



# Blood biomarkers: ready for clinical practice?

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Most people would want to know early, if they had Alzheimer's disease (AD).<sup>1</sup> Potential new treatments, such as lecanemab, require early molecular AD diagnosis.<sup>2</sup> Yet, very few clinic patients receive a molecular diagnosis (only ~1% in the UK), around 40% of people with dementia are never diagnosed and most diagnoses occur relatively late in the course of the illness.<sup>3</sup> Amyloid and tau radionuclide ligands and cerebrospinal fluid (CSF) AD biomarkers are approved by the USA Food and Drug Administration, adopted in National Institute for Health and Care Excellence (NICE) dementia guidelines, and alter clinical management,<sup>4</sup> but they are considered expensive and intrusive, which limits widespread use. Blood biomarkers are a potential solution as they are much easier and cheaper to deliver. In research cohorts, blood biomarkers offer high sensitivity and specificity for AD. However, we require real-world blood biomarker data before validating them for clinical use.<sup>5,6</sup>

To this end, here, we present three papers that illuminate the practical application of blood biomarkers—Altomare *et al*<sup>7</sup> (Geneva Cohort) and Lehman *et al*<sup>8</sup> (BALTAZAR cohort) assess the performance of AD blood biomarkers in memory clinics, and Veria *et al*<sup>9</sup> highlight potential for positive AD blood biomarkers in amyotrophic sclerosis.

Altomare *et al* report on 200 patients with cognitive complaints, who range from cognitively unimpaired to dementia stage, to explore the relationship between plasma biomarkers and the established biomarkers of AD including Amyloid (A $\beta$ 42 or A $\beta$ 42:40 ratio in the CSF or Amyloid Positron Emission Tomography (PET)), Tau (p-tau181 or p-tau231 in the CSF, or Tau-PET imaging) and markers of Neurodegeneration (atrophy on MRI

or hypometabolism on Fluorodeoxyglucose (FDG)-PET).<sup>10</sup> The authors rate diagnostic accuracy defined by area under the receiver operated curve (AUC) of 0.7–0.8 as 'acceptable' and 0.8–0.9 as 'excellent'. AUC for some amyloid and tau measures fell within this range (eg, the best amyloid classification AUC was plasma p-tau231:A $\beta$ 42 compared with CSFA $\beta$ 42=0.87). However, plasma A $\beta$ 42 compared with amyloid PET had an AUC of 0.66, and, likewise, plasma NFL fell below the acceptable range of diagnostic accuracy (when compared with an MRI score of hippocampal atrophy or FDG-PET).

In the BALTAZAR prospective longitudinal study, 476 participants with mild cognitive impairment (MCI) had baseline plasma p-tau181 and were followed over years for conversion to dementia—arguably the gold-standard outcome diagnostically (as well as a subgroup having baseline CSF A $\beta$  assays). Over two-thirds of patients had Amyloid $\beta$ 42:40 ratio <0.1 (A $\beta$ +) at baseline and 30% converted to dementia during a period of up to 3 years. Plasma p-tau181 at baseline was associated (1) with baseline CSF A $\beta$ + status (adding P-tau181 to a model containing age, sex, APOE $\epsilon$ 4 status and Mini-mental State Examination (MMSE) improved AUC from 0.786 to 0.849 (from acceptable to excellent as defined above)) and (2) with conversion to dementia (when added to age, sex, APOE $\epsilon$ 4 status and MMSE, P-tau181 improved AUC from 0.69 to 0.74 (ie, just into the acceptable range)). MCI participants with low serum p-tau181 (<2.32 pg/mL) showed a conversion rate of <20% over 3 years. Serum creatinine and eGFR were associated with plasma levels of p-tau181—and the authors highlight the importance of correcting for renal function to optimise interpretation of p-tau181.

In our third paper, in a cohort of 148 amyotrophic lateral sclerosis (ALS), 12 spinal muscular atrophy, 88 AD and 70 healthy controls, Veria *et al* demonstrate raised blood, but not CSF, p-tau181 in ALS—although less marked than in AD. Given the frequency of behavioural and cognitive changes associated with ALS, and the high prevalence of AD, this study demonstrates the impact of comorbidities

on biomarkers for neurodegenerative diseases—and that our understanding is still evolving.

Interpretation across these studies has limitations—Altomare's manuscript has great strengths due to the in-depth characterisation with multiple biomarkers, but heterogeneity in disease stage of the patients, limited reporting of comorbidities, multiple statistical comparisons that are uncorrected and a relatively small sample all limit inference. Lehman *et al* have a much larger cohort with documented comorbidities, but did not report ptau217,<sup>5</sup> an isoform of p-tau thought better for predicting conversion to dementia than ptau181, and patient characterisation was not based on the Amyloid/Tau/Neurodegeneration (ATN) classification<sup>11</sup> (eg, there was no biomarker of neurodegeneration reported). Veria *et al* included a wider range of neurodegenerative diseases but some groups are small (although numbers are impressive given the rarity of the conditions), and comorbidities are little explored. The cognitive tests differ between the studies—Veria not using and/or reporting standardised cognitive tests, while Altomare and Lehman rely on MMSE (a standard cognitive screening tool relatively insensitive to early disease). Also, the ethnicity of participants was not mentioned in the studies.

These studies are important as they show that blood biomarkers in real-world cohorts mirror more established biomarker results and can predict future cognitive decline. But questions remain—which biomarkers should be used and at what stage of disease, how should comorbidities (including renal function) be considered when interpreting blood biomarker results? More fundamentally, do we think that diagnostic accuracy for AD of 0.7–0.8 compared with gold standard tests is acceptable—or is this really an accuracy level we would accept for patient triage only? In other words, will we always require diagnostic confirmation with amyloid PET or CSF before embarking on Alzheimer-specific treatments—or is it reasonable to aim for diagnosis based solely on blood biomarker tests?

The recently published BIODEGMAR cohort<sup>12</sup> suggested perhaps blood tests could be diagnostic in themselves—comparison between CSF A $\beta$ 42/p-tau and plasma ptau181 achieved AUC=0.94, and p-tau217 achieved AUC=0.94. But our papers, together, suggest we should be cautious. Why do blood biomarkers appear less accurate here? Of course, for the BALTAZAR cohort the main outcome is delayed diagnostic verification, but even

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the cross-sectional comparison suggests lower discrimination by ptau181 than BIODEGMAR. It is likely that demographic and perhaps technical (eg, assay) might have contributed to differences. Patient selection might also be very important for interpretation of these difference cohorts—comorbidities affect diagnostic accuracy and typical research cohorts have fewer comorbidities than patients in real-world clinics.

We need aligned populations, index and reference tests across studies to generate larger real-world datasets, with in-depth patient characterisation, before we can be confident clinically how to use blood biomarkers. We agree with current clinical recommendations suggesting their cautious use only in specialised memory services and confirmation with CSF/PET.<sup>13</sup> Blood biomarkers will transform AD diagnosis, but it looks unlikely they will fully replace more established AD diagnostic biomarkers in the next few years (at least). If memory clinics aspire to deliver disease-modifying therapies in near future, CSF and/or PET scanning will need to become routine.

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REFERENCES

1 ARUK. *The right to know: accurate and earlier diagnosis of dementia*. 2021.

- 2 van Dyck CH, Swanson CJ, Aisen P, *et al*. Lecanemab in early Alzheimer's disease. *N Engl J Med* 2023;388:9–21.
- 3 Cook L. *The 2019 national memory service audit*. 2019.
- 4 Hazan J, Wing M, Liu KY, *et al*. Clinical utility of cerebrospinal fluid biomarkers in the evaluation of cognitive impairment: a systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry* 2023;94:113–20.
- 5 Teunissen CE, Verberk IMW, Thijssen EH, *et al*. Blood-based biomarkers for alzheimer's disease: towards clinical implementation. *Lancet Neuro* 2022;21:66–77.
- 6 Ashton NJ, Leuzy A, Karikari TK, *et al*. The validation status of blood biomarkers of amyloid and phospho-tau assessed with the 5-phase development framework for AD biomarkers. *Eur J Nucl Med Mol Imaging* 2021;48:2140–56.
- 7 Altomare D, Stampacchia S, Ribaldi F, *et al*. Plasma biomarkers for Alzheimer's disease: a field-test in a memory clinic. *J Neurol Neurosurg Psychiatry* 2023;94:420–7.
- 8 Lehmann S, Schraen-Maschke S, Vidal J-S, *et al*. Plasma phosphorylated tau 181 predicts amyloid status and conversion to dementia stage dependent on renal function. *J Neurol Neurosurg Psychiatry* 2023;94:411–9.
- 9 Veria V, Andrea M, Corrado Z. Elevated plasma p-Tau181 levels unrelated to Alzheimer's disease pathology in amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry* 2023;94:428–35.
- 10 Jack CR Jr, Bennett DA, Blennow K, *et al*. A/T/N: an unbiased descriptive classification scheme for Alzheimer disease biomarkers. *Neurology* 2016;87:539–47.
- 11 Jack CR, Bennett DA, Blennow K, *et al*. NIA-AA research framework: toward a biological definition of alzheimer's disease. *Alzheimers Dement* 2018;14:535–62.
- 12 Ashton NJ, Puig-Pijoan A, Milà-Alomà M, *et al*. Plasma and CSF biomarkers in a memory clinic: head-to-head comparison of phosphorylated tau immunoassays. *Alzheimers Dement* 12, 2022. 10.1002/alz.12841
- 13 Hansson O, Edelmayer RM, Boxer AL, *et al*. The Alzheimer's association appropriate use recommendations for blood biomarkers in Alzheimer's disease. *Alzheimers Dement* 2022;18:2669–86. 10.1002/alz.12756