Alzheimer's Disease Biomarkers

- Safety, Cognitive, and Behavioral Outcomes in Patients with Dementia with Lewy Bodies Treated with Nilotinib
- Epigenetic Clocks and Their Prospective Application in the Complex Landscape of Aging and Alzheimer's Disease
- Clinical Management of Cerebral Amyloid Angiopathy
- Investigating Gamma Frequency Band PSD in Alzheimer's Disease Using qEEG from Eyes-Open and Eyes-Closed Resting States
- Associations between objective sleep metrics and brain structure in cognitively unimpaired adults: interactions with sex and Alzheimer's biomarkers
- Clinical features, biomarker profiles, and neuroimaging characteristics in patients from memory clinic in china: The Shanghai Memory Study
- Antiamyloid Monoclonal Antibodies in Alzheimer's Disease Part 2: Challenges in Dementia Care Delivery System Logistics
- Biomarker changes associated with fornix deep brain stimulation in Alzheimer's disease

Biomarkers used for the diagnosis, staging, and monitoring of Alzheimer's disease (AD), categorized using the AT(N) model and including emerging non-invasive markers.

Core Pathological Biomarkers

Biomarker	Clinical Meaning	Sample Type	Clinical Use
Aβ42	↓ in CSF indicates amyloid plaque accumulation	CSF	Early diagnosis
Aβ42/Aβ40 ratio	More accurate than Aβ42 alone	CSF, plasma	Diagnostic accuracy
p-tau 181/217	↑ in AD; reflects tau hyperphosphorylation	CSF, plasma	Staging and progression
t-tau	↑ in AD and other neurodegenerative diseases	CSF	General neuronal damage

Neurodegeneration Biomarkers ("N")

Biomarker	Meaning	Sample Type	Utility
Neurofilament light (NfL)	↑ in axonal degeneration	CSF, plasma	Severity, non-specific
Hippocampal atrophy	MRI finding indicating neuronal loss	MRI	Disease progression marker
FDG-PET	↓ glucose metabolism in temporoparietal regions	PET	Functional damage

Emerging Blood-Based Biomarkers

Biomarker	Comment
Plasma p-tau 181/217	High accuracy, close to CSF values

Biomarker	Comment
Plasma Aβ42/40 ratio	Promising for screening
Plasma GFAP	Reflects astroglial activation, early marker

Peripheral Fluid Biomarkers

Fluid Type	Studied Biomarkers	Remarks
Tears	Aβ, tau, inflammatory markers	Promising (e.g., Kärkkäinen et al. 2025)
Saliva	Lactoferrin, Aβ	Inconsistent results
Urine	Oxidative stress-related markers	Experimental

AT(N) Classification (NIA-AA)

* **A** (Amyloid pathology): ↓ CSF Aβ42 or Amyloid PET + * **T** (Tau pathology): ↑ CSF or plasma p-tau * **N** (Neurodegeneration): ↑ t-tau, NfL, or structural MRI/PET evidence

This classification helps define stages from preclinical to advanced Alzheimer's disease.

Summary Table

Domain	Best Biomarkers
Diagnosis	CSF Aβ42, p-tau, plasma p-tau181
Prognosis	Hippocampal atrophy (MRI), CSF t-tau, NfL
Monitoring	Plasma p-tau, NfL
Non-invasive	Plasma Aβ42/40, GFAP, tear-based markers

Blood biomarkers for Alzheimer's disease.

Cerebrospinal fluid biomarkers for Alzheimer's disease.

In a Prospective Observational Case-Control Study Kärkkäinen et al. aimed to identify neuroinflammation-related proteins in tear fluid (TF) as potential biomarkers for early-stage Alzheimer’s disease (AD). The novelty lies in using a non-invasive biofluid (TF) and applying high-resolution proteomics.

2. Strengths Non-invasive approach: Tear fluid collection via Schirmer strips offers a safe, patient-friendly method ideal for elderly populations.

Mass spectrometry-based proteomics: The use of label-free quantitative proteomics enhances the detection of subtle changes in protein expression without bias toward known candidates.

Clear case-control design: The inclusion of well-defined mild AD patients (CDR 0.5–1, MMSE 23.8 ± 2.8) and cognitively healthy controls (MMSE 28.9 ± 1.4) allows for meaningful comparisons.

Focus on neuroinflammation: Targeting neuroinflammatory pathways aligns with current hypotheses that inflammation plays a central role in early Alzheimer’s disease pathogenesis.

Identified candidate markers: The study reports 14 differentially expressed proteins, several of which (e.g., SERPINA3, ORM1, SPARCL1) have known links to inflammatory and neurodegenerative processes.

3. Limitations Small sample size: With only 19 AD cases and 34 controls, the study is underpowered for broad generalization or robust statistical correction for confounding variables.

Cross-sectional nature: Being observational and cross-sectional, it does not address causality or longitudinal stability of these biomarkers.

Lack of external validation: The findings are not validated in an independent cohort or in cerebrospinal fluid/plasma, limiting translational relevance.

Omission of confounding factors: Factors like dry eye syndrome, medications, systemic inflammation, or comorbidities were not extensively controlled for, which could significantly affect TF protein composition.

Overinterpretation risk: While the link between neuroinflammation and AD is established, asserting that these TF proteins are early biomarkers of AD is premature without longitudinal or mechanistic validation.

Lack of machine learning or biomarker signature development: Despite the proteomic data, no predictive models or ROC analyses were reported to evaluate diagnostic utility.

4. Contribution to the Field This study provides preliminary evidence that tear fluid proteins may reflect neuroinflammatory changes in early AD. It adds to a growing interest in peripheral biomarkers and supports the exploration of eye-brain connections in neurodegeneration.

5. Recommendations for Future Research Conduct longitudinal studies to assess temporal evolution of TF biomarkers in preclinical and prodromal AD.

Validate the identified proteins in larger, multicentric cohorts.

Correlate TF protein changes with CSF biomarkers (Aβ, tau) and neuroimaging findings.

Explore multiplex assays or ELISA-based panels for potential clinical translation.

Include confounder analysis (e.g., ocular surface disease, systemic inflammation).

Conclusion

This study is a promising proof-of-concept for using tear fluid as a diagnostic window into neurodegeneration, particularly AD. However, the small sample size, lack of validation, and cross-sectional design limit its current clinical utility. It should be viewed as a hypothesis-generating work that warrants more rigorous, larger-scale follow-up studies [1)]

1)
Kärkkäinen V, Saari T, Rusanen M, Uusitalo H, Leinonen V, Thiede B, Kaarniranta K, Koivisto AM, Utheim TP. Neuroinflammation Markers in Tear Fluid of Mild Alzheimer's Disease. J Mol Neurosci. 2025 Jun 5;75(2):73. doi: 10.1007/s12031-025-02368-x. PMID: 40471493.