = 48) obtained intermediate results (ratio between 5.4% and 7.2%), indicating positive Aβ PET scans in 52.1%. Notably, in those with a ratio ≥ 7.2%, positive Aβ PET scans were revealed only in 6.4%. Again, the two-cutoff approach acquired a higher NPV (93.6%), while the PPV remained unchanged (91.2%).

In the subgroup of early symptomatic patients with MCI due to AD and mild AD dementia (n = 267), who would be in-label candidates for anti-amyloid therapies, the optimal cutoff for the CSF Aβ42/40 ratio was 5.3% (AUC = 0.89, 95 CI% = 0.83–0.94, P < 0.001). In patients with a negative CSF ratio (i.e., > 5.5%, n = 84) a data-driven cutoff of 7.1% distinguished best between Aβ PET positive and negative cases (AUC = 0.89, 95% CI = 0.81–097, P < 0.001). Using both calculated thresholds, 16.1% of patients showed a CSF ratio in the intermediate range (i.e., CSF Aβ42/40 between 5.3% and 7.1%) with Aβ PET positivity in 62.8% of cases (Figure S3 in supporting information). Above a ratio of 7.1%, 10% of patients exhibited positive Aβ PET scans, resulting in an NPV of 90% and PPV of 93.1%.

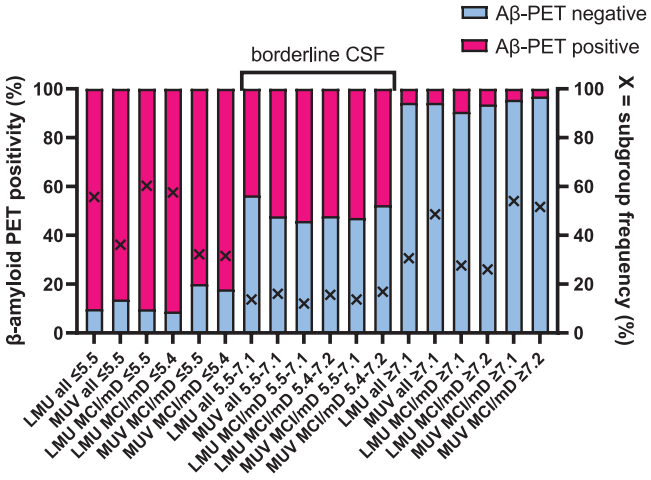

FIGURE 2 Discrepancies of cerebral Aβ status based on PET and CSF results in both cohorts at different cutoffs as well as proportions of Aβ PET positive and negative findings in the proposed borderline range of CSF Aβ42/40. Findings are displayed in both whole cohorts and subsets of early symptomatic patients. Frequencies of each group are illustrated in each bar (marked with X). Aβ, amyloid beta; CSF, cerebrospinal fluid; LMU, Ludwig Maximilian University; MCI, mild cognitive impairment; mD, mild dementia; MUV, Medical University of Vienna; PET, positron emission tomography

In MCI and mild dementia cases of the Austrian cohort (n = 124), a CSF Aβ42/40 threshold of 7.0% resulted in a sensitivity of 93.2%, specificity of 81.3%, NPV of 95.6%, and PPV of 73.2%. Discordant results were obtained in 18 patients (31.2%; Aβ42/40 > 7.0% and positive Aβ PET scan: 4.4%, Aβ42/40 ≤ 7.0% and negative Aβ PET scan: 26.8%). The predefined threshold of 5.4% of the German cohort led to an improvement of the PPV (82.1%), but a deterioration of the NPV (85.9%). The proportion of patients with discordant results remained similar (n = 19, 32%), with more patients exhibiting positive Aβ PET scans and a ratio > 5.4% (14.1%) and fewer patients with a ratio ≤ 5.4% and negative Aβ PET scans (17.9%). When applying both predefined cutoffs (≤ 5.4% and ≥ 7.2%), 21 out of 124 patients (16.9%) ranged between the two cutoffs, with positive Aβ PET scans in 47.6%. Above the ratio of 7.2%, only 3.1% showed positive Aβ PET scans. Compared to the threshold of the Austrian cohort (7.0%), both NPV (96.9%) and PPV (82.1%) were improved. Figure 2 summarizes discrepancies between Aβ status definition by PET and CSF in both cohorts at different cutoffs as well as proportions of Aβ PET positive and negative findings in the proposed borderline range of CSF Aβ42/40.

4 | DISCUSSION

In this retrospective study, we aimed to evaluate the diagnostic workflow for the assessment of cerebral Aβ status in a real-world memory-clinic setting in two independent cohorts. Using Aβ PET as the standard of truth, we identified borderline cases with a high

probability of Aβ PET positivity despite non-diagnostic CSF. By applying a two-cutoff approach based on the CSF Aβ42/40 ratio, we categorized patients as exhibiting a low, intermediate, and high probability of having an abnormal Aβ PET scan that could guide diagnostic algorithms of Aβ status determination in memory clinics.

Recent studies have also proposed the application of a two-cutoff threshold to improve the diagnostic accuracy of fluid biomarkers.[29–31] This would enhance the diagnostic certainty as well as reduce the number of additional confirmatory biomarker testing. The main finding of our study was that in both cohorts, patients with a CSF Aβ42/40 ratio ≥ 7.1% had a low risk of harboring a positive Aβ PET scan, resulting in a high NPV of 94.3%. In line with current proposed European recommendations regarding biomarker-based diagnosis,[1] these results would exclude an underlying AD pathology and require a reconsideration of the diagnostic suspicion.

In both cohorts, a small but relevant proportion of patients (13.7% and 16.0%) showed intermediate results (i.e., CSF Aβ42/40 ratio between 5.5%–7.1%), thus representing a group that should undergo additional Aβ PET imaging after CSF assessment to reevaluate brain amyloidosis and identify those patients who would benefit from anti-amyloid therapies. Future studies may also determine which patients should be referred to Aβ PET directly and which should receive CSF assessment first. Notably, these borderline cases may display patients with intermediate values not just in CSF but across different diagnostic modalities, particularly Aβ PET imaging, which could indicate the presence of an early AD-related neuropathological change in these patients.[29] Quantification of Aβ PET imaging and further standardization of collected data to reduce variability across tracers and sites (i.e., Centiloid Project)[32] may be of benefit in the future.

A CSF Aβ42/40 ratio ≤ 5.5% was considered Aβ positive in both study populations, with just a small proportion of patients exhibiting discordant Aβ PET results (i.e., negative, 9.8% and 13.7%). This may be in line with the hypothesis that a change of CSF Aβ42 and CSF Aβ42/40 occurs before the accumulation of dense, fibrillar Aβ plaques visualized by Aβ PET imaging, as both tests are likely assessing different species and states of Aβ accumulation.[33] In clinical practice, the concomitant assessment of CSF p-tau181 could potentially aid in ascertaining the detected brain amyloidosis as the underlying cause of the cognitive impairment, as tau pathology is the second essential proteinopathy required for the neuropathological diagnosis of AD.[1,17] Furthermore, the Aβ42/p-tau181 ratio has also demonstrated high concordance with Aβ PET imaging and is therefore included in the clinical routine assessments of CSF biomarkers in many memory clinics, particularly when Aβ40 is not available.[2,34–36]

In line with the whole study cohort, the values of the optimized thresholds remained unchanged in the subgroup of patients with cognitive impairment (CSF Aβ42/40 ratio ≤ 5.5% and ≥ 7.1%). The number of patients with intermediate CSF Aβ42/40 results was similar (13.4%), displaying positive Aβ PET scans in half of these cases, further emphasizing the need for additional biomarker testing in this patient group. In patients with a clinical AD diagnosis, the lower threshold for the CSF Aβ42/40 ratio was calculated as 5.3%, while the upper threshold remained the same (≥ 7.1%); 16.5% of patients showed intermediate CSF results with an even higher rate of positive Aβ PET scans in this group. Patients with a CSF Aβ42/40 ratio ≥ 7.1% showed positive Aβ PET results in 9.3% of patients, resulting in a slightly lower NPV of 90.7%, while the PPV was higher than in the whole cohort (93.5%). Similar results were obtained in the group of patients with MCI and mild dementia due to AD. This could be explained by the fact that the prevalence of amyloid positivity was higher in the group of patients with clinically suspected AD compared to the other groups that were analyzed. This led to a distinctly smaller group of amyloid-negative patients, which could potentially influence these results. However, it exemplifies the real-world setting of memory clinics, in which amyloid testing in CSF and PET imaging is not routinely performed in all patients with cognitive impairment.

When focusing on patients with early symptomatic all-cause dementia (i.e., MCI and mild dementia), the data-driven optimal cutoffs of the CSF Aβ42/40 ratio only slightly shifted to 5.4% and 7.2%, which may indicate the need for different thresholds depending on the clinical stage of the disease. The rate of intermediate results remained similar (15.6% and 16.9%), with only a few patients exhibiting a positive Aβ PET scan above the threshold of 7.2% (6.4% and 3.1%, NPV 93.6% and 96.9%).

In terms of predicting Aβ PET positivity, the CSF Aβ42/40 ratio demonstrated higher performance than the individual CSF biomarkers alone, which is consistent with previously published studies and might be explained by the control of interindividual variations regarding the natural fluctuations of the proteins as well as preanalytical factors.[2,35,37]

The recent US Food and Drug Administration approval of disease-modifying therapies in the United States has emphasized the urgent need for an accurate and timely diagnosis of AD pathology in patients with cognitive impairment. The use of currently available biomarkers is still limited due to the high costs of PET imaging and the invasiveness of CSF analysis, which hampers their widespread routine application. Additionally, a biomarker-based approach is reliant on geographic differences, particularly in terms of availability, accessibility, and feasibility.[38–40] Consequently, the decision on which biomarkers to use is frequently guided more by organizational and logistical considerations than by clinical and patient-related factors.[1,41,42] Furthermore, the application of multiple biomarkers may complicate the diagnostic process, making it challenging for clinicians to interpret the results. Thus, it is of great importance to implement an algorithm for routine clinical practice.

Although many studies show a strong concordance between CSF Aβ biomarkers and Aβ PET status, clinicians often encounter discordant results between these two investigations in everyday practice, which causes difficulties in the clinical routine for the specific diagnosis of individual patients. This issue will become even more relevant in the future when targeted therapies depend on it. Blood-based biomarkers may be of great value in the future regarding screening and risk stratification of patients with cognitive impairment but they still need to undergo validation in real-world cohorts before clinical implementation. Hence, appropriate use of available resources is crucial to ensure an accurate diagnosis with the lowest number of examinations.

The proposed workflow with a two-cutoff approach could assist in both confirming (rule in) as well as excluding (rule out) the presence of AD-related amyloid pathology and further identify those patients who would need additional biomarker testing before administration of anti-amyloid therapies. Future steps will need to improve methodologies and harmonize quantitative analyses of fluid biomarkers to establish standardized cutoffs and reference values across different assays and laboratories to grant equivalent and reliable results.[43] Because Aβ PET imaging in clinical practice is visually assessed for the absence or presence of Aβ deposits, interrater variability can display a problem, especially in borderline cases.[44] The implementation of new tracers and additional quantification tools could aid in providing a standardized quantitative measure for amyloid burden, allowing a better comparison across different tracers and sites, and facilitating fast and consistent analysis. In addition, Aβ PET imaging may gain a new significance once anti-amyloid therapies are approved in Europe, as the duration of the administration may depend on the removal of cerebral amyloid plaques visualized and quantified by PET imaging, which could lead to fewer infusions and lower treatment costs.[45–47]

The main strength of our study is the replication of our real-world data in an independent real-world cohort, which supports the generalizability of the proposed two-cutoff approach. This approach is ready to use in imminent anti-amyloid therapy evaluation. However, several limitations must be acknowledged. As classification of Aβ PET scan was assessed through visual read, we did not include quantification data, which would be of special interest in discordant and intermediate results. Furthermore, we did not obtain longitudinal analyses of CSF biomarker concentrations or plasma biomarkers. During the conduct of our study, analyses of core AD biomarkers in CSF were performed with commercially available ELISA in both cohorts. Hence, it would be of great interest to further validate the obtained results on automated platforms.

Due to the cross-sectional design of the study, we lack follow-up data on clinical outcomes to assess future cognitive decline and disease progression in cognitively unimpaired individuals. Our results do not clarify if specific patient subpopulations should undergo Aβ PET imaging before CSF assessment.

5 | CONCLUSION

In conclusion, our data demonstrate the utility of a two-cutoff approach for CSF Aβ42/40 assessment in a real-world setting of two independent cohorts. This approach would enhance the detection and, more importantly, exclusion of underlying amyloid pathology, especially in patients with MCI or mild dementia. Furthermore, we identified patients with borderline CSF results (14%–16%), who would strongly benefit from additional Aβ PET biomarker testing, and ultimately, reduce the number and costs of further examinations.

AUTHOR CONTRIBUTIONS

Matthias Brendel: conceptualization, validation, writing—original draft, visualization, supervision, project administration, funding acquisition; Tandis Parvizi and Johannes Gnörich: methodology, software, formal analysis, writing—original draft, visualization; Christof Elias Topfstedt: investigation, formal analysis; Katharina Buerger: investigation, resources; Daniel Janowitz: investigation, resources; Boris-Stephan Rauchman: investigation, resources; Robert Perneczky: investigation, resources, writing—review & editing, supervision; Carolin Kurz: investigation, resources; Dirk Mehrens: conceptualization, Wolfgang G. Kunz: conceptualization; Julia Kusche-Palenga: methodology, data curation; Agnes Bernadette Kling: methodology, data curation; Antonia Buchal: methodology, software, data curation; Elizabet Nestorova: methodology, software, data curation; Sara Silvaieh: resources; Raphael Wurm: resources; Tatjana Traub-Weidinger: resources; Sigrid Klotz: resources; Günther Regelsberger: resources; Axel Rominger: conceptualization, resources, funding acquisition; Alexander Drzezga: conceptualization, writing—review & editing, project administration; Johannes Levin: conceptualization, writing—review & editing, project administration; Elisabeth Stögmann: conceptualization, writing—review & editing, supervision, project administration; Nicolai Franzmeier: conceptualization, formal analysis, writing—review & editing, supervision, project administration; Günter U. Höglinger: conceptualization, writing—review & editing, supervision, project administration, funding acquisition.

ACKNOWLEDGMENTS

We would like to thank the patients and their families whose help and participation made this work possible. N.F. was funded by the Bright Focus Foundation (A2021026S), the Alzheimer's Association (AARG-22-973496), the Alzheimer Forschung Initiative, and the Hertie Network of Excellence in Neuroscience. R.P. is supported by the German Center for Neurodegenerative Disorders (Deutsches Zentrum für Neurodegenerative Erkrankungen, DZNE), the Hirnliga e.V. (Manfred-Strohscheer Stiftung), the Deutsche Forschungsgemeinschaft (DFG, 1007 German Research Foundation) under Germany's Excellence Strategy within the framework of 1008 the Munich Cluster for Systems Neurology (EXC 2145 SyNergy – ID 390857198), the Davos Alzheimer's Collaborative, the VERUM Foundation, the Robert-Vogel-Foundation, the National Institute for Health and Care Research (NIHR) Sheffield Biomedical Research Centre (NIHR203321), the University of Cambridge–Ludwig Maximilian University Munich Strategic Partnership within the framework of the German Excellence Initiative and Excellence Strategy and the European Commission under the Innovative Health Initiative program (project 101132356).

CONFLICT OF INTEREST STATEMENT

A.D. reports research support by Siemens Healthineers, Life Molecular Imaging, GE Healthcare, AVID Radiopharmaceuticals, Sofie, Eisai, Novartis/AAA, Ariceum Therapeutics as well as speaker honorary/advisory boards by Siemens Healthineers, Sanofi, GE Healthcare, Biogen, Novo Nordisk, Invicro, Novartis/AAA, Bayer Vital, Lilly; stock by Siemens Healthineers, Lantheus Holding, Structured therapeutics, Lilly; and a patent for 18F-JK-PSMA- 7 (Patent No.: EP3765097A1; Date of patent: Jan. 20, 2021). E.S. has received grants from Roche, Eisai, FFG/AAL, Horizon2020, and the Austrian Alzheimer Association

(all to the institution); consulting fees from Biogen, Eisai, and Lilly; support for attending meetings and/or travel from Roche; and has received payment for lectures, presentations, speakers bureaus, manuscript writing, or educational events by Biogen, Roche, Eisai, and Novartis. E.S. has participated on advisory boards (Biogen, Roche, Eisai, Sanofi) and held leadership or a fiduciary role in scientific societies (Austrian Alzheimer Association, the EAN scientific panel dementia). J.L. reports speaker fees from Bayer Vital, Biogen, EISAI, TEVA, Esteve, Zambon, and Roche; consulting fees from Axon Neuroscience, EISAI, and Biogen; author fees from Thieme medical publishers and W. Kohlhammer GmbH medical publishers; and is an inventor in a patent "Oral Phenylbutyrate for Treatment of Human 4-Repeat Tauopathies" (EP 23 156 122.6) filed by LMU Munich. In addition, he reports compensation for serving as chief medical officer for MODAG GmbH, is a beneficiary of the phantom share program of MODAG GmbH, and is an inventor in a patent "Pharmaceutical Composition and Methods of Use" (EP 22 159 408.8) filed by MODAG GmbH, all activities outside the submitted work. M.B. is a member of the Neuroimaging Committee of the EANM. M.B. received speaker honoraria from Roche, GE Healthcare, and Life Molecular Imaging and served as an advisor of MIAC and Life Molecular Imaging. N.F. has received speaker honoraria from Eisai, GE Healthcare, Life Molecular Imaging, and Consulting Honoraria from MSD. R.P. has received honoraria for advisory boards and speaker engagements from Roche, EISAI, Eli Lilly, Biogen, Janssen-Cilag, Astra Zeneca, Schwabe, Grifols, Novo Nordisk, and Tabuk. W.G.K. reports consulting fees from BMS, Boehringer Ingelheim, Need Inc., mintMedical, and FalkFoundation (unrelated to the paper). All other authors declare no competing interests. Author disclosures are available in the supporting information.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study was approved by the Ethics Committee of the LMU Hospital (399-09 and 17-569) and the Medical University of Vienna (EK 1965/2019) and conducted in accordance with the Declaration of Helsinki.

CONSENT STATEMENT

Written informed consent was obtained from all patients.

REFERENCES

1. Frisoni GB, Festari C, Massa F, et al. European intersocietal recommendations for the biomarker-based diagnosis of neurocognitive disorders. *Lancet Neurol*. 2024;23(3):302-312.
2. Doecke JD, Ward L, Burnham SC, et al. Elecsys CSF biomarker immunoassays demonstrate concordance with amyloid-PET imaging. *Alzheimers Res Ther*. 2020;12(1):36.
3. Palmqvist S, Zetterberg H, Blennow K, et al. Accuracy of brain amyloid detection in clinical practice using cerebrospinal fluid β-Amyloid 42: a cross-validation study against amyloid positron emission tomography. *JAMA Neurol*. 2014;71(10):1282-1289.
4. Palmqvist S, Zetterberg H, Mattsson N, et al. Detailed comparison of amyloid PET and CSF biomarkers for identifying early Alzheimer disease. *Neurology*. 2015;85(14):1240-1249.
5. Mattsson N, Insel PS, Landau S, et al. Diagnostic accuracy of CSF Ab42 and florbetapir PET for Alzheimer's disease. *Ann Clin Transl Neurol*. 2014;1(8):534-543.
6. Reimand J, Collij L, Scheltens P, Bouwman F, Ossenkoppele R, Initiative ADN. Association of amyloid-β CSF/PET discordance and tau load 5 years later. *Neurology*. 2020;95(19):e2648-2657.
7. Zwan M, van Harten A, Ossenkoppele R, et al. Concordance between cerebrospinal fluid biomarkers and [11C]PIB PET in a memory clinic cohort. *J Alzheimers Dis*. 2014;41(3):801-807.
8. Mattsson N, Insel PS, Donohue M, et al. Independent information from cerebrospinal fluid amyloid-β and florbetapir imaging in Alzheimer's disease. *Brain*. 2015;138(Pt 3):772-783.
9. de Wilde A, Reimand J, Teunissen CE, et al. Discordant amyloid-β PET and CSF biomarkers and its clinical consequences. *Alzheimers Res Ther*. 2019;11(1):78.
10. 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.
11. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment 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):270-279.
12. Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*. 2011;134(Pt 9):2456-2477.
13. Gorno-Tempini ML, Hillis AE, Weintraub S, et al. Classification of primary progressive aphasia and its variants. *Neurology*. 2011;76(11):1006-1014.
14. Armstrong MJ, Litvan I, Lang AE, et al. Criteria for the diagnosis of corticobasal degeneration. *Neurology*. 2013;80(5):496-503.
15. Höglinger GU, Respondek G, Stamelou M, et al. Clinical diagnosis of progressive supranuclear palsy: the movement disorder society criteria. *Mov Disord*. 2017;32(6):853-864.
16. Sachdev P, Kalaria R, O'Brien J, et al. Diagnostic criteria for vascular cognitive disorders: a VASCOG statement. *Alzheimer Dis Assoc Disord*. 2014;28(3):206-218.
17. Jack CR Jr, 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.
18. Lehrner J, Kogler S, Lamm C, et al. Awareness of memory deficits in subjective cognitive decline, mild cognitive impairment, Alzheimer's disease and Parkinson's disease. *Int Psychogeriatr*. 2015;27(3):357-366.
19. Pusswald G, Moser D, Gleiss A, et al. Prevalence of mild cognitive impairment subtypes in patients attending a memory outpatient clinic—comparison of two modes of mild cognitive impairment classification. results of the Vienna conversion to dementia study. *Alzheimers Dement*. 2013;9(4):366-376.
20. Lehrner J, Krakhofer H, Lamm C, et al. Visuo-constructional functions in patients with mild cognitive impairment, Alzheimer's disease, and Parkinson's disease. *Neuropsychiatrie*. 2015;29(3):112-119.
21. Kühner C, Bürger C, Keller F, Hautzinger M. Reliabilität und Validität des revidierten Beck-Depressionsinventars (BDI-II). *Nervenarzt*. 2007;78(6):651-656.
22. Welsh KA, Butters N, Mohs RC, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part V. A normative study of the neuropsychological battery. *Neurology*. 1994;44(4):609-614.
23. Morris JC, Heyman A, Mohs RC, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical

and neuropsychological assessment of Alzheimer's disease. *Neurology*. 1989;39(9):1159-1165.
24. Hansson O, Batrla R, Brix B, et al. The Alzheimer's Association international guidelines for handling of cerebrospinal fluid for routine clinical measurements of amyloid β and tau. *Alzheimers Dement*. 2021;17(9):1575-1582.
25. Vanmechelen E, Vanderstichele H, Davidsson P, et al. Quantification of tau phosphorylated at threonine 181 in human cerebrospinal fluid: a sandwich ELISA with a synthetic phosphopeptide for standardization. *Neurosci Lett*. 2000;285(1):49-52.
26. Vanderstichele H, Van Kerschaver E, Hesse C, et al. Standardization of measurement of β-amyloid (1-42) in cerebrospinal fluid and plasma. *Amyloid*. 2000;7(4):245-258.
27. Clark CM, Schneider JA, Bedell BJ, et al. Use of Florbetapir-PET for imaging β-Amyloid pathology. *JAMA*. 2011;305(3):275-283.
28. Sabri O, Sabbagh MN, Seibyl J, et al. Florbetaben PET imaging to detect amyloid beta plaques in Alzheimer's disease: phase 3 study. *Alzheimers Dement*. 2015;11(8):964-974.
29. Barthélemy NR, Salvadó G, Schindler SE, et al. Highly accurate blood test for Alzheimer's disease is similar or superior to clinical cerebrospinal fluid tests. *Nat Med*. 2024;30(4):1085-1095.
30. Brum WS, Cullen NC, Janelidze S, et al. A two-step workflow based on plasma p-tau217 to screen for amyloid β positivity with further confirmatory testing only in uncertain cases. *Nat Aging*. 2023;3(9):1079-1090.
31. Hansson O, Blennow K, Zetterberg H, Dage J. Blood biomarkers for Alzheimer's disease in clinical practice and trials. *Nat Aging*. 2023;3(5):506-519.
32. Klunk WE, Koeppe RA, Price JC, et al. The Centiloid Project: standardizing quantitative amyloid plaque estimation by PET. *Alzheimers Dement*. 2015;11(1):1-15.e154.
33. Palmqvist S, Mattsson N, Hansson O; Alzheimer's Disease Neuroimaging Initiative. Cerebrospinal fluid analysis detects cerebral amyloid-β accumulation earlier than positron emission tomography. *Brain*. 2016;139(Pt 4):1226-1236.
34. Willemse EAJ, Tijms BM, van Berckel BNM, 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.
35. Hansson O, Seibyl J, Stomrud E, et al. CSF biomarkers of Alzheimer's disease concord with amyloid-β PET and predict clinical progression: a study of fully automated immunoassays in BioFINDER and ADNI cohorts. *Alzheimers Dement*. 2018;14(11):1470-1481.
36. Schindler SE, Gray JD, Gordon BA, et al. Cerebrospinal fluid biomarkers measured by Elecsys assays compared to amyloid imaging. *Alzheimers Dement*. 2018;14(11):1460-1469.
37. Hansson O, Lehmann S, Otto M, Zetterberg H, Lewczuk P. Advantages and disadvantages of the use of the CSF amyloid β (Aβ) 42/40 ratio in the diagnosis of Alzheimer's Disease. *Alzheimers Res Ther*. 2019;11(1):34.
38. Hlavka JP, Mattke S, Liu JL. Assessing the preparedness of the health care system infrastructure in six European countries for an Alzheimer's treatment. *Rand Heal Q*. 2019;8(3):2.
39. Dubois B, Villain N, Frisoni GB, et al. Clinical diagnosis of Alzheimer's disease: recommendations of the international working group. *Lancet Neurol*. 2021;20(6):484-496.
40. Lang L, Clifford A, Wei L, et al. Prevalence and determinants of undetected dementia in the community: a systematic literature review and a meta-analysis. *BMJ Open*. 2017;7(2):e011146.
41. Bocchetta M, Galluzzi S, Kehoe PG, et al. The use of biomarkers for the etiologic diagnosis of MCI in Europe: an EADC survey. *Alzheimers Dement*. 2015;11(2):195-206. e1.
42. Riello R, Albini C, Galluzzi S, Pasqualetti P, Frisoni GB. Prescription practices of diagnostic imaging in dementia: a survey of 47 Alzheimer's centres in Northern Italy. *Int J Geriatr Psychiatry*. 2003;18(7):577-585.
43. Giangrande C, Delatour V, Andreasson U, Blennow K, Gobom J, Zetterberg H. Harmonization and standardization of biofluid-based biomarker measurements for AT(N) classification in Alzheimer's disease. *Alzheimers Dement*. 2023;15(3):e12465.
44. Yamane T, Ishii K, Sakata M, et al. Inter-rater variability of visual interpretation and comparison with quantitative evaluation of 11C-PiB PET amyloid images of the Japanese Alzheimer's Disease Neuroimaging Initiative (J-ADNI) multicenter study. *Eur J Nucl Med Mol Imaging*. 2017;44(5):850-857.
45. Sims JR, Zimmer JA, Evans CD, et al. Donanemab in early symptomatic Alzheimer disease. *JAMA*. 2023;330(6):512-527.
46. Boustani M, Doty EG, Garrison LP Jr, et al. Assessing the cost-effectiveness of a hypothetical disease-modifying therapy with limited duration for the treatment of early symptomatic Alzheimer disease. *Clin Ther*. 2022;44(11):1449-1462.
47. Ross EL, Weinberg MS, Arnold SE. Cost-effectiveness of aducanumab and donanemab for early Alzheimer disease in the US. *JAMA Neurol*. 2022;79(5):478-487.

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: Brendel M, Parvizi T, Gnörich J, et al. Aβ status assessment in a hypothetical scenario prior to treatment with disease-modifying therapies: Evidence from 10-year real-world experience at university memory clinics. *Alzheimer's Dement*. 2024;16:e70031. https://doi.org/10.1002/dad2.70031