



# Gold standard tests for diagnosing Alzheimer's Alzheimer's Disease

## Overview

Alzheimer disease is a condition in which beta-amyloid plaques and hyperphosphorylated tau proteins accumulate outside and inside nerve cells, causing the neurons in the brain to degenerate. Currently, the treatment for Alzheimer disease aims to detect the disease early, provide symptomatic treatment, and manage health through activities such as exercise to alleviate symptoms and delay progression. However, brain imaging tests can only confirm significant brain atrophy, so research is ongoing to develop tests that can enable early diagnosis of dementia. Therefore, in this chapter, we would like to explore various Alzheimer disease-related tests that can be conducted using blood or cerebrospinal fluid.

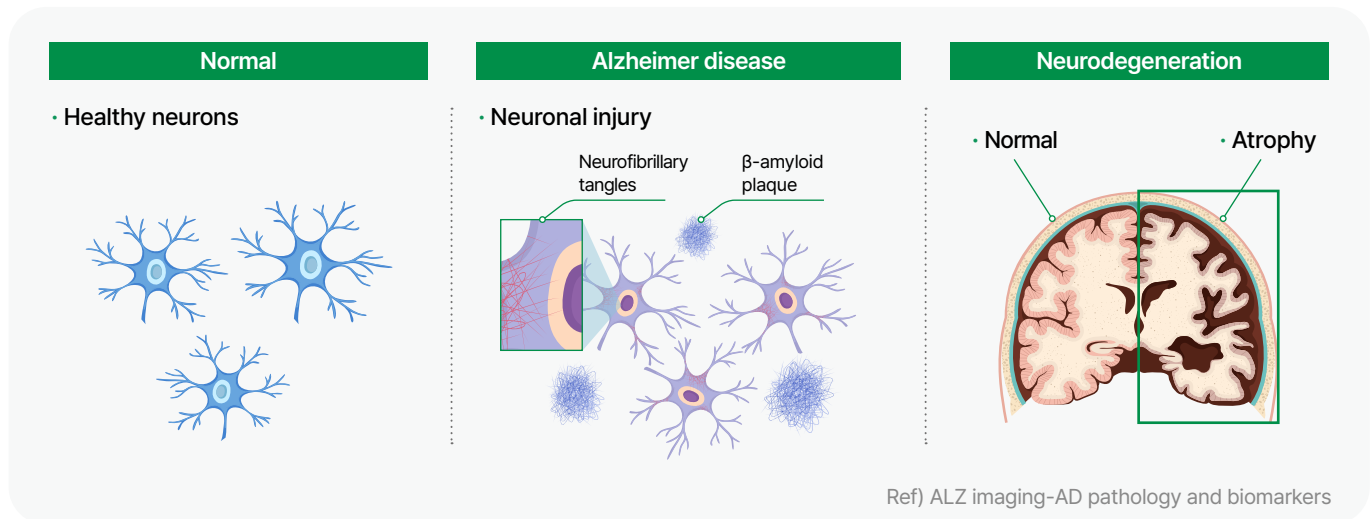
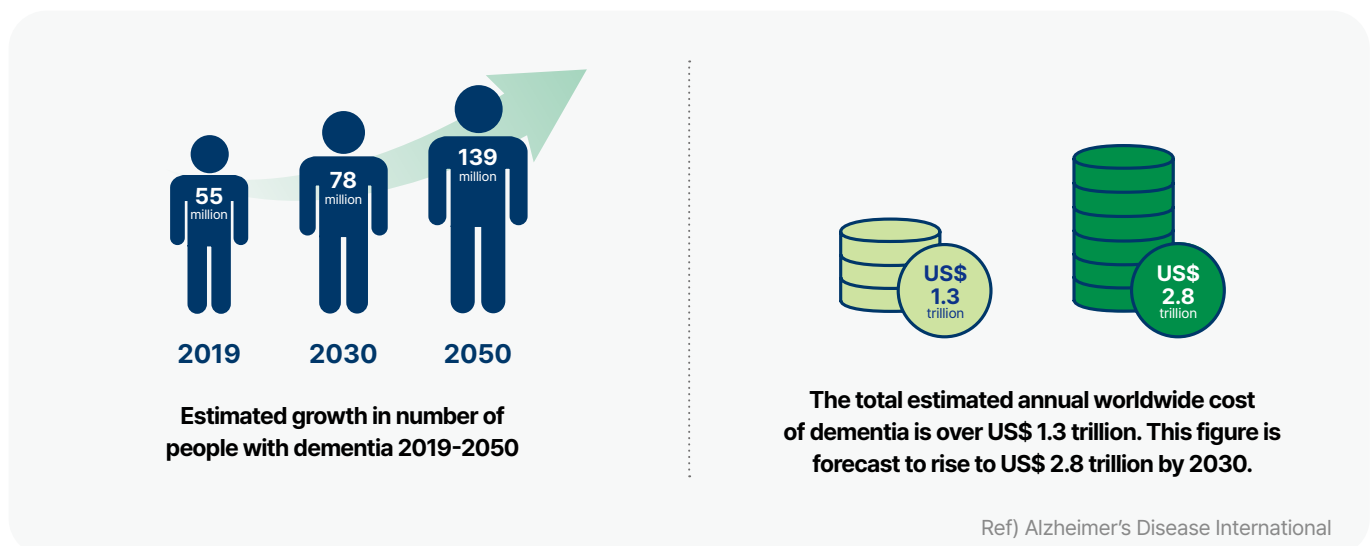


Fig 1. Pathophysiology of Alzheimer disease by beta-amyloid and tau proteins.

Throughout the world, there is a new case of dementia identified for every three seconds. As of 2020, over 55 million people are living with the dementia globally. This number will almost double every 20 years, expected to reach 78 million in 2030 and 139 million in 2050.

The total estimated worldwide cost of dementia was US\$ 818 billion in 2015, which represented 1.09% of global GDP at that time. The annual global cost of dementia is now above US\$ 1.3 trillion and is expected to rise to US\$ 2.8 trillion by 2030.



## $\beta$ -amyloid 1-42, p-tau, p-tau/A $\beta$ 42 ratio

The testing method utilizing this involves measuring the levels of CSF-A $\beta$  and CSF-tau/p-tau. Currently, the average concentrations of beta-amyloid and tau proteins in the cerebrospinal fluid of normal individuals and dementia patients are known, making the development of dementia diagnostic markers using this method the most active field. The p-tau/A $\beta$ 42 ratio cerebrospinal fluid (CSF) analysis has been shown to correlate with amyloid PET by approximately 90%, suggesting that it could be an alternative to PET in Alzheimer disease diagnosis.

Test code	Test item	Specimen(mL)	Test schedule	TAT(day)	Test method
W720	p-tau/Abeta 42 ratio	CSF 2.5	Wed	1	ECLIA & Calculation
W722	Amyloid $\beta$ 1-42	CSF 2.5	Wed	1	ECLIA
W721	P-tau 181	CSF 2.5	Wed	1	ECLIA

## Oligomerized amyloid $\beta$ [ECLIA]

This test quantitatively measures beta-amyloid oligomers in the plasma (heparin) of patients suspected of Alzheimer disease using electrochemiluminescence immunoassay (ECLIA). Beta-amyloid is formed from soluble beta-amyloid monomers (A $\beta$  monomer), dimers, oligomers, and fibrils derived from amyloid precursor protein (APP), ultimately forming insoluble plaques. Since beta-amyloid monomers are non-toxic and can be found in normal individuals, sandwich ELISA method is used to selectively detect toxic oligomers by overlapping the antigen recognition sites of the capture/detection antibodies that react to the antigen.

Test code	Test item	Specimen(mL)	Test schedule	TAT(day)	Test method
W221	Oligomerized amyloid $\beta$	Heparin P 3.0	Mon, Wed	3	ECLIA

## Human amyloid $\beta$ [ELISA]

Beta-amyloid is a peptide composed of 40 or 42 amino acids associated with Alzheimer disease, with plaques mainly known to consist of A $\beta$ 1-42, as well as A $\beta$ 1-40, A $\beta$ 4-38, and others. Many studies have reported an increase in the concentration of A $\beta$ 1-40 in the cerebrospinal fluid and blood of Alzheimer patients, as well as a decrease or mild increase in the concentration of A $\beta$ 1-42, resulting in a decrease in the ratio of A $\beta$ 1-42/A $\beta$ 1-40. This test measures the concentration of beta-amyloid of various sizes using enzyme-linked immunosorbent assay.

Test code	Test item	Specimen(mL)	Test schedule	TAT(day)	Test method
G323	Human Amyloid $\beta$ [ELISA]	EDTA P 0.5	Tue, Thu	2	EIA

## APOE (apolipoprotein E) genotype [Real-time PCR]

Apolipoprotein E (APOE) is a apolipoprotein mainly produced in the liver, which transports cholesterol to nerve cells in the central nervous system. The APOE gene is located on chromosome 19 and has three allelic variants: E2, E3, and E4 (APOE e2, APOE e3, APOE e4). E4 in particular binds to very low-density lipoprotein (VLDL) and is involved in lipid transport, glucose metabolism, brain vascular function, and tau-mediated neurodegenerative processes, showing relevance to various cerebrovascular and neurological disorders such as Alzheimer disease. However, Alzheimer dementia is influenced by multiple genes and environmental factors, so even with a specific APOE genotype, the disease may not develop. Therefore, it can be used as a diagnostic support test for symptomatic patients.

Test code	Test item	Specimen(mL)	Test schedule	TAT(day)	Test method
S875	APOE genotype [Real-time PCR]	EDTA WB 3.0	Mon-Fri	3	PCR with hybridization