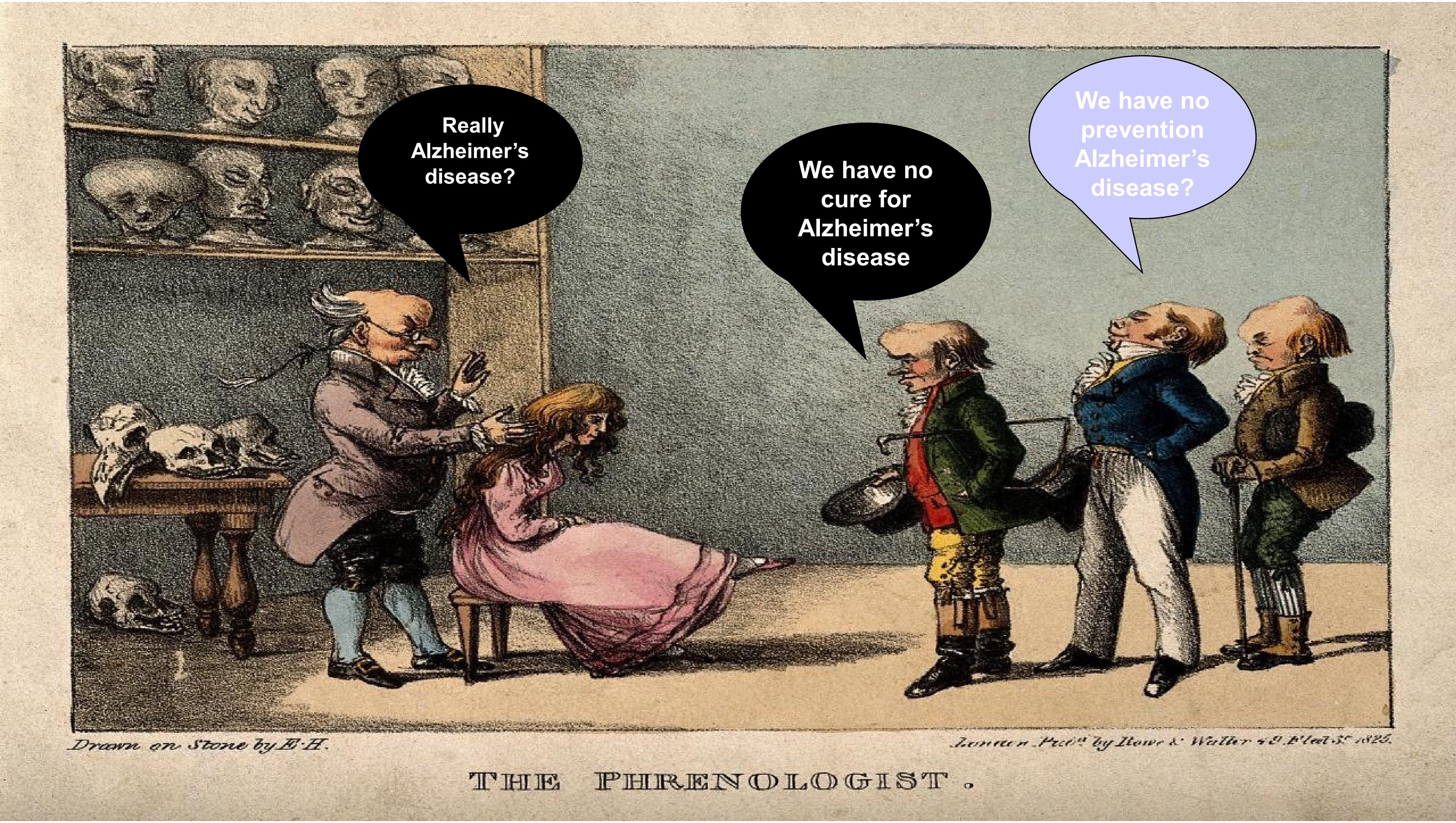
ROMA
17-18 marzo 2026

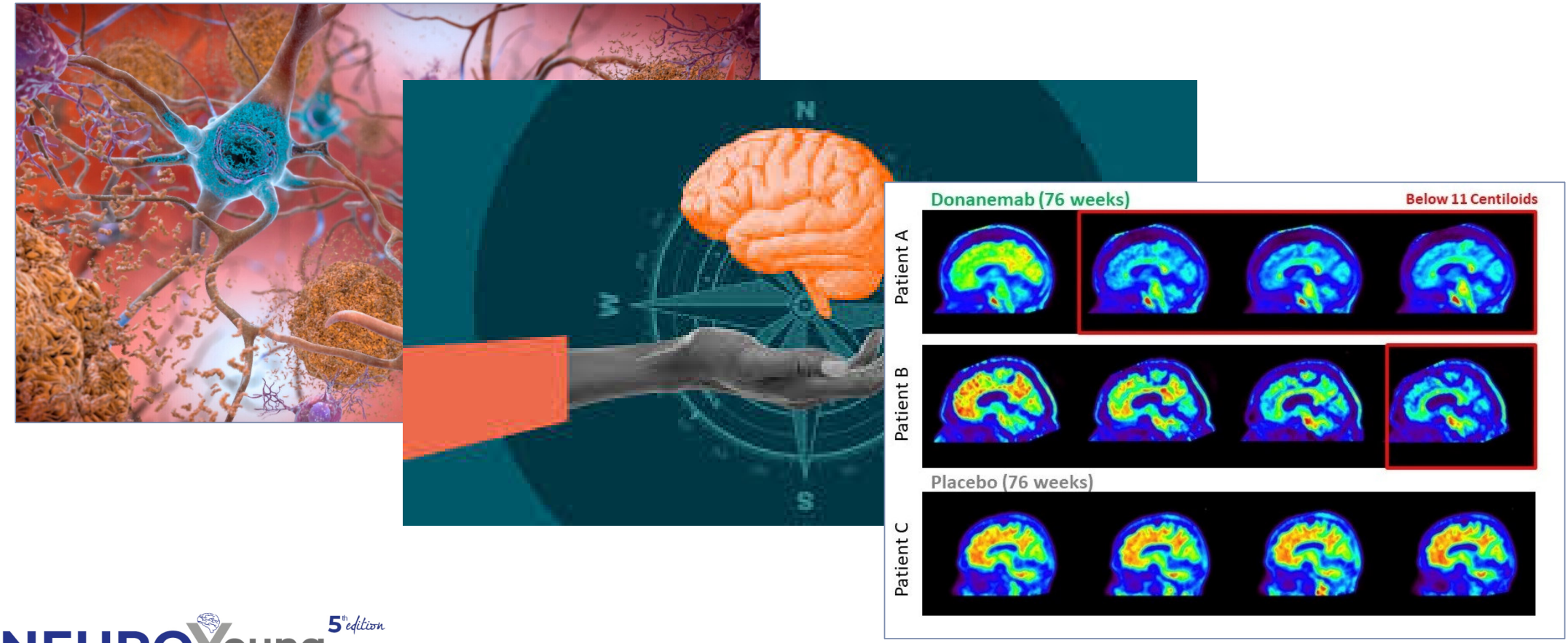
NEUROYoung
next generation in neurologia
5th edition

Introduzione

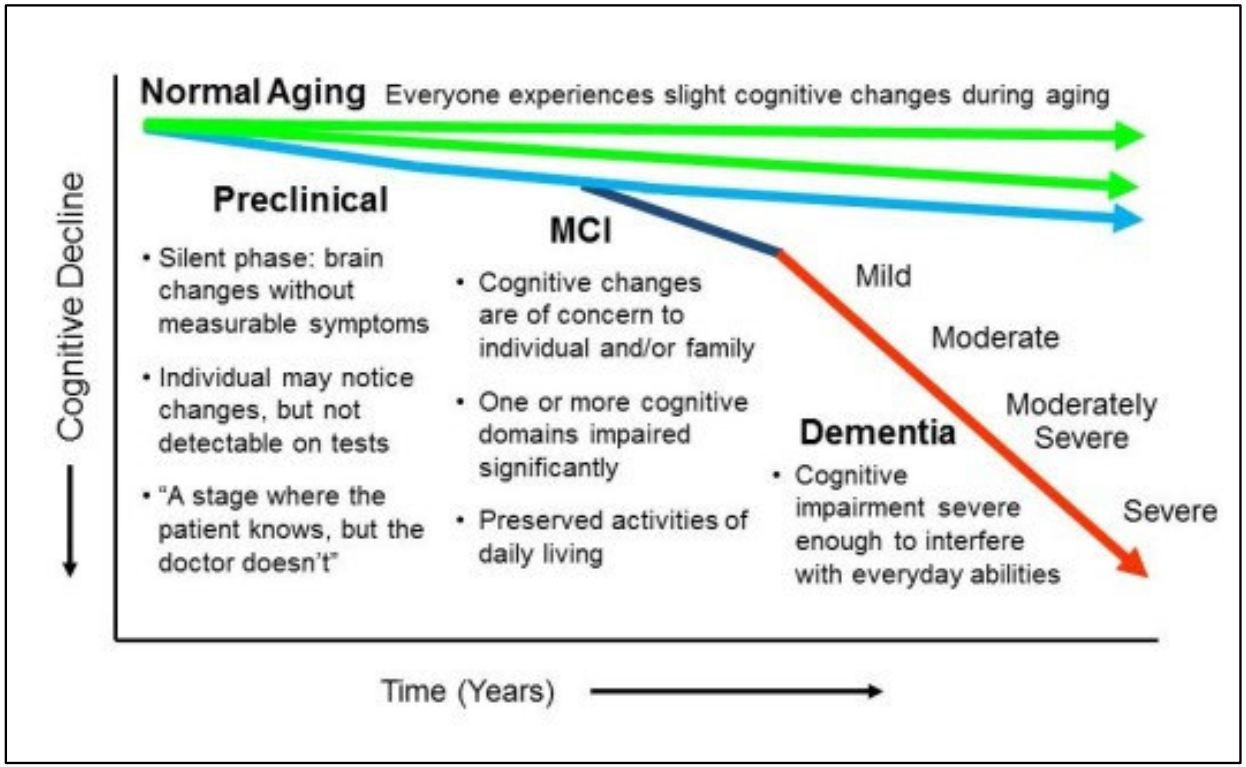
Innocenzo Rainero, MD, PhD
SSD Malattia di Alzheimer e demenze correlate
Università di Torino

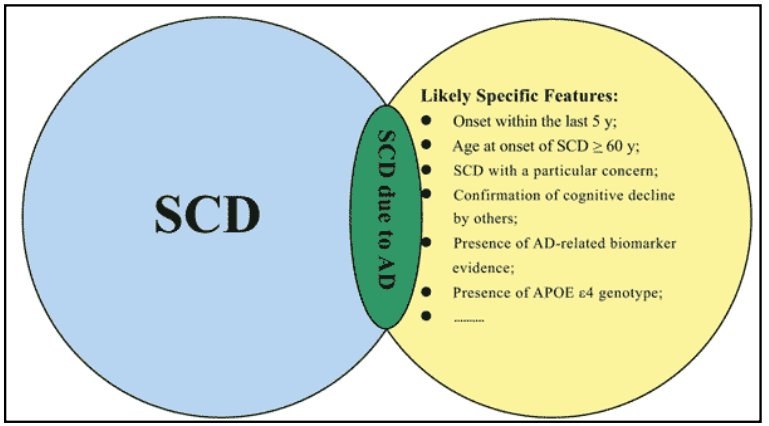

Really Alzheimer's disease?
We have no cure for Alzheimer's disease
We have no prevention Alzheimer's disease?
Drawn on Stone by E.H.
THE PHRENOLOGIST.

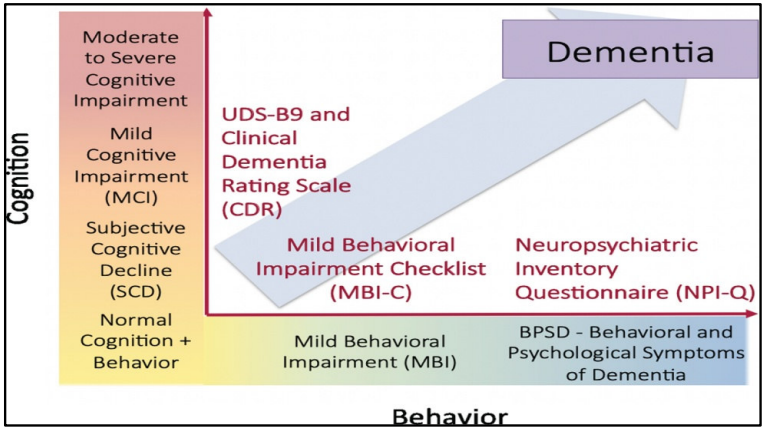
A new era in Alzheimer's disease

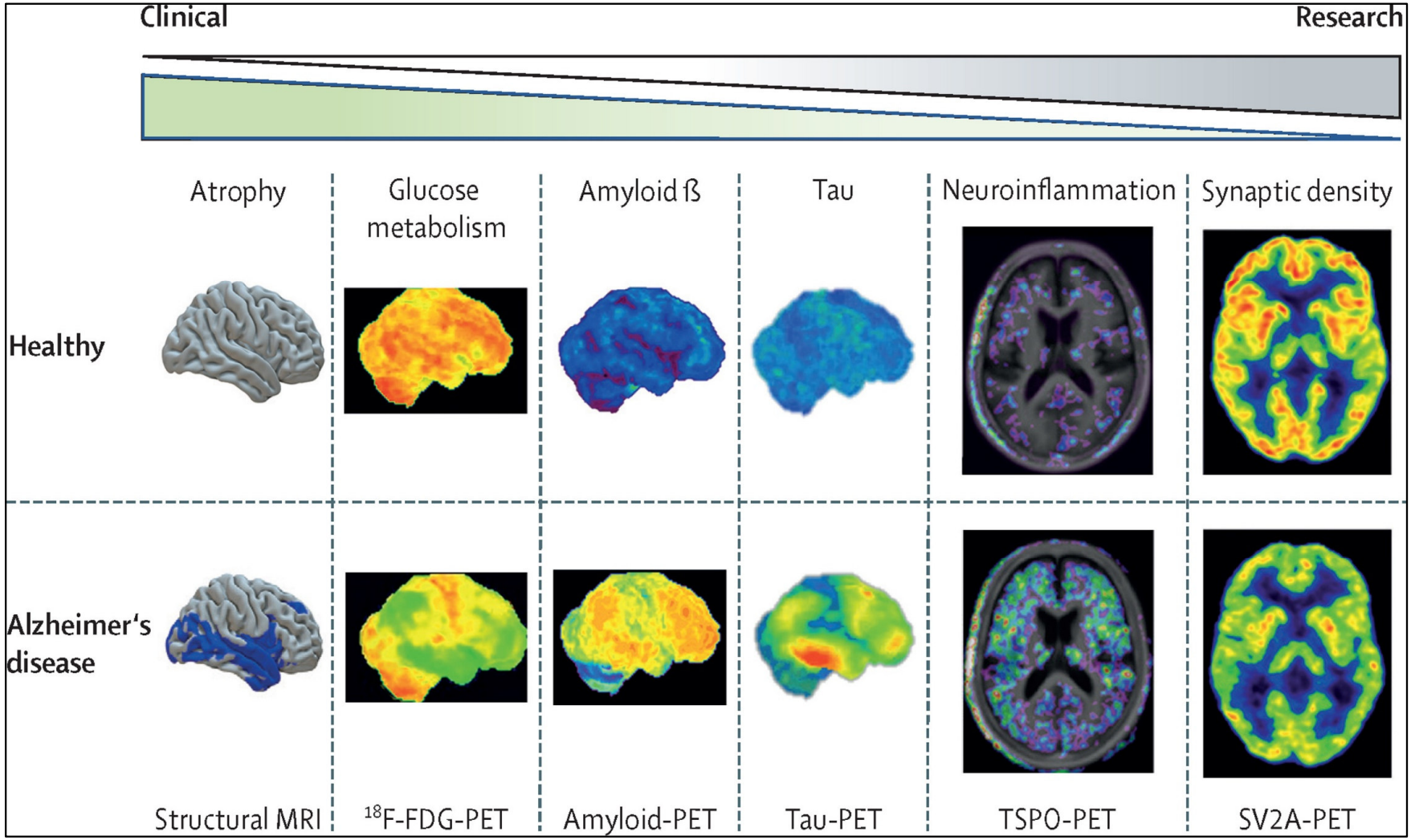


The new clinical scenario



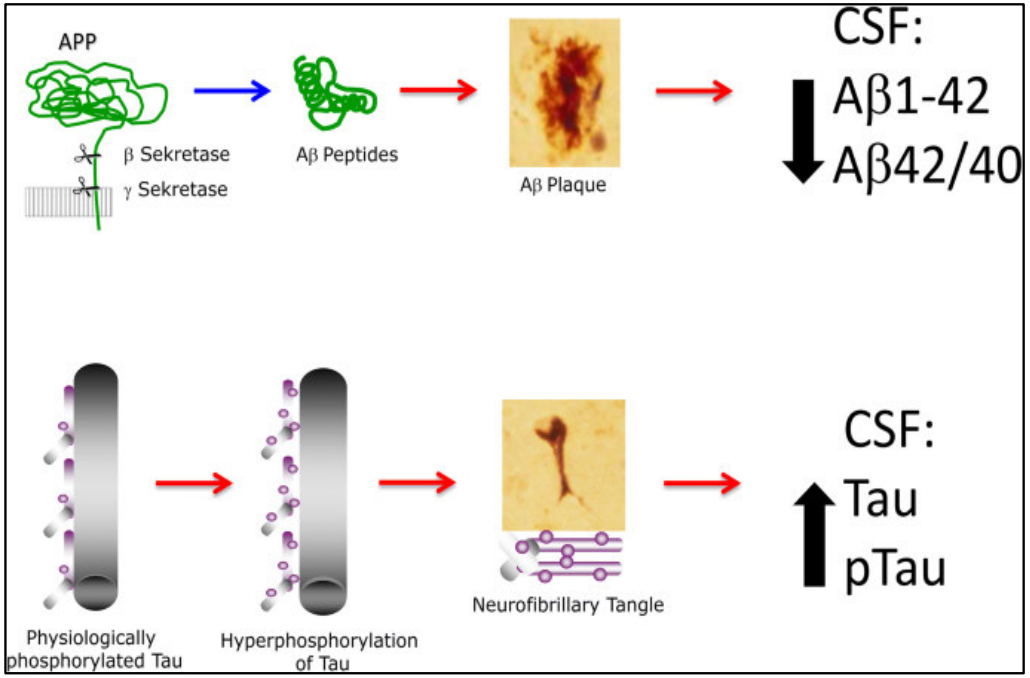


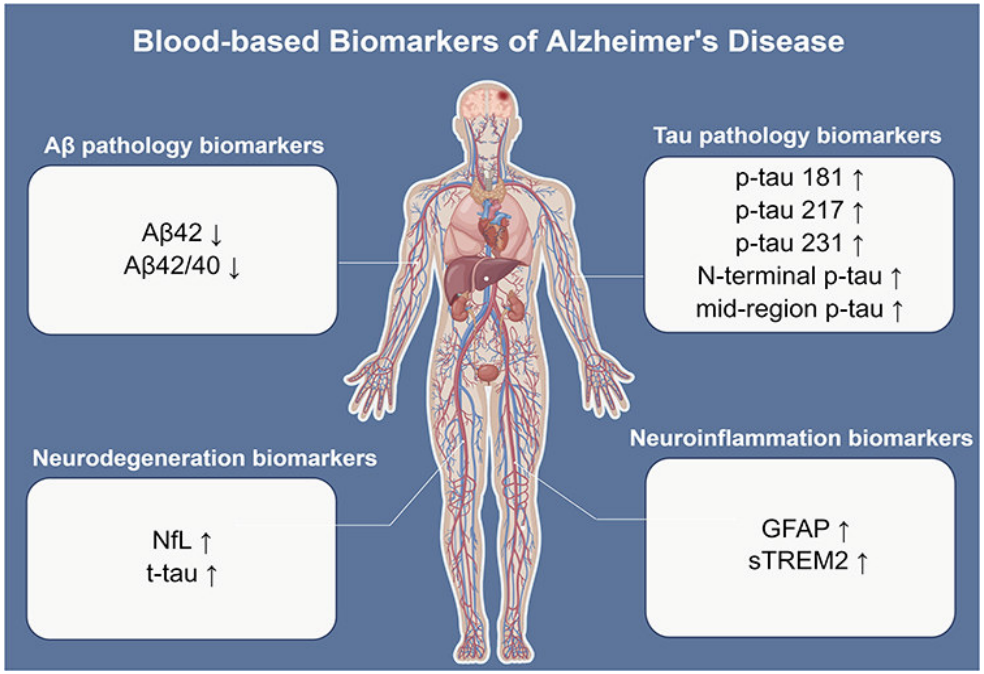




Amyloid -PET and FDG-PET in the diagnosis of AD

Fluid biomarkers in AD





New drugs to treat Alzheimer's disease

FDA APPROVED

- **Aducanumab**
- **Lecanemab**
- **Donanemab**
- **Memantine/Donepezil**

A new landscape in Alzheimer's disease

Have a nice meeting

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La diagnosi biologica della malattia di Alzheimer e le nuove terapie

Innocenzo Rainero, MD, PhD

SSD Malattia di Alzheimer e demenze correlate

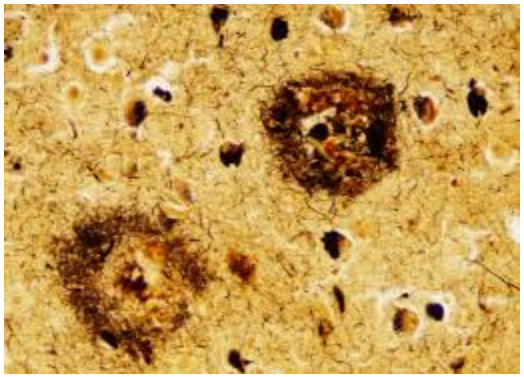
Università di Torino

OUTLINE

- What's Alzheimer's disease?
- Old and new diagnostic procedures
- The Biological Diagnosis of Alzheimer's disease
- New Treatment Options

What’s Alzheimer’s Disease?

What's Alzheimer disease?



The term AD is often used to describe **two very different entities:**

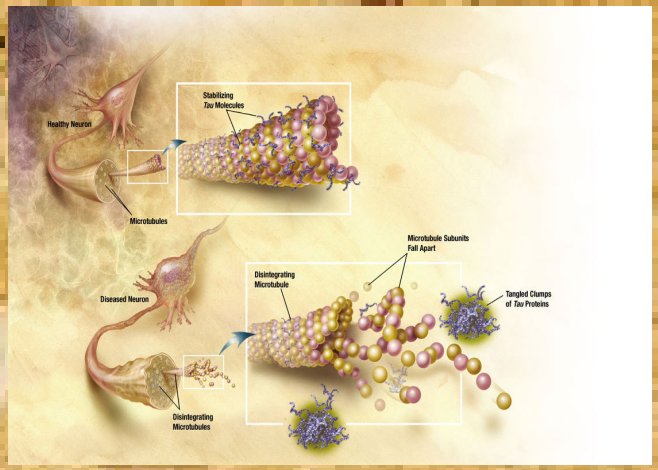
- a prototypical clinical syndrome, mainly characterized by cognitive deficits, but without neuropathologic confirmation.
- a unique disease, showing at neuropathologic examination the presence of plaques and tangles, that is the leading cause of dementia.

Major concerns

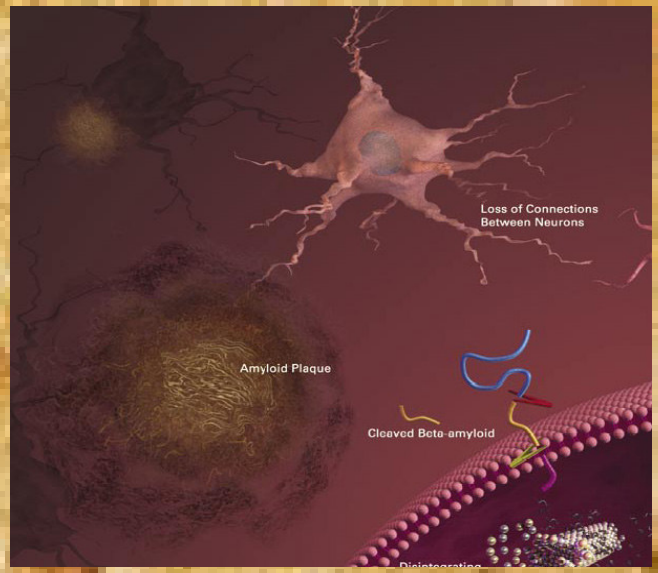
- It is now well established that the prototypical multidomain amnestic dementia historically used to define probable AD is neither sensitive nor specific for AD neuropathologic change: **from 10% to 30%** of individuals clinically diagnosed as AD dementia by experts do not display AD neuropathologic changes at autopsy.

- In addition, AD neuropathologic changes are often present without signs or symptoms, especially in older persons. **Thirty to forty percent** of cognitively unimpaired elderly persons have AD neuropathologic changes at autopsy.

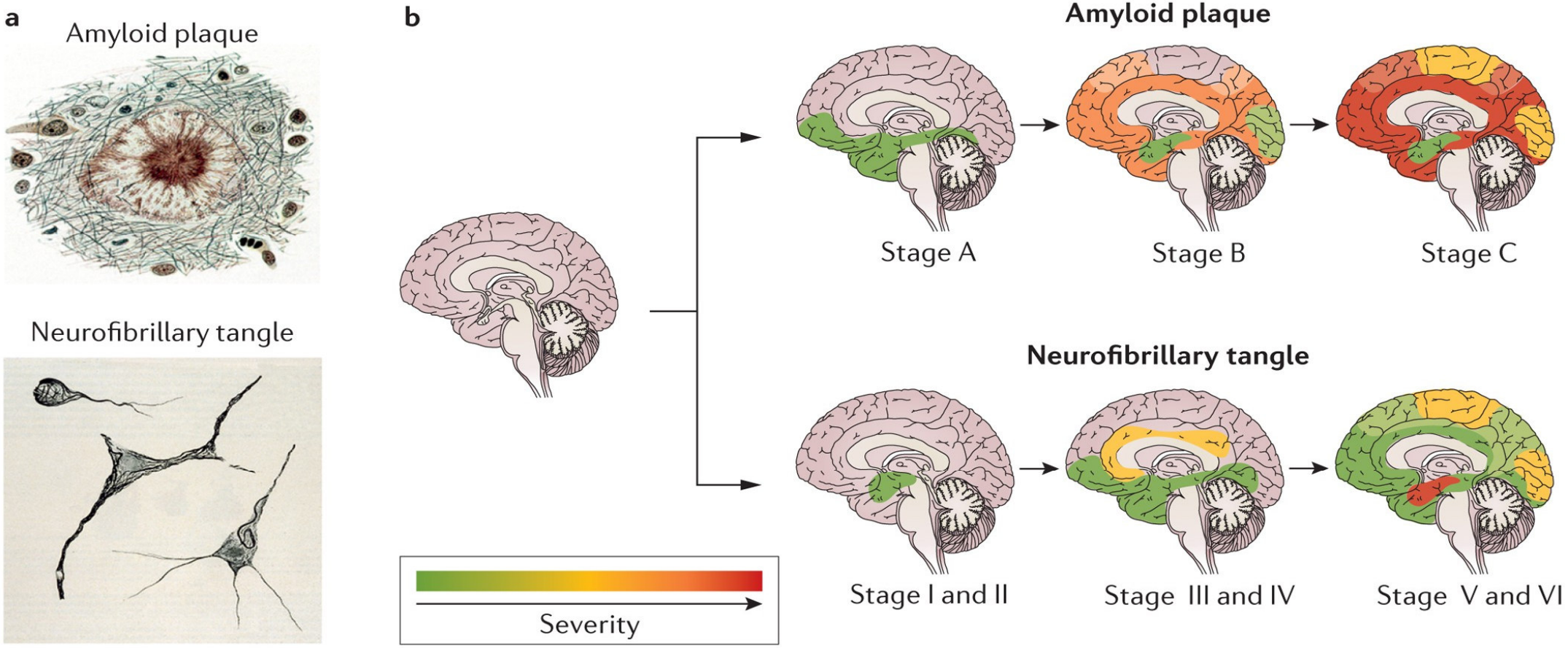
NFT


Healthy Neuron
Stabilizing
Tau Molecules
Microtubules
Diseased Neuron
Disintegrating
Microtubule
Microtubule Subunits
Fall Apart
Tangled Clumps
of Tau Proteins
Disintegrating
Microtubules

Amyloid

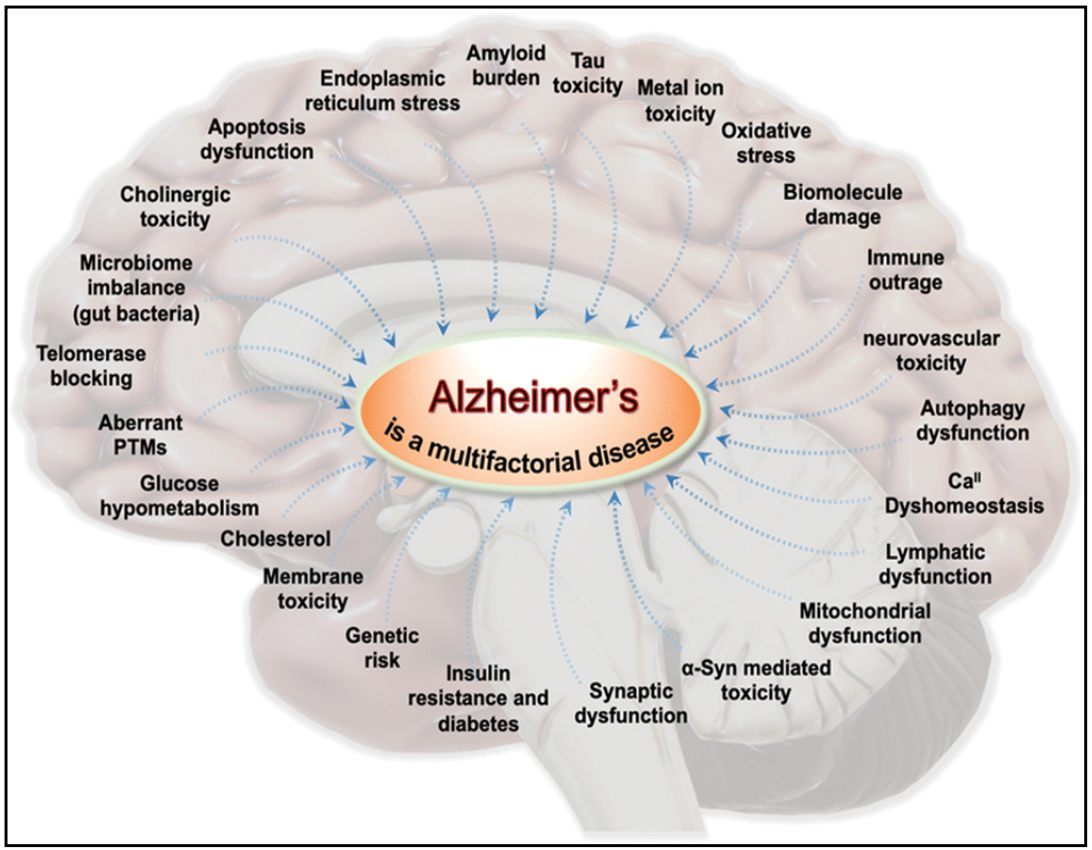

Loss of Connections
Between Neurons
Amyloid Plaque
Cleaved Beta-amyloid

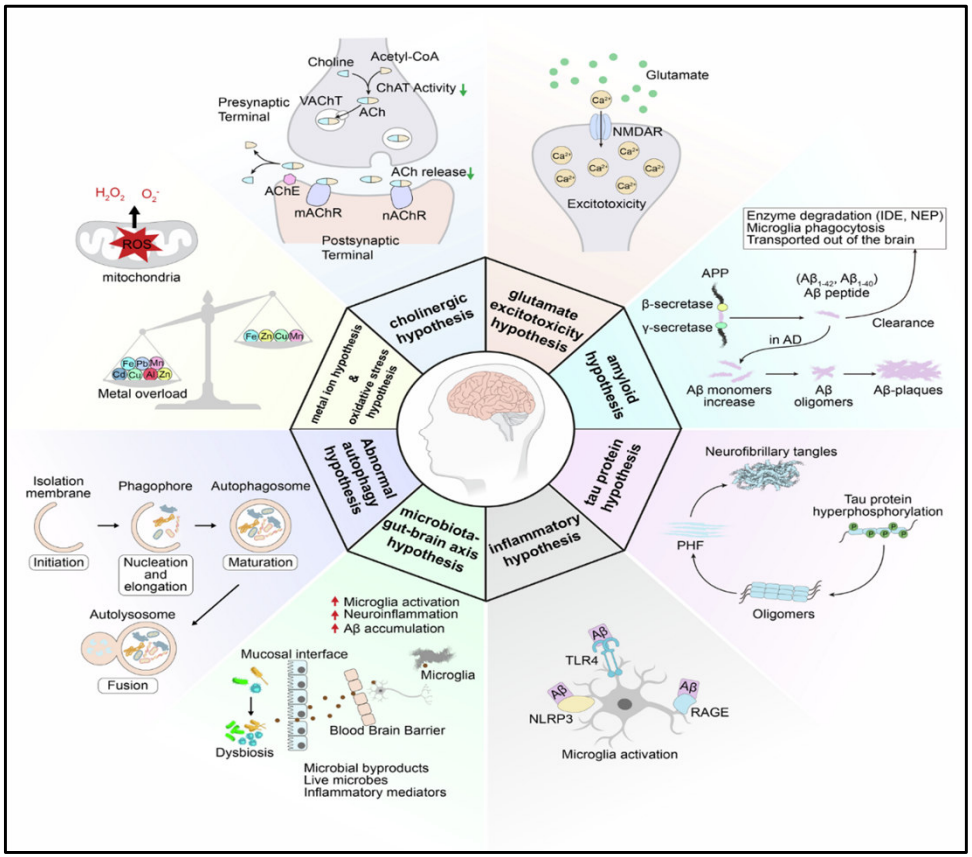
Progression of neuropathological changes in AD



Nature Reviews | Disease Primers

Risk factors and pathogenesis of AD





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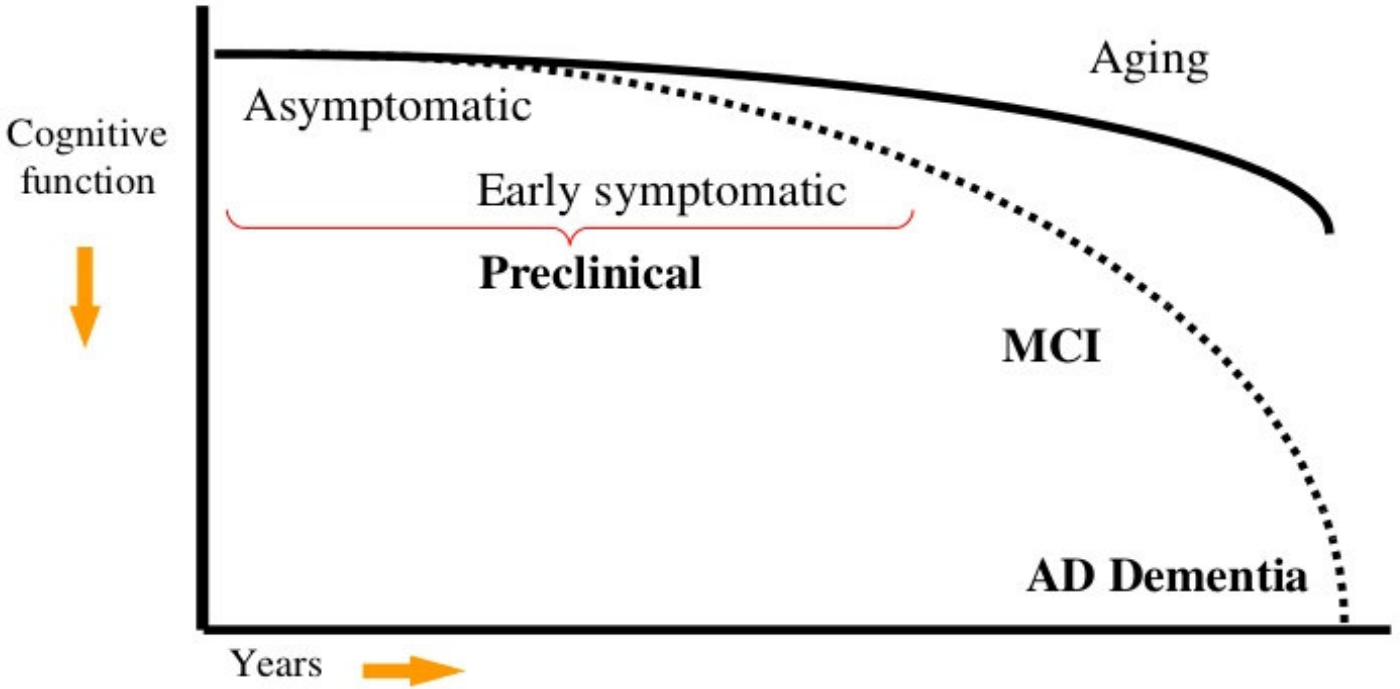
The continuum of Alzheimer's disease



Sperling et al *Alzheimer & Dementia 2011*
NIA-AA Preclinical Workgroup

The **Alzheimer's disease continuum** is a progressive, model spanning years or decades. It represents a gradual, continuous transition from asymptomatic brain changes (amyloid plaques/tau tangles) to cognitive decline, functional impairment, and eventually severe, fatal neurodegeneration.

Old and new diagnostic procedures

Old and new diagnostic procedures

Cognitive Assessments

Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), second level neuropsychological testing

Brain Imaging

MRI, PET scans to identify physical brain changes

Amyloid and Tau PET scans for detecting plaques and tangles

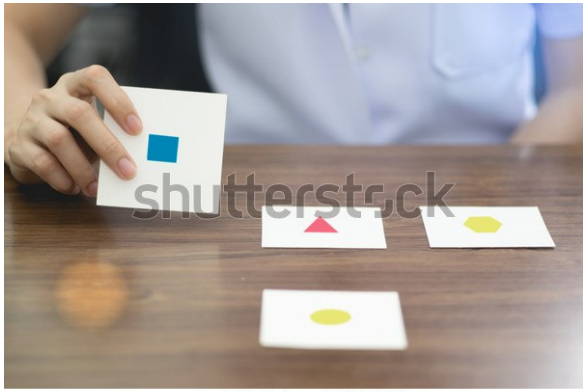
Biomarker and Genetic Testing

Cerebrospinal fluid (CSF) analysis

Blood tests (e.g., tau, beta-amyloid proteins)

Apo E alleles and genotyping for monogenic variants

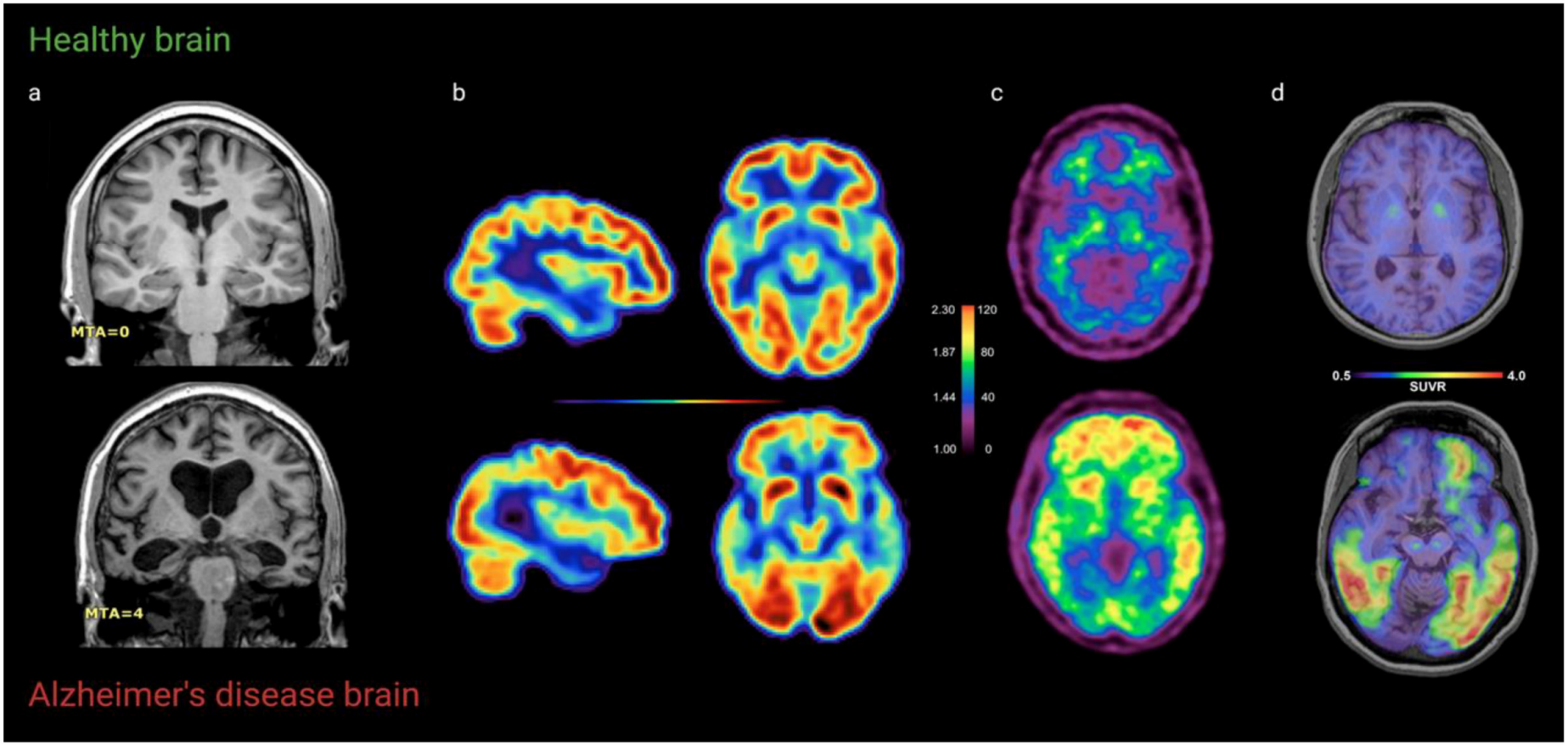
Cognitive Assessment



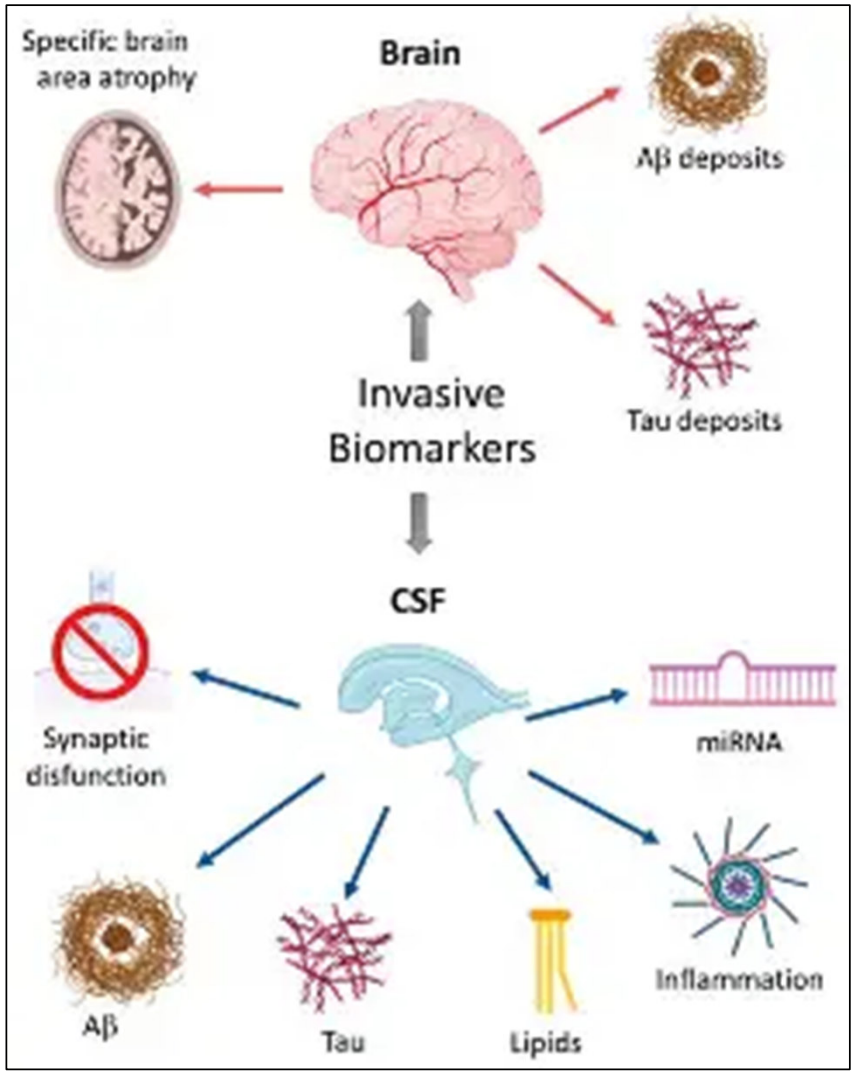
- Neuropsychological evaluation is a **critical** component in supporting early and accurate diagnosis and staging, characterizing the clinical profile, assessing trajectory over time, and providing recommendations specifically tailored to the individual and their care team.

- For any clinician, brief cognitive assessments can provide a quick estimate of an individual's cognitive function and identify those individuals who would benefit from a more detailed cognitive evaluation.

Brain Imaging



Alzheimer's Association, 2023



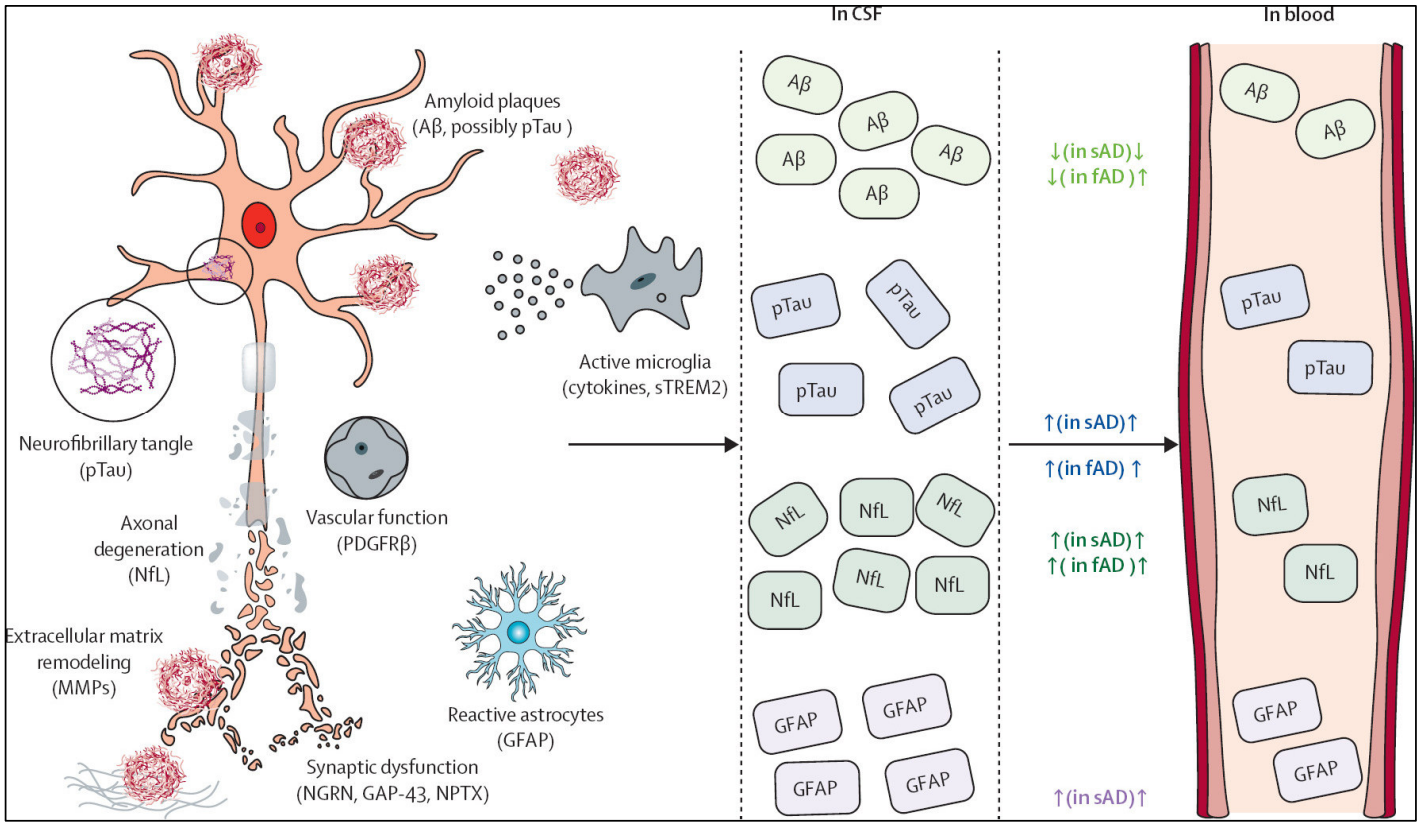
CSF biomarkers

The core CSF biomarkers of neurodegeneration (T-tau, P-tau, and Aβ42) arte strongly associated with **Alzheimer's disease** and the core biomarkers are also strongly associated with **mild cognitive impairment due to Alzheimer's disease.** In addition, CSF Neurofilament light (NFL) are a clear indication of neurodegeneration.

Due to their consistency, T-tau, P-tau, Aβ42, and NFL in CSF should be used in clinical practice and clinical research.

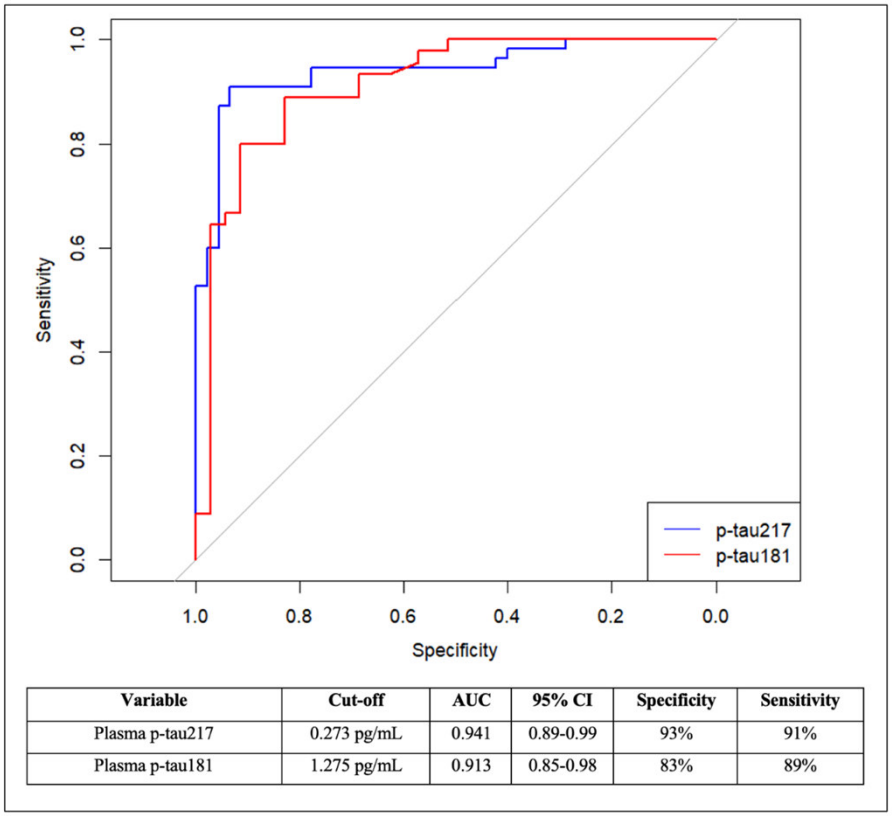
Despite being the **gold standard** for detecting amyloid and tau pathologies in vivo, CSF biomarkers are not widely used in the clinical setting because of invasiveness, high costs, and restricted accessibility.

Plasma biomarkers for early diagnosis

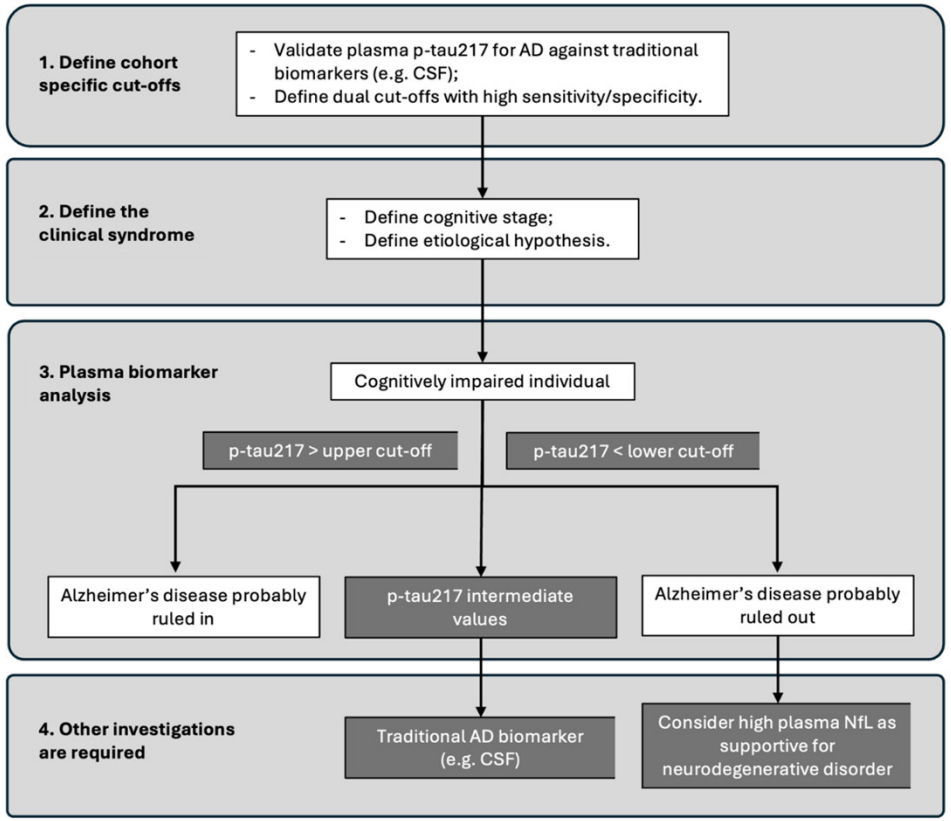


Among the currently available plasma biomarkers, **plasma phosphorylated tau 217** (p-tau217) has consistently shown the highest accuracy in detecting AD pathology.

Plasma biomarkers in real world

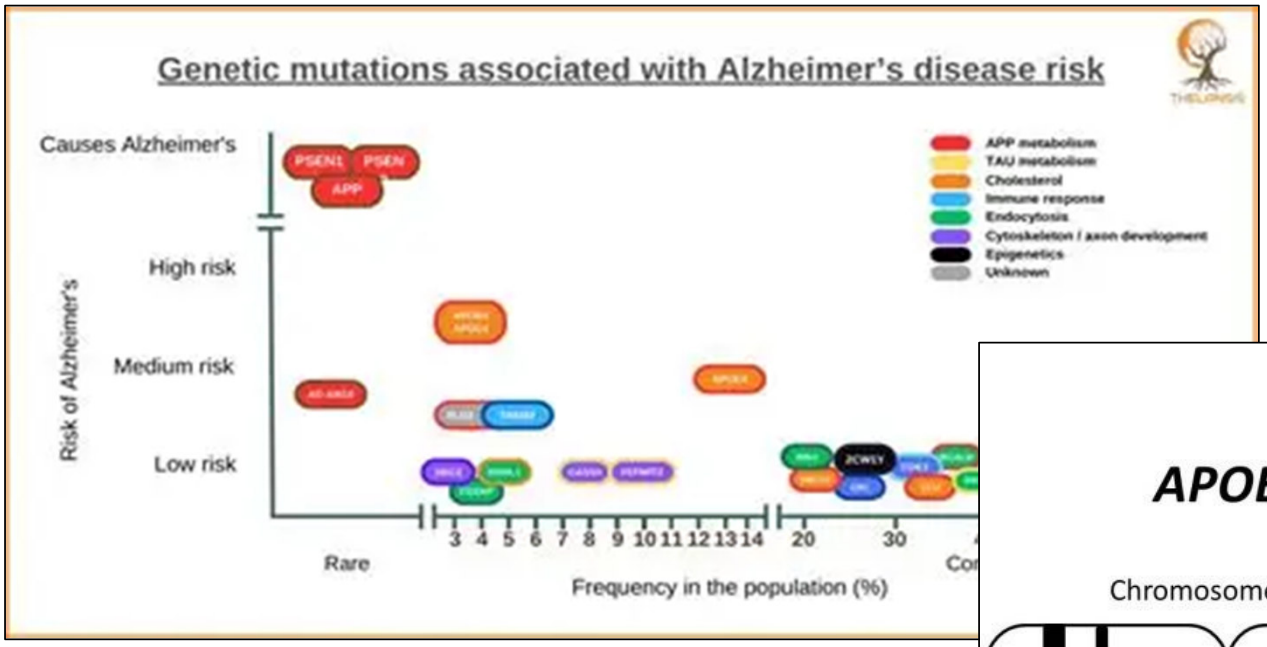


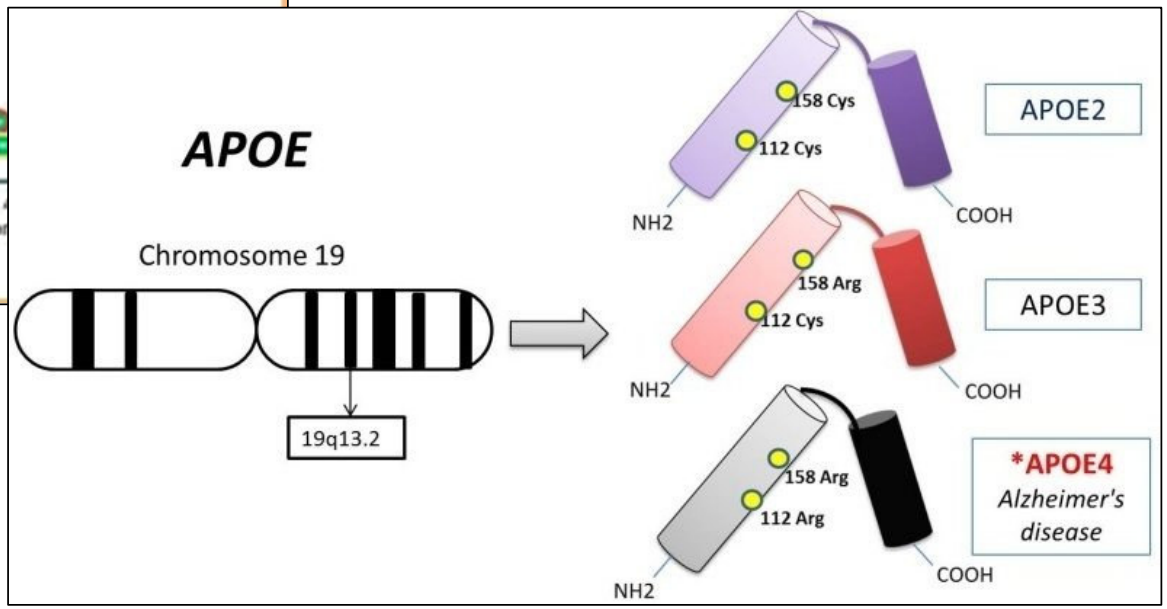
Variable	Cut-off	AUC	95% CI	Specificity	Sensitivity
Plasma p-tau217	0.273 pg/mL	0.941	0.89-0.99	93%	91%
Plasma p-tau181	1.275 pg/mL	0.913	0.85-0.98	83%	89%



Roveta et al, 2025;108:1961-1971

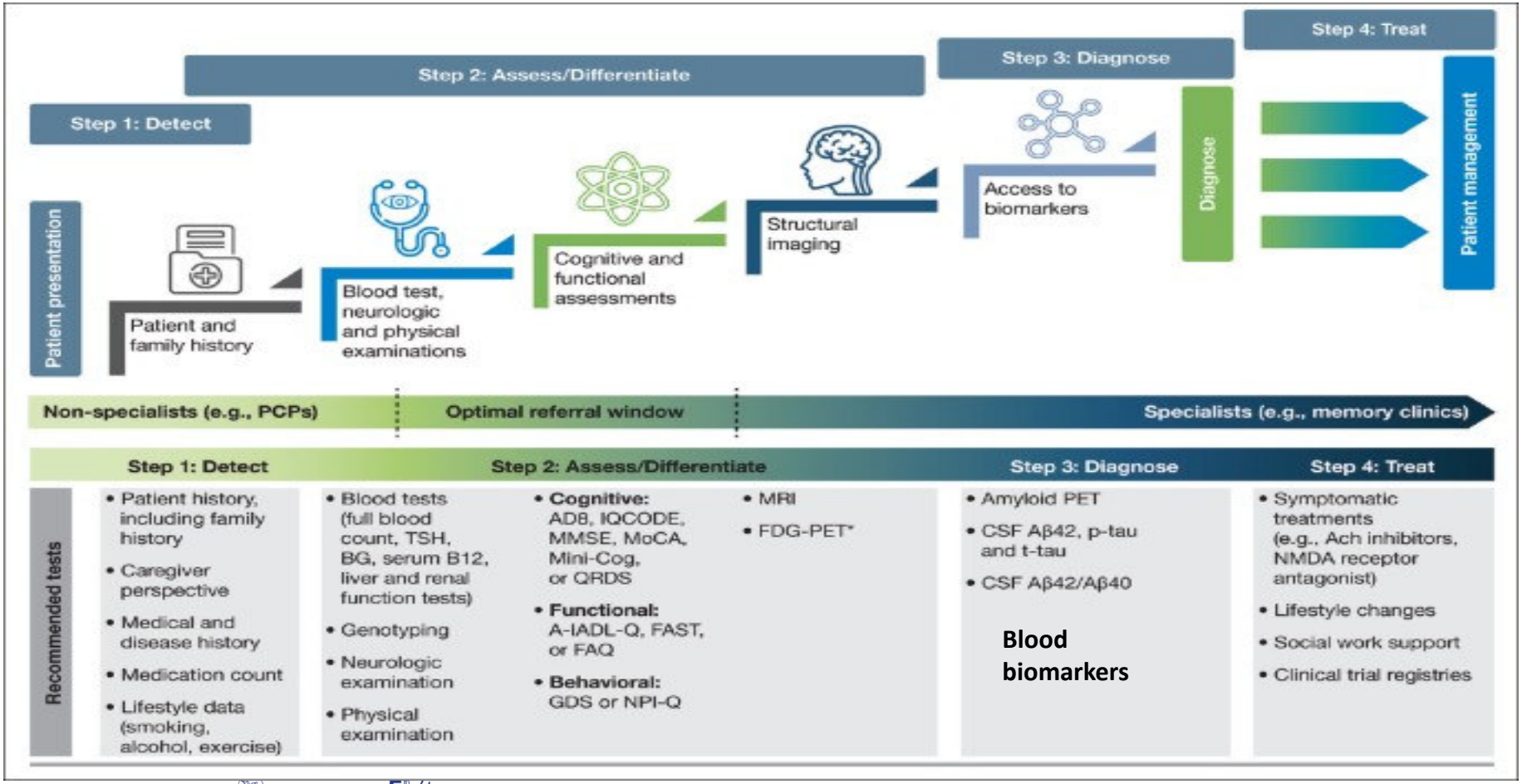
Genetic testing





APOE remains the most robust tic risk factor for AD susceptibility, with the ε4 allele demonstrating profound associations with accelerated symptom manifestation, enhanced disease trajectory, and modified therapeutic responsiveness.

The patient journey



*"Easily accessible blood biomarkers will lead to a new **diagnostic revolution** and bring about major changes in health-care systems worldwide"*

The Biological Diagnosis of AD

The *biological* diagnosis of Alzheimer's disease

• The NIA-AA 2011 approach to incorporating biomarkers into models of AD began with patients' clinical symptoms, which appear relatively late in the disease, and worked backward to relate symptoms to biomarker findings.

• The Research Framework (NIA-AA 2018) recommends a different approach where the neuropathologic changes detected by **biomarkers** define the **disease**.

• Defining AD by biomarkers indicative of neuropathologic change independent from clinical symptoms represents a **profound shift in thinking**.

• We need to distinguish Alzheimer's disease **unambiguously** from other neurocognitive disorders.

• The biological definition explicitly specifies the attributes that together classify Alzheimer's as a unique disease entity: **the intracerebral accumulation of abnormal Aβ and tau**.

ELSEVIER

Alzheimer's & Dementia 14 (2018) 535-562

Alzheimer's & Dementia

2018 National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework

NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease

Clifford R. Jack, Jr.,[a,*], David A. Bennett[b], Kaj Blennow[c], Maria C. Carrillo[d], Billy Dunn[e], Samantha Budd Haeberlein[f], David M. Holtzman[g], William Jagust[h], Frank Jessen[i], Jason Karlawish[j], Enchi Liu[k], Jose Luis Molinuevo[l], Thomas Montine[m], Creighton Phelps[n], Katherine P. Rankin[o], Christopher C. Rowe[p], Philip Scheltens[q], Eric Siemers[r], Heather M. Snyder[d], Reisa Sperling[s]

Contributors[t]**:** Cerise Elliott, Eliezer Masliah, Laurie Ryan, and Nina Silverberg

[a]*Department of Radiology, Mayo Clinic, Rochester, MN, USA*
[b]*Department of Neurological Sciences, Rush University, Chicago, IL, USA*
[c]*Department of Psychiatry and Neurochemistry, University of Gothenburg, Gothenburg, Sweden*
[d]*Medical & Scientific Relations, Alzheimer's Association, Chicago, IL, USA*
[e]*Office of Drug Evaluation, FDA, Silver Spring, MD, USA*
[f]*Biogen, Cambridge, MA, USA*
[g]*Department of Neurology, Washington University, St. Louis, MO, USA*
[h]*Department of Public Health and Neuroscience, University of California Berkeley, Berkeley, CA, USA*
[i]*Department of Psychiatry, University of Cologne, Medical Faculty, Cologne, Germany*
[j]*Department of Medicine, University of Pennsylvania, Philadelphia, PA, USA*
[k]*Prothena Biosciences, Inc., San Francisco, CA, USA*
[l]*BarcelonaBeta Brain Research Center, Pasqual Maragall Foundation and Hospital Clínic-IDIBAPS, Barcelona, Spain*
[m]*Department of Pathology, Stanford University, Standford, CA, USA*
[n]*Formerly at National Institute on Aging, Bethesda, MD, USA*
[o]*Department of Neurology, University of California San Francisco, San Francisco, CA, USA*
[p]*Department of Molecular Imaging, Austin Health, University of Melbourne, Melbourne, Australia*
[q]*Department of Neurology, VU University Medical Center, Amsterdam, Netherlands*
[r]*Formerly at Eli Lilly and Company, Indianapolis, IN, USA*
[s]*Department of Neurology, Brigham and Women's Hospital, Boston, MA, USA*

Abstract In 2011, the National Institute on Aging and Alzheimer's Association created separate diagnostic recommendations for the preclinical, mild cognitive impairment, and dementia stages of Alzheimer's disease. Scientific progress in the interim led to an initiative by the National Institute on Aging and Alzheimer's Association to update and unify the 2011 guidelines. This unifying update is labeled a "research framework" because its intended use is for observational and interventional research, not routine clinical care. In the National Institute on Aging and Alzheimer's Association Research Framework, Alzheimer's disease (AD) is defined by its underlying pathologic processes that can be documented by postmortem examination or *in vivo* by biomarkers. The diagnosis is not based on the clinical consequences of the disease (i.e., symptoms/signs) in this research framework, which shifts the definition of AD in living people from a syndromal to a biological construct. The research framework focuses on the diagnosis of AD with biomarkers in living persons. Biomarkers are grouped into those of β amyloid deposition, pathologic tau, and neurodegeneration [AT(N)]. This

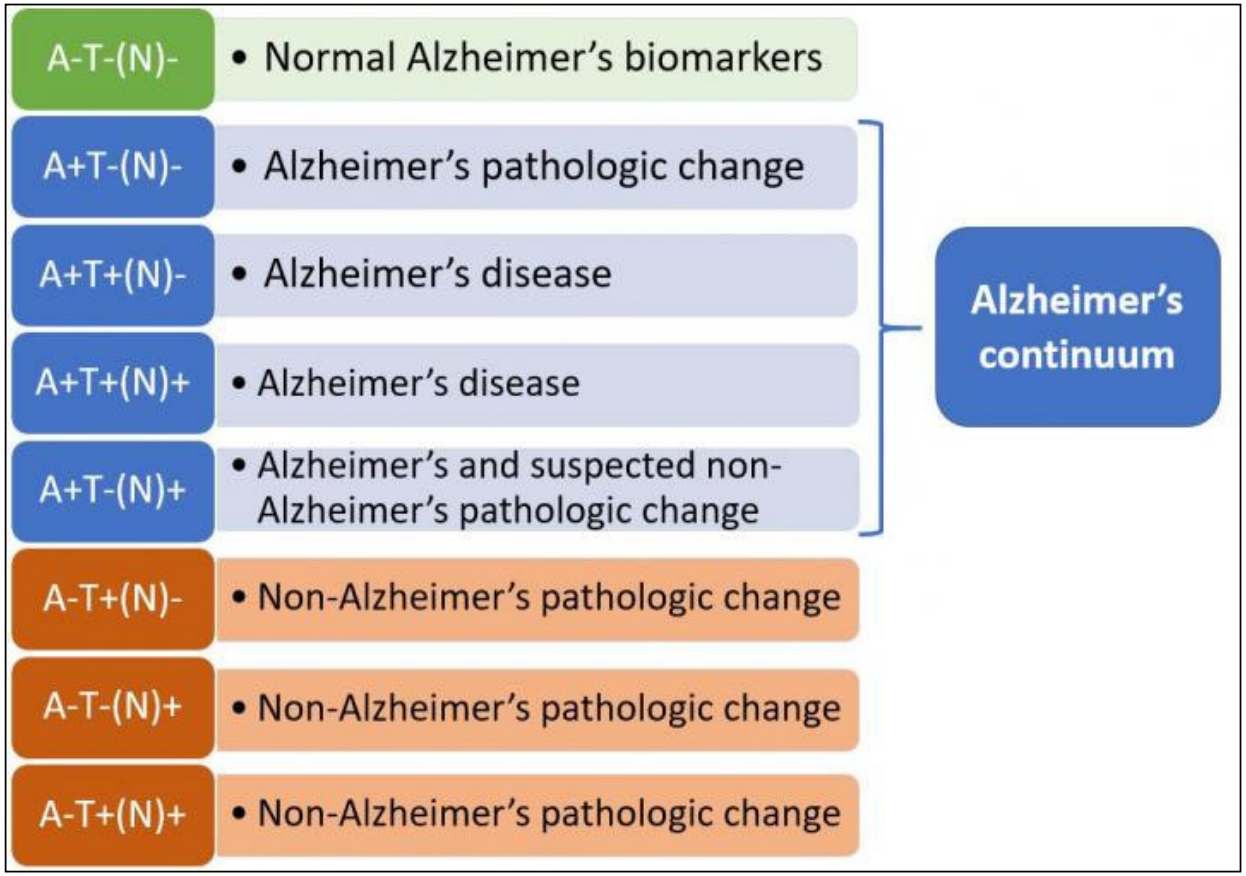
The authors' conflict of interest statements can be viewed online at https://doi.org/10.1016/j.jalz.2018.02.018.

[t]The listed National Institute on Aging program staff are acknowledged for their key contributions in leadership and scientific guidance on this project.

*Corresponding author. Tel.: 507-284-9087; Fax: 507-293-2235.
E-mail address: jack.clifford@mayo.edu

https://doi.org/10.1016/j.jalz.2018.02.018

The A/T/N system



Core AD biomarkers (or specific AD biomarkers)	
Core 1	
A	Aβ proteinopathy: $A\beta_{42}$ (CSF or plasma) and amyloid PET
T_1	Soluble (or secreted) phosphorylated tau proteinopathy: p-tau 181, p-tau 217, p-tau 231(CSF or plasma)
Core 2	
T_2	Insoluble (or aggregated) phosphorylated tau proteinopathy: p-tau205, MTBR-243 (CSF or plasma), and tau PET
Non-specific biomarkers involved in the pathogenesis of AD	
N	Neurodegeneration: NfL (CSF or plasma), anatomic MRI, and FDG PET
I	Astrocytic inflammation and reactivity: GFAP (CSF or plasma)

The revised criteria for Alzheimer's disease and early diagnosis of Alzheimer's disease

Jack et al., 2025

New treatment options

The treatment of Alzheimer’s disease

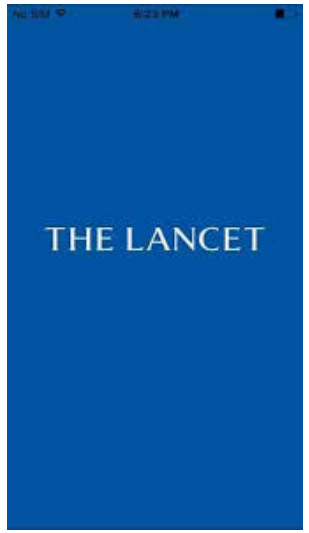
- Over the last two decades, the evidence on how to best treat the cognitive and non-cognitive symptoms of patients with Alzheimer's disease has increased. **Early recognition of Alzheimer's disease** is the first step toward providing patients with optimal therapy and the best opportunity for treatment response.

- Treatment prioritises addressing **social, somatic, and behavioural** problems before targeting cognitive symptoms.

- Pharmacological treatment for Alzheimer's disease primarily focuses on managing symptoms using **cholinesterase inhibitors** (donepezil, rivastigmine, galantamine) for mild-to-moderate stages and **NMDA antagonists** (memantine) for moderate-to-severe stages.

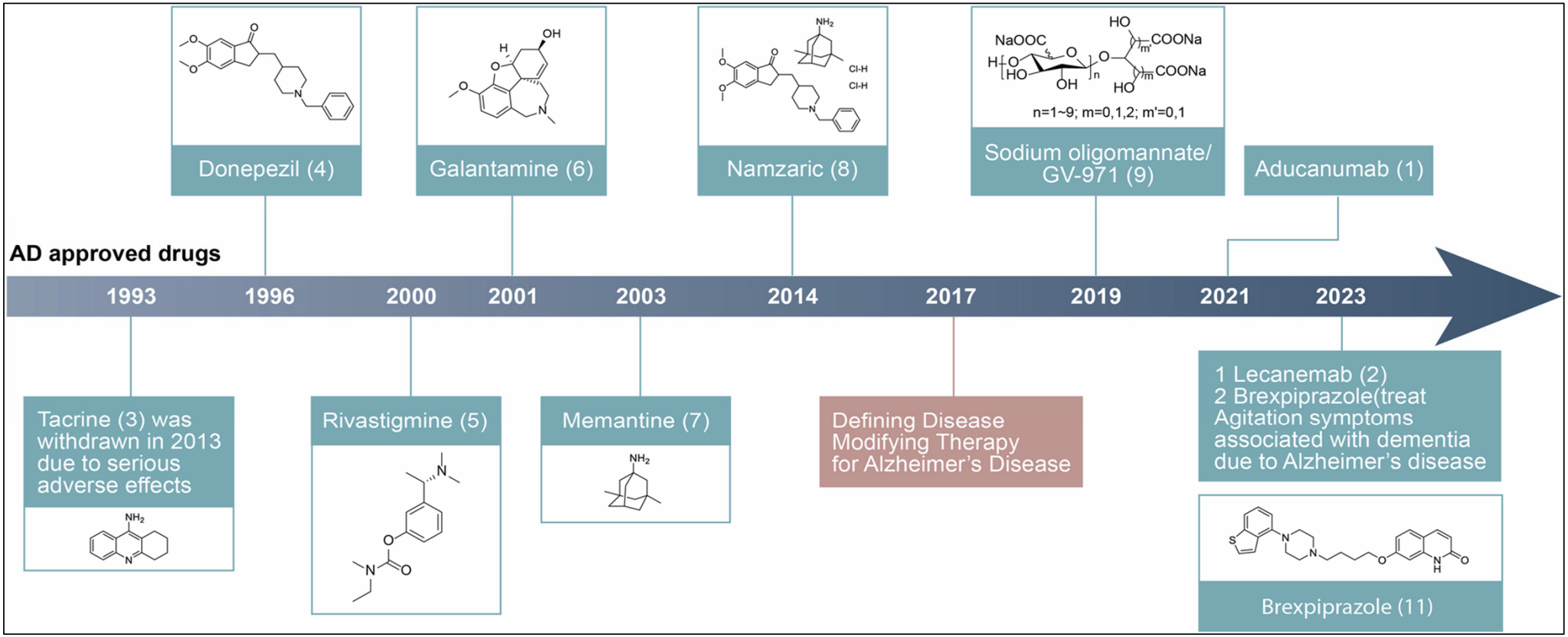
- Recent advances include FDA-approved **disease-modifying therapies**, such as lecanemab and donanemab, which target amyloid plaques to slow progression in early-stage patients.

- In theory, the benefit of symptomatic treatments and disease-modifiers should be additive, and the two types of drugs should be prescribed in association for maximal benefit–risk ratio.



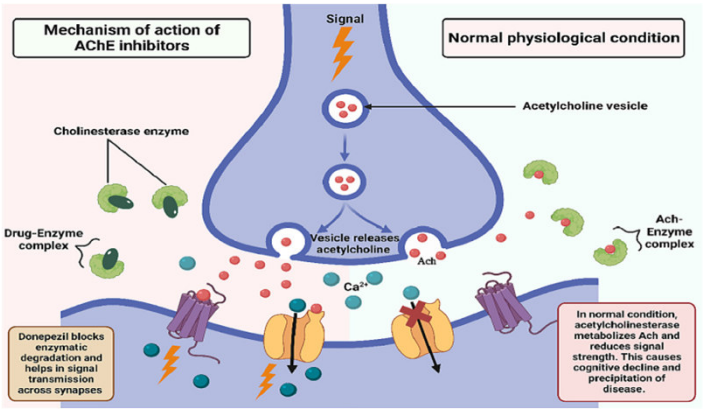
Frisoni et al. 2025

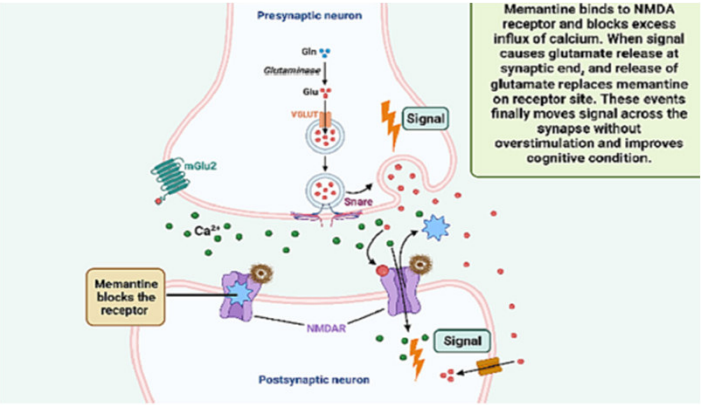
Pharmacological advances in AD



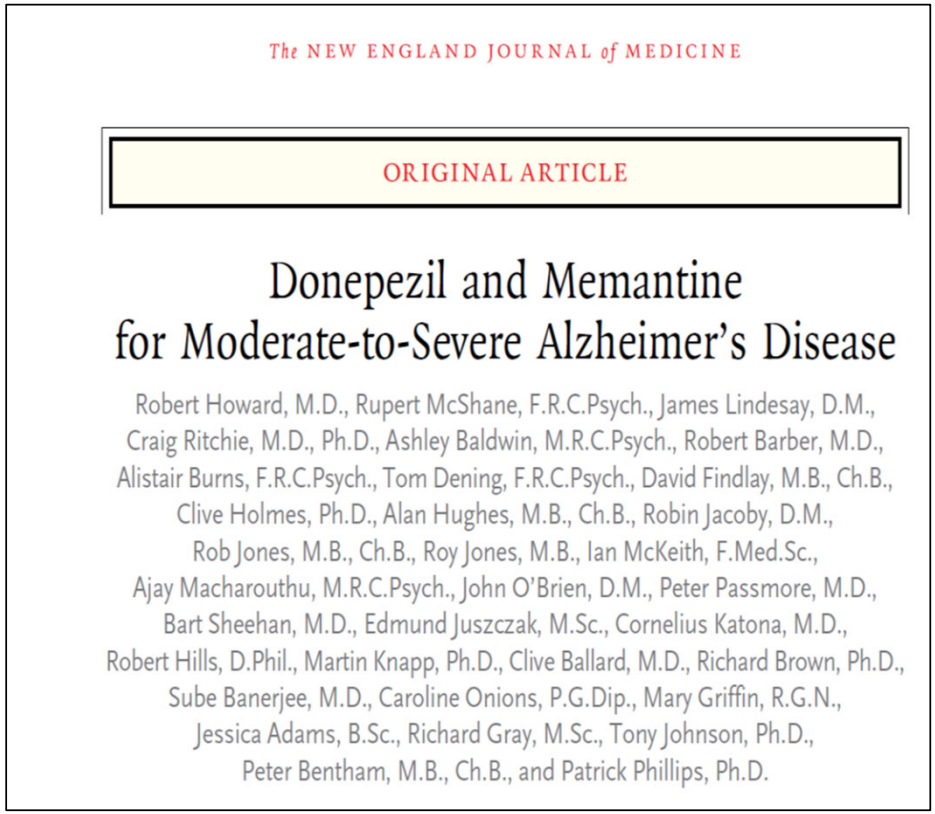
Symptomatic treatment for cognitive impairment

- Treatment with cholinesterase inhibitors or memantine showed a small beneficial effect on cognition in patients with Alzheimer's disease.
- A meta-analysis of patients with Alzheimer's disease treated with cholinesterase inhibitors or memantine suggested a reduction of progression to severe cognitive and functional impairment, all-cause mortality, and stroke.
- The prescription of cholinesterase inhibitors to patients with Alzheimer's disease has also been associated with a lower likelihood of antipsychotic prescription.
- These agents **should remain** part of the Alzheimer's disease pharmacotherapeutic armamentarium moving forward.





Combination therapy



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

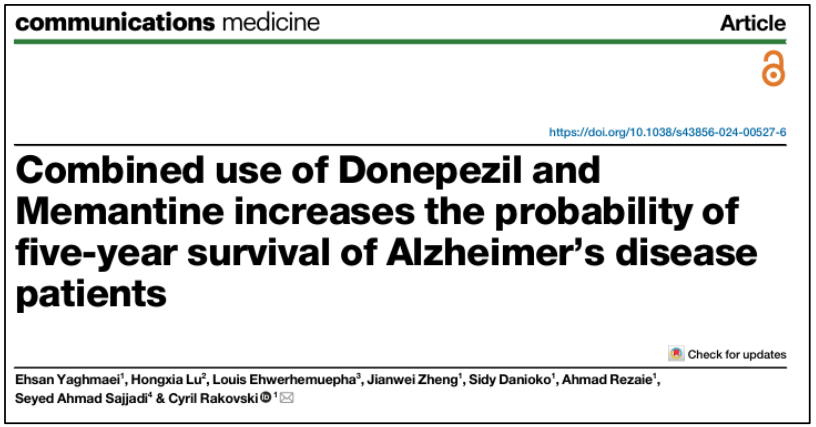
Donepezil and Memantine for Moderate-to-Severe Alzheimer's Disease

Robert Howard, M.D., Rupert McShane, F.R.C.Psych., James Lindesay, D.M., Craig Ritchie, M.D., Ph.D., Ashley Baldwin, M.R.C.Psych., Robert Barber, M.D., Alistair Burns, F.R.C.Psych., Tom Dening, F.R.C.Psych., David Findlay, M.B., Ch.B., Clive Holmes, Ph.D., Alan Hughes, M.B., Ch.B., Robin Jacoby, D.M., Rob Jones, M.B., Ch.B., Roy Jones, M.B., Ian McKeith, F.Med.Sc., Ajay Macharouthu, M.R.C.Psych., John O'Brien, D.M., Peter Passmore, M.D., Bart Sheehan, M.D., Edmund Juszczak, M.Sc., Cornelius Katona, M.D., Robert Hills, D.Phil., Martin Knapp, Ph.D., Clive Ballard, M.D., Richard Brown, Ph.D., Sube Banerjee, M.D., Caroline Onions, P.G.Dip., Mary Griffin, R.G.N., Jessica Adams, B.Sc., Richard Gray, M.Sc., Tony Johnson, Ph.D., Peter Bentham, M.B., Ch.B., and Patrick Phillips, Ph.D.

- We assigned 295 community-dwelling patients who had been treated with donepezil for at least 3 months and who had moderate or severe Alzheimer's disease (a score of 5 to 13 on the Standardized Mini-Mental State Examination to continue donepezil, discontinue donepezil, discontinue donepezil and start memantine, or continue donepezil and start memantine. Patients received the study treatment for 52 weeks.

- In patients with moderate or severe Alzheimer's disease, continued treatment with donepezil was associated with cognitive benefits that exceeded the minimum clinically important difference and with significant functional benefits over the course of 12 months.

Combined use and five-year survival



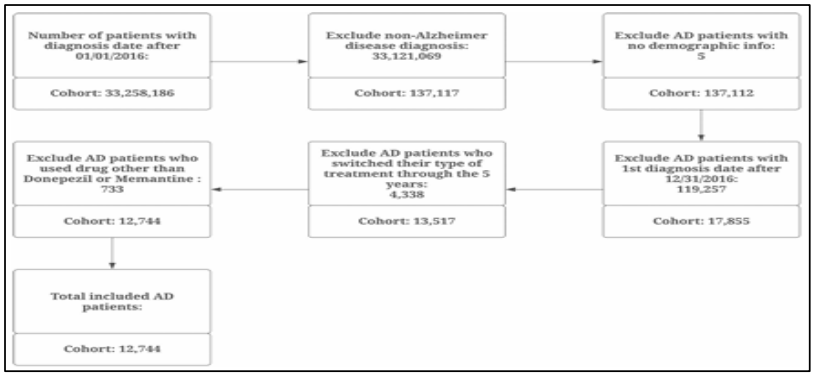
communications medicine — Article

https://doi.org/10.1038/s43856-024-00527-6

Combined use of Donepezil and Memantine increases the probability of five-year survival of Alzheimer's disease patients

Check for updates

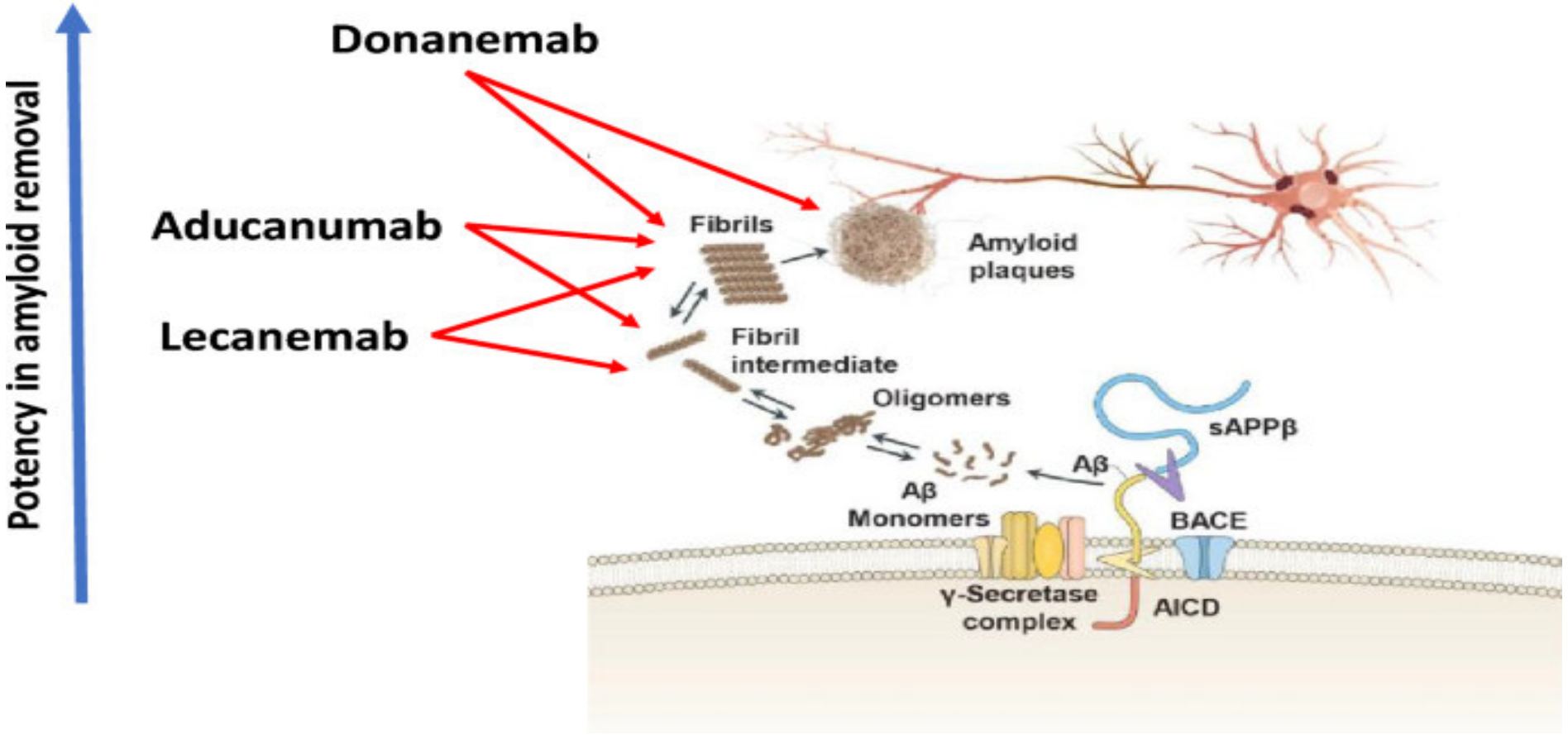
Ehsan Yaghmaei[1], Hongxia Lu[2], Louis Ehwerhemuepha[3], Jianwei Zheng[1], Sidy Danioko[1], Ahmad Rezaie[1], Seyed Ahmad Sajjadi[4] & Cyril Rakovski[1]



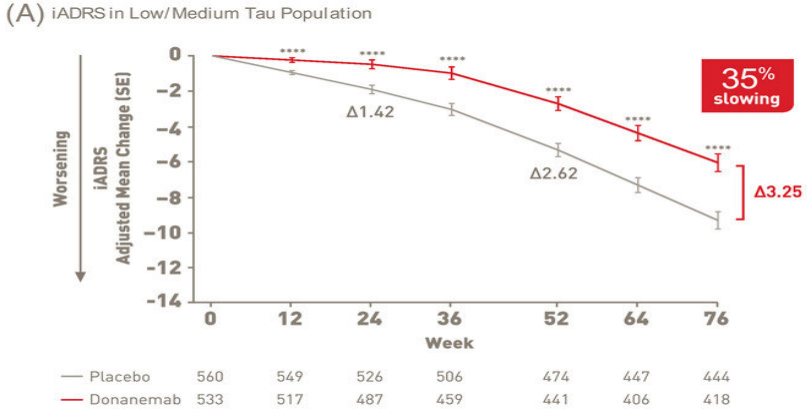
- We conducted a comprehensive causal inference study using one of the largest high-quality medical databases, the Oracle Electronic Health Records Real-World Data. Our work was focused on the estimation of the effects of the two common Alzheimer's disease drugs, Donepezil and Memantine, and their combined use on the **five-year survival** since initial diagnosis of AD patients.
- Here, we show that the combined use of Donepezil and Memantine significantly elevates the probability of five-year survival. In particular, their combined use increases the probability of five-year survival by 0.050 (0.021, 0.078) (6.4%), 0.049 (0.012, 0.085), (6.3%), 0.065 (0.035, 0.095) (8.3%) compared to no drug treatment, the Memantine monotherapy, and the Donepezil monotherapy respectively. We also identify a significant beneficial **additive drug-drug interaction effect** between Donepezil and Memantine of 0.064 (0.030, 0.098).

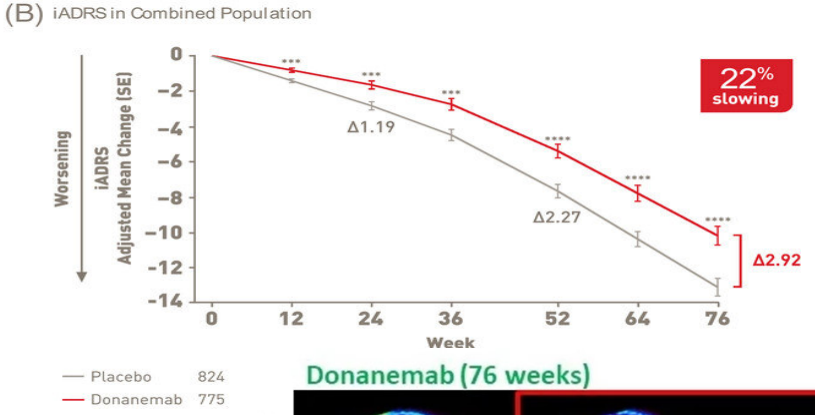
FDA and EMA approved anti-β amyloid monoclonal antibodies

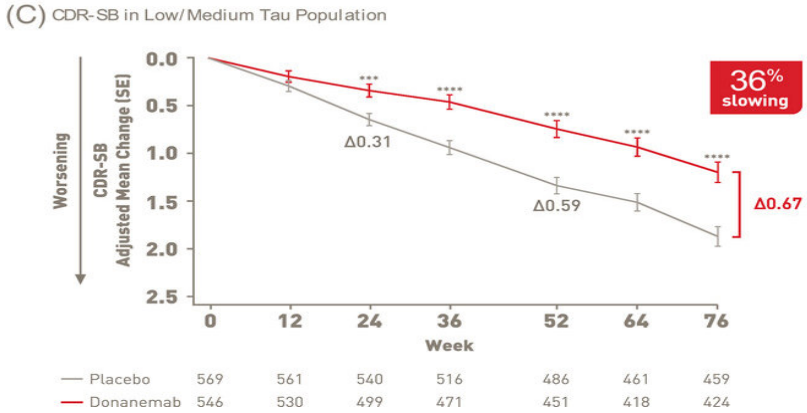
Molecular Targets of Anti-Amyloid Monoclonal Antibodies

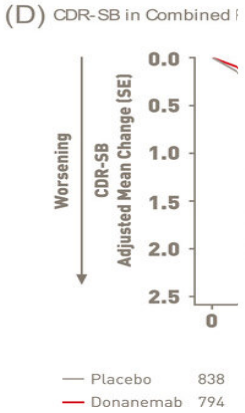


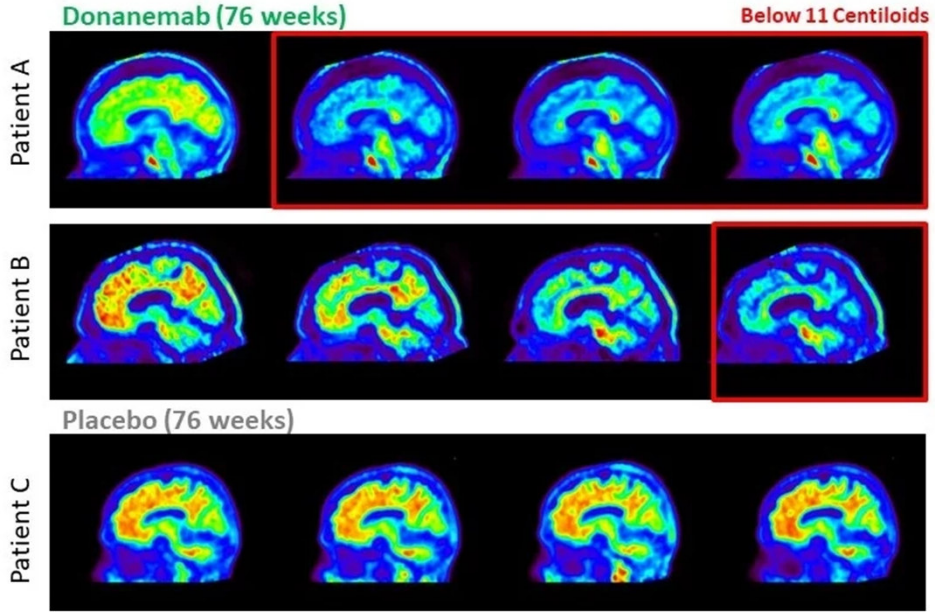
Donanemab for Alzheimer's disease











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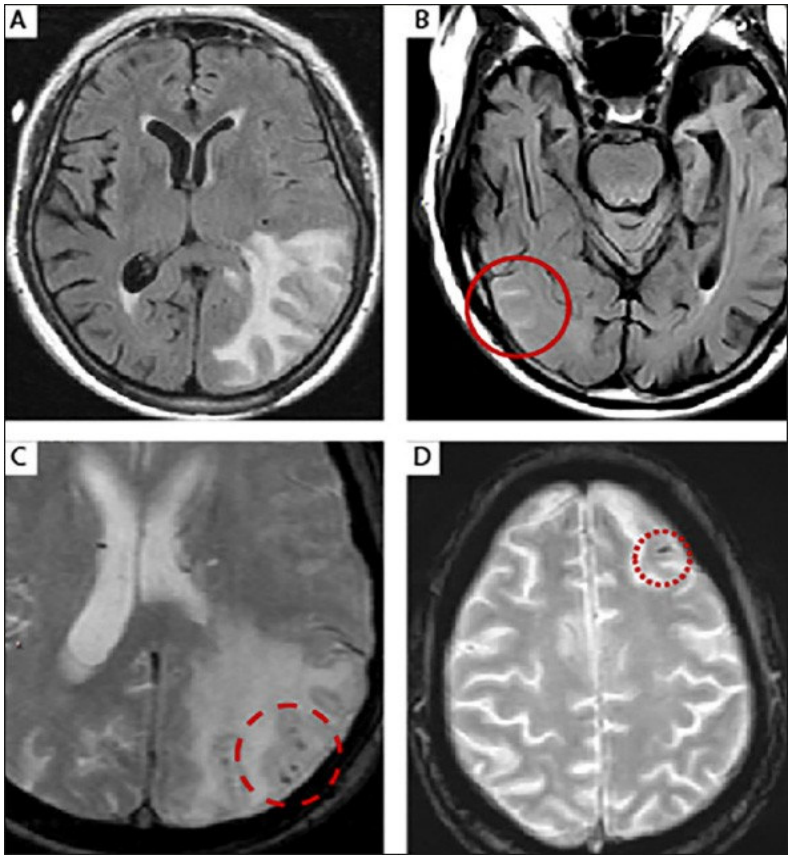
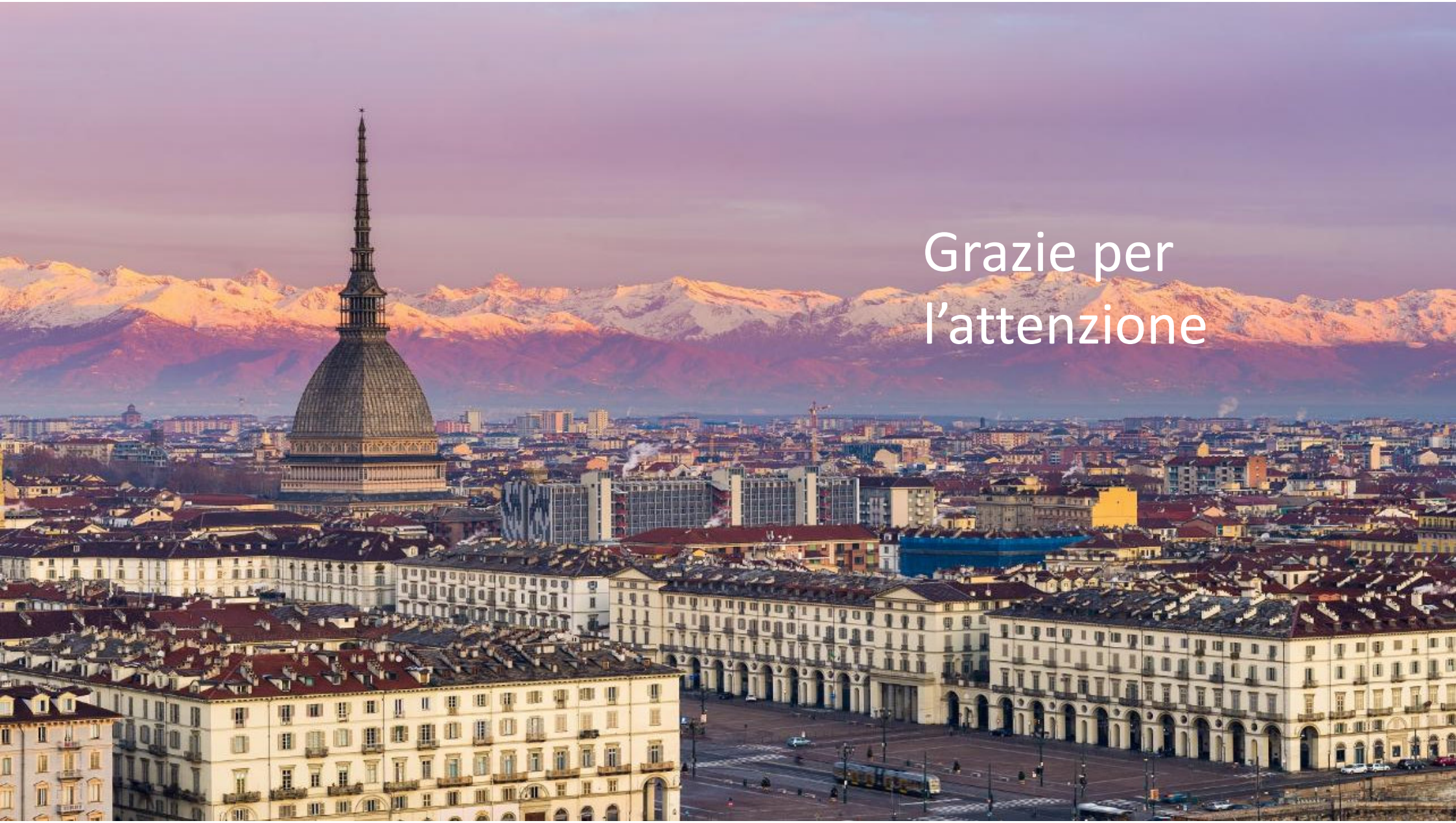
Anti-Amyloid therapy: the side-effects



- ARIA-E is identified as vasogenic edema in the brain parenchyma or sulcal effusions in the leptomeninges/ sulci.
- ARIA-H is hemosiderin deposits presenting as microhemorrhages or superficial siderosis.
- The debate on the clinical meaningfulness of the effect of anti-β amyloid monoclonal antibodies, their cost–benefit ratio, the appropriateness of resource allocation, and the benefit to the quality of life of society at large will engage the community of Alzheimer's disease experts and decision makers for years to come.

Take Home messages

- The new diagnostic criteria define AD biologically, by neuropathologic change or biomarkers, and treats cognitive impairment as a symptom/sign of the disease rather than the definition of the disease.
- Structured non-pharmacological programmes are being used for the management of BPSDs along with better tolerated drugs than those used previously.
- Symptomatic drugs for cognitive impairment, although with limited efficacy, have forced health-care systems to organise dedicated expert care networks, thus facilitating access to diagnosis and care.
- Anti-β amyloid monoclonal antibody treatment for Alzheimer's disease represents the latest tool and promise long-term improvements of patients' quality of life.


Grazie per
l’attenzione

Progressive Stages of Alzheimer's Disease

- No symptoms.
- Changes in the brain related to Alzheimer's begin.

- Very mild symptoms.
- Memory lapses.
- Changes in cognitive functions may be measurable.

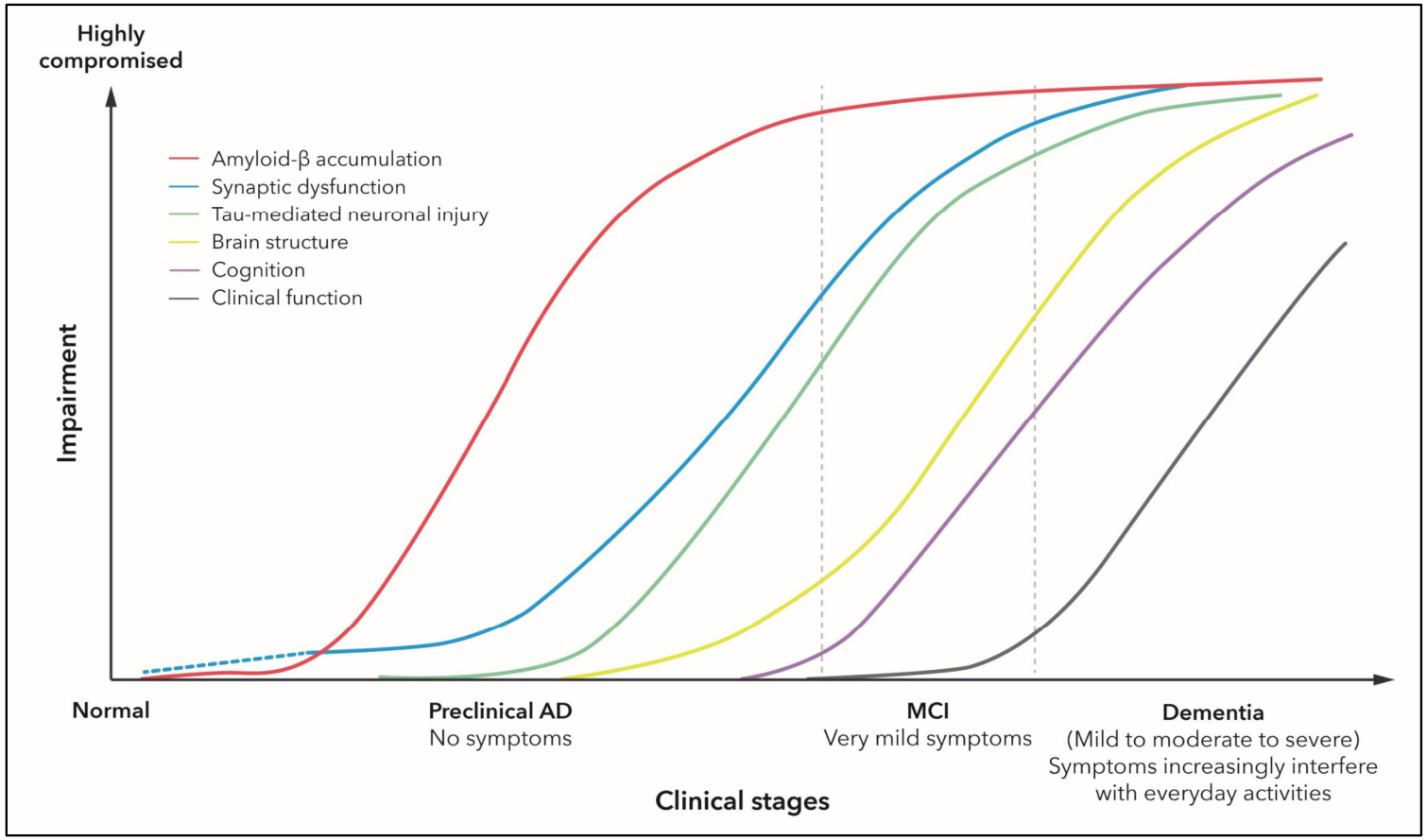
- Memory loss becomes more noticeable.
- Difficulty in organizing and expressing thoughts.
- Getting lost or misplacing belongings.

- Greater memory loss and confusion.
- Significant assistance required for daily activities.
- Changes in sleep patterns, personality, and behavior.

- Nearly total memory loss.
- Loss of ability to communicate.
- Need for full-time assistance.

MCI: Mild Cognitive Impairment
AD: Alzheimer's Disease

New landscape in the therapy of Alzheimer's disease



Early diagnosis of Alzheimer’s disease is a process involving recognizing of subtle cognitive and behavioral changes, and then using tests such as blood tests, genetic tests and brain scans to confirm the diagnosis and monitor the disease's progression.

Frisoni et al., 2025