# Clinical Practice Aid: Biomarker Testing in Alzheimer's Disease

## Introduction: How Is Biomarker Testing Important Across the Alzheimer's Continuum?[1]

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by the accumulation of amyloid plaques and neurofibrillary tangles in the brain. It is a clinical continuum, with a **preclinical phase** marked by abnormal biomarker changes in asymptomatic individuals, progressing to **mild cognitive impairment (MCI)**, and eventually, leading to **dementia**. Early and accurate diagnosis of AD is important to enable comprehensive care planning with patients and their families, while the patient still has capacity and insight to be involved. It also enables offering appropriate therapies within the optimal treatment window to help maintain patient quality of life and, with certain treatments, slow disease progression.

## What Are the Recommended Steps in Evaluating a Patient With Cognitive Decline in a Memory Clinic in Europe?[2]

*The European intersocietal recommendations* for biomarker-based diagnosis of neurocognitive disorders propose a structured workflow for patients with neurocognitive decline who are referred to specialized memory clinics following initial evaluation by a primary care physician.

**Wave 0 (staging):** Initial assessment of patient concerns, clinical history (family, medical, social, cognitive), and examination (neurological, physical, cognitive screening, daily function, and behavioral/psychological symptoms) in a specialized outpatient setting to stage MCI or mild dementia

**Wave 1 (clinical syndromes):** Categorization into clinical syndromes based on clinical, cognitive, and imaging features. This includes routine blood tests (to rule out secondary causes), comprehensive neuropsychological assessment, MRI or CT, and resting EEG if required

**Wave 2 (first-line biomarkers) and Wave 3 (second-line biomarkers):** Wave 2 comprises of first-line biomarker testing and a second-line biomarker testing is applied in wave 3, if results are inconclusive

CT, computed tomography; EEG, electroencephalogram; MCI, mild cognitive impairment; MRI, magnetic resonance imaging.

## What Are the Methods of Biomarker Testing in AD?[3,4]

Positron emission tomography (PET) imaging and cerebrospinal fluid (CSF) biomarkers are well-validated diagnostic tools that allow *in vivo* detection of cerebral amyloid beta (Aβ) and tau pathology and provide valuable insights into disease mechanisms, even at the preclinical and MCI stages. They support timely diagnosis, prognostication, monitoring and treatment with high but not absolute concordance, requiring careful interpretation to avoid false positives. Blood-based biomarkers are evolving as a minimally invasive, accessible, and accurate approach, and the first test has been approved in the United States. Future workflows may incorporate blood-based biomarkers alongside CSF biomarkers and PET imaging.

## How Can a Diagnosis of AD Be Confirmed for a Patient With Cognitive Impairment?[4]

If a clinical profile is consistent with Alzheimer's disease, the presence or absence of Alzheimer's pathology can be established by testing for specific Core 1 biomarkers: Aβ proteinopathy and phosphorylated and secreted AD tau. These are the earliest biomarkers to become abnormal in AD and the presence of either is sufficient to make an AD diagnosis. The modalities used to detect these biological markers are analysis of CSF (and in some locations blood), and imaging with amyloid-PET or tau-PET.

## What Are the Typical Fluid Biomarker Findings That Indicate a Positive Result for AD?[2-4]

In CSF, decreased levels of Aβ42 indicate amyloid plaques are accumulating in the brain, and elevated tau indicates accumulating tau pathology. Absolute values are subject to variability, and diagnostic accuracy is increased by using ratios. For example, the p-tau/Aβ42 ratio captures the opposing trends and amplifies the signal.

| Biomarkers[3] | Pathological Indicator[3] | Typical Finding in AD[3] |
|---|---|---|
| Aβ42 | Amyloid-β plaques | ↓ Decreased |
| Aβ42/Aβ40 ratio | Normalizes Aβ42 to total Aβ | ↓ Decreased |
| t-tau | Neuronal injury | ↑ Increased |
| p-tau | Tau tangles | ↑ Increased |
| **p-tau/Aβ42 ratio** | **Composite for AD pathology** | **↑ Elevated** |

AD, Alzheimer's disease; Aβ42, amyloid-beta 42; Aβ42/40 ratio, amyloid-β42 to amyloid-β40 ratio; p-tau, phosphorylated tau; t-tau, total tau.

## What Are the Advantages and Disadvantages of CSF Biomarker Testing?[3]

| Advantages | Disadvantages |
|---|---|
| • Cost-effective<br>• Accessible<br>• Useful for differential diagnosis of non-AD dementias<br>• Provides quantitative measures of amyloid, tau isoforms, and neuronal injury biomarkers within a single test<br>• Fewer logistical barriers (radioactive tracers or specialized imaging equipment are not required)<br>• May detect abnormalities earlier than PET even in the preclinical phase of disease | • Invasive (lumbar puncture required)<br>• Higher rate of patient-reported adverse events (headache, back pain; rarely infection/bleeding), than PET imaging<br>• Influenced by comorbidities, which may yield false positives<br>• Contraindicated in patients with spinal issues, taking anticoagulation, or with intracranial masses |

AD, Alzheimer's disease; PET, positron emission tomography.

## What Are the Advantages and Disadvantages of PET Imaging in Biomarker Testing for AD?[3]

| Advantages | Disadvantages |
|---|---|
| • Direct visualization and quantification of regional cerebral amyloid and tau deposition<br>• Minimally invasive<br>• Allows longitudinal monitoring of treatment-related changes<br>• Useful in clinical trials<br>• Lower risk for adverse events compared with lumbar puncture<br>• Tau PET can inform disease severity and progression[4,5] | • Expensive<br>• Restricted availability<br>• Radiation exposure and claustrophobia may be concerns.<br>• May yield misleading signals in patients with CAA<br>• Contraindicated with radiotracer hypersensitivity |

AD, Alzheimer's disease; CAA, cerebral amyloid angiopathy; PET, positron emission tomography.

## References

1. Porsteinsson AP, et al. J Prev Alzheimers Dis. 2021;8:371-386.
2. Frisoni GB, et al. Lancet Neurol. 2024;23:302-312.
3. Leuzy A, et al. Alzheimers Dement. 2025;21:e14528.
4. Jack CR Jr, et al. Alzheimers Dement. 2024;20:5143-5169.
5. Rabinovici GD, et al. Alzheimers Dement. 2025;21:e14338.

*Independently developed by Medscape LLC and supported by an independent educational grant from Lilly.*