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Cracking the Alzheimer's code: Emerging blood biomarkers for clinical diagnosis

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Dementia is the most common clinical feature of neurodegenerative diseases and currently more than 55 million people worldwide live with dementia[1]. Among its various causes, Alzheimer's disease (AD) is the most prevalent, accounting for 60–70% of cases[1]. AD is an intricate condition characterized by two pathological hallmarks: amyloid-beta (Aβ) plaques and neurofibrillary tangles, whose formation leads to a longstanding cascade involving neuroinflammation, reactive astrogliosis, and progressive synaptic and neuronal loss. This process begins years before the apparent clinical symptoms of the disease and progresses in a consistent pattern, resulting in a clinical continuum.

AD pathology often co-occurs with other neurodegenerative and vascular diseases, and while memory loss (amnestic syndrome) is the typical presentation, many patients show non-amnestic cognitive changes. These differences in symptoms and underlying pathology make diagnosis and treatment challenging. Disease-modifying therapies are being developed to target AD across these diverse presentations, but they are most effective when started early. Several agents are in clinical trials, and two antibody-based drugs have already been approved by the U.S. Food and Drug Administration (FDA). Therefore, accurate and timely diagnosis is critical to identify patients who can benefit from these treatments.

What are AD blood biomarkers, and where do we stand?

The biological determination of disease has long been a standard framework, and since AD is a dual proteinopathy, Positron Emission Tomography (PET) imaging and Cerebrospinal fluid (CSF) biomarkers are FDA-approved for its diagnosis2. However, their invasiveness, high cost, and limited availability restrict routine clinical use. This has led to a shift toward blood biomarkers, which are more accessible and scalable. Several highly sensitive immunoassays have been developed to reflect core AD pathology, including plasma amyloid-β42, the Aβ42/Aβ40 ratio, phosphorylated tau at threonine 181 (p-tau181), p-tau217, p-tau231, brain-derived tau (BD tau), and microtubule-binding region tau243 (MTBR-tau243). Plasma Aβ42 depletion and a reduced Aβ42/Aβ40 ratio can be detected in preclinical AD, though small differences between individuals and production from extracerebral tissues can complicate testing. All p-tau assays measure phosphorylated tau using antibodies targeting the N-terminus or mid-domain. Plasma p-tau181 correlates with both Aβ plaque and tau tangle burden and can distinguish AD from other dementias. Plasma p-tau217 is emerging as a leading biomarker, showing diagnostic performance comparable to CSF biomarkers and tau-PET[3]. The plasma p-tau217/Aβ42 ratio was recently FDA-approved for biological AD diagnosis, demonstrating excellent accuracy compared to amyloid and tau PET[4]. Other plasma biomarkers include MTBR-tau243, indicating tau toxicity; neurofilament light chain (NfL), a marker of neurodegeneration; and glial fibrillary acidic protein (GFAP), a marker of neuroinflammation, which together can help define the biological diagnosis of AD.

Why plasma p-tau217 is a front-runner biomarker for AD

Plasma p-tau217 shows the highest relative concentrations among p-tau variants in AD and has diagnostic performance comparable to CSF biomarkers and tau-PET imaging[3,5,6]. It begins to change earlier than other p-tau forms, rising during both preclinical and prodromal stages, and can accurately predict future cognitive decline along the AD continuum. Multiple studies, including our own, comparing plasma p-tau with CSF biomarkers and neuropathological diagnosis, confirm that p-tau217 is a reliable marker for both screening and confirmatory AD diagnosis[3, 5, 6]. We evaluated two assays against autopsy-confirmed diagnoses: the ALZpath p-tau217 assay using SIMOA and the Lumipulse p-tau217 immunoassay. The ALZpath assay achieved an area under the curve (AUC) of 0.94, while the Fujirebio p-tau217 assay demonstrated an AUC of 0.90. Both assays support a three-range approach, resulting in an intermediate zone encompassing 15%–30% of cases that require confirmation by PET or CSF testing[3,6].

Blood biomarkers must be interpreted carefully in clinical practice

The recently published Alzheimer's Association clinical practice guideline addresses the use of blood biomarkers for diagnosing suspected AD and related disorders[7]. In patients with objective cognitive impairment presenting to specialized memory centers, these biomarkers may be used as part of the diagnostic workup. The guideline recommends using a highly accurate plasma biomarker (≥90% sensitivity, ≥75% specificity) as a triaging tool to rule out AD pathology, with positive results confirmed by CSF or amyloid PET. Blood biomarkers with both high sensitivity and specificity (≥90% for each) may also serve as confirmatory tests, although the certainty of evidence is currently low.

The guideline emphasizes that blood biomarker testing should follow a thorough clinical evaluation and be interpreted within the broader clinical context. Results may be unreliable in patients with reversible cognitive impairment or certain medical conditions or medications that can alter biomarker levels. Overall, blood biomarkers are reshaping the diagnostic landscape of AD, enabling earlier detection, improving clinical trial recruitment, and supporting more precise use of emerging disease-modifying therapies.

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