Alzheimer's Disease Clinical Trials

Innovative laboratory solutions to accelerate progress

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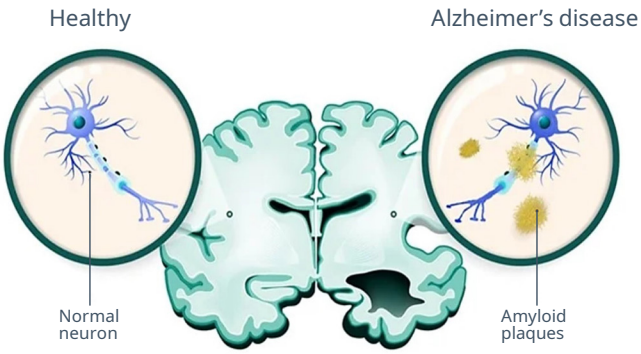
Alzheimer's disease (AD) remains an area of severe unmet need and decades of research, but significant progress was recently made with innovative treatments. Following the FDA approval aducanumab (Leqembi™) from Eisai and donanenab-azbt (Kisunla™) from Eli Lilly[1,2] aiming at addressing underlying disease biology are now marketed. Similarly, impactful advancement was made in the discovery and the validation of laboratory tests to assist with disease diagnostics and to evaluate disease progression.

At the beginning of 2024, there were 127 drugs in 164 trials across the AD pipeline: of these, 32 drugs were in 48 Phase 3 trials, 81 drugs were in 90 Phase 2 trials, and 25 drugs were in 26 Phase 1 trials.[3] Around 75% of AD drug candidates (biologics and small molecules) are aimed at disease modification, 10% are intended as cognitive-enhancing agents, and the remaining 14% are designed to reduce neuropsychiatric symptoms.[3]

Based on recent demonstration of clinical utility, soluble protein biomarkers are being used more frequently in AD clinical trials. This insight brief describes the potential to advance AD trials through validation and deployment of innovative soluble protein biomarker assays.



Adapted from https://www.news-medical.net/health/Is-Alzheimers-Disease-Transmissible.aspx

ABOUT ALZHEIMER'S DISEASE

Over 55 million people worldwide were suffering of dementia in 2020. This number is expected to almost double every 20 years, reaching 78 million in 2030 and rising to 139 million in 2050.[4] The worldwide cost of dementia is estimated at US$1.3 trillion and is expected to rise to US$ 2.8 trillion by 2030.[4]

AD is the most common form (60-80%) of dementia ranging from a preclinical stage without symptoms to a prodromal stage with mild cognitive impairment, followed by the dementia stage with functional impairment.[5] Advanced age is the predominant risk factor for AD, manifesting mainly in individuals aged 65 years and older. The percentage of individuals with AD increases with age, representing approximately 5%, 13%, and 33% of people aged 65 to 74 years, 75 to 84 years, and 85 years and older, respectively, and is one of the top 10 causes of death worldwide.[5,6] Due to the aging world population, the societal burden of AD will surely increase in the future.

It is estimated that 75% of people with dementia have not received a diagnosis, preventing access to proper care.[4] AD is associated with the accumulation of amyloid beta (Aß) protein forming amyloid plaques and/or abnormal filaments of the hyperphosphorylated tau protein (Neurofibrillary Tangles: NFTs) which impair cognitive function leading to premature death.[7]

The recent discovery that soluble protein biomarkers can be used to complement conventional imaging technology such as with positron-emission tomography (PET) to diagnose and monitor AD progression is very promising. However, ability to detect AD at preclinical stage brings new challenges related to trial design, study endpoints and safety/risk ratio of investigational therapies.

AD Physiopathology

In AD, first the aggregation of Aß proteins in plaques occurs, then the formation of NFTs from phosphorylated tau proteins in the brain, followed by the appearance of symptoms.[8] Although these findings were reported almost a century ago, biomarkers that could be measured in vivo were only identified in the 1980s with the purification of the plaque cores and the identification of Aß proteins.[9]

The multifactorial nature of AD has become apparent as more information has become available. The major risk factors identified thus far include genetic predisposition, cardiovascular and cerebrovascular diseases, traumatic brain injury, recurrent depression, gut microbiome disturbances, and other theoretically preventable environmental factors such as educational level or cultural enrichment. However, the precise etiology remains unknown.

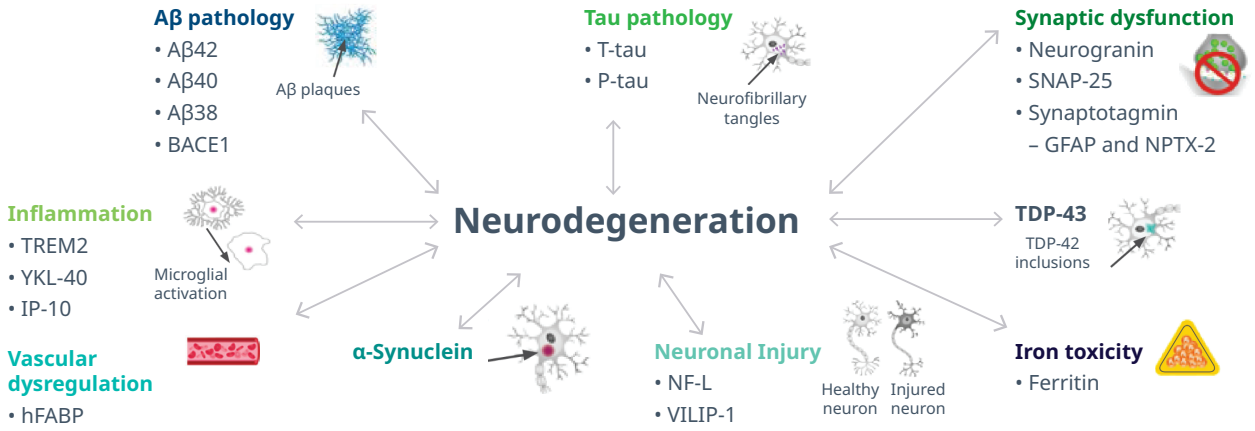
Multiple causative mechanisms have been identified. The various hypotheses and percentage of clinical trials targeting each of these hypotheses are listed in Table 1.[10] The presenting condition is likely the result of a combination of these mechanisms, leading to two major difficulties: (1) differences in presentation of the disease across individuals, and (2) the effectiveness of any single treatment.

Research continues in efforts to uncover the causes for AD. The known pathological mechanisms involved in sporadic, and to certain extent, in familial cases of AD are summarized in Figure 1.[10] Briefly, neurodegeneration is the primary cause of AD and could be manifested via several modalities such as Aβ pathology, tau pathology, synaptic dysfunction, iron toxicity, inflammation, and vascular dysfunction. AD has been associated with more than 20 different genetic loci. Among these, four genes have been analyzed extensively: apolipoprotein E (APOE), amyloid precursor protein encoding gene (APP), presenilin1 (PSEN1), and presenilin2 (PSEN2).

Table 1. Hypotheses for causes of AD and percentage of clinical trials targeting each one[4]

HYPOTHESES DRIVING CLINICAL TRIALS	PERCENTAGE OF CLINICAL TRIALS TARGETING EACH HYPOTHESIS
Amyloid as target	22.3
Neurotransmitter approaches	19.0
Mitochondrial cascade and related cell degeneration	17.0
p-tau propagation	12.2
Neurovascular targets	7.9
Physical activity (as prevention or stabilization)	6.6
Anti-inflammation	4.6
Diabetes as adjunct condition	2.3
Antivirals	0.5
Others	7.6

Figure 1. Pathological mechanisms implicated in AD and associated fluid biomarkers[8,10]



The strongest genetic risk factor identified for AD is the Ɛ4 allele of apolipoprotein E (APOE), with Apo Ɛ4 homozygosity recently being proposed as a distinct genetic form of AD[16]. Screening for APOE (Ɛ4) homozygous/heterozygous genotypes has already been utilized in AD clinical trials for enrichment of the enrollment. Mutations of APP, PSEN1 and PSEN2 account respectively for ~14%, ~80% and ~6% of known AD cases.[11] Therefore, screening entire populations for genetic mutations causing AD is not feasible.

AD pathology specific neuro-and inflammatory biomarkers

The use of biomarkers collected from cerebrospinal fluid (CSF) such as Aβ42/Aβ40 or Aβ42/phosphorylated-tau (pTau), p-tau181/Aβ42, or total tau/Aβ42 which correlate strongly with Aβ PET and disease progression is well established.[12,13] Since 2020, we have witnessed a major breakthrough with the demonstration of the clinical utility of measuring non-invasive blood-borne biomarkers, most notably pTau217 and pTau231 while interestingly, Aβ42/ Aβ40 level has limited predictive value[12,14,15] Additionally, the National Institute on Aging and the Alzheimer's Association revised criteria for diagnosis and staging of AD, published in July 2024, now recommends incorporating blood biomarkers for diagnostic and pharmacodynamic (PD) purpose in clinical trials.[13]

IQVIA laboratories has extensive experience supporting AD clinical trials offering a broad range of biomarkers

Over the years, and keeping up with innovation, we have validated and deployed a comprehensive portfolio of assays detecting AD biomarkers, AD genetic markers and inflammation markers to support clinical trials (Table 2). Selected markers can be used for different contexts of use ranging from exploratory purpose, primary/secondary PD endpoints to inclusion/exclusion criteria during patient enrolment. It is of note that each assay must be used in accordance with regulatory and industry guidelines in each local jurisdiction including FDA final rule for Laboratory Developed tests (LDTs) and the European In Vitro Diagnostic Medical Devices Regulation (IVDR).

Table 2: Conventional serology assay testing

	ANALYTES	SAMPLE TYPES
AD BIOMARKERS	p-tau 181	CSF, Plasma, Serum
	p-tau 217	CSF, Plasma, Serum
	Total tau	CSF, Plasma, Serum
	Aβ40	CSF, Plasma, Serum
	Aβ42	CSF, Plasma, Serum
	Aβ42/Aβ40	CSF
	Aβ42/Aβ40/Tau	Plasma
	BDNF	Plasma, Serum
	GFAP	CSF, Plasma, Serum
	GFAP/NfL	Plasma, Serum
	GPNMB/ Osteoactivin	CSF, Plasma, Serum
	Nfl	CSF, Plasma, Serum
	pNfH	CSF, Plasma, Serum
	Neurogranin	CSF
	NPTX2	CSF
	Progranulin	Plasma, Serum
	TREM-1	CSF, Plasma, Serum
	TREM-2	CSF, Plasma, Serum
	α-Synuclein	CSF, Plasma, Serum
	β2 microglobulin	Serum
	sCD33	CSF, Plasma, Serum
AD GENETIC BIOMARKERS	ApoE	Whole-Blood
	APP	Whole-Blood
	PSEN1	Whole-Blood
	PSEN2	Whole-Blood
	Microbiome 16S rRNA	Stool
INFLAMMATION BIOMARKERS	C3	Serum
	C3a	Plasma, Serum, Urine
	C4	Serum
	C4a	Plasma, Urine
	C5a	Plasma
	C5b	Plasma
	sC5b-9 (TCC)	Plasma, Urine
	IL-1b	Plasma, Serum
	IL-2	Plasma, Serum
	IL-6	Plasma, Serum
	IL-17a	Plasma, Serum
	IL-22	Plasma, Serum
	IP-10	Serum
	MCP-1	Plasma, Serum, Urine
	S100B	Serum
	TNF-α	Plasma, Serum
	YKL-40	CSF, Plasma, Serum

About IQVIA Laboratories

IQVIA laboratories global experience in neurodegenerative diseases reference testing services coupled with IQVIA's Contract Research Organization (CRO) expertise makes this collaboration uniquely poised to provide services for AD-related clinical trials. The synergistic relationship between IQVIA laboratories and IQVIA's Neurology Center of Excellence (CNS-CoE) offers a wealth of knowledge and experience for customers seeking laboratory solutions for AD clinical trials. IQVIA laboratories' ability to validate innovative diagnostic biomarkers along with CNS-CoE's medical expertise will provide an asset to manage Phase I through Phase IV studies.

IQVIA laboratories offers state-of-the-art technologies, capacity, and high-quality infrastructure to support AD testing needs. As a leading clinical trial laboratory services organization, we can offer end-to-end laboratory services along with secure, enterprise-wide biospecimen and consent management solutions. With a relentless focus on quality and innovation, IQVIA laboratories leverages global experience and scientific expertise to transform science and data into actionable medical insights that help customers improve human health.

About the authors

PATRICE HUGO, PH.D.
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Dr. Patrice Hugo has more than 30 years of senior scientific leadership experience in laboratory operations, drug target and biomarker discovery & assay validation applied to drug development and diagnostics. He has published more than 75 scientific publications in internationally renowned journals and has been invited to speak at over 200 conferences. He currently leads the scientific strategy and medical affairs for the global Central Laboratories and specialty testing services including routine safety, Companion Diagnostics, Pathology, Genomics, Molecular, Vaccine, Flow Cytometry, Proteomics, Translational Science, Antibody¬ drug discovery, Bioanalytical PK, immunogenicity and ADME. Dr. Hugo holds a Ph.D. in Experimental Medicine & Immunology at McGill University and held post-doctoral positions at the WEHI, Australia, and Howard Hughes Medical Institute, USA.

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Dr. Marek Bieniek is a board-certified neurologist, with over 25 years of experience in neurology practice, over 10 years of Medical Affairs experience in pharmaceutical industry, primarily related to multiple sclerosis and Alzheimer's disease, and over 6 years' experience in clinical research industry. His research interests were focused primarily on the use of MRI imaging in understanding MS pathology in different clinical phenotypes. He is currently a part of IQVIA CNS Center of Excellence, where he applies his practical knowledge related to all stages of medicines' life cycle to support development of innovative therapies for neurological disorders.

References

1. FDA Converts Novel Alzheimer's Disease Treatment to Traditional Approval | FDA
2. FDA approves treatment for adults with Alzheimer's disease | FDA
3. Cummings, J. et al. Alzheimer's disease drug development pipeline: 2024. Alzheimer's Dement. 2024;10:e12465. https://alz-journals.onlinelibrary.wiley.com/doi/epdf/10.1002/trc2.12465
4. http://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf; www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf:https://; http://www.ncbi.nlm.nih.gov/; www.ncbi.nlm.nih.gov/ pmc/articles/PMC11095490/pdf/ALZ-20-3708.pdf
5. IQVIA_Institute_alzheimers-disease-an-update-on-treatment-options-and-pipeline-developments.pdf
6. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death
7. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7764106/pdf/molecules-25-05789.pdf
8. https://www.nature.com/articles/d41586-024-02535-x
9. https://www.nature.com/articles/d41586-024-02119-9
10. Molinuevo JL, Ayto S, Bartla, R, Et.al: Current state of AD fluid markers. Act. Neuropathologica (2018) 1346: 821-853
11. Liu P, Xie Y, Meng X-Y, et.al Signal Transduction and Targeted Therapy (2019) 4:29; https://doi.org/10.1038/s41392-019-0063-8
12. Nature_Blood biomarkers for Alzheimer's disease in clinical practice_trials.pdf
13. Alzheimer s Dementia - 2024 - Jack - Revised criteria for diagnosis and staging of Alzheimer s disease Alzheimer s.pdf
14. Plasma p-tau231 and p-tau217 as state markers of amyloid-β pathology in preclinical Alzheimer's disease | Nature Medicine
15. https://jamanetwork.com/journals/jama/fullarticle/2821669
16. Fortea et al.APOE4 homozygosity represents a distinct genetic form of Alzheimer's disease. Nat Med 30, 2093 (2024) https://doi.org/10.1038/s41591-024-02931-w

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