ID AD

IDENTIFY ALZHEIMER'S DISEASE EARLIER

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Biomarker testing in the diagnosis of Alzheimer's disease (AD)

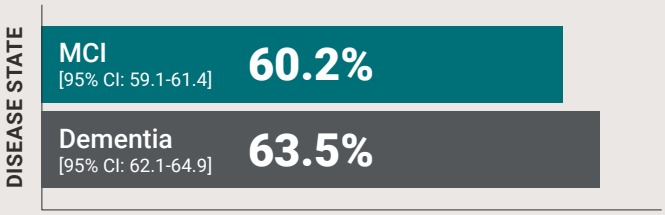
Biomarker testing may inform diagnosis and change patient care[1]

The IDEAS Study, a longitudinal study of 11,409 patients, investigated whether amyloid biomarker testing via positron emission tomography (PET) imaging changed the diagnosis and management of patients with mild cognitive impairment (MCI) or dementia of uncertain etiology.

Over 60% of patients experienced a change in clinical management after amyloid biomarker testing[1]

Primary endpoint: Change in patient management* between pre- and post-PET imaging.

CHANGE IN MANAGEMENT



N=11,409; *P*<0.001

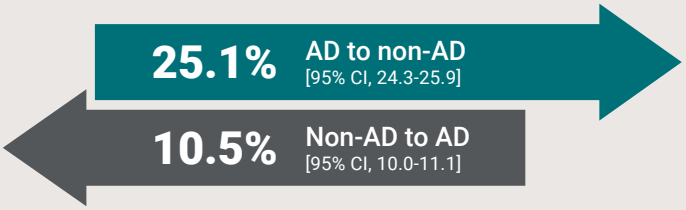
- Results significantly exceeded the target of 30.0% composite change in each group (*P*<0.001, 1-sided)

*As assessed by a composite outcome that included Alzheimer's disease drug therapy, other drug therapy, and counseling about safety and future planning.[1]

Over 35% of patients received a change in diagnosis after biomarker testing[1]

Secondary endpoint: Proportion of changes in diagnosis from AD to non-AD and vice versa between pre- and post-PET imaging.

CHANGE IN DIAGNOSIS

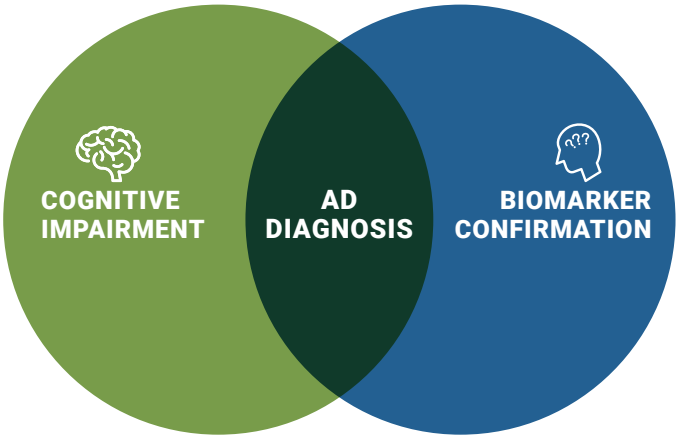


2021 International Working Group (IWG) Recommendations[2]

Alzheimer's disease is a clinical and biological disease. Recent IWG recommendations state:

"The diagnosis of Alzheimer's disease is clinical–biological. It requires the presence of both a specific clinical phenotype of Alzheimer's disease and biomarker evidence of Alzheimer's disease pathology."

Dubois B, Villain N, Frisoni GB, et al. Clinical diagnosis of Alzheimer's disease: recommendations of the International Working Group. *Lancet Neurol*. 2021;20(6):484-496.



Classifying and evaluating biomarkers of AD pathology

The ATN Classification System[3]

The ATN Classification System categorizes AD biomarkers into three groups used to evaluate neuropathologic changes. AD-specific biomarkers are useful because neurodegeneration and injury may occur in non-AD conditions, particularly in elderly individuals with comorbidities.

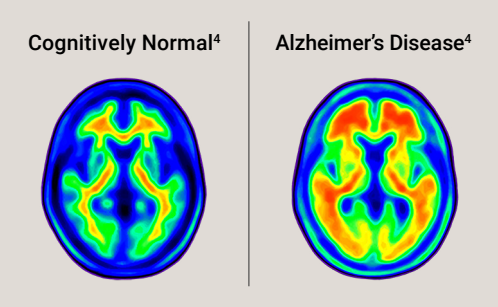
Aβ=amyloid beta; ATN=amyloid plaques, tau neurofibrillary tangles, and neurodegeneration; CSF=cerebrospinal fluid; FDG=fluorodeoxyglucose; MRI=magnetic resonance imaging.

ATN Biomarker Grouping[3]

A	T	N
Aggregated Aβ or associated pathologic state	**Aggregated hyperphosphorylated tau (neurofibrillary tangles) or associated pathologic state**	**Neurodegeneration or neuronal injury***
CSF $A\beta_{42}$, or $A\beta_{42}/A\beta_{40}$ ratio Amyloid PET	CSF phosphorylated tau (p-Tau) Tau PET	Anatomic MRI FDG PET CSF total tau (t-Tau)

*Neurodegeneration is not specific to AD.

Evaluating AD Biomarkers with PET imaging

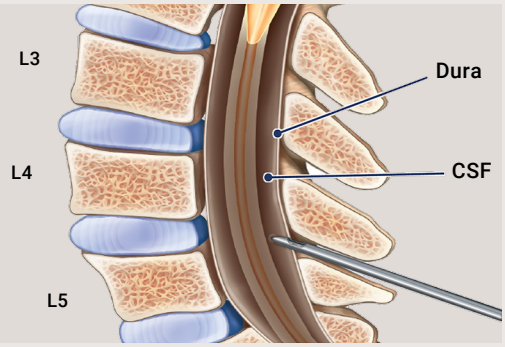


Amyloid PET imaging of Aβ aggregation. Images from Huang CC, et al, used under CC by 4.0. https://creativecommons.org/licenses/by/4.0/.

PET imaging uses radiotracers to bind to amyloid plaques or tau in the brain.[5]

- Offers high diagnostic accuracy and localized information[5]
- Provides an opportunity to visually assess AD pathology in the brain[5]
- May be used to establish biomarker relationships with changes in cognition and neurodegeneration[6]

Evaluating AD biomarkers with CSF testing via lumbar puncture



CSF is collected between the L3 and L4 or L4 and L5 vertebrae.[8]

CSF analysis enables assessment of brain pathology and can measure Aβ and tau biomarkers from the same collection.[3,5]

- Levels of Aβ in CSF are inversely related to the extent of cerebral Aβ deposits[7]
- CSF p-Tau is a biomarker of the abnormal pathophysiology specifically associated with neurofibrillary tangles in AD. It is not elevated in primary tauopathies, head injury, or stroke[3]
- CSF t-Tau is a biomarker of neuronal degeneration; it is less specific for AD[3]

Studies have shown a strong correlation between CSF biomarkers and PET scan results.[5]

References: 1. Rabinovici GD, Gatsonis C, Apgar C, et al. Association of amyloid positron emission tomography with subsequent change in clinical management among Medicare beneficiaries with mild cognitive impairment or dementia. *JAMA*. 2019;321(13):1286-1294. **2.** Dubois B, Villain N, Frisoni GB, et al. Clinical diagnosis of Alzheimer's disease: recommendations of the International Working Group. *Lancet Neurol*. 2021;20(6):484-496. **3.** Jack CR Jr, Bennett DA, Blennow K, et al. NIA-AA research framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement*. 2018;14(4):535-562. **4.** Huang CC, Hsiao IT, Huang CY, et al. Tau PET with 18F-THK-5351 Taiwan patients with familial Alzheimer's disease with the APP p.D678H mutation. *Front Neurol*. 2019;10:503. doi:10.3389/fneur.2019.00503. **5.** Porsteinsson AP, Isaacson RS, Knox S, Sabbagh MN, Rubino I. Diagnosis of early Alzheimer's disease: clinical practice in 2021. *J Prev Alzheimers Dis*. 2021;8(3):371-386. **6.** Jack CR, Knopman DS, Jagust WJ, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. *Lancet Neurol*. 2013;12(2):207-216. **7.** Blennow K, Mattsson N, Scholl M, Hansson O, Zetterberg H. Amyloid biomarkers in Alzheimer's disease. *Trends Pharmacol Sci*. 2015;36(5):297-309. **8.** Engelborghs S, Niemantsverdriet E, Struyfs H, et al. Consensus guidelines for lumbar puncture in patients with neurological diseases. *Alzheimers Dement (Amst)*. 2017;8:111-126.

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