

Are we close to using Alzheimer blood biomarkers in clinical practice?

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Alzheimer's disease (AD) is a progressive neurodegenerative disease histologically characterized by the presence of extraneuronal plaques, mainly formed by the 42-aminoacid isoform of amyloid- β ($A\beta_{1-42}$), and by intraneuronal neurofibrillary tangles, mainly formed by the tau protein and its hyperphosphorylated isoforms (p-tau). AD is the most common cause of dementia, with an estimated lifetime risk of about 1 in 10 for men and 1 in 5 for women. As of 2020, there were approximately 50 million people living with dementia worldwide, a number set to increase to 152 million by 2050 (Scheltens et al., 2021). Two forms of AD exist. The most common form is late-onset AD with onset at ≥ 65 years which in most cases is a sporadic disorder with a number of genetic risk factors (e.g., *APOE*, *CLU*, *CR1*, *TREM2*, and *PICALM*). Early-onset AD occurs at ≤ 65 years and accounts for 5% to 6% of total cases of which about 10% have an autosomal-dominant form associated with point mutations of genes codifying for amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*) and presenilin 2 (*PSEN2*), which are involved in $A\beta$ production. Clinical features of sporadic and autosomal-dominant AD are similar, with early and prominent episodic memory loss (Scheltens et al., 2021). The $A\beta$ cascade hypothesis of AD postulates that the accumulation of $A\beta$ in the brain is the initial causative event of the disease process, starting 15–20 years before the onset of clinical symptoms. The accumulation of $A\beta$ in the brain would trigger the aggregation of tau protein in neurofibrillary tangles. These effects are interconnected with microglial activation and astrocyte reactivity leading to neuritic dystrophy and disease progression. Over the past 30 years, this hypothesis has inspired intense research efforts to develop and test compounds that counteract the accumulation of $A\beta$ in the brain (Karran et al., 2022).

In June 2021, the Food & Drug Administration has granted accelerated approval of aducanumab, an anti- $A\beta$ monoclonal antibody selective for aggregated forms of $A\beta$, for the treatment of early AD based on its ability to robustly lower brain plaque load. Lecanemab, a monoclonal antibody selective for $A\beta$ -protofibrils, was approved by the Food & Drug Administration in January 2023 based on a modest beneficial effect on the rate of cognitive and clinical decline in individuals with early AD (van Dyck et al., 2023). Donanemab, a monoclonal antibody selective for $A\beta$ -plaques, is expected to be approved in the near future based on relatively positive results in a large trial conducted in early symptomatic AD participants (Sims et al., 2023).

In this Perspective, we briefly summarize the latest advances in the field of AD blood biomarker research and discuss the feasibility of their clinical implementation in individuals with relatively advanced age and in those at risk of developing

AD. We will also provide the rationale for a new biological classification of AD through the blood AT(N) framework that could improve AD diagnosis, personalize treatment, and improve risk estimation of disease progression.

AD biomarkers and the AT(N) classification system: The current biological diagnosis of AD is based on the measurement of three classes of biomarkers detected in cerebrospinal fluid (CSF) or through brain imaging techniques that estimate brain amyloid- β ($A\beta$) deposition ("A"), tau pathology ("T"), and neurodegeneration ("N"). This approach is called the AT(N) classification system with "A" and "T" indicating the prototypical pathological hallmarks of the disease ($A\beta$ and tau) and "N" indicating the evidence of neuronal damage. "N" is indicated in parenthesis since its positivity is optional for the biological diagnosis of AD.

Pathology studies have shown that both brain $A\beta$ -positron emission tomography ($A\beta$ -PET) imaging and CSF concentrations of $A\beta_{1-42}$ are reliable biomarkers of brain $A\beta$ pathology. Other studies have also shown that tau-PET imaging or CSF hyperphosphorylated tau isoforms (p-tau217, p-tau181, p-tau231, p-tau205, and MTBR-tau243) are efficient biomarkers of tau pathology both in terms of diagnosis and of prediction of clinical course (Figure 1). Neurodegeneration status can be effectively tracked by volumetric magnetic resonance imaging measuring total and regional brain atrophy, [18F]fluorodeoxyglucose (FDG)-PET imaging measuring brain regional glucose utilization or CSF concentrations of neurofilament light chain (NfL), a marker of neuroaxonal injury. The AT(N) matrix is now being expanded towards an ATX(N) system, where "X" represents a biomarker for other neuropathological components including neuroinflammation [glial fibrillary acidic protein (GFAP) for reactive astrogliosis or soluble triggering receptor expressed on myeloid cells 2 (sTREM2) for microglial activation], or a marker of synaptic damage (neurogranin or growth-associated protein 43 or neuronal pentraxin receptor).

In the last 10 years, AD blood-based biomarkers have been developed and extensively tested in individuals with mild-to-moderate AD, in individuals with early AD, and in cognitively normal individuals at risk of developing AD. AD blood biomarkers are much less invasive and less costly than CSF or imaging biomarkers and can be easily repeated in the same individuals. Promising blood biomarkers for each of the AT(N) categories have been identified ($A\beta_{1-42}/A\beta_{1-40}$ ratio, p-tau isoforms, and NfL, respectively). An AT(N) system has been proposed in which "I" represents a biomarker for neuroinflammation (GFAP) (Imbimbo et al., 2023). Longitudinal studies have shown that blood AD biomarkers can predict the onset of clinical symptoms in AD and can help identify individuals

on the early path of the disease and, therefore, amenable to therapeutic intervention prior to irreversible neurodegeneration. AD biomarkers can also be useful for optimizing the enrollment of individuals in clinical trials of novel drugs and for tracking therapeutic response.

What has changed in our understanding of AD blood biomarkers in recent years? Cross-sectional and longitudinal studies have shown that the combination of blood biomarkers tracking neuroaxonal injury (NfL) and neuroinflammatory pathways (GFAP) can enhance the sensitivity and specificity of AD clinical diagnosis and improve the prediction of AD onset and progression (Stocker et al., 2023). Microtubule-binding region (MTBR) of tau containing the residue 243 (MTBR-tau243) was shown to be a specific CSF biomarker for insoluble tau aggregates (Horie et al., 2023a). MTBR-tau243 was most strongly associated with PET and cognition and was proposed to represent insoluble tau aggregates ("T") in the AT(N) classification. Interestingly, a recent study has shown that plasma levels of MTBR-tau243 strongly correlated with tau-PET during the clinical symptomatic phase of AD (Horie et al., 2023b). Plasma MTBR-tau243 was also found to be inversely associated with cognitive performance (as measured with the Mini-Mental State Examination) in amyloid-positive participants. These encouraging results need to be validated in larger cohorts and tested in longitudinal studies.

The clinical response of early AD individuals to anti- $A\beta$ monoclonal antibodies was shown to be potentially dependent on tau pathology status at baseline. Concerning lecanemab, a better clinical response, as measured by the Clinical Dementia Rating-Sum of Boxes scale, was observed in individuals showing lower tau burden at baseline, as assessed by tau-PET. In the phase 3 study with donanemab, baseline plasma p-tau217 concentrations predicted therapeutic response. Although these observations involve post hoc analyses of small numbers of participants from large trials and need to be replicated in future controlled studies, the perspective that baseline tau biomarkers may predict cognitive and clinical response to anti- $A\beta$ monoclonal therapy is very attractive from a clinical standpoint because it can pave the way to therapy optimization on an individual basis.

Is there enough evidence on AD blood biomarkers to influence clinical practice? A recent longitudinal study conducted in 1712 cognitively unimpaired individuals, found that serum GFAP concentrations at baseline were associated with a hazard ratio of 1.38 for incident dementia, and 2.76 for dementia-specific mortality, thus indicating that circulating GFAP may provide useful clinical insight regarding dementia risk and prognosis (Cronjé et al., 2023). An analysis conducted within the ESTHER cohort, a German population-based prospective cohort study of community-dwelling older individuals, disclosed a considerably earlier association (within 9–17 years before clinical diagnosis) of plasma GFAP with AD incidence than NfL and p-tau181 (within 9 years of diagnosis) (Stocker et al., 2023). These results highlighted a possible role of GFAP as a superior prognostic biomarker for incident AD dementia

compared with NfL (Verberk et al., 2021). A recent study has shown that brain A β is associated with increased plasma hyperphosphorylated tau only in individuals with abnormally high blood GFAP (Bellaver et al., 2023). Overall, the above-reported outcomes suggest a potential role for GFAP as an early blood-based biomarker of reactive astrogliosis associated with A β pathology in preclinical AD, thus it may be used to recognize individuals at risk of AD, before clinical symptoms onset (Chatterjee et al., 2021).

A study with 912 participants found that algorithms using plasma p-tau217 can accurately identify most A β -positive individuals and may substantially reduce the number of invasive and costly confirmatory tests (including tau-PET imaging) required to identify individuals who would likely benefit from anti-amyloid immunotherapies. These results were validated in an independent cohort of 118 individuals (Mattsson-Carlgrén et al., 2023).

The potential clinical use of the AT(N) classification system: Recommendations have been published by the Alzheimer's Association for blood-based biomarkers, highlighting that longitudinal and observational clinical trials should establish the overtime changes in blood biomarkers in AD patients and monitoring changes in clinically relevant outcomes, such as cognition and motor functions (Hansson et al., 2022).

Longitudinal studies recruiting large cohorts of individuals with accurate clinical characterizations have identified blood GFAP as an efficient and predictive biomarker of neuroinflammation in AD. GFAP well tracks reactive astrocytes and can identify A β -positive cognitively unimpaired individual who have initial p-tau pathology (Bellaver et al., 2023) and predicts the risk of clinical AD diagnosis within 17 years (Stocker et al., 2023). Thus, plasma GFAP represents the most promising neuroinflammation biomarker for subjects with early AD and for those at risk of developing AD. The plasma AT(N) framework, together with APOE genotyping and cognitive testing, offers a basis for individualized assessment toward a biomarker-driven individualization of therapy for patients with AD (Imbimbo et al., 2023). From a clinical practice perspective, a multi-stage and multi-marker diagnostic model is foreseen. Individuals with cognitive complaints undergo initial clinical assessment and cognitive testing. Those individuals with confirmed cognitive impairment may have a blood draw to assess the presence of AD pathology according to the AT(N) classification system. Based on the outcome of the blood biomarker assays, individuals are classified as high, intermediate, or low risk. For individuals at high-risk profile, the clinical AD diagnosis is supported. For individuals at intermediate risk, further biomarker evaluation in CSF and/or PET imaging may be considered. For individuals at low risk, alternative clinical diagnosis should be investigated (Figure 2). Once the diagnosis is defined, therapeutic interventions can be initiated. Such a combined multi-step/multi-modal biomarker-based diagnostic model can assist primary healthcare physicians when deciding which patients should be moved to more specialized clinics for ultimate diagnosis

and beginning of treatments. In addition, it can represent a cost-effective means for effective biomarker-based patient stratification as well as a refined model for novel targeted interventions also in the setting of clinical trials. In this diagnostic scenario, supplementary studies will be needed to find the best combination of blood biomarkers with other scalable and inexpensive indicators, including magnetic resonance imaging modalities and cognitive examinations, and refine algorithms that can predict cognitive deterioration and disease clinical advancement (thus, they will be relevant in non-demented individuals with memory complaints).

Use of blood biomarkers in diagnosis, prognosis, and patient selection in AD trials: Blood biomarkers may help diagnosis, prognosis, and patient selection for anti-amyloid drugs. Indeed, AD diagnosis may be supported by measuring plasma A β_{1-42} /A β_{1-40} ratio and p-tau217 levels (Hansson et al., 2022). However, plasma A β_{1-42} /A β_{1-40} ratio is a less robust brain A β pathology biomarker than CSF A β_{1-42} /A β_{1-40} ratio due to the small fold change between A β -positive and A β -negative individuals (an 8–15% reduction compared with 40–60% in CSF). In the memory clinic setting, the diagnostic performance of plasma p-tau217 has been shown to be similar to both CSF biomarkers and tau-PET imaging (Hansson et al., 2022). Kits for measuring A β_{1-42} /A β_{1-40} and p-tau217 in blood are currently commercially available, but they do not provide a diagnosis; they simply estimate the risk of developing AD. In terms of prognosis, plasma p-tau217 was shown to be the best biomarker to predict cognitive decline as measured with modified Preclinical Alzheimer Cognitive Composite and the Mini-Mental State Examination in A β -positive cognitively unimpaired individuals (Mattsson-Carlgrén et al., 2023). Power calculations for enrichment in hypothetical clinical trials revealed large relative reductions in sample sizes when using plasma p-tau217 to enrich cognitively unimpaired individuals likely to experience cognitive decline over time (Mattsson-Carlgrén et al., 2023).

Current challenges and limitations: AD blood biomarker profiling is expected to facilitate diagnosis, predict disease progression, and devise individualized therapeutic interventions in the AD continuum. At present, the most promising blood AD biomarkers are A β_{1-42} /A β_{1-40} , p-tau217, NfL, and GFAP. However, while plasma p-tau217 and p-tau181 efficiently reflect amyloid burden in the AD brain, they do not accurately track the accumulation of tau pathology. Recently, a preliminary study has shown that plasma levels of MTBR-tau243 strongly correlated with tau-PET during the clinical symptomatic phase of AD (Horie et al., 2023b). However, these results need to be validated in future studies. A further point of attention is that no reliable blood biomarkers have been identified to track activated microglia and synaptic damage.

Scientific interpretation of the central trends (means or medians or Log-transformed means) of blood biomarkers is quite clear. However, interpreting blood biomarker profile for a single individual is clinically challenging due to the

high variability (Brum et al., 2023). Indeed, no internationally accepted cut-offs have been identified for AD blood biomarkers. Furthermore, AD often presents multiple overlapping pathologies linked to other neurodegenerative diseases and this complicates the interpretation of blood biomarkers.

In 2017, a five-phase roadmap for the clinical validation of biomarkers in AD has been proposed (Frisoni et al., 2017). Phase 1 is represented by preclinical exploratory studies; phase 2 by clinical assay development for AD pathology; phase 3 by retrospective studies of longitudinal data available in repositories; phase 4 by prospective diagnostic accuracy studies; and phase 5 by disease burden reduction studies. We believe that sufficient evidence has accumulated for plasma A β_{1-42} /A β_{1-40} , p-tau 217, NfL, and GFAP to meet phases 1, 2, 3, and partially phase 4 while there is not yet sufficient evidence for their clinical utility (phase 5). These limitations prevent the use of blood biomarkers in routine clinical settings.

Conclusions: Several large longitudinal studies have found that blood biomarkers can efficiently detect A β and tau pathology and estimate the degree of neurodegeneration. When combined, blood AD biomarkers can reliably and effectively predict brain pathology in individuals with mild cognitive impairment and clinical progression to AD dementia and distinguish AD dementia from other types of dementia. Interpreting results of blood candidate biomarkers simultaneously in a clinical context in a single individual with cognitive complaints is challenging due to high individual variability, lack of clear cut-offs, and differential diagnosis. A decision algorithm could aid in the interpretation, tailored to the following clinically relevant questions. Although blood-based AD biomarkers have great potential in the diagnostic workup for AD, evidence of their utility in terms of patient clinical outcome is not yet available, hampering their widespread clinical implementation.

BPI is an employee at Chiesi Farmaceutici. He is listed among the inventors of a number of Chiesi Farmaceutici's patents of anti-Alzheimer drugs. SL, CI, and RN have no conflicts of interest to declare.

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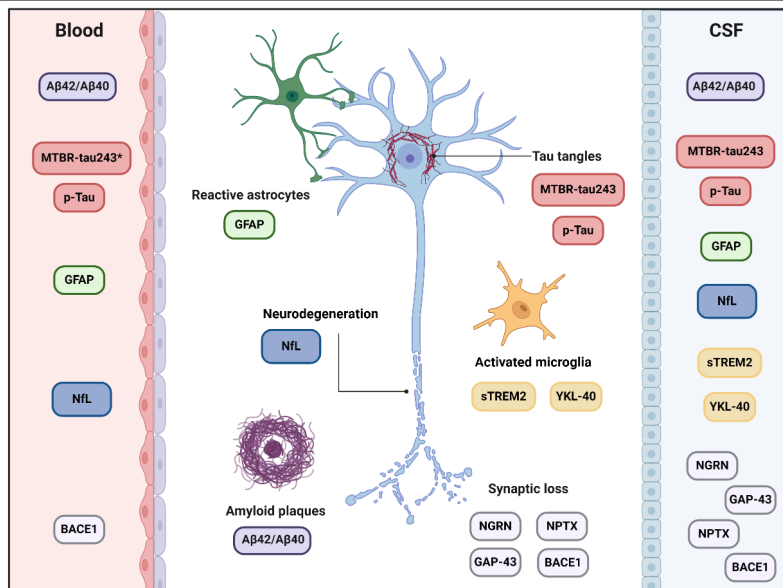


Figure 1 | Pathological mechanisms involved in Alzheimer's disease and their associated fluid-based biomarkers. Aβ, p-tau isoforms, NFL, GFAP, and BACE1, can be reliably measured both in CSF and in blood. sTREM2, YKL-40, MTBR-tau243, NGRN, GAP-43, and NPTX are additional valuable biomarkers that can be measured in CSF. *Preliminary evidence indicates that MTBR-tau243 can be measured also in blood. Created with BioRender.com. Aβ: Amyloid-β; BACE1: β-amyloid precursor protein cleaving enzyme; CSF: cerebrospinal fluid; GAP-43: growth-associated protein 43; GFAP: glial fibrillary acidic protein; MTBR-tau243: microtubule-binding region of tau containing the residue 243; NFL: neurofilament light chain; NGRN: neurogranin; NPTX: neuronal pentraxin receptor; p-Tau: hyperphosphorylated tau; sTREM2: soluble triggering receptor expressed on myeloid cells 2; YKL-40: chitinase-3-like protein 1.

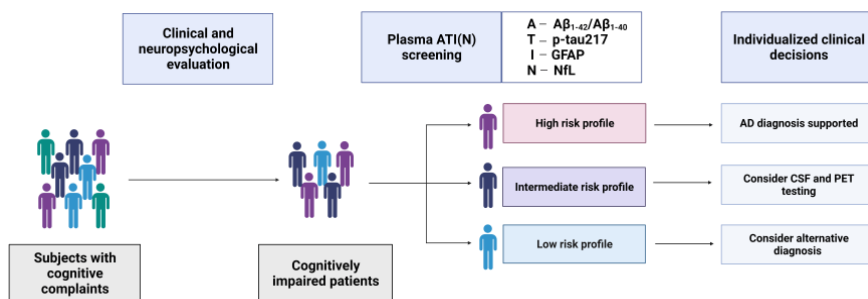


Figure 2 | Blood-based screening approach for a patient with cognitive complaints.

Simplified illustration of a multi-step, multi-modal biomarker-based diagnostic model. After clinical and neuropsychological evaluation of individuals presenting with subjective memory complaints, those with confirmed memory impairment may undergo a blood-based screening panel composed of biomarkers evaluating Aβ pathology (A), tau pathology (T), neurodegeneration (N), and neuroinflammation (I). Based on the outcome of the blood biomarker assays, individuals are classified at high (A⁺ and T⁺), intermediate (A⁺ or T⁺ or I⁺, N⁺/N⁻), or low (A⁻, T⁻, I⁻, N⁺/N⁻) risk profile. For subjects with a high AT(N) risk profile, the AD diagnosis is supported. For individuals with intermediate AT(N) risk profile, CSF sampling for biomarker assay and PET imaging may be considered. For individuals with a low AT(N) risk profile, an alternative diagnosis may be considered. AD: Alzheimer's disease; Aβ: amyloid-β; Aβ₁₋₄₂/Aβ₁₋₄₀: ratio between amyloid-β₁₋₄₂ and amyloid-β₁₋₄₀; CSF: cerebrospinal fluid; GFAP: glial fibrillary acidic protein; NFL: neurofilament light chain; PET: positron emission tomography; p-tau217: hyperphosphorylated tau at position 217.

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