Abstract. An accurate and early diagnosis of Alzheimer’s disease (AD) is important to select optimal patient care and is critical in current clinical trials targeting core AD neuropathological features. The past decades, much progress has been made in the development and validation of cerebrospinal fluid (CSF) biomarkers for the biochemical diagnosis of AD, including standardization and harmonization of (pre-) analytical procedures. This has resulted in three core CSF biomarkers for AD diagnostics, namely the 42 amino acid long amyloid-beta peptide (Aβ1-42), total tau protein (T-tau), and tau phosphorylated at threonine 181 (P-tau181). These biomarkers have been incorporated into research diagnostic criteria for AD and have an added value in the (differential) diagnosis of AD and related disorders, including mixed pathologies, atypical presentations, and in case of ambiguous clinical dementia diagnoses. The implementation of the CSF Aβ1-42/Aβ1-40 ratio in the core biomarker panel will improve the biomarker analytical variability, and will also improve early and differential AD diagnosis through a more accurate reflection of pathology. Numerous biomarkers are being investigated for their added value to the core AD biomarkers, aiming at the AD core pathological features like the amyloid mismetabolism, tau pathology, or synaptic or neuronal degeneration. Others aim at non-AD neurodegenerative, vascular or inflammatory hallmarks. Biomarkers are essential for an accurate identification of preclinical AD in the context of clinical trials with potentially disease-modifying drugs. Therefore, a biomarker-based early diagnosis of AD offers great opportunities for preventive treatment development in the near future.

Keywords: Alzheimer’s disease, amyloid, biomarkers, cerebrospinal fluid, dementia, diagnosis, mild cognitive impairment, neuropathology, tau

INTRODUCTION

An accurate and early diagnosis of Alzheimer’s disease (AD) is important to select the optimal patient care and is critical in current clinical trials targeting core AD neuropathological features. Its value will grow even more so when a disease modifying treatment is available. To date, diagnosis of AD is still based on a full clinical work-up, including neuropsychological testing [1] and brain imaging such as magnetic resonance imaging (MRI). However, clinical dementia diagnosis does not always correspond to the neuropathological definite diagnosis with clinical diagnostic accuracy levels ranging between 82% and...
When a clinician should discriminate AD from a non-AD dementia relying on (non-biomarker based) clinical diagnostic criteria, 16% are misdiagnosed and 16% of the patients have a doubtful AD versus non-AD diagnosis [2, 4, 5]. Therefore, it is important to increase the clinical diagnostic accuracy, which will even be harder at an early stage of the disease. Since biochemical changes are believed to take place and be detectable through biomarkers around two decades before clinical symptom onset [6], they will be important tools in the clinical setup for early and differential diagnosis of AD.

Several attempts have been made to counteract the effects of amyloid-β (Aβ) mismetabolism, which is assumed to be one of the key pathogenic events in AD. However, all but one clinical trials have failed to reverse or slow down cognitive decline [7]. Possible reasons for the failures may be that non-homogeneous groups of patients have been included in the trials, the treatment has been administered too late in the course of the disease or has been too short, and/or that the Aβ aggregation is not the key event in AD.

Also driven by the need of clinical trials to select ‘pure’ AD subjects early in the course of the disease, much effort has been put in developing biomarkers for AD during the past two decades (see Alzforum biomarker database and meta-analyses at http://www.alzforum.org/alzbiomarker) [8]. This has resulted in three core cerebrospinal fluid (CSF) biomarkers for AD diagnostics, namely the 42 amino acid long amyloid-beta peptide (Aβ1-42), total tau protein (T-tau), and tau phosphorylated at threonine 181 (P-tau181) [9]. A biomarker classification scheme, which is based on the early findings and interpretations of the above CSF biomarkers by Blennow et al. [10], has been suggested as a tool to assess the pathophysiology in the brain independent of the clinical evaluation. This so called “A/T/N” system, captures the three main neuropathological findings related to AD. The A refers to the Aβ pathology measured by either amyloid PET or CSF Aβ1-42, T represents tangle pathology and is assessed by either tau PET or CSF P-tau, and N stands for neurodegeneration or neuronal injury detected by either [18F]-fluorodeoxyglucose-PET, structural MRI, or CSF T-tau [11].

Biomarkers have been incorporated into research diagnostic criteria for AD [12–14] and, although the clinical examination (including full neuropsychological evaluation) is still the basis for AD diagnosis [1], these biomarkers are being introduced in daily clinical practice as in vivo surrogate markers for the confirmation of AD neuropathology. The core CSF AD biomarkers increase the diagnostic accuracy for diagnosing AD (mainly in cases with atypical presentations), also in its prodromal phase (mild cognitive impairment (MCI) due to AD) [15, 16] and are able to differentiate between AD and psychiatric disorders [17]. The CSF biomarkers are useful to diagnose AD in patients with ambiguous clinical dementia diagnoses [4] and in cases with mixed brain pathology like AD with cerebrovascular disease [5, 18, 19].

During ten years of CSF AD biomarker analyses, the number of samples referred to the BIODEM lab at UAntwerp from clinical centers has increased with 238% [20]. Due to the revisions of diagnostic criteria for AD diagnosis and the herein described use of CSF biomarkers [12–14], confidence in the importance of biomarkers has grown. Not only are they used more often by clinicians, they are also useful in clinical trials as enrichment strategy or outcome measures due to their in vivo pathophysiological characteristics [21]. However, there is a general shift from samples referred for neurochemical confirmation of AD diagnosis to referrals for differential AD versus non-AD dementia diagnosis. This may be due to the growing scientific support for biomarker-based differential diagnosis between AD and non-AD dementias [22], also in the prodromal phase [23].

**BIOMARKER ASSOCIATION WITH NEUROPATHOLOGY AND DETECTION OF DEFINITE AND CLINICAL AD**

A biomarker should be readily accessible, accurately indicating a biological or pathological state and preferably inexpensive. In case of neurodegenerative biomarkers, the choice of CSF over blood biomarkers, at least in the case of Aβ1-42, is mainly based on the fact that the central nervous system is secluded from the systemic circulation, which precludes direct translation of biomarker findings of the brain to the periphery. This has been supported by studies in plasma showing conflicting results, and in the case of Aβ1-42 for instance no overall difference between AD and controls were found in a meta-analysis [8] (http://www.alzforum.org/alzbiomarker). Furthermore, no correlation between plasma and CSF levels of the Aβ1-42 biomarker has been found [24, 25]. Tau on the other hand have shown more potential as a plasma or serum biomarker for the differentiation between AD and controls [8] (http://www.alzforum.org/alzbiomarker);
however, speaking against a direct translation of CSF values into plasma is the finding that nor
tau CSF levels correlate with its plasma counter-
part [26]. Nevertheless in CSF, Aβ1-42, T-tau, and
P-tau181 have shown to be consistently altered in
AD versus controls, also in the prodromal phase [8]
(http://www.alzforum.org/alzbiomarker).

The BIODEM lab was the first to demonstrate
the diagnostic value of the CSF biomarkers Aβ1-42,
T-tau, and P-tau181 in clinical AD using the neu-
ropathological diagnosis as a reference [2, 27]. The
study demonstrated that all three biomarkers provide
useful information, showing promising sensitivity
and specificity values that systematically exceed the
80% threshold. The use of a biomarker-based model
in patients with a clinically ambiguous diagnosis,
resulted in a correct diagnosis in the majority of
autopsy-confirmed AD and non-AD cases, indicat-
ing that biomarkers have an added diagnostic value
in these cases [1, 2, 4].

Moreover, Aβ1-42 has proven its potential to mir-
ror the build-up of plaques, which is supported by
the inverse correlation between the CSF Aβ1-42 lev-
els and the amount of amyloid plaques found at
neuropathological examination of AD brains [28] as
well as the in vivo association with cortical amyloid
load as measured by amyloid PET in patients with
AD [29–31]. The present core AD CSF biomarkers,
including Aβ1-42, T-tau, and P-tau181, have recently
been incorporated into the research diagnostic criteria
of AD, with a CSF profile suggestive for AD being
low Aβ1-42 in combination with high T-tau and/or
P-tau181 levels [14].

THE ADDED VALUE OF CSF
BIOMARKERS FOR EARLY AND
DIFFERENTIAL AD DIAGNOSIS

It should be emphasized that biomarkers are espe-
cially important for the selection of preclinical AD
subjects (who are asymptomatic at risk for AD or
subjects who suffer from subjective cognitive decline
[SCD] due to AD) and for the selection of patients
in the earliest symptomatic stages of AD (prodrom-
al AD or MCI due to AD). SCD and MCI are both
very heterogeneous syndromes and when assessed in
a large clinical cohort less than 25% of the subjects
converted to dementia after an extensive follow-up
period of 6 years. The majority of these SCD and
MCI subjects (42%) developed dementia due to AD,
while subjects with mixed AD with cerebrovascular
disease and pure vascular dementia (VaD) were the
second most common diagnoses representing about a
quarter each of the converters [32]. In this particular
setting, CSF Aβ1-42 would portrait as a very attrac-
tive biomarker for early AD detection since both CSF
T-tau and P-tau181 alterations seem to occur at a later
time point in the disease process closer to clinically
detectable dementia [33]. However, it has previously
been suggested and shown that a combination of the
core AD biomarkers is superior compared with the
single biomarkers alone, especially for differential
diagnosis [2]. Investigating autopsy-confirmed AD
and non-AD dementia patients has also improved
our knowledge and insights with regard to the dif-
ferential diagnostic value of the existing AD CSF
biomarkers. An added discriminatory value for AD
versus non-AD dementia was shown for P-tau181 to
the panel of Aβ1-42 and T-tau [34, 35] and, fur-
thermore, that the ratio of Aβ1-42/P-tau181 has shown a
higher diagnostic accuracy than Aβ1-42, T-tau, and
P-tau181 alone, but also than the Aβ1-42/T-tau ratio
to discriminate between AD and non-AD dementias.
This clearly shows the importance of P-tau181 in
the biomarker panel for differential dementia diagnosis
[2, 4, 20, 35].

Although there is strong evidence for the impor-
tance of CSF Aβ1-42 as a biomarker for early AD
detection, there are still limitations to be overcome.
One such limitation is the overlap of CSF Aβ1-42
different neurodegenerative disorders. For instanc,
decreased CSF levels of Aβ1-42 have also been
observed in patients with prodromal and mani-
fest (subcortical) VaD [34, 36, 37], dementia with
Lewy bodies (DLB) [34, 38], Creutzfeldt–Jakob
disease (CJD) [34, 39], and frontotemporal lobar
degeneration (FTLD) [34, 40] compared with healthy
individuals. Though the Aβ1-42 levels are most often
still lower in AD compared with VaD and DLB, a
significant overlap nevertheless limits the discrimi-
nation. Concomitant AD pathology in DLB has been
shown to occur in 72% of autopsy-confirmed DLB
patients, which was reflected by low CSF Aβ1-42
values [38]. While AD pathology is often found in
combination with both DLB and cerebrovascular dis-
ease [2, 38], decreased Aβ1-42 levels in CSF of
patients with pure VaD (related to subcortical small
vessel disease), CJD or FTLD may on the other hand
be related to other pathophysiological characteristics
than plaque burden.

The introduction of Aβ peptide ratios was prop-
osed already in the late 1990s to improve the AD
differential diagnosis [41, 42]. It has previously been
shown that CSF Aβ_{1–42} and florbetapir-PET showed a nonlinear association with pathological values of CSF Aβ_{1–42} preceding PET abnormalities [29] and it has been suggested that CSF Aβ_{1–42} is an earlier marker of brain amyloid pathology compared with PET [43]. However, this has more or less been disputed by the finding that the CSF Aβ_{1–42}/Aβ_{1–40} ratio shows a higher concordance with amyloid load in the brain as assessed by PET compared with Aβ_{1–42} alone [31, 44, 45]. The Aβ_{1–42}/Aβ_{1–40} ratio is decreased in AD and more accurately differentiates between AD and controls, FTLD, VaD, and DLB, due to the latter four groups having ratios that approach control levels because of decreased concentrations in both Aβ_{1–42} and Aβ_{1–40}. This finding supports the increased association of the CSF Aβ_{1–42}/Aβ_{1–40} ratio to pathology as the above non-AD dementias are not affected by plaque pathology in their purest forms [44]. Furthermore, the ratio shows a high concordance with PET, also in subjects with subjective cognitive decline and mild cognitive impairment (AUC ≥ 0.93), indicating a high agreement at the early stages of disease [46]. However, more comparative studies are needed to investigate the biomarker characteristics for early pre-clinical detection of amyloid pathology with regard to the timing of CSF Aβ_{1–42}/Aβ_{1–40} ratio and amyloid PET. The Aβ_{1–42}/Aβ_{1–40} ratio has also been shown to perform equally well as the combination of Aβ_{1–42}, P-tau_{181}, and T-tau in differentiating between AD and other non-AD dementias [47]. In another study, it was shown that adding the Aβ ratio to the core biomarkers improved the accuracy when distinguishing between definite AD and non-AD dementias in cases with intermediate P-tau_{181} [48], indicating its potential usefulness as a biomarker for differential dementia diagnosis. Along the same line, the added value to the core biomarkers has also been assessed in a clinical setting where it was shown that in cases with a discrepancy in the AD core biomarker profile, the Aβ_{1–42}/Aβ_{1–40} ratio was in agreement with the clinical diagnosis in over 50% of the cases [49]. All together, these findings speak in favor of the added value of the Aβ_{1–42}/Aβ_{1–40} ratio for differential diagnosis, when alterations in CSF tau are yet to be seen. Other ratios that have been less well investigated but still show potential as biomarkers are Aβ_{1–42}/Aβ_{1–38} and Aβ_{1–42}/Aβ_{1–37} [35]. In this study, it was concluded that Aβ_{1–42}/Aβ_{1–38} ratio performed the best for the separation between AD and DLB, and that it outperformed the single AD biomarkers. Also, Aβ_{1–42}/Aβ_{1–37} was shown to have an added value for the differentiation between AD and FTLD [35]. More studies are needed in order to determine which Aβ peptide ratios achieve the best separation in different diagnostic settings.

The CSF Aβ_{1–42}/Aβ_{1–40} ratio has been shown to be superior to Aβ_{1–42} alone when concerned with the distinction between MCI patients who progress to AD dementia and MCI patients who remain stable [50]. The early diagnostic value of the existing biomarker panel might be improved by the addition of Aβ_{1–40}, since formation of amyloid-plaques is believed to be initiated up to twenty years before the onset of the clinical symptoms. The use of low CSF Aβ_{1–42} and the CSF Aβ_{1–42}/Aβ_{1–40} ratio opens new possibilities for the accurate identification of ‘asymptomatic at risk for AD’ subjects for clinical trials.

**NEW AD AND NON-AD RELATED BIOMARKERS FOR IMPROVED DIFFERENTIAL DIAGNOSIS**

Numerous biomarkers have been investigated for their added value to the core AD biomarkers in early detection or differential diagnosis of AD. Several of those have aimed at the AD core pathological features like the amyloid mismetabolism, tau pathology, or synaptic or neuronal degeneration. Others have aimed at non-AD neurodegenerative, vascular, or inflammatory hallmarks.

More or less overlapping results have been found for the differentiation of AD and non-AD dementias including DLB, FTLD, and VaD using the core AD biomarkers Aβ_{1–42}, T-tau, and P-tau_{181}. When concerned with FTLD-tau, tau CSF levels are usually intermediate ranging from normal to abnormal, precluding its usability as a biomarker for differential diagnosis [51]. Other tau species, with for instance different modifications, may be more specific for either AD or FTLD-tau pathology increasing its clinical utility. Based on this thought, an assay measuring non-phosphorylated tau at positions T175 and T181 was developed, which was highly accurate at detecting MCI due to AD when compared to healthy controls [52]. However, there was no added value compared with the core AD biomarkers for the differential diagnosis of AD with regard to non-AD neurodegenerative diseases, including FTLD and DLB. Neither was there any added value for the differentiation of AD or FTLD from healthy controls [40].
Other core AD biomarker than Aβ1-42 representing Aβ or amyloid-β protein precursor (AβPP) metabolism have also been investigated for their ability to discriminate AD from healthy controls, such as Aβ1-40 and Aβ1-38 peptides as well as soluble AβPPα and β protein fragments. They have shown to be unaltered in AD [8, 53, 54], but decreased levels have been associated with inflammation, cerebrovascular disease, and white matter lesions [54, 55]. As mentioned before, the CSF Aβ1-42/Aβ1-40 ratio is likely to perform with a higher specificity than for instance Aβ1-42/P-tau181 to discriminate between AD and VaD [56] as well as FTLD and DLB [35]. These findings are of outermost importance for the accuracy of detection of amyloid plaque pathology that characterizes AD, both for clinical practice as well as for patient inclusion into clinical trials. Furthermore, these biomarkers may contribute to detect cerebrovascular disease that may also affect the trajectory of AD under the influence of mixed pathology.

As synaptic and neuronal degeneration is assumed to correlate with cognitive decline in AD, being able to monitor neurodegeneration through synaptic function would be an important advantage, both clinically and in clinical trials to detect disease progression or treatment efficacy. For this purpose, the postsynaptic protein neurogranin has been investigated and was found to be increased in CSF of patients with MCI and dementia due to AD as compared with healthy controls [26, 57], while in paired plasma samples no difference was found [26]. As CSF neurogranin and tau has been found to correlate strongly, its added value to the core biomarkers needs further attention as well as the relation to clinical parameters [26, 57].

Neurofilament light (Nf-L) is another marker of neuronal integrity reflecting axonal damage of the subcortical white matter. Nf-L is therefore considered as a candidate biomarker for subcortical small vessel disease and related dementia [58–60] as it has been found to be associated with white matter hyperintensities [55, 61]. Nf-L has been found to be elevated in CSF from patients with subcortical VaD and mixed AD with subcortical small vessel disease as well as in FTLD [36, 37, 62]. However, it has also been proposed as a biomarker for AD [8], if Nf-L in this case is related to concomitant cerebrovascular disease remains to be clarified. The relation to cerebrovascular disease has also been corroborated by findings of increased levels in stroke [63]. So far, Nf-L is the only marker that has been shown to be directly transferrable from CSF to plasma and show potential as a clinical tool to predict cognitive decline and brain atrophy in AD [64]. Another marker reflecting axonal damage or remodeling of the myelin sheet is myelin basic protein (MBP), which has also been found to be increased in subcortical VaD and stroke [37, 63] and associated with white matter lesions [55]. If MBP more specifically reflects white matter lesions related to subcortical VaD than Nf-L remains to be shown.

Other markers that have been proposed to improve the differential diagnosis between AD and (subcortical) VaD are biomarkers reflecting blood-brain barrier (BBB) dysfunction, such as albumin ratio, and markers related to inflammation and opening of the BBB [58, 59]. The albumin ratio has consistently been found to be increased in subcortical VaD compared with AD and healthy controls [36, 37, 62]. Moreover, matrix metalloproteinases (MMP-9) known to be associated with BBB opening has been found to be increased in subcortical VaD together with its endogenous inhibitor, the tissue inhibitor of metalloproteinases 1 (TIMP-1) compared with AD and healthy controls [37]. TIMP-1 has also been shown to correlate with white matter lesion volume and albumin ratio, while MMP-9 has been shown to be associated with white matter lesion progression [37, 55]. These markers and other markers related to inflammation and cerebrovascular disease needs further attention for their role to reflect subcortical small vessel disease [60].

Major molecular pathologies underlying FTLD include aggregation of transactive response DNA-binding protein of 43 kDa (TDP-43, FTLD-TDP), and tau (FTLD-tau) [65]. Having the potential to be a specific biomarker for FTLD-TDP, a lot of research was done on TDP-43. Because of low absolute levels, quantitative analysis of TDP-43 in biofluids will require a very sensitive immunoassay, preferably specific for pathological TDP-43 [66]. So far, research has not been translated into a sensitive and specific biomarker for TDP-43. The only FTLD-specific biomarker is progranulin, showing decreased concentrations in serum or plasma of subjects with GRN mutation-related FTLD (a subgroup of FTLD-TDP) [67, 68]. The diagnostic value of CSF progranulin levels is a matter of debate.

The discovery of α-synuclein (α-syn) as a major component of Lewy bodies, which is the neuropathological hallmark of Parkinson’s disease (PD) and DLB, initiated research on α-syn as a potential CSF biomarker. α-syn is as well a constituent of glial inclusions in multiple system atrophy (MSA). Large variations in the absolute levels of α-syn in CSF and serum have been revealed, even when the same
types of α-syn isoforms were detected [69]. Differences in values are related to differences in analytical procedures, stressing the need for standardization of procedures [70]. CSF α-syn levels are decreased in PD and DLB but also in MSA [69] as compared to AD where increased levels have been reported, correlating with tau and thus possibly with neurodegeneration [71]. These data show the (differential) diagnostic potential of α-syn as a biomarker.

Fast progressive AD phenotypes often pose a diagnostic challenge and may be confused clinically with CJD. The major biological diagnostic biomarker for identifying CJD, 14-3-3 protein in CSF, unfortunately lacks specificity when confronted with a rapid dementia presentation [72, 73]. Very high T-tau concentrations may be found in AD in CSF (>1200 pg/ml), but are also indicative of CJD. In case of suspicion of CJD, analysis of the total concentration of prion protein (t-PrP) in CSF has been shown to be useful to increase the diagnostic accuracy [39]. The use of CSF t-PrP levels may be beneficial in clinical practice in addition to the current classic biomarkers.

**IMPROVEMENT AND HARMONIZATION OF AD CSF BIOMARKER MEASUREMENTS**

Even with an elevated confidence in the use of CSF biomarkers for the clinical work-up of dementia diagnosis, multicenter trials have shown that there is a substantial center-to-center variation [9].

Due to its favorable diagnostic characteristics and the relative inexpensive costs, much effort has been put into making Aβ_{1-42} manageable as an AD biomarker worldwide to be used in daily clinical dementia practice as *in vivo* surrogate marker for plaque pathology [20]. Though the absolute measurements of Aβ_{1-42} in CSF show inter-laboratory variability, mainly due to differences in pre-analytical and analytical procedures, which also includes the performance of different assays utilizing different calibrators. This causes an important concern as direct comparisons of measurements between laboratories and across techniques are not reliable, hampering biomarker development and their utility for clinical routine diagnosis. Storage in different tubes, different aliquot volumes, and number of freeze-thaw cycles are factors that significantly influence CSF biomarker concentrations, stressing the need for standard operating procedures for pre-analytical sample handling [74–76]. However, it has previously been suggested [77] and verified by us that the Aβ_{1-42}/Aβ_{1-40} ratio is a more robust measurement compared with Aβ_{1-42} alone as it corrects for intra-individual confounding factors and minimizes variability due to for instance adsorption of Aβ peptides to storage tubes [76]. An exploratory study in MCI patients, on the other hand, with clinical follow-up and autopsy-confirmed AD patients provided evidence that, for a specific context of use, the impact on clinical diagnostic accuracy of biomarker concentration shifts might be lower than originally expected [78]. However, standardization of (pre)analytical sample handling as well as the cut-off thresholds should be accomplished as they influence biomarker results [74–76, 79].

Major efforts are undertaken to overcome these problems by introducing a certified reference material and a certified reference method that can be used for value assignment of the assay calibrators [79–81]. Also, the Alzheimer’s Association external quality control (QC) program monitors site-to-site and batch-to-batch CSF measurement variability for the purpose of enabling the participating laboratories to synchronize their procedures [82]. These efforts will lead to precise and reliable measurements between laboratories that will enable the introduction of a worldwide cut-off point for CSF Aβ_{1-42}, T-tau and P-tau_{181} measurements for the purpose of clinical diagnostics and patient stratification in clinical trials.

With this in mind, several programs for standardization and harmonization were set up, such as the QC program of the Alzheimer’s Association, as well as the Alzheimer Biomarker Standardization Initiative (ABSI) and the JPND BIOMARKAPD consortium [79, 82–84].

**CONCLUDING REMARKS**

Over the past decades, much progress has been made in the development and validation of three core CSF biomarkers for the biochemical diagnosis of AD, including standardization and harmonization of (pre-) analytical procedures. One of the most important recommendations with a significant effect on pre-analytical variability is likely to be the implementation of the Aβ_{1-42}/Aβ_{1-40} into the clinical diagnostic work-up. This is especially important since Aβ_{1-42} has proven to be the earliest marker to reflect AD related pathological changes take place in the brain and the ratio show a higher concordance with amyloid pathology. At present, low CSF Aβ_{1-42}
concentration is an inclusion criterion for several clinical trials with potential disease-modifying drugs that target AD in its earliest (and even preclinical) stages. Hence, biomarkers reflecting the pathology targeted by specific clinical trials are essential for inclusion but also to monitor treatment effects. Early clinical detection is also likely to become more important as soon as disease-modifying pharmacological treatment for AD is available as medications that halt or prevent the disease are likely to be most effective at an early stage, when neurodegeneration has not become too severe. The validated core AD CSF biomarkers have an added value in the early and differential diagnosis of AD and related disorders, including mixed pathologies, atypical presentations of AD, and in case of ambiguous dementia diagnosis.

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