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PERSPECTIVE

Clinical application of CSF biomarkers for Alzheimer's disease: From rationale to ratios

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Abstract

Biomarker testing is recommended for the accurate and timely diagnosis of Alzheimer's disease (AD). Using illustrative case narratives we consider how cerebrospinal fluid (CSF) biomarker tests may be used in different presentations of cognitive impairment to facilitate timely and differential diagnosis, improving diagnostic accuracy, providing prognostic information, and guiding personalized management in diverse scenarios. Evidence shows that (1) CSF ratios are superior to amyloid beta (Aβ)1-42 alone; (2) concordance of CSF ratios to amyloid positron emission tomography (PET) is better than Aβ1-42 alone; and (3) phosphorylated tau (p-tau)/Aβ1-42 ratio is superior to p-tau alone. CSF biomarkers are recommended for the exclusion of AD as the underlying cause of cognitive impairment, diagnosis of AD at an early stage, differential diagnosis of AD in individuals presenting with other neuropsychiatric symptoms, accurate diagnosis of AD in an atypical presentation, and for clinical trial enrichment.

KEYWORDS
Alzheimer's disease, cerebrospinal fluid biomarkers, diagnosis, mild cognitive impairment

Highlights:

- Cerebrospinal fluid (CSF) Alzheimer's disease (AD) biomarker testing may be underused outside specialist centers.
- CSF biomarkers improve diagnostic accuracy, guiding personalized management of AD.
- CSF ratios (amyloid beta [Aβ]1-42/Aβ1-40 and phosphorylated tau/Aβ1-42) perform better than single markers.
- CSF ratios produce fewer false-negative and false-positive results than individual markers.
- CSF biomarkers should be included in diagnostic work-up of AD and mild cognitive impairment due to AD.

1 | INTRODUCTION

Diagnosis of mild cognitive impairment (MCI) and Alzheimer's disease (AD) has evolved from a traditional description based on a clinical syndrome, to encompass a more detailed assessment of etiology, and biologic characterization of the disease using specific biomarkers (amyloid beta [Aβ] and tau), as described in the most recent criteria from the National Institute on Aging–Alzheimer's Association (NIA-AA) and the International Working Group (IWG).[1–3] Aβ and tau biomarkers can be measured in the cerebrospinal fluid (CSF); however, use of testing may be limited outside specialist and academic centers[4] because of barriers, such as reluctance to use a perceived invasive procedure like lumbar puncture, unfamiliarity with interpretation of test results, and skepticism about the clinical value of knowing an individual's biomarker status.[2,5] Ideally, physicians and their patients would like clear negative or positive results from diagnostic testing, but guidelines and uniformity in reporting test results from laboratory to physician and from physician to patients are still under development.[6,7] Studies of CSF biomarkers in regular clinical practice are under way.[8,9]

Previous reviews have indicated advantages and disadvantages of different biomarker strategies in dementia.[10,11] In this paper, we consider whether and how physicians should use CSF biomarkers in memory and dementia clinics beyond the academic and research settings. We present clinical cases to examine how CSF biomarkers could inform clinical practice decisions, by facilitating timely and accurate diagnosis, providing prognostic information, and guiding personalized management. We also consider the limitations of current biomarkers and look to future innovations.

RESEARCH IN CONTEXT

1. Systematic Review: We searched PubMed and other literature sources to evaluate the practical application and limitations of cerebrospinal fluid (CSF) biomarker tests in Alzheimer's disease (AD) or dementia so that we could provide relevant case studies to illustrate key issues hampering adequate application in clinical practice.
2. Interpretation: Although some physicians may be reluctant to use CSF biomarker tests routinely in patients with cognitive impairment, we illustrate with case descriptions how the advantages of testing outweigh possible disadvantages and skepticism about the value of knowing biomarker status.
3. Future Directions: Use of CSF biomarker tests optimizes patient management, including precise selection for novel disease-modifying drugs. New biomarker development should focus on minimizing invasive procedures and improving the detection of specific pathologic processes more accurately.

2 | METHODS

We searched PubMed in February 2021 using the terms: "dementia," "Alzheimer's disease," "prodromal Alzheimer's disease," "mild cognitive impairment," and "subjective cognitive decline"; "biomarker," "amyloid," "amyloid beta," "tau," "tau/amyloid beta ratio"; "amyloid beta42/amyloid beta40 ratio"; "lumbar puncture," "complications," and "safety"; "neuropsychology," "diagnosis," "differential diagnosis," "communication," "clinical decline," and "conversion to dementia." The search objective was to identify practical applications and limitations of biomarker tests in clinical practice to develop illustrative case studies based on experiences with real-life subjects in memory clinics. Background information and clinical details have been changed to protect anonymity while maintaining clinical authenticity.

3 | WHICH CSF BIOMARKERS ARE CURRENTLY RECOMMENDED?

CSF AD biomarkers provide a continuous, quantitative measure of AD-related proteins; the three core CSF biomarkers currently used for AD diagnostics are the 42 amino acid-long amyloid-beta peptide (Aβ1-42), total tau protein (t-tau), and tau phosphorylated at threonine 181 (p-tau181).[12] CSF biomarker testing has been improved by international quality programs[13] and immunoassays that run on fully automated analyzers that can measure multiple biomarkers (e.g., Elecsys® and Lumipulse®).[14,15]

3.1 | International guidelines recommend use of clinical symptoms and CSF biomarkers

Neuropsychological exam is the cornerstone for clinical diagnosis and can determine whether individuals have normal cognition, cognitive impairment, and/or dementia.[1] Table 1 summarizes current international guidelines for using CSF biomarkers as part of the diagnosis and classification of AD.[3,13,16,17] Core CSF biomarkers (Aβ1-42, t-tau, and p-tau) provide objective information about underlying disease pathology to support clinical work-up, and are recommended for timely and accurate diagnosis, for differential diagnosis, and to predict the risk and rate of clinical decline.[18,19]

Importantly, recent iterations of criteria from the IWG and NIA-AA research framework include recommendations for using clinical findings and abnormal biomarkers (Aβ and tau; Table 1).[1,3] These biomarkers define AD biologically throughout the disease continuum.[1,3] Biomarker testing is recommended for clinically symptomatic individuals where neuropsychological workup is indicative of cognitive decline. Biomarker testing is not routinely indicated for individuals with a normal neuropsychological examination because of the difficulty in classifying cognitively unimpaired biomarker-positive cases.[1]

TABLE 1 Recommendations from international guidelines for the use of biomarkers in the diagnosis of suspected AD[a]

Guideline	Diagnostic criteria for AD	Appropriate use criteria for CSF biomarkers in the differential diagnosis of cognitive impairment
IWG 2021[1]	AD diagnosis is restricted to people who have positive biomarkers together with specific AD phenotypes Biomarker-positive cognitively unimpaired individuals should be considered only at risk for progression to AD	Biological requirements: Aβ marker (CSF or PET) and tau marker (CSF or PET)
NIA-AA research framework[3]	AD should be defined as a biologic construct that is identified by biomarkers in living people Only biomarkers that are specific for hallmark AD proteinopathies (i.e., Aβ and pathologic tau) should be considered potential biomarker definitions of the disease	A: Aβ biomarkers determine whether an individual is in the AD continuum. T: Pathologic tau biomarkers determine whether someone who is in the AD continuum has AD. A and T indicate specific neuropathologic changes that define AD Neurodegenerative/neuronal injury biomarkers (N) and cognitive symptoms (C) are not specific to AD
Alzheimer's Association[16]	CSF biomarker testing is appropriate for specific clinical indications	Appropriate use of LP and CSF testing in the diagnosis of AD: • Patients with SCD considered at increased risk for AD • MCI that is persistent, progressing, and unexplained • Patients with symptoms that suggest possible AD • MCI or dementia with an onset at an early age (<65 years) • Patients meeting core clinical criteria for probable AD with typical age of onset • Patients whose dominant symptom is a change in behavior and where AD diagnosis is being considered
WFSBP Task Force[13]	The potential role of CSF biomarkers in early (predementia) diagnosis, differential diagnosis, prognosis, and selection for clinical trials is noted	• CSF alterations typical for AD have good diagnostic accuracy of more than 80% in discriminating MCI subjects who would convert to AD from those who remain stable or would progress to other dementias
BIOMARKAPD[17]	CSF AD biomarkers are recommended as a supplement to clinical evaluation	• CSF AD biomarkers are recommended to identify or exclude AD as the cause of dementia, for prognostic evaluation, and for guiding management of patients, particularly in atypical and uncertain cases • CSF biomarkers are recommended to predict the rate of clinical decline

[a]All guidelines also include recommendations for core clinical criteria and neuroimaging evidence to be used in the diagnosis of AD, which is not included here.

Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease; BIOMARKAPD, Biomarkers for AD and Parkinson's disease; CSF, cerebrospinal fluid; IWG, International Working Group; LP, lumbar puncture; MCI, mild cognitive impairment; NIA-AA, National Institute on Aging and Alzheimer's Association; SCD, subjective cognitive decline; WFSBP, World Federation of Societies of Biological Psychiatry.

3.2 | CSF biomarker ratios improve agreement with amyloid imaging

Diagnostic criteria for AD recognize both CSF biomarkers obtained by lumbar puncture and positron emission tomography (PET) imaging, which measures amyloid in cortical brain tissue and can detect deposition in different brain regions.[11] Table 2 summarizes positive and negative agreement values between core CSF biomarker results and amyloid PET imaging in studies using fully automated assay platforms.[14,15,20–24] Overall, 90% or more of subjects with a positive CSF Aβ test were also positive using amyloid PET imaging, whereas the degree of agreement between those testing negative both with CSF biomarkers and PET varied between 51% and 81%. These findings support CSF biomarkers as a convenient and cheaper alternative to amyloid PET imaging.[1]

Interestingly, studies found CSF biomarker ratios (Aβ1-42/1-40, p-tau/Aβ1-42, and t-tau/Aβ1-42) performed better than individually measured values.[14,20–23] For example, Schindler et al. used the fully automated Elecsys assays to compare CSF biomarker ratios to amyloid PET imaging in samples from 200 individuals enrolled in studies of normal aging and dementia.[23] The overall percent agreement ([PET-positive and CSF biomarker-positive individuals] plus [PET-negative

TABLE 2 CSF PET agreement in studies reporting individual biomarkers and biomarker ratios using automated assay platforms

				Individual CSF biomarkers				CSF biomarker ratios		
Reference	Study objective	Platform	Measure	p-tau	t-tau	Aβ1-42	Aβ1-40	p-tau/Aβ42	t-tau/Aβ42	Aβ1-42/Aβ1-40
Schindler et al. 2018[23]	To measure relationship between CSF biomarkers and amyloid PET	Elecsys	PPA	82%	68%	90%	60%	92%	92%	96%
			NPA	76%	83%	73%	58%	89%	85%	82%
			OPA	78%	79%	77%	59%	89%	87%	86%
			AUC	0.84	0.81	0.85	0.60	0.96	0.95	0.93
Doecke et al. 2020[14]	To measure concordance between CSF biomarkers and pathological AD via PET imaging	Elecsys	PPA	81%	86%	81%		90%	83%	90%
			NPA	77%	66%	81%		91%	97%	90%
			OPA	79%	75%	81%		91%	91%	90%
			AUC	0.84	0.81	0.86		0.94	0.94	0.94
Willemse et al. 2020 (abstract)[24]	To measure CSF biomarkers compared to amyloid PET imaging	Elecsys	PPA			91%		96%		96%
			NPA			75%		89%		80%
			OPA							
			AUC							
	To measure CSF biomarkers compared to amyloid PET imaging	Lumipulse	PPA			91%		97%		99%
			NPA			73%		91%		83%
			OPA							
			AUC							
Keshaven et al. 2020[21]	To measure concordance between CSF biomarkers and PET imaging	Lumipulse	PPA	100%	54%	100%		100%	92%	100%
			NPA	66%	82%	74%		94%	90%	94%
			OPA							
			AUC	0.879	0.665	0.891		0.966	0.955	0.966
Alcolea et al. 2019[20]	To determine cut-offs between PET and CSF biomarkers	Lumipulse	PPA	80%	75%	95%		93%	81%	88%
			NPA	83%	83%	51%		80%	83%	77%
			OPA	81%	78%	79%		88%	82%	84%
			AUC	0.84	0.80	0.76	0.59	0.88	0.87	0.86
Kaplow et al. 2020[15]	To determine concordance of CSF biomarker ratios with amyloid PET (test cohort A/B)	Lumipulse	PPA		74.1%	98.8%			97.5%	
			NPA		89.8%	75.5%			89.8%	
			OPA		80.0%	90.0%			94.6%	
			AUC		0.87	0.92			0.95	
Moon et al. 2021[22]	To evaluate concordance of CSF biomarkers and PET imaging	Lumipulse	PPA	79.5%	59.0%	79.5%		84.6%	84.6%	84.6%
			NPA	78.6%	89.3%	88.1%		92.9%	88.1%	91.7%
			OPA							
			AUC	0.839	0.791	0.857		0.840	0.842	0.856

Notes:
PPA: positive percent agreement (defined as the percent of PET-positive individuals also positive by a CSF biomarker measure).
NPA: negative percent agreement (defined as the percent of PET-negative individuals also negative by a CSF biomarker measure).
OPA: overall percent agreement (defined as the sum of the PET-positive individuals also positive by a CSF biomarker measure and the PET-negative individuals also negative by a CSF biomarker measure divided by the entire cohort size.
AUC: area under the receiver operator curve for PPA on the Y axis and 1 – NPA on the X axis; AUC 1 represents a 'perfect test,' where there is 100% agreement between CSF biomarker and PET imaging results.
Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease; CSF, cerebrospinal fluid; LP, lumbar puncture; PET, positron emission tomography; p-tau, phosphorylated tau; t-tau, total tau.

and CSF biomarker-negative individuals]/total number of individuals) values were better for CSF ratios (86% for Aβ1-42/1-40, 89% for p-tau/Aβ1-42, and 87% for t-tau/Aβ1-42) than for the individual marker values (77% for Aβ1-42, 78% for p-tau, and 79% for t-tau).

From a clinical perspective, these results mean fewer false-negative and false-positive results using CSF ratios than individual markers. An evidence-based review concluded that the CSF Aβ1-42/1-40 ratio, rather than the absolute value of CSF Aβ1-42, should be used when analyzing CSF AD biomarkers to improve the percentage of appropriately diagnosed patients.[11] Similarly, CSF p-tau/Aβ1-42 or t-tau/Aβ1-42 ratios perform better than p-tau or t-tau alone, respectively,[14,23] and Aβ1-42 alone in terms of PET concordance,[19,24] potentially allowing detection of tau accumulation at an earlier stage than with PET imaging in individuals positive for Aβ.[25] CSF Aβ1-42/1-40 and CSF p-tau/Aβ1-42 or t-tau/Aβ1-42 ratios appear to perform equivalently.[11]

Abnormalities in core CSF and PET AD biomarkers are caused by the hallmark AD pathologies of amyloid plaque formation and neurofibrillary tangles. An increased amyloid burden is indicated by decreased CSF Aβ1-42 levels or by uptake of specific PET tracers. On the other hand, an increase in levels of CSF tau reflects neuronal injury and neurodegeneration, while an increase of tau PET indicates tangles pathology. These biomarker changes, which begin many years before clinical symptoms, do not necessarily occur simultaneously.[26] Aβ deposition detected by PET provides different information than Aβ processing reflected by CSF biomarkers. CSF biomarker changes may precede PET biomarker changes; for example, elevation of p-tau in the CSF may precede PET-tracer positivity in the progression of AD pathogenesis and related cognitive decline.[27] This may explain some of the discordance between CSF and PET biomarkers[27,28] that are found in ≈12% of cases.[15] Differences between biomarker tests may reflect disease pathology at specific time points and the likely evolution of disease, although discrepancies may also result from inter-individual variability in the production and clearance of Aβ, and variance in different measures rather than reflecting real discordance.[11,27] Interestingly, CSF ratios (Aβ1-42/1-40 or Aβ1-42/1-38) may correct for inter-individual differences in total Aβ levels.[11]

Using information both from CSF biomarkers and PET imaging may be helpful in some unclear cases. For example, a mismatch between the primary clinical diagnosis and CSF Aβ1-42/tau ratio was the main reason for requesting a subsequent Aβ PET scan.[29] Other indications for a PET scan after CSF biomarker testing include incongruent magnetic resonance imaging (MRI) findings, an unusual clinical presentation, and young age at presentation.[29]

Combining results from CSF Aβ and tau assays may be more informative than individual CSF biomarker results because the ratios provide a more detailed snapshot of different underlying disease process.[23] p-tau is the most helpful biomarker for differential diagnosis of AD from non-AD dementia.[30] Furthermore, CSF Aβ1-42/1-40 and tau/Aβ1-42 ratios are reliable markers of AD, at both the preclinical and clinical stages of disease, and can differentiate between AD and non-AD causes of cognitive decline.[31] Importantly, brain pathologies not specific to AD may be associated with reduced Aβ1-42 levels in the CSF, whereas biomarker ratios are not similarly affected.[11]

As CSF AD biomarker ratios correct for the potentially confounding influence of variance in CSF protein turnover between individuals, they may add relevant information in the differential diagnosis of neurodegenerative diseases associated with low levels of Aβ1-42. For example, CSF amyloid ratio (Aβ1-42/Aβ1-40) is superior to Aβ1-42 to differentiate patients with AD from those with vascular dementia, dementia with Lewy bodies, and non-AD dementia,[31] while CSF p-tau/Aβ1-42 ratio performed better than p-tau or Aβ1-42 in differentiating AD from other types of dementia.[32] CSF p-tau/Aβ1-42 ratio may be useful in clinical practice to exclude underlying AD pathology in the differential diagnosis of frontotemporal lobar degeneration.[33] In addition, CSF ratios can predict the risk of progression from MCI to AD.[18]

Despite evidence-based recommendations for CSF biomarkers in the diagnostic workup of suspected AD, there remains a degree of reluctance to use them in routine clinical practice.[5] The following authentic case narratives show how CSF biomarkers may be used in different clinical scenarios to improve the accuracy of diagnosis and to inform clinical management decisions.

4 | CASE 1: THE MAN WITH A LARGE HEAD

4.1 | Background

Mr. B is 61 years old and works in an abattoir. He never learned to read or write. Although he has no cognitive complaints and his activities of daily living appear normal, his wife, who has always arranged household, finances, and clothing, is concerned because he has become forgetful over the last 2 to 3 years and often tells the same stories twice. His personality has also changed, he is often agitated, talks to strangers, and has become dysfunctional at work.

4.2 | What did the initial assessment show and why did the physician order specialist tests?

Neurological examination showed Mr. B has a large head circumference (>97th percentile reference); however, initial cognitive tests and further neuropsychological testing (Table 3) were deemed unreliable because of his limited education. Computed tomography (CT) showed enlarged ventricles, probably long standing, considering the large skull. There was no evidence of hippocampal atrophy, although definitive assessment was difficult because of enlarged ventricles. As diagnosis was uncertain from initial assessments, additional tests were done to explore different possible causes of cognitive decline including hydrocephalus, depression, other psychiatric disorders, or AD.

4.3 | How did biomarker and other tests improve diagnostic accuracy?

PET scanning using the Pittsburgh compound B (PiB) tracer showed no evidence of Aβ take-up and AD was excluded (Table 3). CSF

TABLE 3 Summary of biomarker test findings in case studies

Case	CSF test findings	PET test findings	Neuropsychology testing	AD diagnosis
#1 Mr B	Not done	Aβ negative	MMSE 19/30 CAMCOG 67 (cut-off >84) Frontal assessment battery 12/18	AD excluded
#2 Mr C	Glucose 4.0mmol/L Proteins 0.40g/L t-tau 594ng/L (cut-off <360)[a] p-tau 81ng/L (cut-off <60) [a] Aβ1-42 611ng/L (cut-off >450) [a] t-tau/Aβ1-42 0.972 (cut-off <0.28) p-tau/Aβ1-42 0.133 (cut-off <0.02)	Not done	Examination abandoned because patient was distracted and anxious	MCI due to AD
#3 Mrs N	Aβ1-42 498 pg/ml (cut-off >1000) t-tau 635 pg/ml (cut-off <235) p-tau-181 73 pg/ml (cut-off <19) t-tau/Aβ1-42 1.275 (cut-off <0.28) p-tau/Aβ1-42 0.147 (cut-off <0.02)	Not done	MMSE 26/30 Deficits in memory tasks	MCI due to AD
#4 Mr G	Aβ1-42 567 pg/ml (cut off >1000) t-tau 364 pg/ml (cut off <235) p-tau-181 36 pg/ml (cut off <19) t-tau/Aβ1-42 0.642 (cut-off <0.28) p-tau/Aβ1-42 0.063 (cut-off <0.02)	Aβ +	MMSE 26/30 CAMCOG 91 (cut-off >84)	PCA due to AD
#5 Mr T	Aβ1-42/1-40 (cut-off >0.046) 0.037 at 62 years 0.037 at 66 years p-tau181/ Aβ1-42 ratio (cut-off <0.038) 0.042 at 62 years 0.045 at 66 years	Aged 62 years: Aβ+ (centiloid of 91.6) Aged 70 years: Aβ + (centiloid of 113.1) Tau +	Aged 62-72: MMSE 30/30 Aged 72: MMSE 30/30 Delayed recall (Rey Auditory Verbal Learning Test and the Logical Memory I and II subtests of the Wechsler Memory Scale-Revised)	Aged 62 and 66 years: At risk for AD Aged 72 years: MCI

[a]ELISA assay.
Abbreviations: CAMCOG, Cambridge Cognitive Examination; PCA, posterior cortical atrophy.

biomarkers could have been used to test for Aβ to exclude AD, but PET was used in this case because of the presence of enlarged ventricles. In such cases, individual biomarker levels could be decreased overall, which may result in a false-negative normal (low) Aβ level, whereas CSF AD biomarker ratios could be useful because they control for this confounding finding.

4.4 | How did tests help to guide management of the patient?

After exclusion of AD, further psychiatric evaluation revealed prior psychotrauma related to childhood sexual abuse that the patient and caregiver were not able to discuss during the first visit. The final diagnosis was post-traumatic stress disorder (PTSD). Treatment with antidepressants and psychotherapy markedly improved cognitive function. Mr. B's case shows biomarker testing can rule out AD as the primary cause of cognitive deterioration, providing a clear direction for subsequent treatment, and even improvement of his cognitive complaints. Many cases of dementia are not caused by AD and may be reversible with adequate treatment.

The diagnostic value of biomarkers is increased in cases in which medical history provides limited objective clinical information, for example, in individuals with low education, a previous psychotic disease, no informant, or with language barriers.

5 | CASE 2: PROFESSIONAL BURNOUT

5.1 | Background

Mr. C is the 61-year-old son of working-class parents. After compulsory schooling, he completed an apprenticeship as a craftsman, a profession he practiced for a few years before training as a policeman. He has been in this profession for 12 years and is responsible for a team of 12 people. He lives with his wife and son. He enjoys cooking, walking, watching TV, playing computer games, and reading the newspaper. His parents are alive and there is no family history of dementia nor known history of cognitive impairment in close relatives. His father has memory problems, but no diagnosis has been made. Mr. C sought medical help for evaluation of memory impairment after professional burnout,

linked to overwork, a chronic shortage of staff, and an increasing workload.

5.2 | What did the initial assessment show and why did the doctor order specialist tests?

During the first consultation by dementia specialists Mr. C spontaneously described professional overwork, feeling "confused in his head" and slowed down, while being less efficient doing certain tasks. He described himself as very stressed in the workplace, with the feeling that he is performing less well than before, "putting pressure on himself," and "being apprehensive of doing wrong." He mentioned occasional forgetfulness about where he puts his things (misplacing his glasses). His wife is worried about him and confirmed these problems. Outside work, he is self-sufficient in all activities of everyday life. He drives and makes his payments on the internet without difficulties. Until recently Mr. C had a stable and resilient personality, with no evidence of anxiety or depressive episodes, and no need for psychological/psychiatric therapy or psychotropic drugs.

On a scale assessing change in cognitive functioning (IQ-CODE = 3.25, not significant), his wife described a slight decline in his ability to learn new things, recall recent events, and remember where things are stored. Behaviorally, she finds him much calmer. These disorders first appeared about 2 years previously, after a malaise, possibly associated with an event diagnosed as a transient ischemic attack. Mr. C also had two episodes of malaise 4 hours apart 3 years earlier, although no CT scan was done then. Mr. C is in good physical health overall and laboratory tests a year ago were normal. He is currently on aspirin, rosuvastatin, and irbesartan.

Neurological examination was unremarkable. The neurologist's MRI report was within the normal range, except for very discrete white matter signal abnormalities at the supratentorial level reportedly of ischemic origin. During neuropsychological evaluation and psychiatric assessment Mr. C was distractible, verbalizing, and showing significant anxiety related to the testing situation, which led to several tasks being abandoned and significantly limited the examination. He expressed a lack of confidence in his own abilities, apprehension of doing the wrong thing, and low self-esteem related to overwork. There was no evidence of psychotic features.

Mr. C was given a diagnosis of cognitive impairment due to anxiety and lack of confidence in his cognitive abilities in the context of professional burnout. The dementia specialists recommended adopting a healthier lifestyle (via diet, sleep, smoking cessation, and physical activity), psychological care focused on stress management, greater involvement in stimulating cognitive and social activities, and regular monitoring of vascular risk factors. However, his wife was not convinced that his condition was entirely caused by anxiety, as the neuropsychologist and medical specialist had implied, and she asked for a second opinion. Biomarker testing was therefore done to help answer outstanding questions: is the MRI normal and can the cognitive impairment be due only to anxiety or is there AD pathology?

5.3 | How did biomarker and other tests improve diagnostic accuracy?

Closer examination of the MRI scans showed a posterior atrophy pattern with milder medial temporal involvement. Microvascular changes were clinically irrelevant. CSF biomarkers showed abnormalities in Aβ1-42 and t-tau (Table 3).

Based on clinical symptoms and abnormalities in Aβ1-42 level and p-tau/Aβ1-42 and t-tau/Aβ1-42 ratios, Mr. C was diagnosed with MCI due to AD (also known as prodromal AD[1]).

5.4 | How did tests help to guide management of the patient?

Mr. C's prognosis changed after diagnosis. He and his family were informed that cognitive impairment was due to a neurodegenerative disease and would progress in the coming months and years. A biomarker-confirmed diagnosis of MCI due to AD and worsening of Mr. C's condition supported consideration of drug therapy for symptomatic management.[34]

The possibility of participating in a clinical trial of a novel disease-modifying drug was discussed because CSF biomarkers and clinical conditions showed that he met the eligibility criteria.

6 | CASE 3: WORRYING SIGNS OF DEPRESSION

6.1 | Background

Mrs. N is a 63-year-old retired secondary school teacher. After retiring at age 60, she enjoyed 2 years adjusting to her new routine and taking the opportunity to read more books. During the third year of retirement, her partner noticed that she had missed important appointments and was finding it difficult to follow or discuss the books that she was reading. She started to experience more notable memory problems 6 months before seeking medical help, at which point she was showing signs of depression. Her partner confirmed that progressive amnesia was affecting her moods and ability to enjoy retirement.

6.2 | What did the initial assessment show and why did the physician order specialist tests?

Neuropsychological examination showed deficits in memory tasks (Table 3), indicative of amnestic MCI. MRI scan showed a medial temporal atrophy (MTA) score between 0 and 1, indicating only a minor degree of atrophy, normal for her age (MTA score ranges from 0 [no atrophy] to 4 [severe atrophy] and may be used to predict AD in patients with MCI). There was no vascular damage evident on the MRI. As the initial tests proved inconclusive, additional investigation with CSF biomarkers was indicated to make a differential

diagnosis between AD and depression as the underlying cause of cognitive impairment.

6.3 | How did biomarker and other tests improve diagnostic accuracy?

CSF biomarker results showed abnormal levels of Aβ1-42, t-tau, and t-tau/Aβ1-42, consistent with a diagnosis of AD (Table 3).

One year later, Mrs. N had deteriorated and was having problems using the telephone and finding her way in her home village. Neuropsychological examination showed Mini-Mental State Examination (MMSE) was 23/30 and MRI revealed progression of hippocampal atrophy (MTA score between 1 and 2). Mrs. N was diagnosed with dementia due to AD. In this case, both CSF biomarker abnormalities and progressive hippocampal atrophy occurring within 1 year of her first presentation indicated AD as the underlying neurodegenerative process. Importantly, changes in CSF biomarkers identified AD a year before neurodegeneration was shown by hippocampal atrophy.

6.4 | How did tests help to guide management of the patient?

Mrs. N's case shows how biomarkers may inform the diagnosis and management of patients presenting with cognitive impairment with mood changes and no dementia. Late-life depression and cognitive impairment are commonly encountered neuropsychiatric disorders, and may coexist with AD, making diagnosis challenging for physicians.[35] In Mrs. N's case, CSF biomarkers identified AD pathology as the underlying cause for cognitive decline, allowing her management to be adapted appropriately.

7 | CASE 4: THREE NEW PAIRS OF GLASSES IN 2 YEARS

7.1 | Background

Mr. G is 58 years old and was recently dismissed from his job as an electrical engineer because of poor performance. He became worried about progressive impairments in spatial orientation, which started 2 years before presentation and increased after he experienced retinal detachment. He was also concerned about his eyesight because he needed to buy three new pairs of glasses in 2 years. In addition, he noticed problems with planning, reading, and driving.

Mrs. G confirmed his medical history and reported that her husband was showing more dependent behavior than before his health problems started. However, Mr. and Mrs. G found it difficult to describe his cognitive complaints, so clinicians were unable to develop a complete picture of his medical history.

7.2 | What did the initial assessment show and why did the physician order specialist tests?

Neurological examination showed Mr. G's memory and language were intact; however, he exhibited slight dyspraxia affecting his physical coordination; severe spatial and visuo-perceptive problems, shown by an inability to draw a clock or pentagons; and an inability to perceive multiple objects simultaneously (simultanagnosia). He underwent a full neuropsychological examination (Table 3).

A clinical diagnosis of posterior cortical atrophy (PCA) was made. In most cases PCA is caused by underlying AD; however, other neurodegenerative diseases, such as Lewy body dementia or Creutzfeldt-Jakob disease, may also cause this clinical syndrome.[36]

7.3 | How did biomarker and other tests improve diagnostic accuracy?

Amyloid PET imaging using the PiB tracer confirmed amyloid pathology and Mr. G was diagnosed with PCA due to AD.

For research purposes, CSF biomarkers were measured and confirmed abnormalities consistent with a diagnosis of AD (Table 3). There was good agreement between the different approaches, in line with studies showing concordance between amyloid PET and CSF biomarkers, particularly when CSF biomarker ratios are measured (see Table 2).

7.4 | How did tests help to guide management of the patient?

Biomarker tests are particularly useful in atypical presentations of AD. Biomarker tests provide useful information about prognosis,[36] allowing the physician to counsel the patient about what to expect in terms of increasing cognitive dysfunction and other cognitive domains over the coming years.

8 | CASE 5: AN INCREASED RISK FOR DEMENTIA

8.1 | Background

Mr. T, a 72-year-old, former office manager fills his retirement time traveling, playing golf, and socializing. He presented with a subjective complaint of memory loss. His father had been diagnosed with AD aged 75 years, so Mr. T was increasingly concerned about his forgetfulness. Ten years previously, Mr. T had joined a long-term registry study because he felt at increased risk of dementia. At the start of the study, he had no memory or cognitive complaints nor major health issues besides being moderately overweight (body mass index 27) and mildly hypertensive. He was identified as apolipoprotein E ε4 positive (3/4). He attended his first study visit for neuropsychological assessment and diagnostic tests soon after his 62nd birthday.

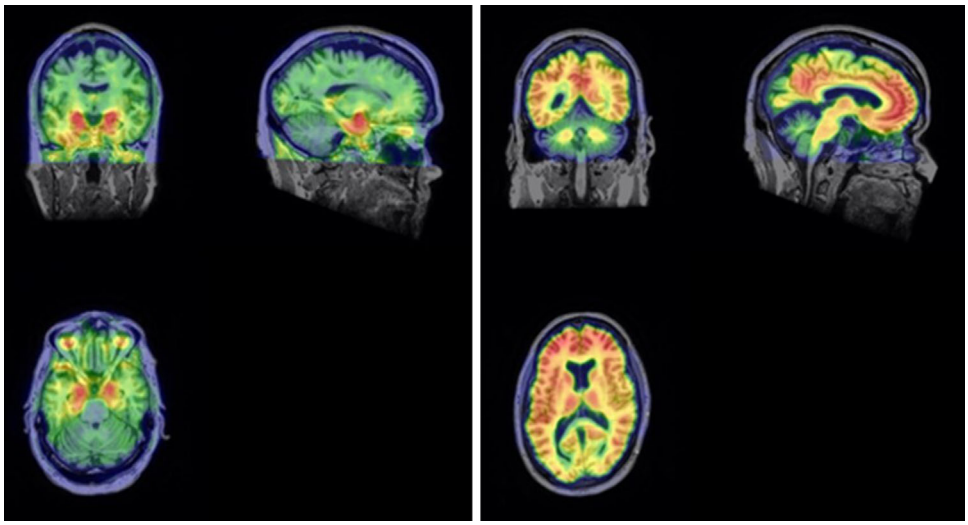

FIGURE 1 Tau positron emission tomography imaging (left set of orthogonal views) and amyloid imaging (right set of orthogonal views) were taken when Mr. T was aged 70 years. He had prior amyloid imaging at age 62 years (not pictured) together with cerebrospinal fluid sampling and both demonstrated amyloid positivity at least 10 years before his diagnosis of mild cognitive impairment at age 72

8.2 | What did the initial assessment show and why did the physician order specialist tests?

Routine neuropsychological assessments on previous visits, when Mr. T was aged 62, 64, and 66 years, had not shown evidence of cognitive abnormalities of concern. On this occasion, aged 72 years, testing revealed psychometric evidence of decline from the previously measured higher level of cognitive functioning. Although his MMSE was 30/30 he performed in the impaired range on tests of delayed recall for word lists and stories (Table 3). Other aspects of cognition were in the high average to superior range. This pattern of performance together with the subjective complaint in the context of otherwise intact cognition and no substantial functional impairment indicated a diagnosis of MCI.

8.3 | How did biomarker and other tests improve diagnostic accuracy?

Biomarkers and PET imaging were done as part of the research study. Mr. T had lumbar puncture procedures when aged 62 and 66 years, which were analyzed using an exploratory multi-panel of CSF biomarkers (Neurotoolkit; Van Hulle et al.[49]). Interestingly, Aβ1-42/1-40 ratios were positive for both lumbar punctures (Table 3). p-tau181/Aβ1-42 ratios were also positive, whereas p-tau181 alone was negative and neurofilament light and neurogranin were normal at all time points.

Early evidence of biomarker changes was also seen on brain imaging (Figure 1). Amyloid PET with [C-11]PiB was positive and increased progressively from his first PiB scan at age 62 years to his most recent PiB scan at age 70 years (Table 3). He was also tau PET positive using the radioligand [F-18]MK6240 at 70 years (Figure 1). The signal was most evident in the bilateral amygdala, with additional signal in the entorhinal cortex and fusiform more left than right. At his second scan the angular gyrus on the right was also focally positive (Figure 1).

8.4 | How did tests help to guide management of the patient?

Mr. T's MCI was first apparent on clinical findings at age 72 years, while his CSF was positive for amyloid 10 years earlier. This case illustrates the potential of CSF biomarkers to assess risk of AD based on early detection of specific pathologic changes associated with AD before clinical symptoms become apparent.[1] This is compelling for researchers but how does the clinician use this information to help their patient when proven disease-modifying therapies are not widely available?

A timely diagnosis provides an opportunity for physicians to encourage lifestyle changes and cognitive training to improve overall health.[37] A Lancet Commission report suggests that modifying 12 risk factors might prevent or delay up to 40% of dementias.[38] In addition, CSF biomarker testing provides a useful tool for clinical trial enrichment.[2] However, the impact on risk stratification of biomarker positivity is beyond the scope of this paper. Risk profiling in individuals with a family history is not currently recommended in the clinic and guidelines do not advocate routine testing of individuals like Mr. T.

9 | CSF AD BIOMARKERS IN TRIAL ENRICHMENT AND TREATMENT SELECTION

CSF biomarkers are promising for enrichment of clinical trials with subjects showing AD pathology and, in the future, it is likely that accurate diagnostic tests will be needed to select appropriate patients for novel

therapies based on specific target pathologies, for example the presence of amyloid or tau aggregates.[2] Recently, the US Food and Drug Administration (FDA) conditionally approved aducanumab (a monoclonal antibody therapy that targets Aβ) for selected patients with MCI or mild AD dementia. The benefit of this novel disease-modifying therapy is based on a surrogate endpoint (reduction of Aβ plaque in the brain). We recommend that careful patient selection using biomarkers will be crucial in providing access to this drug.

10 | BARRIERS AND LIMITATIONS TO CSF AD BIOMARKERS IN CLINICAL PRACTICE

Clear guidelines and uniform reporting are required to facilitate appropriate use of CSF AD biomarkers in clinical practice so physicians can communicate the potential benefits.[5] Physicians need to counsel their patients about whether they would like to know their prognosis or would prefer to "wait and see." In addition, it is important to provide adequate psycho-education both for caregivers and the patients.[39]

CSF biomarker tests involve a perceived invasive procedure (lumbar puncture) that may limit participation in clinical research and reduce acceptance in clinical practice, particularly among some ethnic groups.[4,40] The procedure is easy and safe when performed following state of the art protocols[41] and collection of up to 30mL of CSF appears well tolerated.[42] The most common side effects of lumbar puncture are back pain and headache, which are easily managed, while serious complications (infections, spinal and subdural cerebral hematoma, and cerebral venous thrombosis) are very rare (prevalence <0.01%).[41–43] Guidelines have been developed to reduce the risks of complications when lumbar puncture is used in daily neurological practice and highlight the need to use atraumatic needle tips.[41] Providing up-to-date education and audio-visual information to physicians and patients can allay common misconceptions about the acceptability and safety of lumbar puncture.[16,44]

Previously, different methodologies and lack of standardization added to the complexity of performing and interpreting CSF biomarker tests.[45] Today, uniform protocols and standards have been agreed,[46] while fully automated testing procedures are now available. These advances mean that CSF biomarker tests can be considered for use in routine clinical practice.[45] The tests provide simple positive or negative results for amyloid isoforms and (p)tau based on standardized cut-off values, which can be used alongside neuropsychological evaluation consistent with the latest international clinical diagnostic criteria.[1,3] While a positive biomarker test supports the diagnosis of AD, it is important to remember that a biomarker profile that is negative for AD does not exclude other dementias.

Experts recommend CSF ratios to improve the timeliness and accuracy of diagnosis of AD, and to predict progression from MCI to AD.[3,11] Importantly, CSF biomarkers provide information on both amyloid and tau biomarkers. The additional financial cost of using CSF ratio tests is considerably lower (10–15 times) than PET imaging;[11] however, it may take time to obtain CSF analysis results from a clinical chemistry laboratory.

11 | NOVEL BIOMARKERS IN DEVELOPMENT

The rationale for new biomarkers includes minimizing invasive procedures, making tests more widely available, and improving the ability to detect specific pathologic processes more accurately.[47]

Blood-based biomarkers may be attractive in primary care because of the familiarity and ease of obtaining blood and plasma samples in this setting.[13] In the first steps of the diagnostic process, blood-based biomarkers could be used alongside cognitive testing to improve referral to specialists. Plasma Aβ and tau biomarkers could indicate a need for testing in specialized clinics, including CSF or PET biomarkers to confirm amyloid positivity. Additional research is warranted to scale-up clinical use of blood-based biomarkers for AD, particularly in relation to validation with existing large sample sets and ethnically diverse populations.[48] Similarly, biomarkers measured in other fluids (eyes, mouth, ears, and nose) offer relatively non-invasive methods, but their potential remains to be realized.

Novel biomarkers that track different aspects of AD pathology, including synaptic dysfunction, neuro-inflammation, and glial activation,[49] may be useful for early diagnosis of MCI and AD, and differential diagnosis of AD from other neurodegenerative diseases (see supporting information). Digital tools may also contribute to screening and diagnostic pathways in AD.[50]

12 | CONCLUSIONS

We recommend that CSF AD biomarkers should be part of the standard of care for the work-up of MCI and dementia patients. The case narratives show how CSF AD biomarkers may be useful at different stages of AD diagnosis and across different ages (see Box A).

In regular clinical practice, standardized reporting of CSF AD biomarker tests should be an important part of the diagnostic pathway and help to answer patients' questions about what their cognitive complaints mean for them. Tests revealing normal Aβ and tau levels show there is no evidence of AD pathology, whereas abnormal levels indicate a risk of AD independently of clinical stage. CSF Aβ1-42 assays have good agreement with amyloid PET imaging, while Aβ1-42/1-40 and tau/Aβ1-42 ratios have superior performance to Aβ1-42 alone.

While timely and precise diagnosis can improve clinical management of patients with suspected AD, the negative predictive value of CSF AD biomarkers is also clinically important and can be psychologically reassuring for patients and clinicians. Biomarker tests are important for patients because by being better informed they can take steps to plan their future lives. In the future, appropriate use of biomarker testing will be essential for the careful selection of patients to receive disease-modifying therapies, such as aducanumab, which was approved based on surrogate benefits.

Box A. Uses of CSF AD biomarker testing as shown by the case narratives

In the clinic

Exclusion of AD as the underlying cause of dementia, helping Mr. B to receive appropriate therapy for a psychiatric condition.

Diagnosis of AD at an early stage (MCI due to AD/prodromal AD), enabling Mr. C to start symptomatic treatment for cognitive impairment and planning for future life changes (early retirement).

Accurate and prompt diagnosis in individuals such as Mr. G with relatively young-onset AD.

Differential diagnosis of AD in individuals presenting with other neuropsychiatric symptoms, and accurate diagnosis of AD despite an atypical presentation, allowing Mrs. N and Mr. G, respectively, to benefit from appropriate clinical management plans.

For research

Detection of therapeutic target for future treatments (anti-amyloid immunotherapies).

Determination of prevention or lifestyle interventions, for example, Mr. T, whose heightened risk state could be assessed in the context of a research program, where amyloid changes could be detected 10 years before clinical diagnosis.

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CONFLICTS OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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