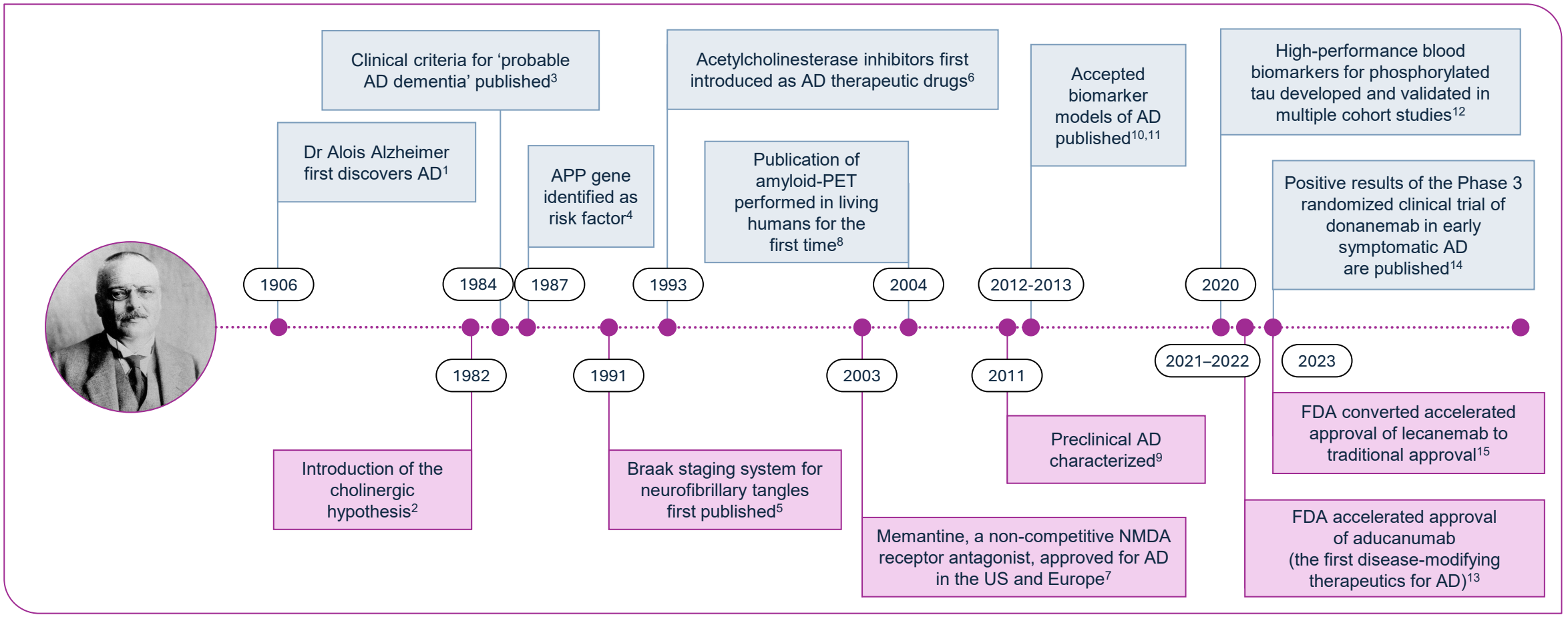
Advances in the Diagnosis and Treatment of Alzheimer’s Disease

Wendell R. Helveston, MD

Alzheimer's disease research timeline



Alzheimer’s disease is not synonymous with dementia

- Dementia is an umbrella term used to describe a state where an individual has lost the ability to carry out daily life activities independently,[1,2] because of cognitive impairment that is not due to an underlying psychiatric condition[3]
- There are many types and causes of dementia. The most common ones are:[1,2]
  - Alzheimer’s disease (AD)
  - Vascular dementia
  - Dementia with Lewy bodies
  - Frontotemporal dementia
- AD refers to the abnormal presence of Aβ and tau proteins,[4,5] which define AD among many other neurodegenerative diseases[5]
- Some individuals may have dementia without Aβ or tau pathology, while others may have no clinical symptoms, even in the presence of Aβ and tau pathology[4,5]

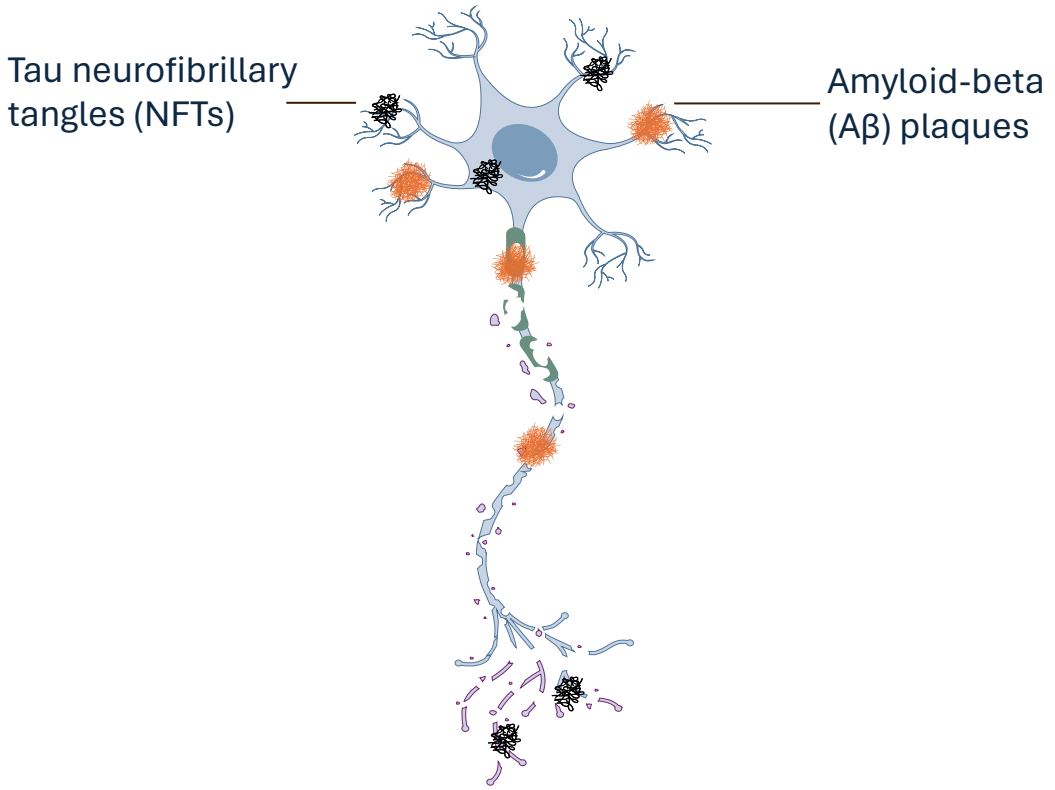
Between 50–80% of all dementia cases are caused by AD[2,6]

Overall, AD and vascular dementia are responsible for up to 90% of all dementia cases, even though the boundaries between the different types may not be definite[7]

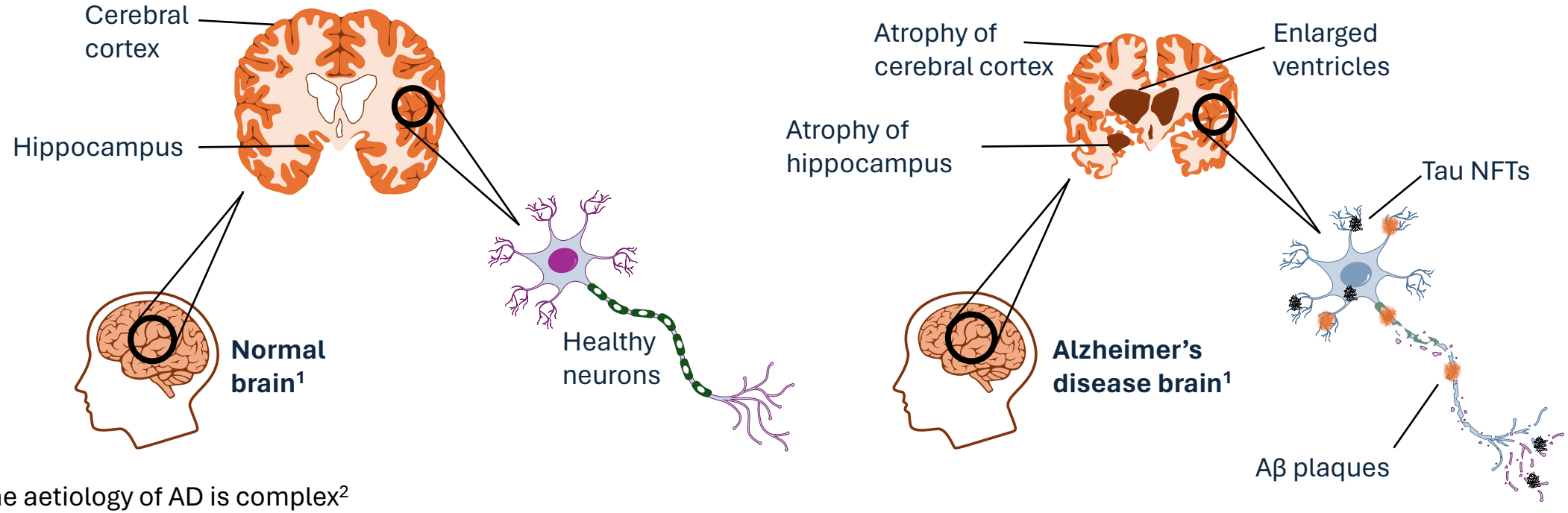
Alzheimer’s disease is a neurodegenerative disease

- AD is a complex progressive neurodegenerative disease characterized by the accumulation of Aβ plaques and tau NFTs, which are considered to result in neuronal loss and cognitive decline[1-5]
- Both Aβ plaques and NFTs seem to be aggregating for many years before the clinical symptoms of AD emerge[1-5]
- There are many factors that contribute to the development of the disease, including neuroinflammation, cerebrovascular disease, and other proteins, such as α-synuclein and TDP-43 (TAR DNA-binding protein 43)[6-8]

Alzheimer’s disease neuron[2]



The etiology of Alzheimer's disease is complex



The aetiology of AD is complex[2]

AD is a progressive neurodegenerative disease, which is defined biologically by:[2-6]

- The extracellular accumulation of Aβ protein plaques
- Intracellular tau NFTs
- Neuronal and synaptic loss

Amyloid hypothesis

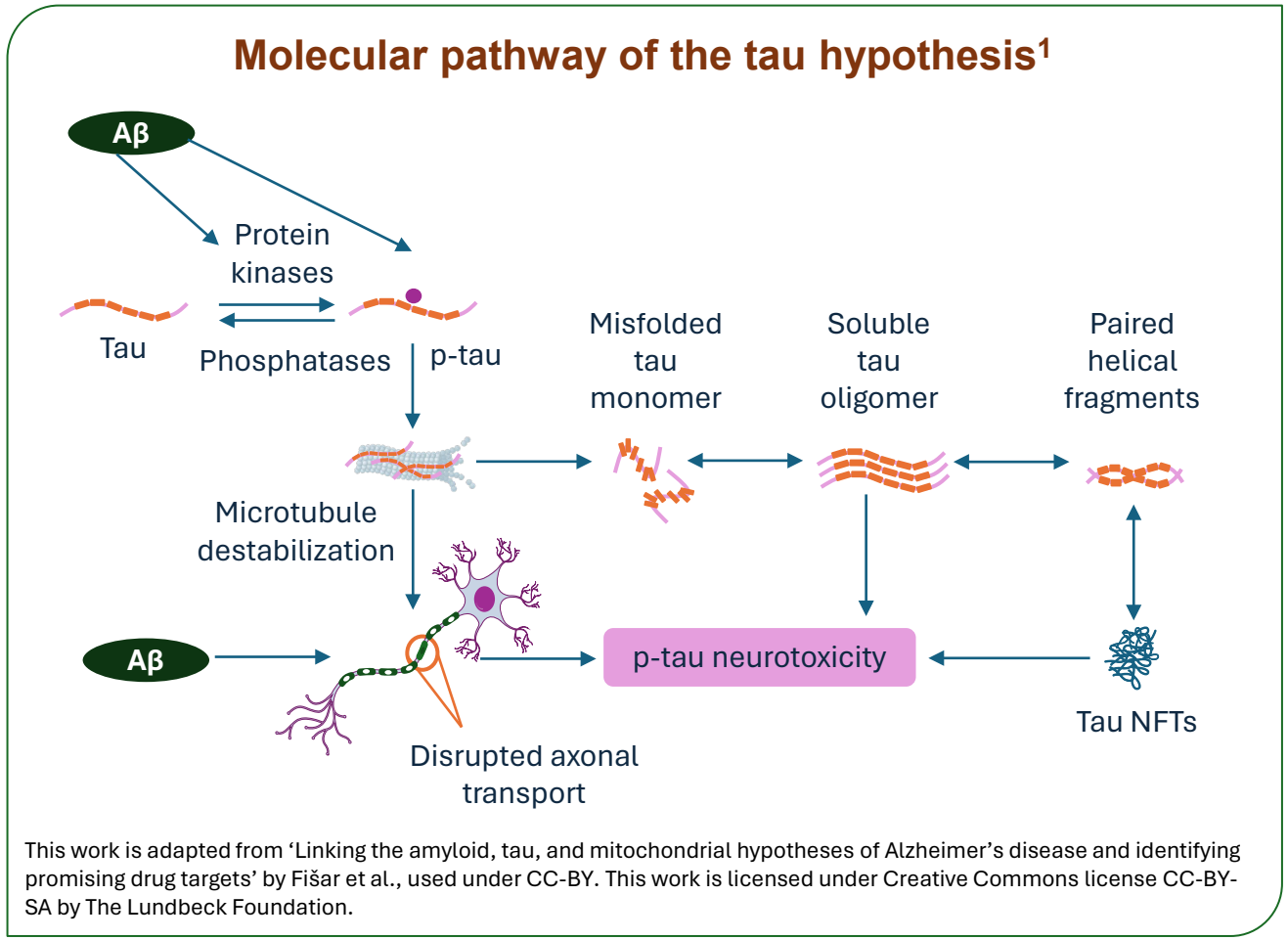
Aβ pathology is one of the criteria for AD types of dementia[1,2]

According to the amyloid hypothesis, an imbalance between the generation and clearance of Aβ protein deposits leads to a gradual accumulation of Aβ plaques, giving rise to other pathological processes such as neocortical tau pathology and neurodegeneration[3-5]

The amyloid hypothesis suggests that Aβ accumulation in the brain, which occurs over decades before symptoms appear, also precedes subsequent pathological mechanisms of AD, such as NFTs and neuronal loss[3-5]

Evidence for the amyloid hypothesis comes from the penetrance of APP, PSEN1, and PSEN2 mutations, which alter Aβ metabolism and cause aggregation of Aβ into plaques that precede symptoms[6]

Tau hypothesis

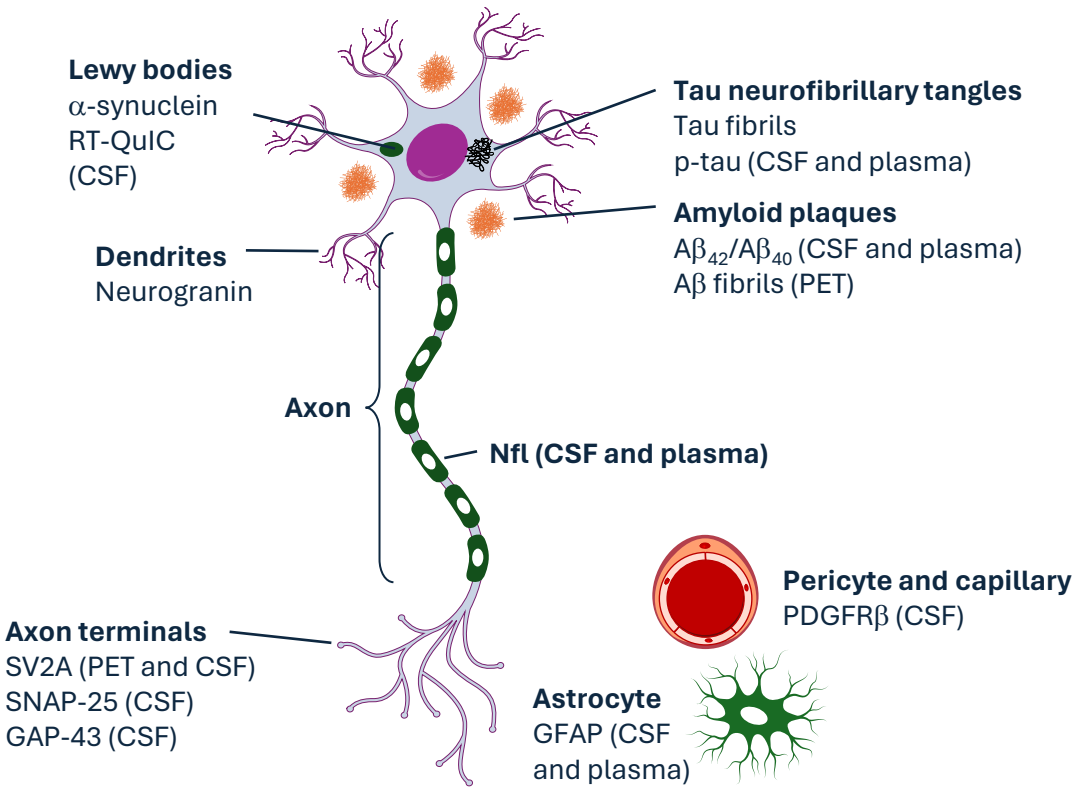


This work is adapted from 'Linking the amyloid, tau, and mitochondrial hypotheses of Alzheimer's disease and identifying promising drug targets' by Fišar et al., used under CC-BY. This work is licensed under Creative Commons license CC-BY-SA by The Lundbeck Foundation.

- Tau is a microtubule-associated protein involved in stabilizing microtubules in the axon of a neuron[2]
- In AD, tau becomes abnormally hyperphosphorylated, resulting in misfolding and aggregation into NFTs[2]
- Hyperphosphorylated and misfolded tau form NFTs in specific parts of the brain, which is a core part of AD and correlates with clinical symptoms of the disease[2-5]
- While some hypotheses suggest tau as an initiating event in AD,[4] most animal and human studies suggest that tau pathology aggregation and spreading happens following Aβ aggregation[6-7]

What are biomarkers?

Biomarkers for neurodegenerative disease[1]



- According to the Biomarkers Definitions Working Group, a biological marker (biomarker) is:

  "A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention"[2]

- Biomarkers of AD can be grouped into neuroimaging (such as MRI, PET) and fluid (CSF, plasma) biomarkers[3]
- Currently, available evidence suggests fluid biomarkers can successfully identify the presence/absence of AD, whereas imaging biomarkers can stage disease severity as well[1,4,5]

Potential use of accessible and cost-effective biomarkers in primary care[1]

Patient populations in primary care are more heterogeneous compared with specialized clinics

Patients with relevant cognitive and neurological symptoms

Clinical investigation in primary care using cost-effective and time-efficient assessments of symptoms

Interpretation of clinical findings

Diagnostic algorithms based on blood biomarkers and clinical tests can be used to determine the likelihood of neurodegenerative disease at an individual level

Patients with lower probability of neurodegenerative disease

Follow-up in primary care

Patients with higher probability of neurodegenerative disease

Referral to specialized care

Currently, clinically available AD biomarkers include:

- CSF p-tau and $A\beta_{42}$[2]
- Amyloid-PET[3]
- Tau-PET[4]

JAMA Neurology | Original Investigation

Diagnostic Accuracy of a Plasma Phosphorylated Tau 217 Immunoassay for Alzheimer Disease Pathology

Nicholas J. Ashton, PhD; Wagner S. Brum; Guglielmo Di Molfetta, MSc; Andrea L. Benedet, PhD; Burak Arslan, MD; Erin Jonaitis, PhD; Rebecca E. Langhough, PhD; Karly Cody, PhD; Rachael Wilson, PhD; Cynthia M. Carlsson, PhD; Eugeen Vanmechelen, PhD; Laia Montoliu-Gaya, PhD; Juan Lantero-Rodriguez, PhD; Nesrine Rahmouni, MSc; Cecile Tissot, PhD; Jenna Stevenson, PhD; Stijn Servaes, PhD; Joseph Therriault, PhD; Tharick Pascoal, MD, PhD; Alberto Lleó, MD, PhD; Daniel Alcolea, MD, PhD; Juan Fortea, MD, PhD; Pedro Rosa-Neto, MD, PhD; Sterling Johnson, MD, PhD; Andreas Jeromin, PhD; Kaj Blennow, MD, PhD; Henrik Zetterberg, MD, PhD

Findings

This cohort study found that the P-Tau 217 immunoassay showed similar accuracies to cerebrospinal fluid biomarkers in identifying abnormal amyloid beta and tau pathologies

Meaning

The wider availability of high-performance assays may expedite the use of blood biomarkers in clinical settings and benefit the research community.

Early Alzheimer's Disease: Developing Drugs for Treatment

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Office of Communications, Division of Drug Information at 855-543-3784 or 301-796-3400 or (CBER) Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

March 2024
Clinical/Medical

AD is a complex neurodegenerative disease with multifactorial aetiology and is thought to result from many interrelated components[1,2]

The risks of inheriting AD are relatively high,[3] with the APOE ε4 allele constituting the most important genetic risk factor in older adults for AD[4]

The amyloid hypothesis suggests that Aβ accumulation is a major upstream event in the pathogenesis of AD, leading to tau accumulation and neurodegeneration.[5] Unlike Aβ, tau pathology is more closely associated with symptoms[6]

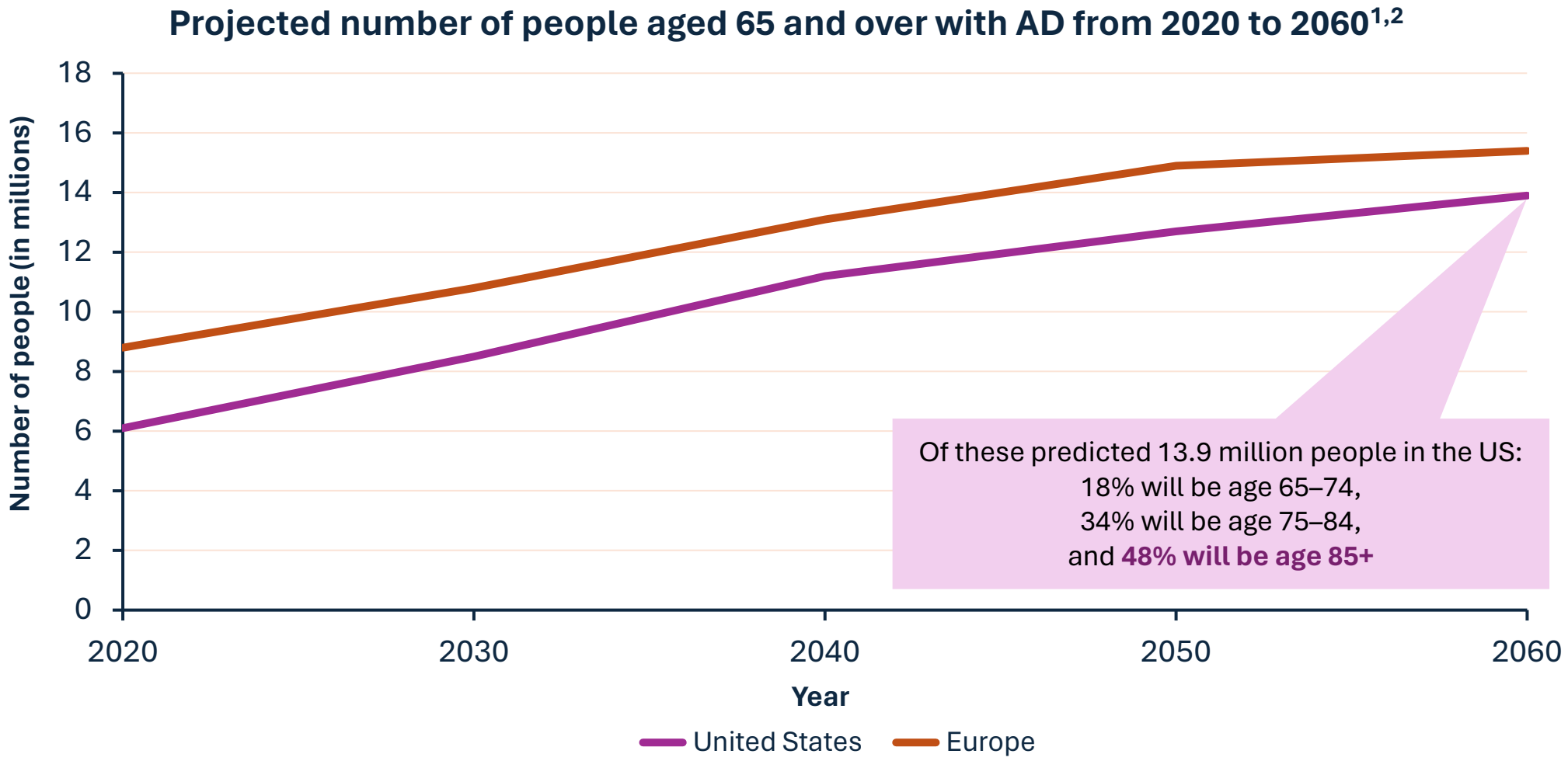
Because of the disparity between clinically defined "probable AD" and biological AD,[7] biomarkers have revolutionized the study of AD and have provided evidence that pathological changes begin approximately two decades before the onset of dementia[8,9]

Biomarkers may be used to identify eligible individuals for disease-modifying clinical trials to target the engagement of a therapy.[10] In specialist centers, biomarkers may be used in the *in vivo* diagnosis of AD[11]

Using biomarkers, individuals with preclinical AD can be identified as eligible for disease-modifying therapeutic trials[12]

Blood-based biomarkers may revolutionize the diagnosis of AD by making AD biomarkers more cost-effective and less invasive[13]

Projected increase in the prevalence of Alzheimer's disease dementia



Dementia has a significant impact on society

Globally, dementia costs **$1.3 trillion** annually[1]

Predicted to increase to **$2.8 trillion** by 2030[1]

20% of these expenses are directly related to medical costs[1]

AD management involves multiple expenses

Medical services include:

- Doctor visits
- In-hospital stays
- Emergency room admissions
- Long-term care (nursing homes and home healthcare)
- Skilled nursing care
- Medications

In 2022, caregivers (usually family members) of individuals living with AD provided an estimated **18 billion hours of unpaid care**[2]

Social care provided by professionals in care settings also incurs high costs[1]

Indirect costs include:[3]

- Decreased **productivity** for the person affected
- Decreased **quality of life**
- Increased **reliance** on others

The **progressive nature** of AD, combined with the **lack of widely available disease-modifying treatments**, place a significant economic and social strain on the healthcare system[3]

Number of deaths related to all-cause dementia or AD dementia is rising, making it the **7th most common cause of death** globally[4]

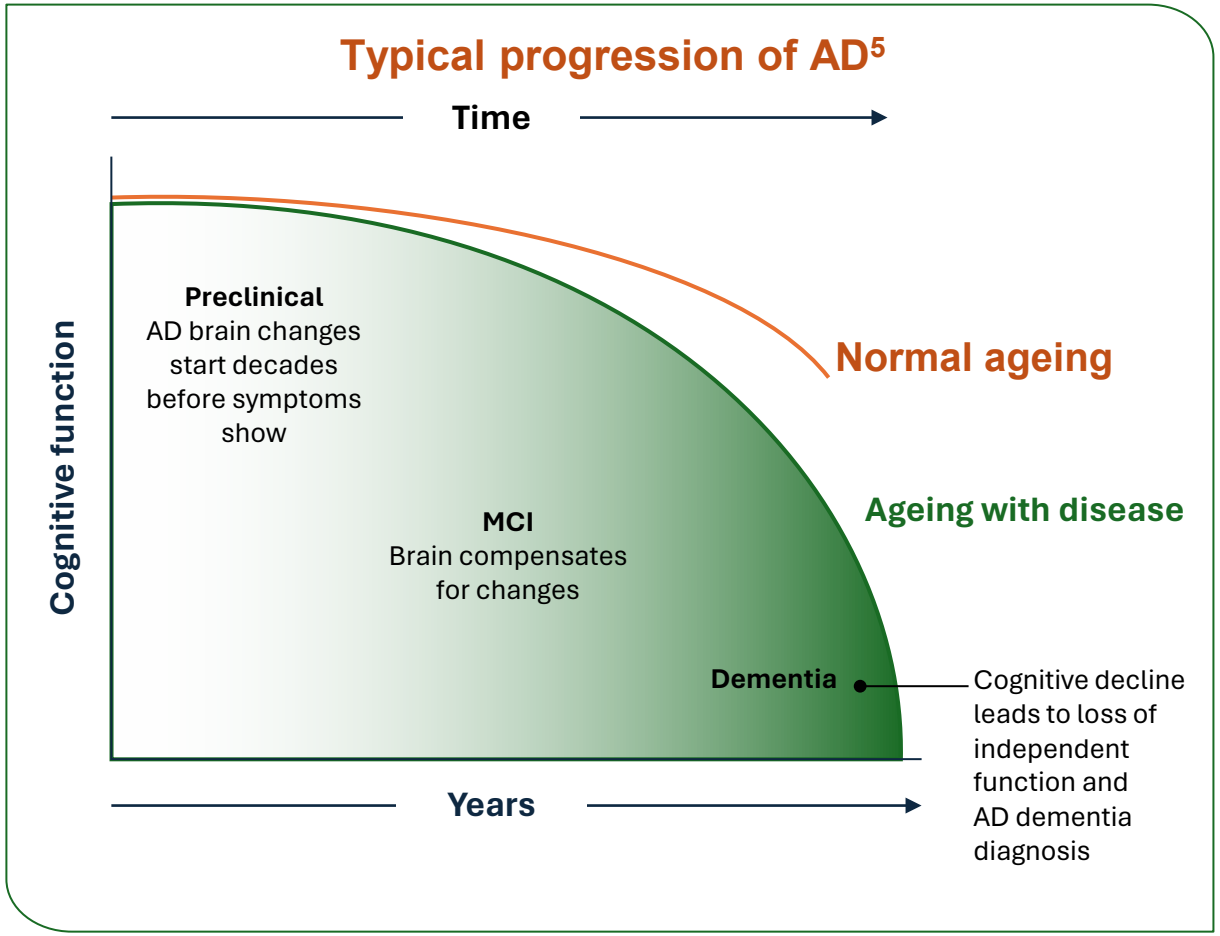
Course, natural history, prognosis and their clinical significance

- The course of a disease is the length of time for which the disorder is present, its natural progression, and, if applicable, its recurrence over time[1]
- The natural history of the disease refers to its progression in the absence of treatment[2], while prognosis, which may be used to weigh the benefits of different treatment options, refers to the likely outcome at specific points in the disease course[3]
- There are two types of AD staging
  - Clinical staging is based on the severity of cognitive impairment, ranging from no impairment to severe dementia[4]
  - Biological staging is based on the severity of biological changes in the brain.[5] In AD, biological disease progression precedes clinical impairment[4]

- Clinical staging tools assess disease severity and help plan for future disease progression and management[4]
- Understanding disease progression is valuable for the patient and their families and caretakers; their ability to carry out daily activities impacts their quality of life[6]
- Timely diagnosis and staging of the disease provide an objective measure for clinical progression during medical visits, and are critical for interventions which may delay progression[7]

The typical course of Alzheimer's disease

- Studies indicate that biological changes begin approximately two decades before the clinical onset of AD symptoms[1]
- AD can be characterized by three main phases:
  1. **Preclinical AD**: Abnormal AD biomarkers but no clinical symptoms[2]
  2. **MCI**: Individuals are mildly symptomatic but do not have dementia.[3] MCI denotes cognitive decline without impairment in activities of daily living[4]
  3. **Dementia**: Individuals show progressive loss of cognitive function and the ability to live independently[5]
- Anosognosia, impaired illness awareness, is a common feature of AD.[6] Hence, it is beneficial to interview an informant who knows the patient to understand the stage of the individual in the AD continuum[5]



Clinical staging of dementia

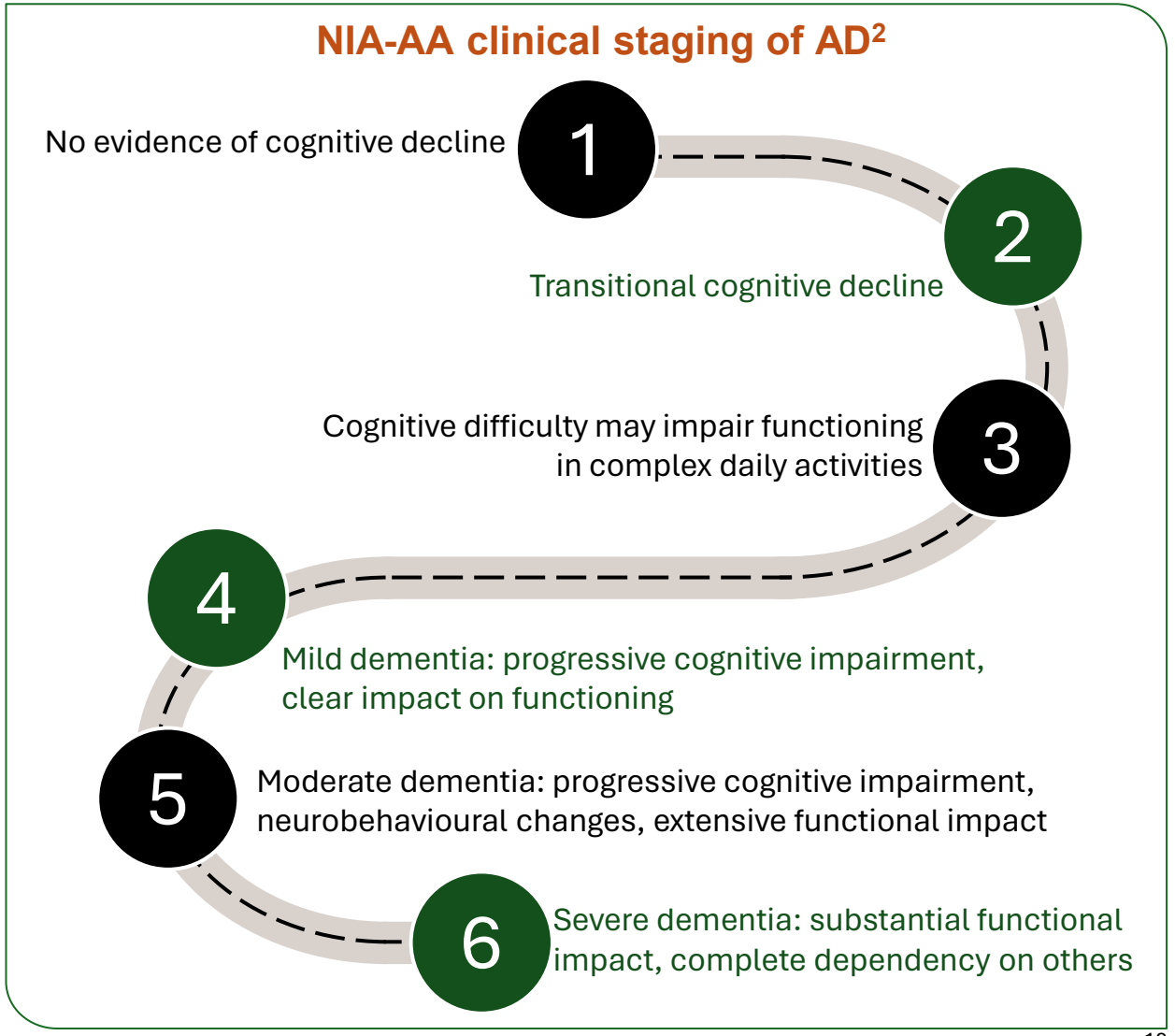
- The Global Deterioration Scale, developed in 1982, was widely used in categorizing cognitive and functional severity into seven stages, from no cognitive decline to severe cognitive decline[1]
- Today, clinical staging of dementia can be done using staging scales that measure cognitive and functional impairment in persons with dementia[2], as an unbiased staging of the disease is important for personalized clinical management[3]
- Commonly used clinical staging scales include[2]
  - Clinical Dementia Rating (CDR) Scale was designed for MCI and mild dementia[4]
  - Global Deterioration Scale (GDS) has seven stages and is suitable for the full range of MCI and dementia[1]
  - Functional Assessment Staging (FAST) has seven stages, focuses on function in activities of daily living[5]

The progression and severity of functional decline are the basis of clinical staging[6]

The rate of progression through clinical stages is variable and may depend on comorbid medical conditions[7]

New clinical staging of Alzheimer's disease

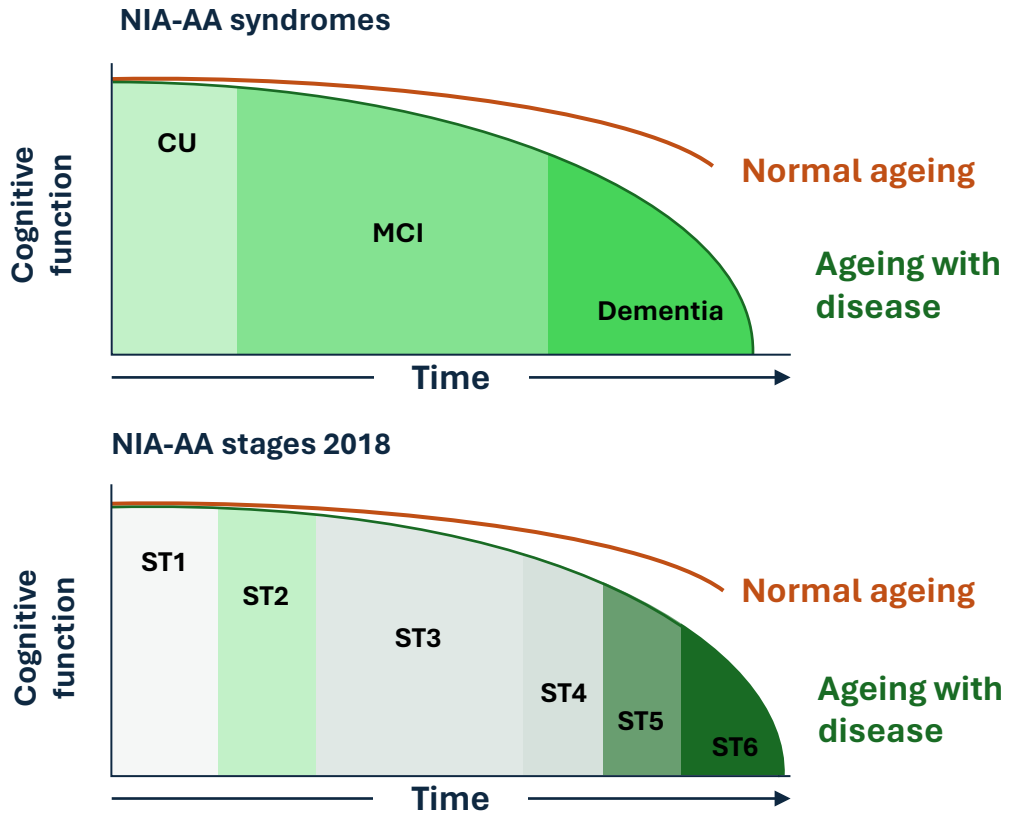
- A variation to the clinical staging of AD was proposed by the National Institute on Aging – Alzheimer's Association (NIA-AA) working group using six clinical stages for persons who are amyloid positive[1,2]
- The NIA-AA Research Framework describes AD as a biological construct that can be identified in living persons via Aβ and tau biomarkers[2]
- In the NIA-AA framework, biomarkers are used to identify the presence of AD, with clinical stages used to indicate disease severity[1,2]



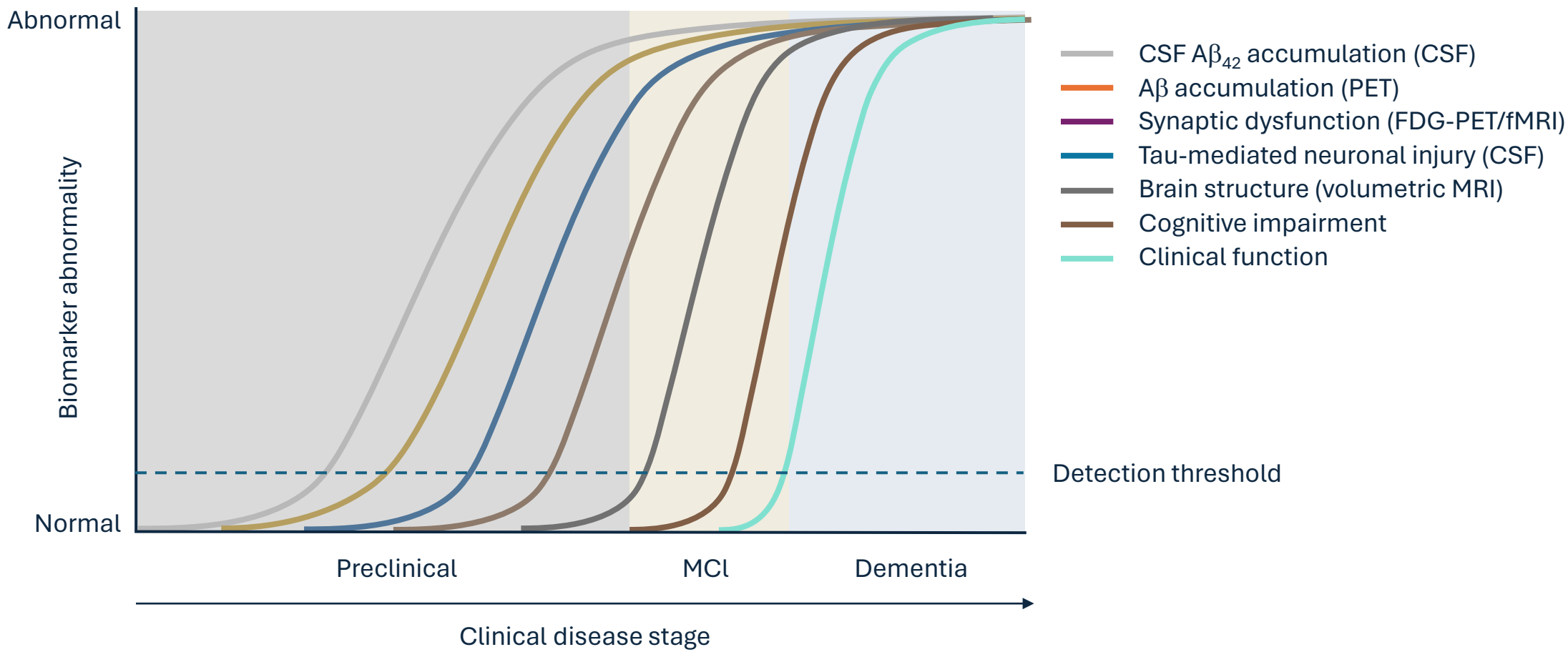
Characterizing the progression of cognitive impairment

- Progression in the severity of cognitive impairment in the clinical continuum, from CN to MCI and to dementia, has been classified and named differently by different diagnostic manuals and groups[1]
- IWG's "asymptomatic at-risk" stage has no correspondence in the DSM-5, as the latter only describes symptomatic states as "mild NCD" and "major NCD".[1,2] These two corresponding stages are called "prodromal" and "dementia" stages, as per IWG[1]
- The NIA-AA AD framework describes six stages for individuals with abnormal Aβ biomarkers (ST1-ST6)[3]
- Within the NIA-AA framework, MCI overlaps with both stages 2 and 3[1]

Clinical continuum[1]



Hypothetical biomarker model of Alzheimer's disease pathophysiology



Medical treatment of Alzheimer's disease

Therapeutic approaches to AD can be divided into three categories[1]

Symptomatic

AD-specific medications with beneficial effects on cognition and function[1]

Treatments can alleviate various symptoms, including agitation and sleep disturbances[1]

- Widely used current treatments are symptomatic[1]

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Disease-modifying

Treatments that can delay the onset, slow progression of cognitive and functional decline[1,2]

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- Disease-modifying treatments are being developed, with some recently approved in the United States only[2]

Medical treatment of Alzheimer's disease

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Disease-modifying

Treatments that can delay the onset, slow progression of cognitive and functional decline[1,2]

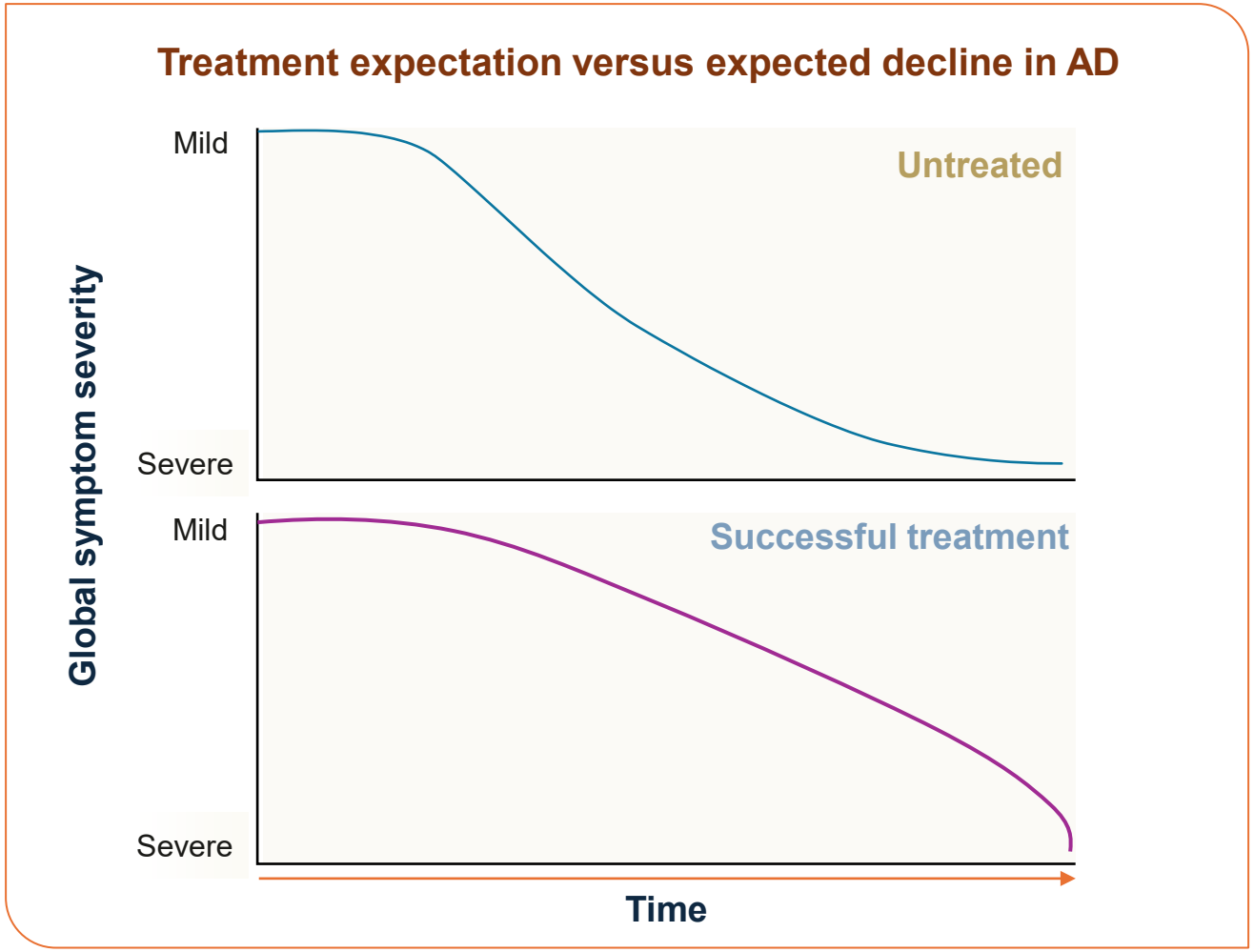
Regenerative

Treatments aimed at replacing lost neurons and networks[1]

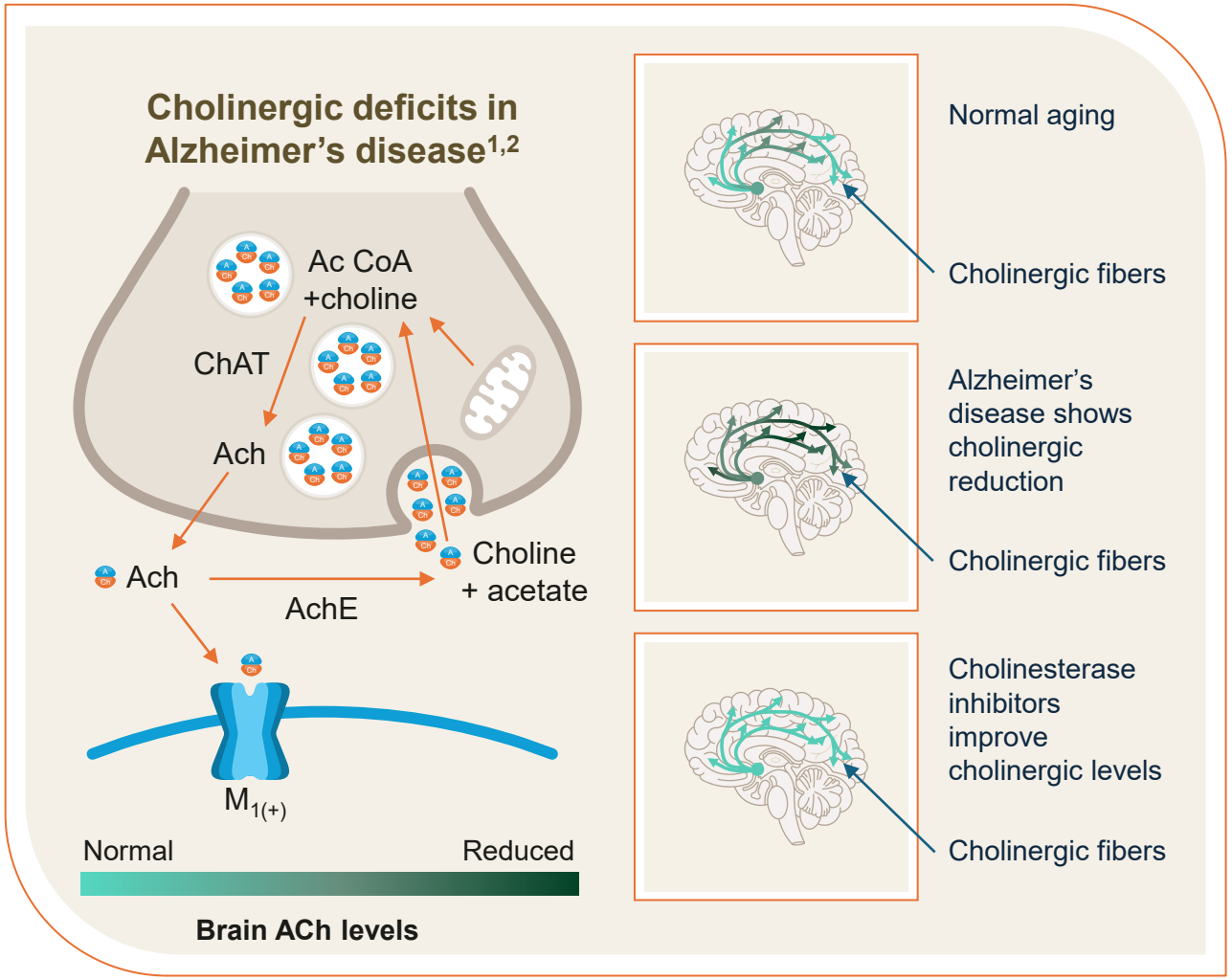
- Widely used current treatments are symptomatic[1]
- Disease-modifying treatments are being developed, with some recently approved in the United States only[2]
- No regenerative treatments have proven successful yet, and it remains a hypothetical approach[1]

Treatment goals of symptomatic treatment for Alzheimer's disease

- AD is a progressive disease with patients experiencing cognitive decline over time
- A successful treatment will shift the curve to the right, representing both short-term improvement and long-term slowed progression of symptoms. This would increase a patient's time in milder stages relative to no treatment
- The difference between the 'untreated' and 'successful treatment' curves represents the benefit of the treatment. This benefit is maximized with early initiation of therapy
- At present, AD treatments have not been shown to prolong life. Consequently, the trajectories of treated and untreated patients will converge in the later stages of the disease when treatment no longer provides measurable benefits



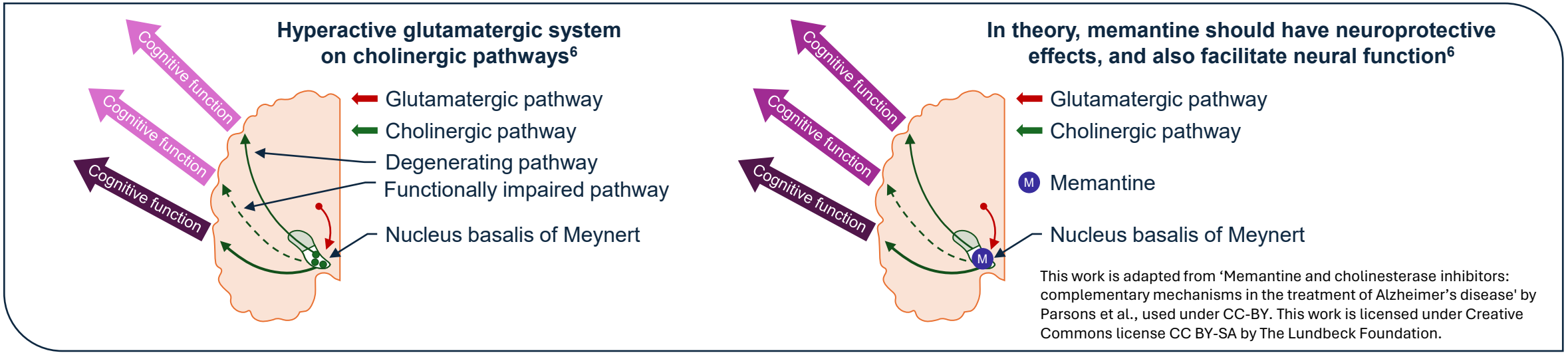
Treatment with cholinesterase inhibitors



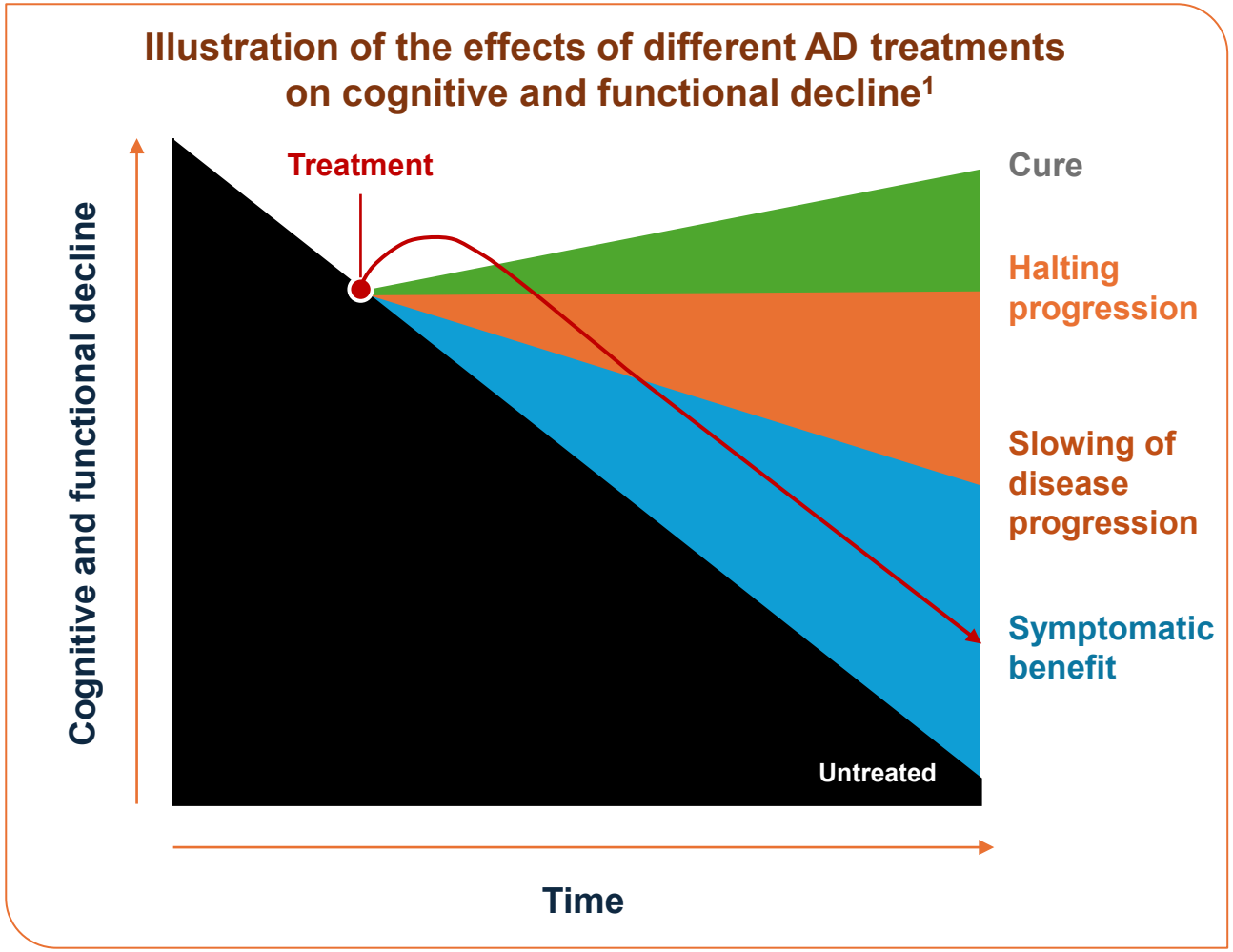
- Acetylcholine is a major neurotransmitter in the brain[1]
- In patients with AD, cholinergic neurons are progressively lost, reducing levels of acetylcholine[1]
- ChEIs target cholinesterase enzymes (AChE and BuChE) and inhibit the breakdown of acetylcholine.[1-3] This increases the availability of acetylcholine at the cholinergic synapses[1,2]
- Currently available FDA-approved ChEIs for the treatment of mild, moderate and severe AD are donepezil, rivastigmine, and galantamine[1]
- These drugs improve cognition, daily and global function, and some behavioural manifestations of AD, compared with placebo treatment[2-4]

Treatment with NMDA receptor antagonists

- Overstimulation of the NMDA receptors by glutamate is implicated in neurodegenerative disorders, including AD[1]
- The NMDA receptor antagonist memantine is approved for the treatment of moderate/severe AD alone or in combination with cholinesterase inhibitors[2-4]
  - Memantine has been shown to reduce clinical deterioration in moderate/severe AD[1]
- Furthermore, treatment with memantine has been shown to reduce symptoms such as agitation, aggression, irritability, and appetite disturbances[5]



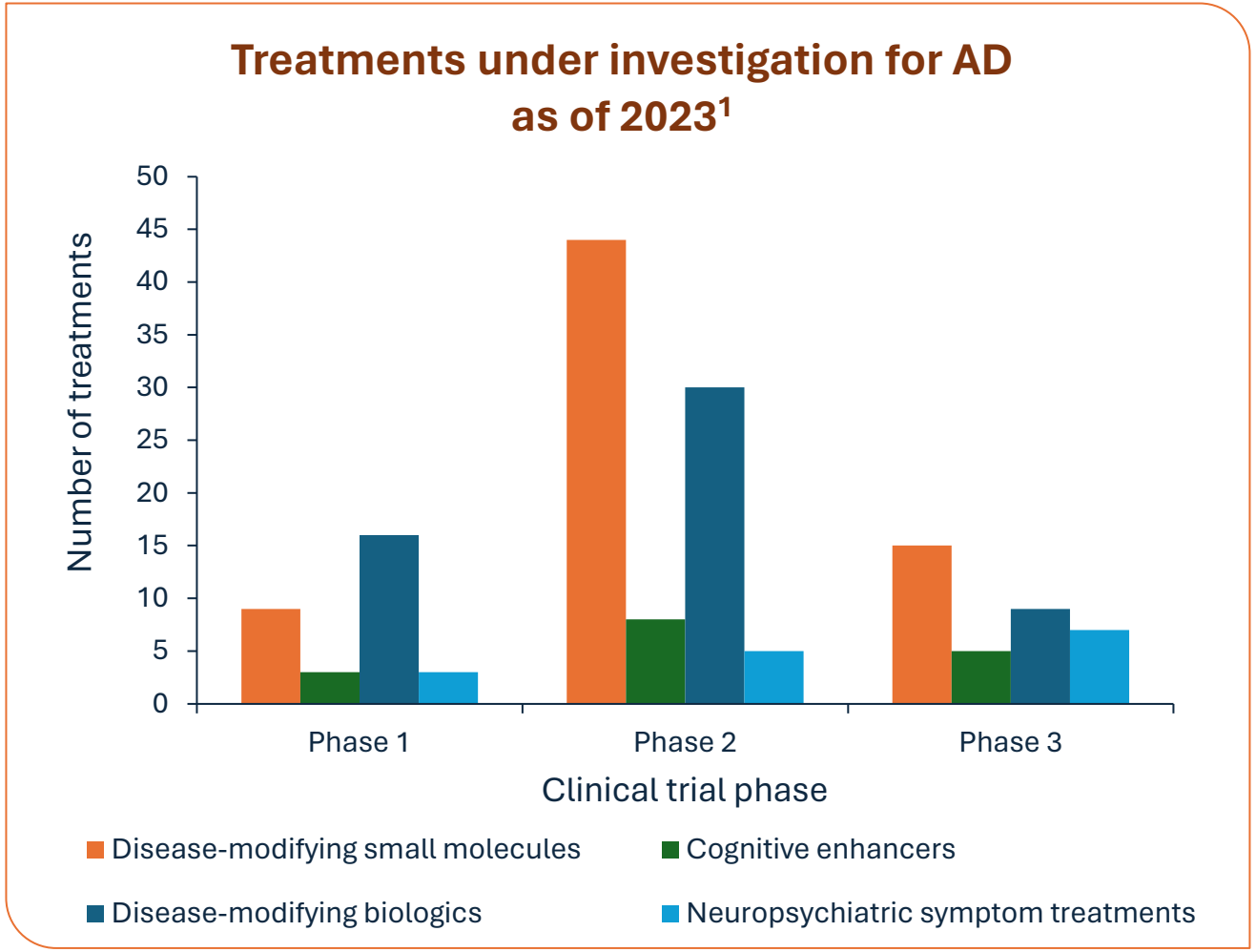
Treatment goals of disease-modifying treatments



- A treatment that modifies the disease would either halt or delay the gradual deterioration of the patient's health[2]
  - As a result, the patient's rate of decline would be less steep, deviating at a sharp angle from that of an untreated patient[2]
  - The more pronounced the effect of DMTs, the more significant the deviation, and the sooner the benefits of the treatment would be noticeable from a clinical perspective[2]
- New DMTs are being developed to affect the disease's underlying pathology[3]
- DMTs are not expected to fully restore a patient's function to its pre-disease state[2]
- Thus, symptomatic therapies still hold a critical role in patient care[2]

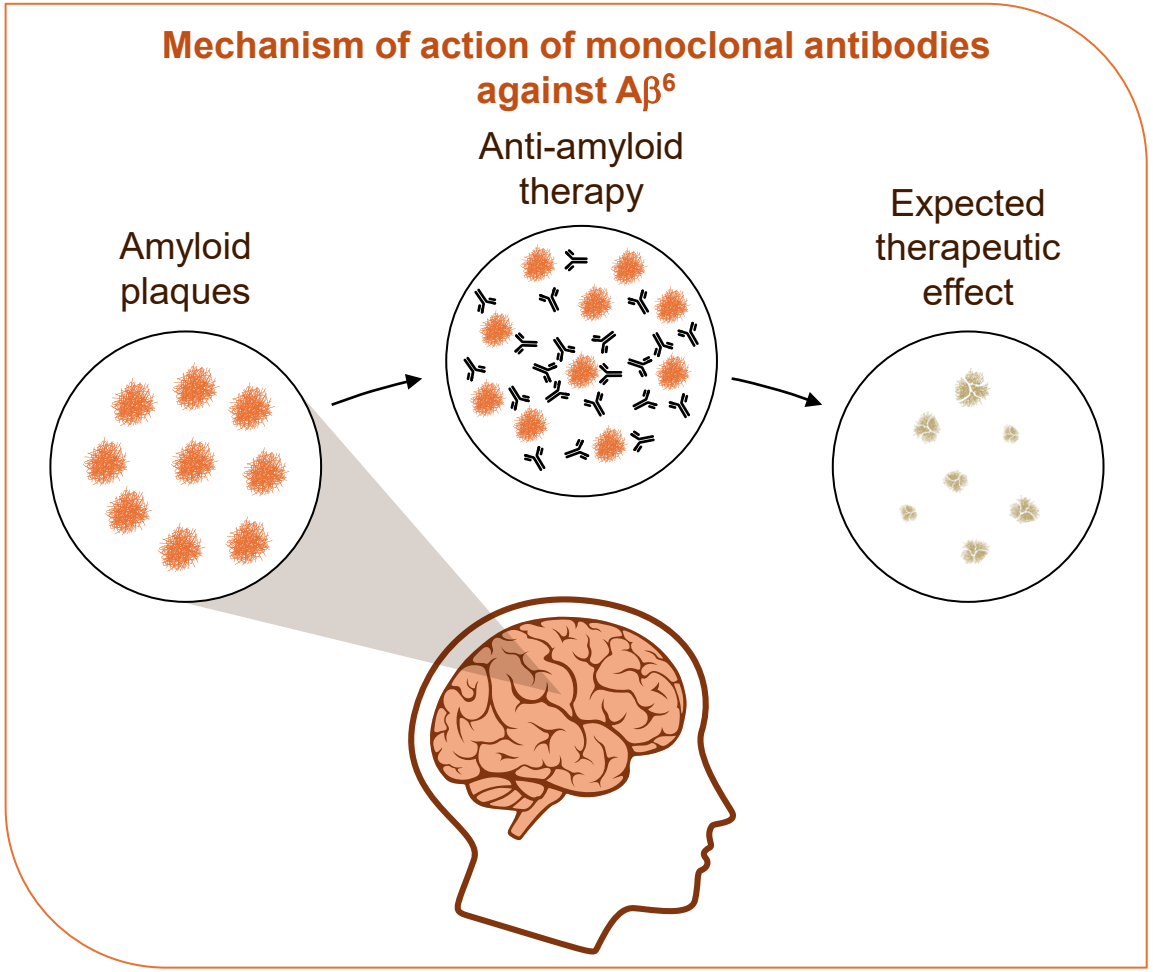
Several DMTs are being investigated

- DMTs targeting many different components of the pathology of AD are currently being investigated, among others, agents targeting amyloid accumulation, tau pathology, etc.[1]
- Several agents are in ongoing Phase 3 trials[1]
- An overview of the Alzheimer's drug development pipeline is published annually by Cummings et al.
- The primary outcome measure in the clinical studies can vary; one example is CDR-SB, which assesses function and cognition.[2,3] Another example is iADRS, which also measures cognition and function[4]



Current DMTs are targeting amyloid pathology

- In June 2021, the US FDA approved aducanumab, a treatment targeting amyloid pathology, for the treatment of AD[1]
- In January 2023, the FDA approved lecanemab, which like aducanumab, is a treatment targeting Aβ[2]
- The primary end-point in the trials investigating the effect of aducanumab,[3] lecanemab,[4] and most recently donanemab,[5] was the reduction of Aβ or slowing of cognitive and functional decline assessed on different scales[3-5]
- ARIA, which can manifest as brain oedema or microhaemorrhages, have been described as adverse events for aducanumab, lecanemab, and donanemab requiring brain MRI monitoring under treatment[3-5]



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Aducanumab to Be Discontinued as an Alzheimer's Treatment

Treatments for Alzheimer's

Aducanumab (Aduhelm®), which received accelerated approval as a treatment for Alzheimer's disease from the U.S. Food and Drug Administration (FDA) in 2021, will be discontinued by its manufacturer (Biogen) in 2024.

JAMA Network

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Medical News in Brief

July 19, 2023

Alzheimer Drug Lecanemab Gains Traditional FDA Approval

Emily Harris

JAMA. 2023;330(6):495. doi:10.1001/jama.2023.12548

Lecanemab

- Slows deterioration as determined by CDR Sum of Boxes by 27% over 18 months
- Slows ADL progression by 30% at 18 months
- Significantly decreases brain amyloid at 18 months
- Main complications: ARIA

FDA full prescribing info

ALZHEIMER'S ASSOCIATION®

Donanemab for Treatment of Early Alzheimer's Disease — News Pending FDA Review

Alzheimer’s Disease Work Up

Individuals < 65

- MMSE of 22 or greater or MOCA of 17 or greater.
- PrecivityAD2 (If positive, refer to Neurology)
- MRI brain without contrast. Specify SDAT work up in notes. Must have 4 or fewer microhemorrhages.
- APO-E Alzheimer's risk
- CBC, CMP, Vitamin B12, TSH

Individuals > 65

- MMSE of 22 or greater or MOCA of 17 or greater.
- Amyloid PET

  or

  Lumbar puncture with: Beta amyloid 42/40 ratio & routine CSF labs
- MRI brain without contrast. Specify SDAT work up in notes. Must have 4 or fewer microhemorrhages.
- APO-E Alzheimer's risk
- CBC, CMP, Vitamin B12, TSH