# Alzheimer's and Neurodegenerative Diseases
## in Global Clinical Trials


eurofins | BioPharma Services

# Integrated Lab Performance and BioPharma Solutions From the Organization You Trust

From compound discovery and clinical research through manufacture and release of commercial product and post approval/marketing, Eurofins BioPharma Services provides seamless, end-to-end solutions to help clients progress through the drug development cycle through a single, experienced provider. Our integrated solutions deliver the most comprehensive range of state-of-the-art analytical technologies with an expansive geographic reach in order to support our clients' specialized testing needs and stringent quality and safety requirements around the world.

## Introduction

Alzheimer's Disease is a brain disease that is known as neurodegenerative, meaning it gets worse over time. Thought to begin in the brain twenty years before symptoms arise, Alzheimer's Disease goes unnoticed until the individual's case becomes hard to treat. It is also the most common cause of Dementia, accounting for 60 to 80 percent of cases.

Dementia is the loss of cognitive functioning - known as thinking, remembering, and reasoning - as well as behavioral abilities to such an extent that it interferes with a person's daily life.

Symptoms begin to occur with Alzheimer's as nerve cells (neurons) in parts of the brain involved in thinking, learning, and memory (cognitive function), have been damaged or destroyed. As the disease progresses, neurons in other parts of the brain are damaged and destroyed making it increasingly difficult for the person to carry out basic bodily functions, such as walking or swallowing. In later stages of Alzheimer's, individuals require constant care until the disease is ultimately fatal.

Though up to half of all people aged 85 and older may have some sort of dementia, Alzheimer's Disease is not a normal part of aging.


## Causes of Dementia

Though Alzheimer's Disease accounts for the majority of dementia cases, there are several other neurodegenerative diseases that can result in dementia as well.

**Cerebrovascular disease** refers to the process by which blood vessels in the brain are damaged and/or brain tissue is injured from not receiving enough blood, oxygen, or nutrients. Only 5 to 10 percent of individuals with dementia show evidence of vascular dementia. It is more common, however, as a mixed pathology, with most people living with dementia showing the brain changes of cerebrovascular disease and Alzheimer's disease.

**Lewy body disease** occurs when Lewy bodies develop in a part of the brain called the cortex. People with DLB have some of the same symptoms common in Alzheimer's but are more likely to have initial or early symptoms of sleep disturbances, hallucinations, and visual impairment.

**Fronto-temporal lobar degeneration (FTLD)** includes dementias such as behavioral-variant FTLD, primary progressive aphasia, Pick's disease, corticobasal degeneration, and progressive supranuclear palsy. Unlike Alzheimer's, memory is typically spared in the early stages of this disease.

**Parkinson's disease** includes problems with movement, such as slowness, rigidity, tremors, and changes in gait, with cognitive symptoms developing just before them or later in the disease.

**Hippocampal sclerosis (HS)** is the hardening of tissue in the hippocampus in the brain, which plays a crucial role in forming memories. The most pronounced symptom of HS is memory loss, making it easy for individuals suffering from this disease to be misdiagnosed with Alzheimer's.

Mixed pathologies are when an individual shows the brain changes of more than one cause of dementia. More common than previously recognized, more than 50 percent of individuals with dementia who were studied at Alzheimer's Disease Centers have pathologic evidence of more than one cause of dementia.

Finally, Alzheimer's disease is the most common cause of dementia, accounting for 60 to 80 percent of cases. The hallmark pathologies of Alzheimer's are the accumulation of the protein fragment beta-amyloid (plaques) outside neurons in the brain and twisted strands of the protein tau (tangles) inside neurons. These changes accompanied by the death of neurons and damage to brain tissue. It is a slowly progressive brain disease that begins many years before symptoms emerge.

# Alzheimer's and Neurodegenerative Diseases
## in Global Clinical Trials

### Continuum

The Alzheimer's disease continuum is what describes the progression of Alzheimer's from brain changes that are unnoticeable to brain changes that cause problems with memory and eventually physical disability.

The continuum includes three phases: pre-clinical Alzheimer's disease, mild cognitive impairment (MCI) due to Alzheimer's disease, and dementia due to Alzheimer's disease. Dementia due to Alzheimer's disease phase is then further broken down into the stages of mild, moderate, and severe. This reflects the degree to which symptoms interfere with the individual's ability to carry out everyday activities.


In this first phase, individuals have measurable brain changes that indicate the earliest signs of Alzheimer's disease, known as biomarkers), but have not yet developed symptoms like memory loss. When the early changes of Alzheimer's occur, the brain compensates for them, enabling individuals to continue functioning normally. While research settings have the tools and expertise to identify some of the early brain changes, additional research is needed to fine-tune the tool's accuracy before they become available for widespread use.

Individuals with MCI due to Alzheimer's disease have biomarker evidence of brain changes in addition to subtle problems with memory and thinking. These changes do not interfere with their ability to carry out everyday activities but may become noticeable to family and friends. Among those with MCI, not all individuals will develop Alzheimer's or dementia. Identifying which individuals with MCI are more likely to develop Alzheimer's or other dementias is a major goal of current research.

Dementia due to Alzheimer's disease is characterized by noticeable memory, thinking, or behavioral symptoms that impair a person's ability to function in daily life, along with evidence of brain changes. The pace at which symptoms of dementia develop from mild to moderate to severe varies based on the individual.

## Dementia Due to Alzheimer's Disease

### Mild Alzheimer's Dementia

In this stage, most people are able to function independently in most areas but may require assistance with some activities. They may still be able to drive, work, and participate in other everyday activities.

### Moderate Alzheimer's Dementia

Often the longest stage, those dealing with moderate Alzheimer's stage have difficulty communicating and performing routine tasks; including everyday activities, becoming incontinent, and begin having personality and behavioral changes.

### Severe Alzheimer's Dementia

In the severe Alzheimer's stage, individuals need help with everyday activities and will most likely need around-the-clock care. The effects of Alzheimer's disease also become apparent in this stage, with many individuals becoming bed-bound.

2020 Alzheimer's Disease Facts and Figures Report, Alzheimer's Association

# Alzheimer's and Neurodegenerative Diseases
## in Global Clinical Trials

### Diagnosis

There is no single test for dementia due to Alzheimer's disease. Usually, physicians will use a variety of approaches to make a diagnosis. These can include the following:

- Understanding the patient's medical and family history, including psychiatric, cognitive, and behavioral changes.
- Asking a family member to provide input on cognitive and behavioral changes.
- Conducting problem-solving, memory, and other cognitive tests with the patient.
- Undergo blood tests and brain imaging to rule out other potential causes of dementia symptoms.
- Using PET imaging of the brain to determine if the patient has high levels of beta-amyloid, which is a hallmark of Alzheimer's.
- Using lumbar puncture to determine the levels of beta-amyloid and certain types of tau in CSF.

Over the past few years, the Alzheimer's and dementia fields have developed improved techniques and technologies aimed at early diagnosis and detection of Alzheimer's disease and related dementias. The field has seen remarkable growth in research using clinical assessments, psychometric testing, cerebrospinal fluid (CSF) and blood-based biomarkers, magnetic resonance imaging (MRI), and positron emission tomography (PET) imaging of the brain to detect hallmarks of neurodegenerative diseases at its earliest stages.

### Alzheimer's Clinical Trials Pipeline

While we have numerous symptomatic treatments today, there is still no cure for neurodegenerative diseases such as Parkinson's and Alzheimer's. There are more than 600 neurodegenerative diseases alone that affect the brain, spine, and peripheral nervous system. While diseases like Parkinson's affect motor functions, Alzheimer's is a progressive disease that destroys memory and other mental functions.

Currently, there are more than 5.5 million people in the United States alone who suffer from Alzheimer's related symptoms, with an additional 6.3 million estimated worldwide suffering from Parkinson's disease.

The identification of biomarkers for Alzheimer's enables early detection of the disease and will accelerate the development of new therapies by ensuring that appropriate people are enrolled in clinical trials. With the discovery that Alzheimer's may begin 20 years or more before the onset of symptoms, a substantial window of time has been open to intervene in the progression of the disease. In the future, more will be understood about which therapies will be most effective at which points in the Alzheimer's disease continuum.

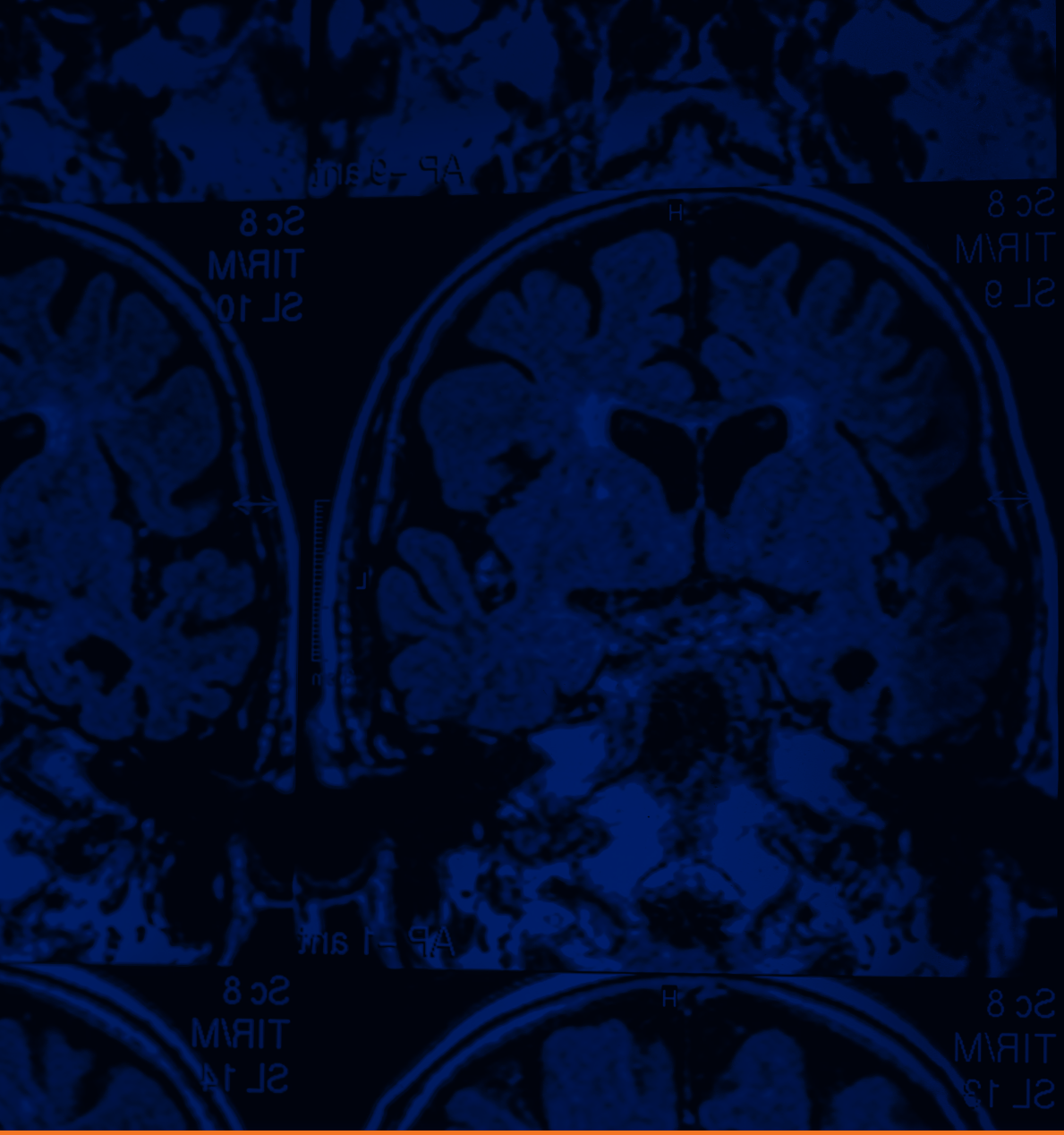
This is why Eurofins Central Laboratory is pleased to participate in industry-leading, innovative analysis of both curative and symptomatic treatments for neurodegenerative diseases.

## Capabilities

Eurofins BioPharma Services provides seamless, end-to-end solutions to help clients progress through the drug development cycle through a single, experienced provider. Our integrated solutions deliver the most comprehensive range of state-of-the-art analytical technologies, with an expansive geographic reach in order to support our clients' specialized testing needs, stringent quality and safety requirements around the world. Whether your trial requires neurodegenerative specific biomarkers, like cerebrospinal fluid (CSF), Aβ, tau, phosphorylated tau and other neuronal proteins, PET tracers for Aβ, tau and glucose uptake or genomic-based biomarkers, like APOE, PICALM, CLU, and BIN1; Eurofins BioPharma Services will collaborate with your research and development team, every step of the way.

Eurofins Central Laboratory supports the determination and analysis of neurodegenerative disease biomarkers in Serum, Plasma, and CSF deploying the following methodology: ELISA, Multiplex Immunoassay, Electrochemillumniscense Immunoassay, Nephelometry, and Immunoturbidimetric.

| Analyte | Methodology | Matrix |
|---|---|---|
| Amyloid Beta (1-42) | Electrochemiluminescence Immunoassay | CSF |
| Total Tau | Electrochemiluminescence Immunoassay | CSF |
| Phospho-Tau (181p) | Electrochemiluminescence Immunoassay | CSF |
| Alpha-Synuclein | ELISA | CSF |
| Neurogranin | ELISA | CSF |
| IFN-gamma | ELISPOT | PBMC |
| Neurofilament Light Chain | Digital ELISA | CSF/Serum |
| Phosporylated Neurofilament Heavy Chain (pNF-heavy) | Digital ELISA | CSF/Serum |
| Cytokine 10 Plex Panel: IFN-gamma, IL-1ß, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNF-a | MSD multiplex | Serum |
| Amyloid Beta Panel (Abe-ta38/40/42) | MSD Multiplex | CSF |
| Neurology 4-PLEX PanelA (Nf-L, TAU, GFAP, UCHL-1) | Digital ELISA | CSF/Serum |
| ApoE Genotype | PCR/Sequencing | Whole Blood (EDTA) |
| Neurology Panel: Sequencing and CNV Analysis | "Next Generation Sequencing and Copy Number Analysis" | Whole Blood (EDTA) |



eurofins | BioPharma Services