Biomarcatori e terapia della malattia di Alzheimer

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- Terminologia

Alzheimer's Association Workgroup 2024 Revised Criteria
An integrated biological and clinical staging scheme with six clinical stages (graphically represented in left-to-right columns) and 4 biological stages (top-to-bottom rows). Biological Alzheimer's disease stage and clinical severity are related, but do not travel in lockstep. The typical or average relationship between biology and symptoms can be envisioned as moving along an upper left to lower right diagonal, following the steps of the amyloid cascade (from A−T− to A+T− to A+T+ in the medial temporal lobe, A+T+ with moderate neocortical burden, A+T+ with high neocortical burden. A=β-amyloid, and T=tau pathology). The criteria are conceptual and await validation.

Mild cognitive impairment (MCI)
A syndrome referring to acquired and progressive cognitive impairment. The person may be slower and less efficient but can still function independently. In older age, it is commonly associated with neuropathology (eg, Alzheimer's disease), but it could be due to anything, including physical and psychiatric conditions. Mild neurocognitive disorder is the synonym to MCI in DSM-5.

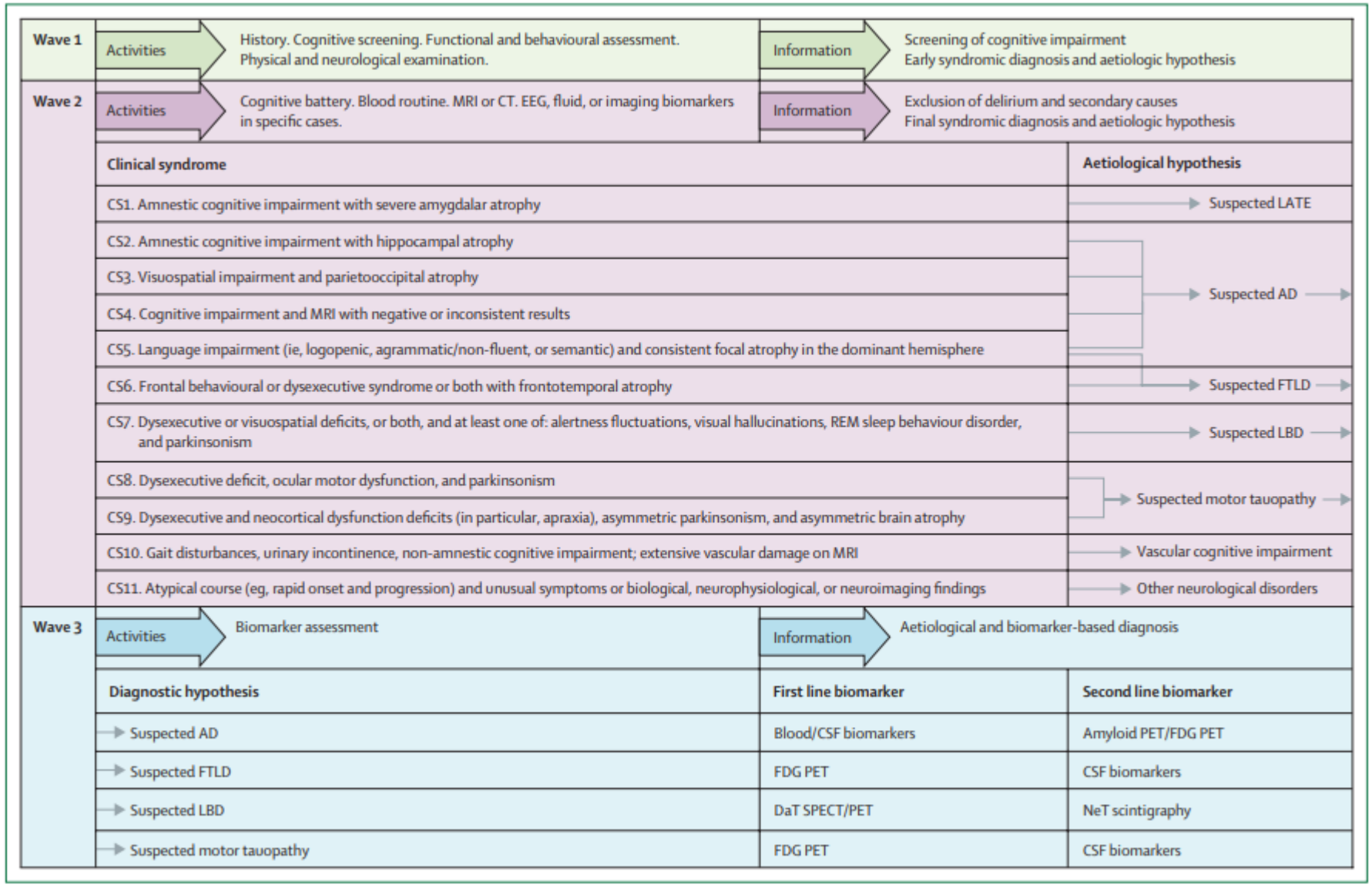
Alzheimer's disease
There is no unanimity on the epistemological definition of Alzheimer's disease, reflected in sets of different diagnostic criteria (Alzheimer's Association Workgroup 2024 Revised Criteria and International Working Group 2024 diagnostic criteria). Disagreements extend to the existence of presymptomatic or preclinical Alzheimer's disease and the interpretation of Alzheimer's disease biomarker positivity in the absence of objective cognitive impairment or deterioration. However, for all practical purposes in clinical practice, Alzheimer's disease can be operationalised as cognitive impairment due to Alzheimer's disease pathology, evolving in stages of increasing cognitive and functional severity.

Cognitive disorders
All conditions that can cause cognitive impairment. These include neurodegenerative conditions such as Alzheimer's disease, but also vascular disease, traumatic brain injury, substance use, infections, disturbances of cerebrospinal fluid dynamics, psychiatric conditions, secondary or reversible cognitive disorders, and more. DSM-5 refers to "neurocognitive disorders" to differentiate the cognitive impairment of psychoses. We believe that the "neuro" prefix does not add meaningful information as, by definition, the brain is the organ responsible for all cognitive disorders.

Subjective cognitive decline (SCD)
A clinical construct referring to complaints of progressive cognitive problems with formal cognitive testing revealing unimpaired performance. SCD plus refers to certain features of SCD, which increase the likelihood that this condition is related to Alzheimer's disease pathology and that there is a higher risk of objective cognitive decline in the future. The currently proposed SCD plus criteria are: subjective decline in memory irrespective of function in other cognitive domains, onset of SCD within the past 5 years, onset of SCD at 60 years and older, concern (worry) associated with SCD, persistence of SCD over time, seeking of medical help, and confirmation of cognitive decline by an observer.

Worried well
Individuals who do not experience SCD themselves but are concerned about cognitive deterioration or Alzheimer's disease in the future. The label is controversial in the literature as it might lead to genuine concerns or pathology being dismissed.

Lancet 2025; 406: 1389–407 Published Online September 22, 2025 https://doi.org/10.1016/ S0140-6736(25)01294-2



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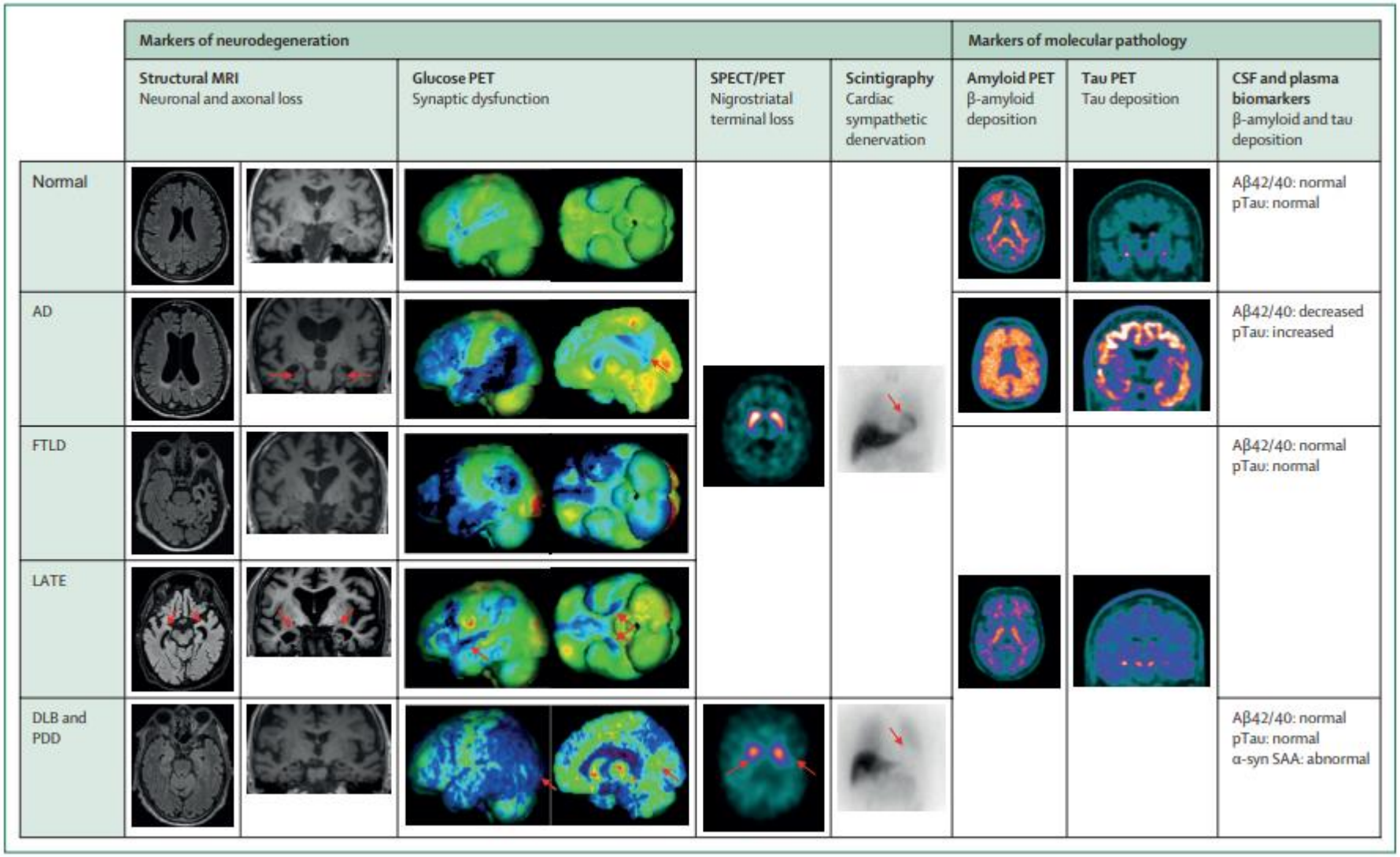

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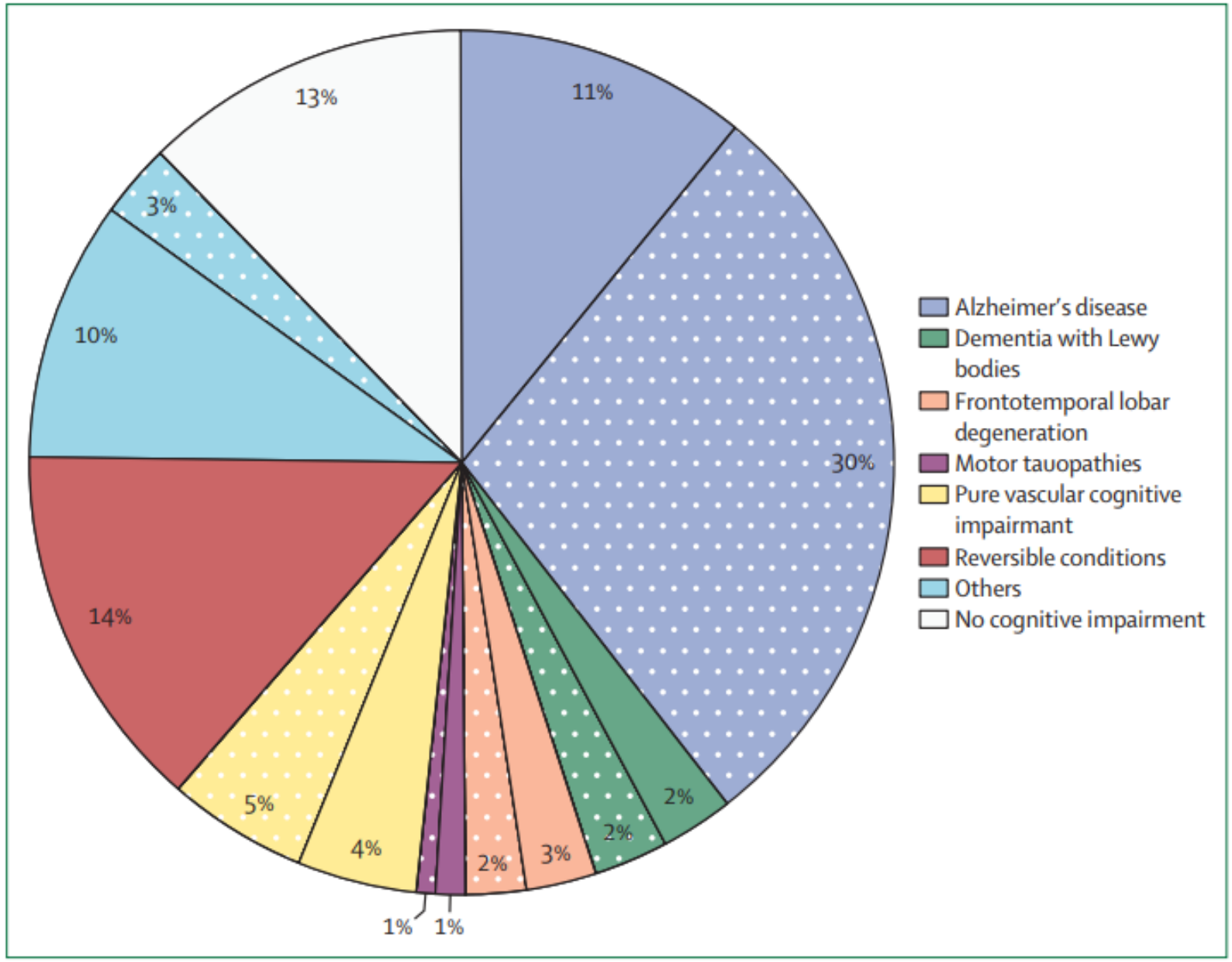
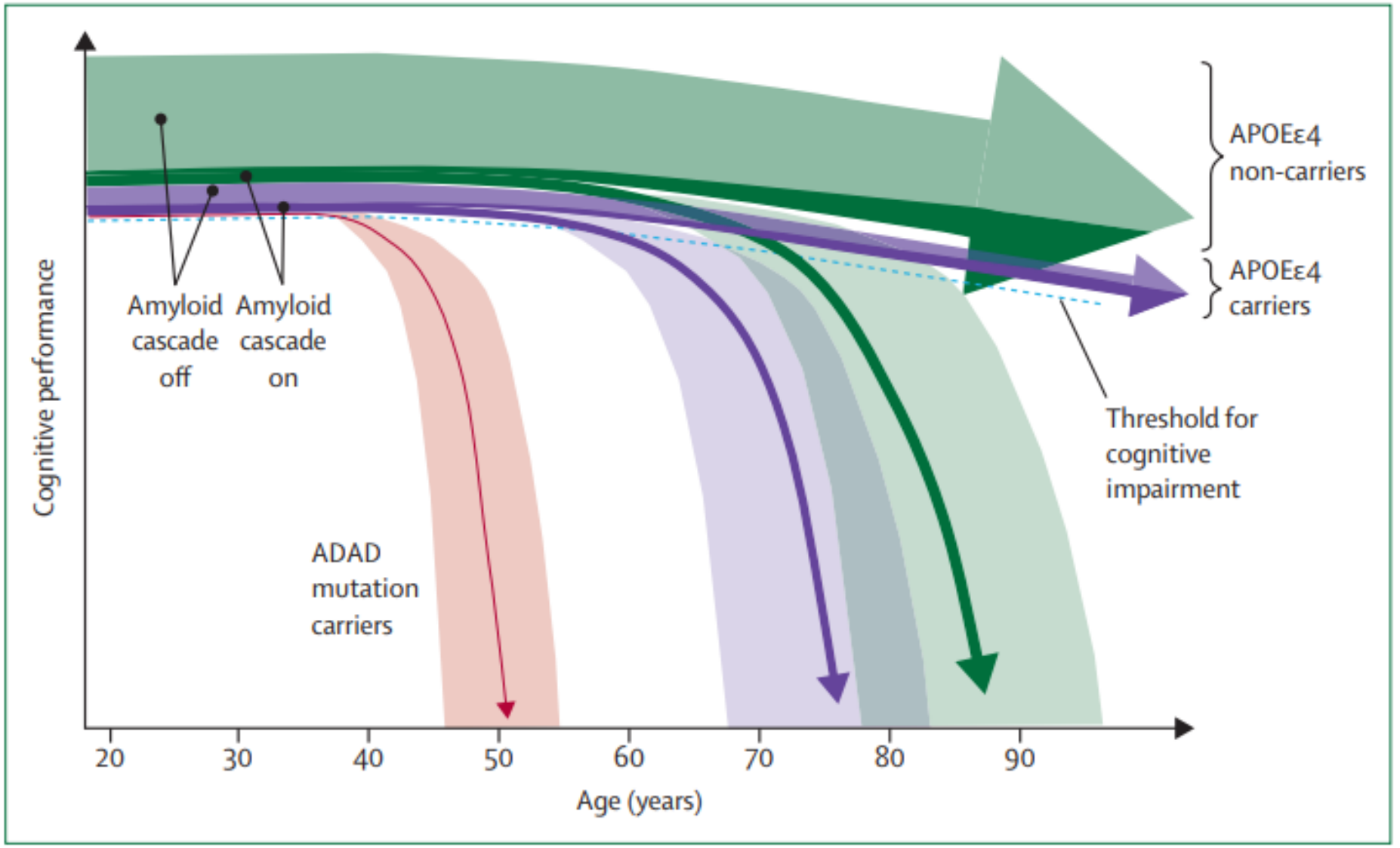


Lancet 2025; 406: 1389–407 Published Online September 22, 2025 https://doi.org/10.1016/ S0140-6736(25)01294-2

- Rischio genetico e proteomica



- Lancet 2025; 406: 1389–407 Published Online September 22, 2025 https://doi.org/10.1016/ S0140-6736(25)01294-2

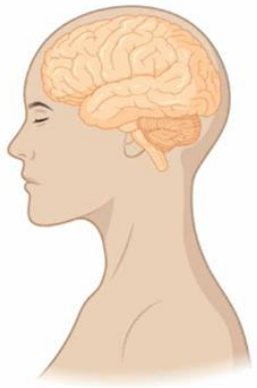
INTERAZIONE TRA INVECCHIAMENTO FISIOLOGICO E ALZHEIMER

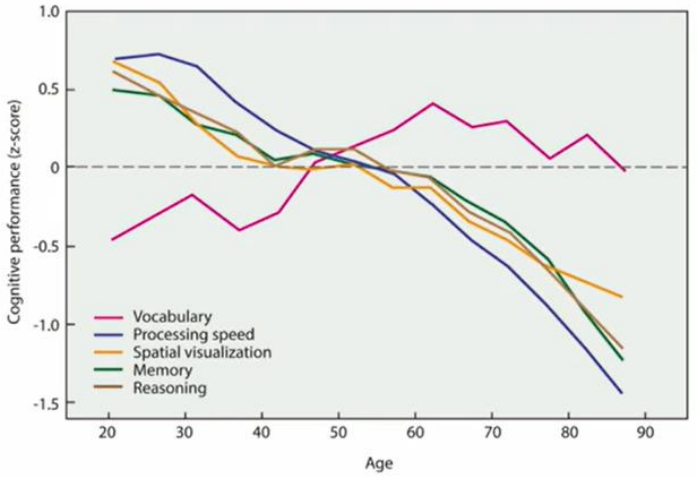
- L'invecchiamento cerebrale fisiologico è caratterizzato da declini graduali nella **plasticità sinaptica**, riduzione dell'efficacia dei circuiti neuronali (ad esempio nell'ippocampo) e accumulo di **danno ossidativo e senescenza cellulare**, che generano un ambiente a bassa resilienza nei tessuti cerebrali .

- Parallelamente, si verifica un fenomeno di **"inflammaging"**: attivazione cronica, sterile e subclinica del sistema immunitario (microglia e inflammasomi), che favorisce la secrezione di citochine pro-infiammatorie (IL-1β, IL-6, TNF-α), danneggiando la neuroplasticità e aumentando la vulnerabilità alla neurodegenerazione

- Questi processi aumentano la suscettibilità sinaptica, specie in regioni critiche per la memoria, dove Aβ e tau operano sinergicamente per indurre **disfunzione sinaptica**, accelerare la perdita cognitiva e innescare meccanismi neurodegenerativi tipici dell'Alzheimer

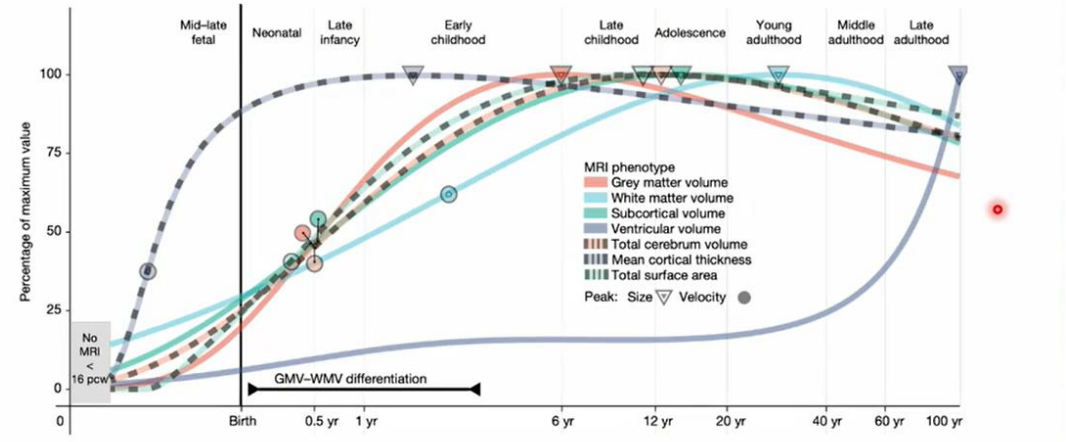
The human brain deteriorates as we age





W. Eikelenboom et al., 2020

Structural decline of the human brain

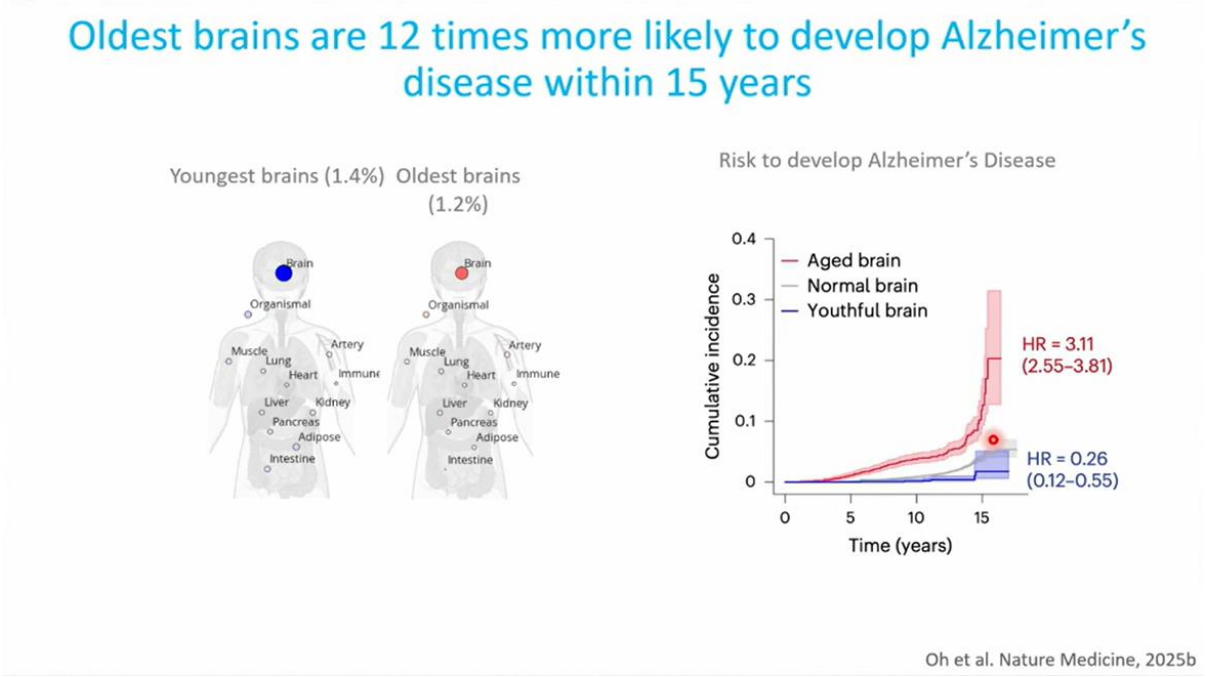


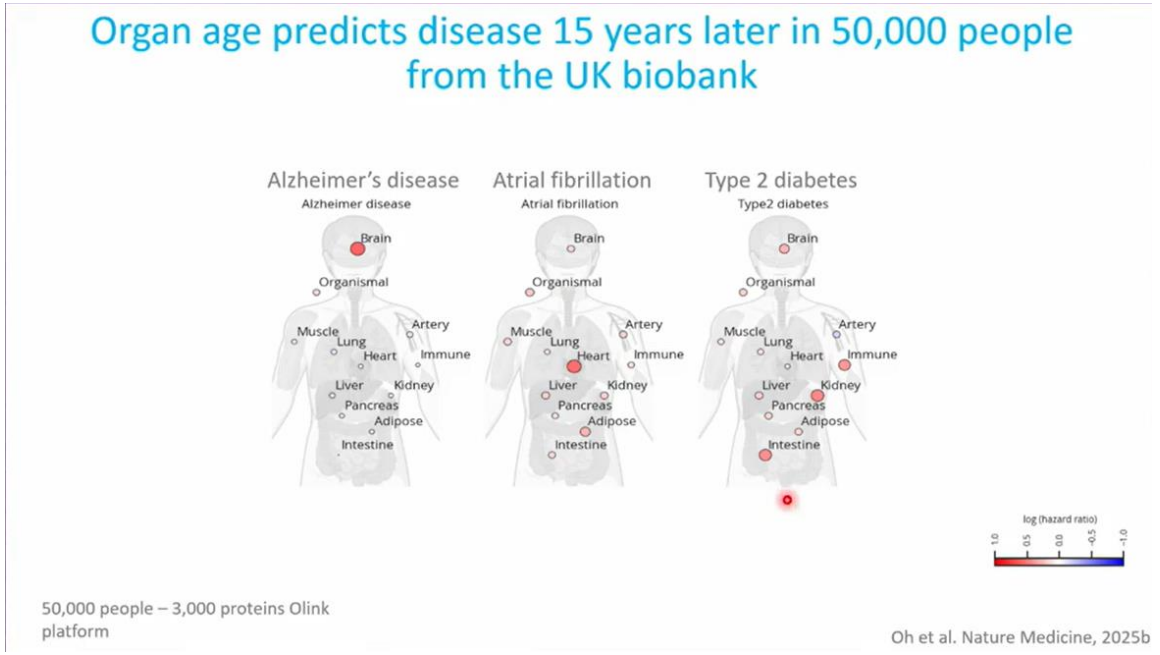
Data from >100,000 individuals and MRI brain scans

Bethlehem et al., Nature 2022

BIOBANCHE E TRAIETTORIE LONGITUDINALI: DAL PLASMA AL LIQUOR PER VALUTARE L'INVECCHIAMENTO D'ORGANO

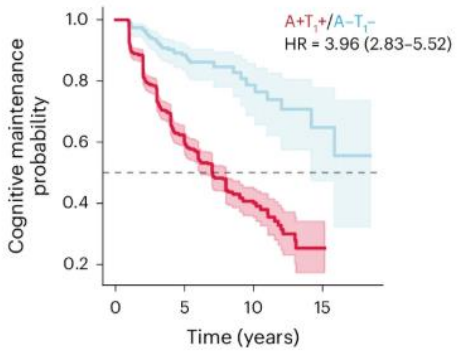
- Biobanche estese come ADNI, BioFINDER o altri studi di proteomica su larga scala consentono il tracciamento di biomarcatori nel sangue e nel liquor nel corso degli anni. Questo permette di definire curve normative d'invecchiamento per organi diversi — cervello, cuore, reni, sistema vascolare — mediante proteomiche plasmatiche e CSF.
- Per esempio, l'invecchiamento cardiaco accelerato comporta un rischio 250 % maggiore di insufficienza cardiaca, e che il "brain aging" predice la progressione dell'Alzheimer tanto quanto i biomarcatori p-tau181 plasmatici. Allo stesso modo, il monitoraggio di biomarcatori in questi fluidi consente di posizionare ogni paziente lungo la traiettoria di invecchiamento prevista per il suo organo specifico — individuando così chi devia prematuramente dalla norma e potrebbe beneficiare di interventi personalizzati.

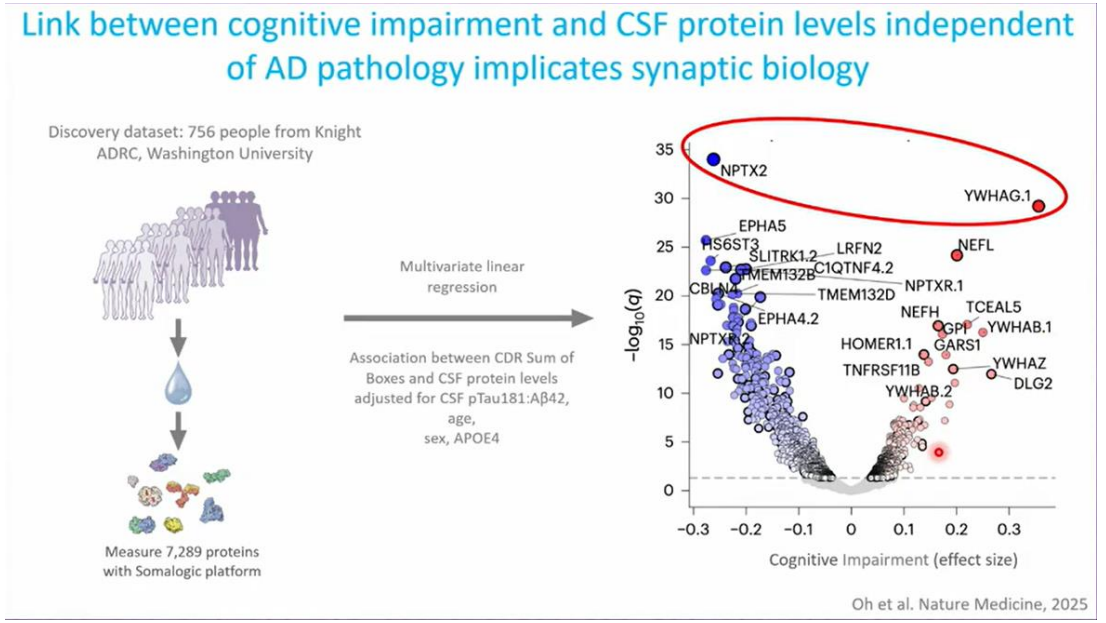


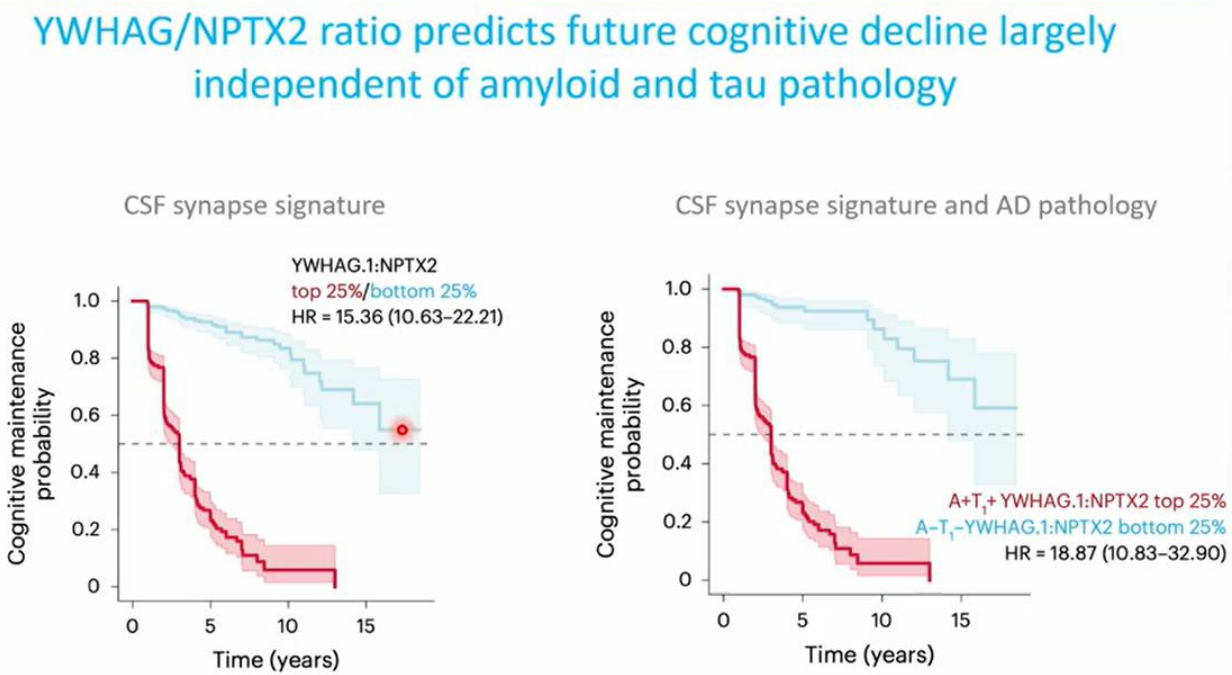


YWHAG : NPTX2 – BIOMARCATORI SINAPTICI NELL'INVECCHIAMENTO E ALZHEIMER

- Il rapporto tra i livelli di **YWHAG** e **NPTX2** nel liquor cerebrospinale si rivela un indicatore eccezionale della salute sinaptica e dell'evoluzione cognitiva. Questo indice aumenta progressivamente con l'età — già a partire dai 20–30 anni — e accelera drasticamente fino a 20–25 anni prima dei sintomi clinici nei portatori di mutazioni AD autosomiche dominanti.
- La ratio YWHAG:NPTX2 è in grado di spiegare fino al **27 % della variabilità** del decadimento cognitivo, superando altri biomarcatori consolidati come p-tau/Aβ, tau-PET, NfL, neurogranin, e GAP-43
- Inoltre, un aumento di una deviazione standard di YWHAG:NPTX2 è associato a un **rischio triplo di conversione da cognitivamente normali a MCI**, e più che doppio (HR ≈ 2,2) di evoluzione da MCI a demenza nel corso di 15 anni.
- Il fatto che tale rapporto sia associato al declino prima ancora dell'emergere dei depositi amiloide-tau lo rende un potente predittore di resilienza cognitiva e un possibile strumento per identificare precocemente chi è a rischio







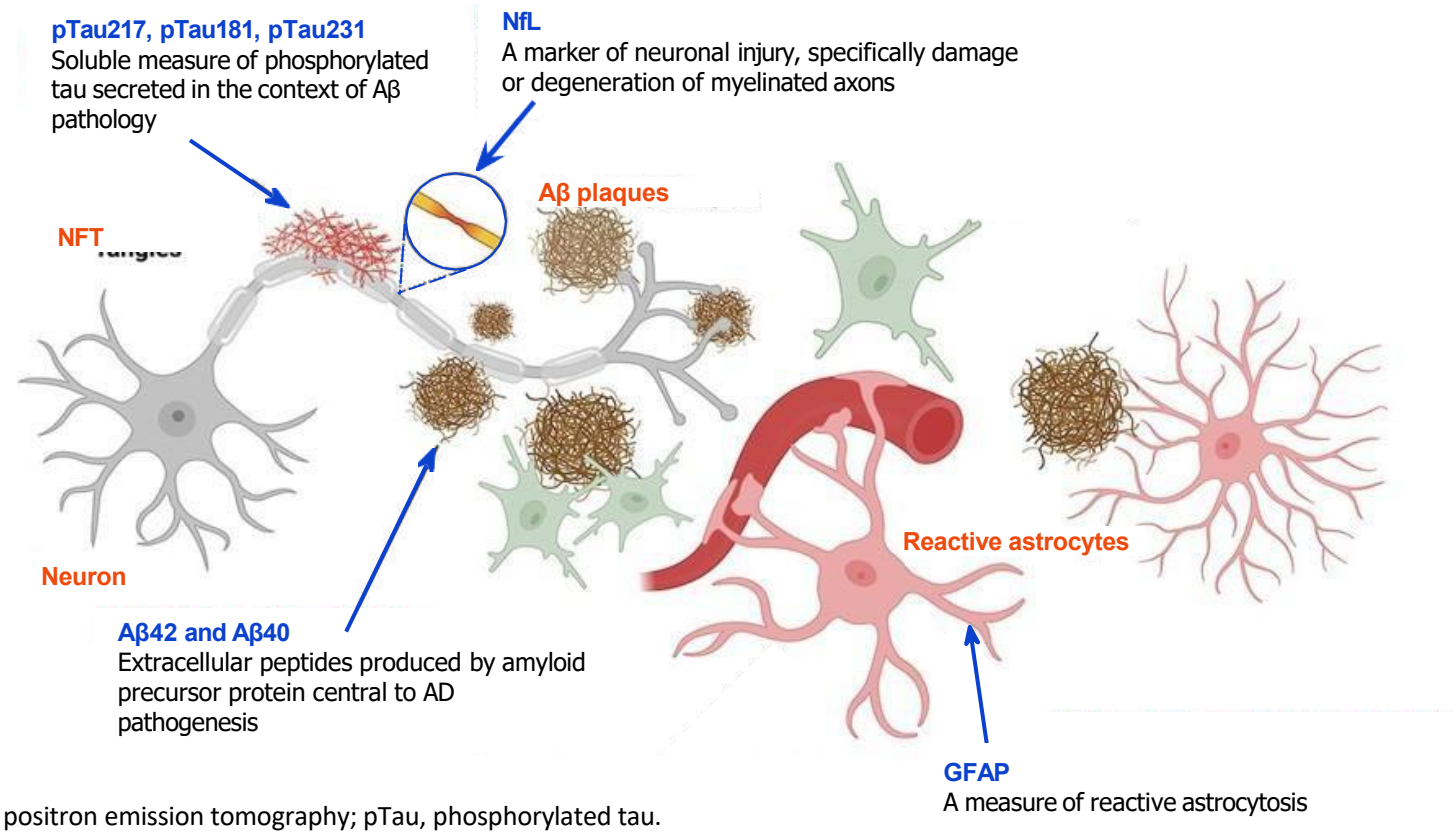
- Biomarcatori plasmatici

AD pathology comprises both amyloid and tau pathology

The two prominent neuropathological features of AD are extracellular aggregated Aβ and intracellular aggregated tau in the form of NFTs

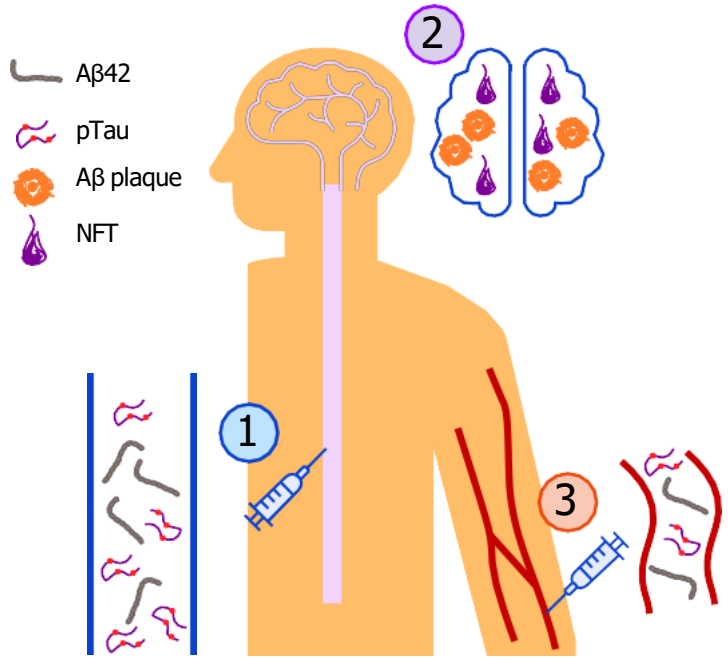
The amyloid, tau and neurodegenerative pathological processes that occur in AD can be detected using:

- CSF biomarkers
- PET imaging biomarkers
- Plasma biomarkers
- Structural MRI



MRI, magnetic resonance imaging; NFT, neurofibrillary tangle; PET, positron emission tomography; pTau, phosphorylated tau.
Dark HE, et al. Arch Clin Neuropsycho 2024;39:313–24.

Biomarkers can be used to detect changes indicative of amyloid and tau pathology



	Pathology	Biomarker[1–3]	In AD[1–3]
1. CSF	Amyloid	Aβ42, Aβ42/40 ratio pTau181, pTau181/Aβ42 ratio, tTau/Aβ42 ratio	↓ ↑
	Tau	pTau181, pTau217, pTau231	↑
2. PET	Amyloid	Tracer binding to Aβ plaques	↑
	Tau	Tracer binding to NFTs	↑
3. Plasma	Amyloid	Aβ42, Aβ42/40 concentration	↓
	Tau	pTau181, pTau217, pTau231, pTau205, MTBR-tau243	↑

MTBR-tau243, microtubule-binding region (MTBR) of tau containing the residue 243

1. Iaccarino L, et al. J Prev Alzheimers Dis 2023;10:426–42; 2. Ossenkoppele R, et al. Lancet Neurol 2022;21:726–34; 3. Fagan AM, et al. Arch Neurol 2007;64:343–9.

Plasma biomarkers are an alternative to CSF and PET for detection of amyloid pathology

Plasma biomarkers are a **less invasive** approach with **greater patient preference** than CSF and PET testing, plasma biomarkers are also more **cost-effective** and widely available globally[1]

Plasma biomarkers are **more scalable** than CSF and PET, and can meet the increasing need for testing in both **primary** and **secondary care**[2]

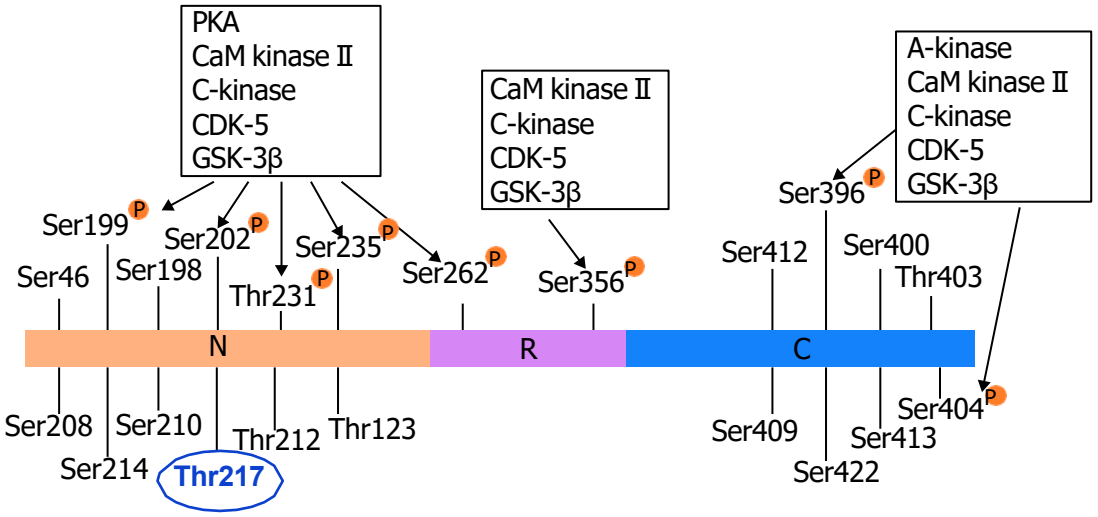
In the future, **plasma biomarkers** have the potential to be used as a **triage** test before subsequent confirmatory testing (amyloid-PET or CSF biomarkers), as a **confirmatory** test, or for monitoring disease and/or treatment progression[1,2]

1. Hampel H, et al. Nat Aging 2022;2:692–703; 2. Schindler SE, et al. Nat Rev Neurol 2024;20:426–39.

pTau217 is a specific plasma biomarker for AD pathology

pTau217 is tau protein that has been **phosphorylated at threonine 217**[1]

Tau phosphorylation sites and associated kinases[2]



pTau217 is a **promising plasma biomarker for AD**, as demonstrated by:

- High diagnostic accuracy (AUC=0.89)[3]
- Strong correlations with amyloid pathology[1,4–6]
- Correlation with established CSF biomarkers for detecting amyloid-PET positivity[1,7–9]

Other pTau biomarkers of AD pathology include **pTau181** and **pTau231**[3,10,11]

C-kinase, creatine kinase; CaM kinase, calmodulin-dependent protein kinase; Ser, serine; Thr, threonine.

1. Palmqvist S, et al. JAMA 2020;324:772–81;
2. Kawashima M, et al. J Biologic Chem 1995;270:823–9; 3. Janelidze S, et al. Brain 2022;146:1592–601; 4. Therriault J, et al. JAMA Neurol 2022;80:188–99; 5. Thijssen E, et al. Lancet Neurol 2021;20:739–52;
6. Salvadó G, et al. EMBO Mol Med 2023;46:1–16; 7. Therriault J, et al. Alzheimer's Dement 2023;19:4967–77; 8. Ashton NJ, et al. Alzheimer's Dement 2022;19:1913–24;
9. Ashton NJ, et al. JAMA Neurol 2024;81:255–63; 10. Ashton NJ, et al. Acta Neuropathol Commun 2019;7:1–25; 11. Janelidze S, et al. Nat Med 2020;26:379–86.

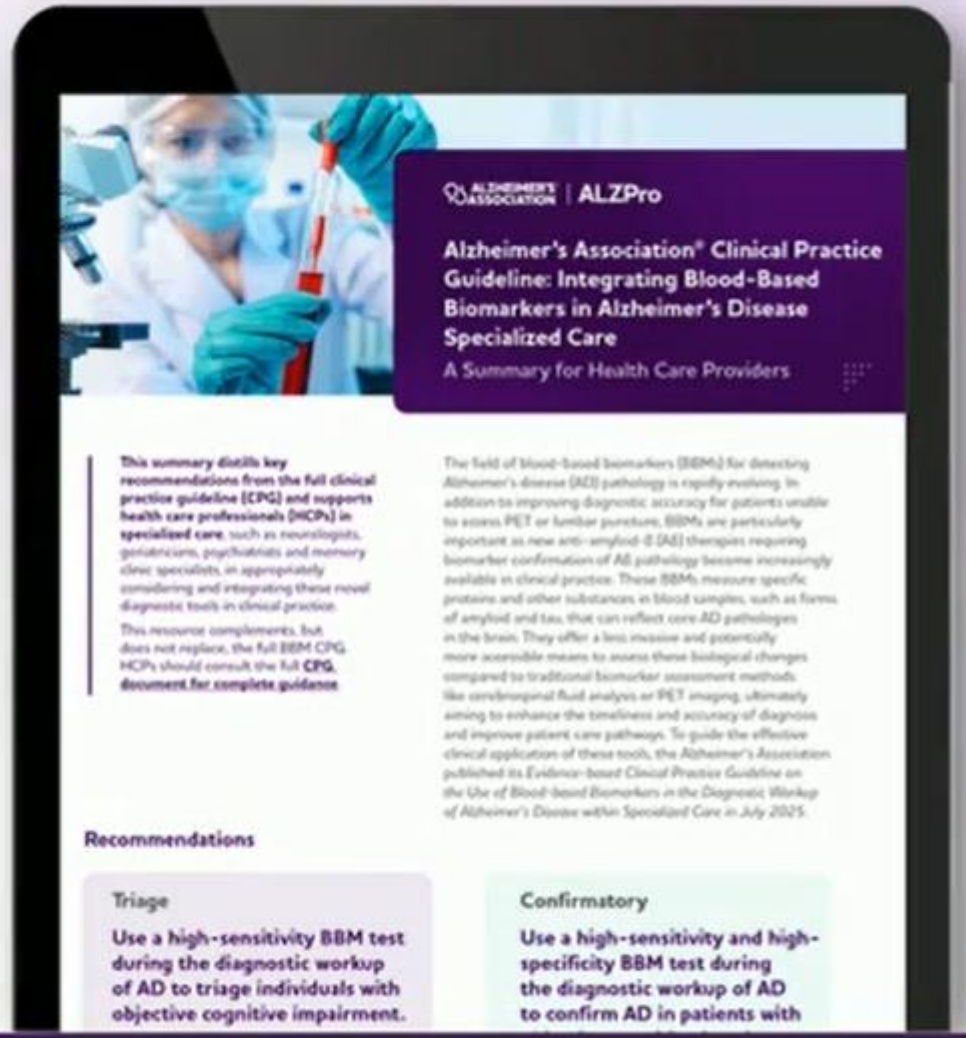
Good Practice: Clinical Context

A BBM test should NOT be obtained before a comprehensive clinical evaluation. Clinical context is paramount.

When to avoid testing OR interpret results with extra caution

- Patient preference/refusal
- Obvious modifiable or temporary causes
- Limited life expectancy
- Interfering conditions/factors

Blood-Based Biomarker CPG: Resources to Support Implementation



Key Tools

- Executive Summary

Clinical Relevance

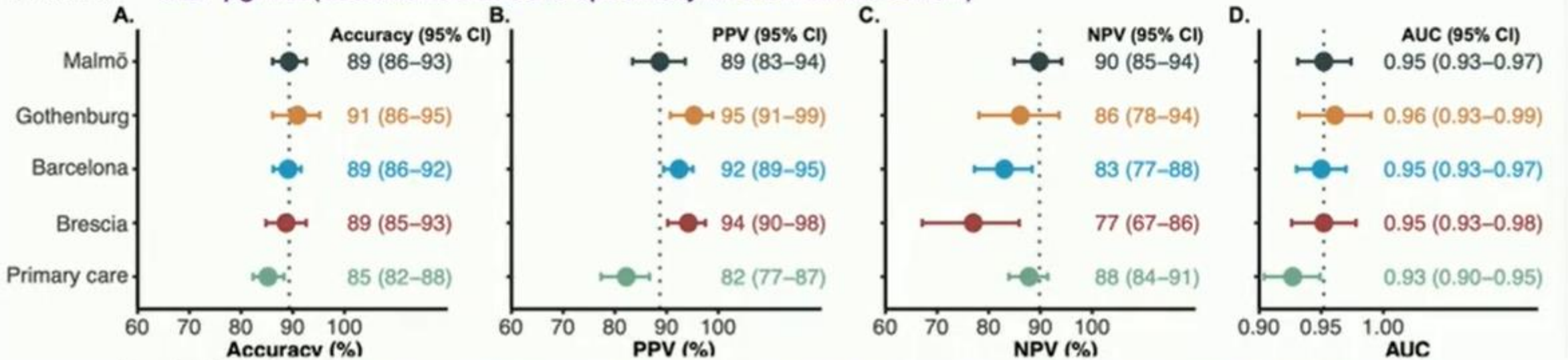
- **Guides clinical integration** of blood-based biomarkers in specialized care.
- **Provides clear pathways** for using BBM tests as triage or confirmatory tools.

Access

- alz.org/BloodCPG

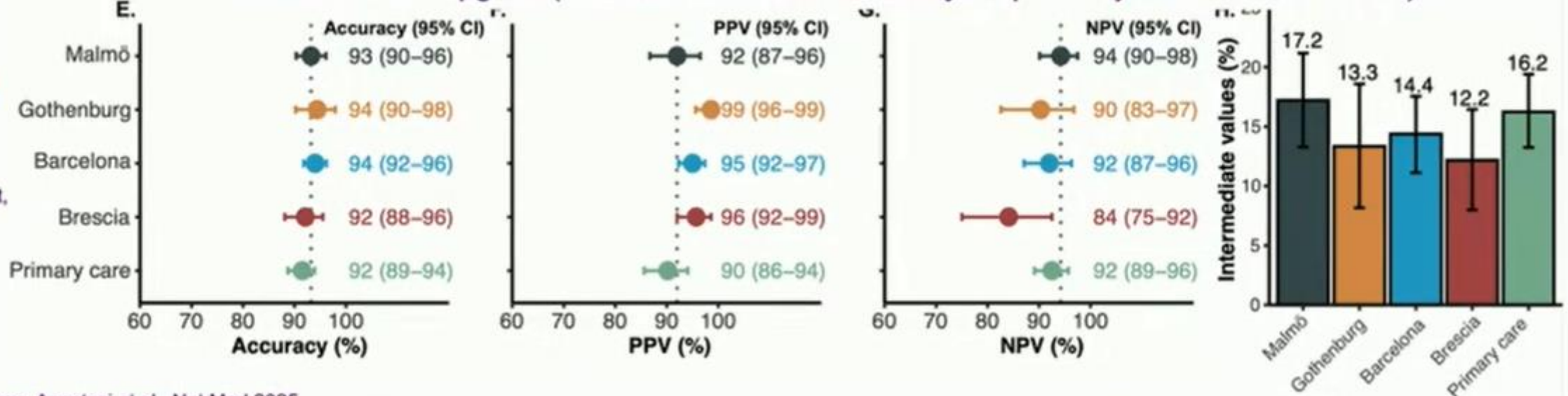
Performance of plasma p-tau217 (Lumipulse)

1 cutoff > 0.27 pg/mL (established at 90% specificity in the Malmö cohort)



2 cutoffs < 0.22 & > 0.34 pg/mL (established at 95% sensitivity & specificity in the Malmö cohort)

Sebastian Palmqvist, M.D., Ph.D.



Palmqvist, Warmenhoven, Anastasi et al., Nat Med 2025

- Terapie farmacologiche: novità

TRAILBLAZER RESULTS

Met Primary Endpoint, Showing Highly Statistically Significant Reduction of Clinical Decline

Primary Endpoint

Reduced clinical decline on iADRS (Alzheimer's Disease Rating Scale), compared with placebo at 76 weeks from baseline

35% reduced decline

Key Secondary Endpoints

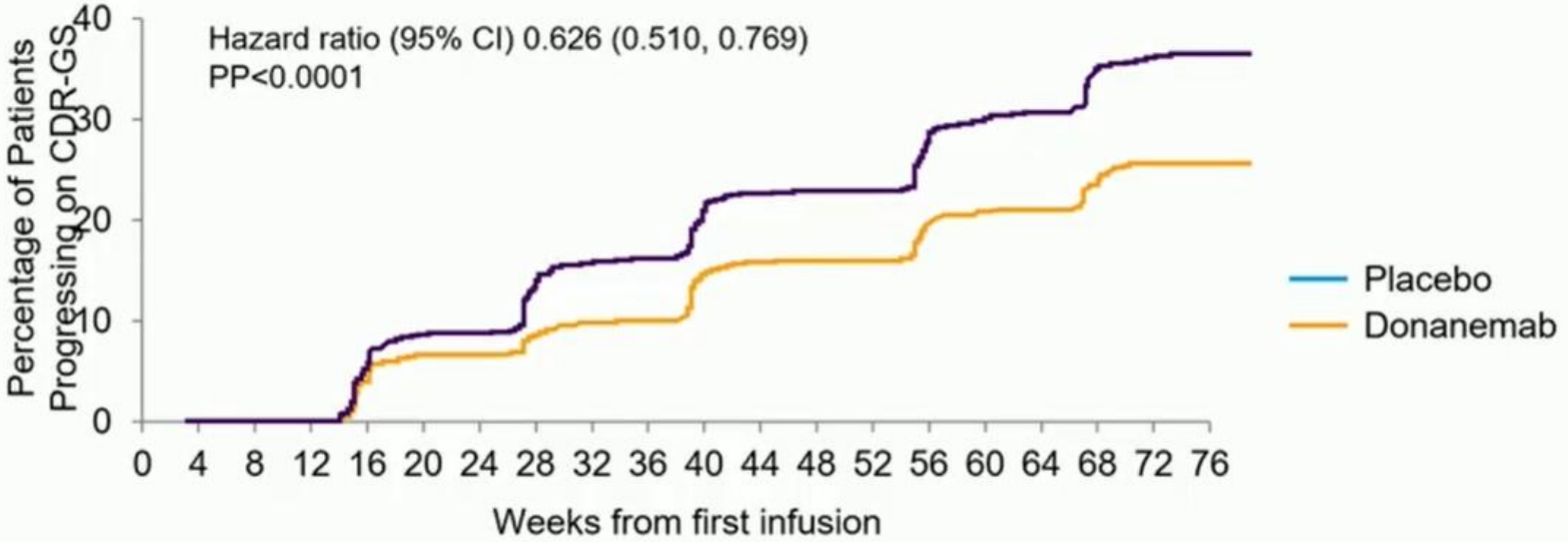
All key secondary endpoints also met, demonstrating highly statistically significant results (P<0.01)

Safety

ARIA-E: 15.7%
ARIA-H: 26.8%

JAMA. 2023;330(6):512-527. doi:10.1001/jama.2023.13239

Donanemab treatment lowered risk of AD progression: CDR-Global Score (overall population)



Reduced risk of progression to the next stage of Alzheimer's disease by 37% by CDR-GS at 76 weeks
CDR-GS = Clinical Dementia Rating Global Score

BACKGROUND

TRAILBLAZER-ALZ 6, a phase 3b trial, assessed the impact of different donanemab dosing regimens on ARIA-E frequency and amyloid reduction

1:1:1:1 Randomization stratified by *APOE* and by baseline amyloid PET

Cumulative donanemab exposure was the same for the 4 dosing regimens by week 16.

Primary Outcome

	Visit Number	1	2	3	4	5	6	7	8	9	10	11	**12**
	Study Week	Screening	0	2	4	6	8	10	12	14	16	20	**24**
Treatment Arm (mg)	**Standard**		700	PBO	700	PBO	700	PBO	1400	PBO	1400	1400	1400
	Modified Titration		350	PBO	700	PBO	1050	PBO	1400	PBO	1400	1400	1400
	Dose Skipping		700	PBO	PBO	PBO	1400	PBO	1400	PBO	1400	1400	1400
	Cmax		350	350	350	350	350	350	700	700	1400	1400	1400
	Amyloid PET	√											√
	MRI	√			√				√				√

Placebo was given at the indicated visits to preserve the blind for the different dosing regimens.

After week 16, all participants received 1400 mg of donanemab monthly until dose stopping criteria were met or until the end of the study.

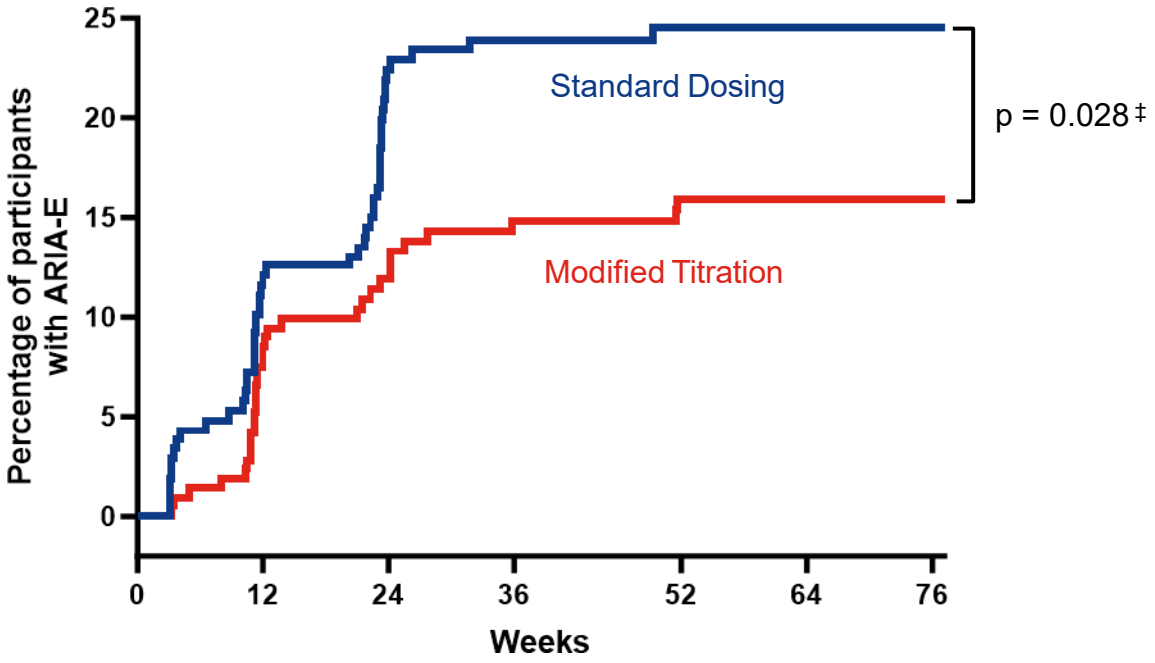
Figure modified from Wang H, et al. Alzheimers Dement. 2025.

Abbreviations: APOE=apolipoprotein E; ARIA-E=amyloid-related imaging abnormalities with effusion/edema; MRI=magnetic resonance imaging; PET=positron emission tomography.

SIGNIFICANTLY LOWERED ARIA-E RISK OVER TIME IN THE MODIFIED TITRATION ARM

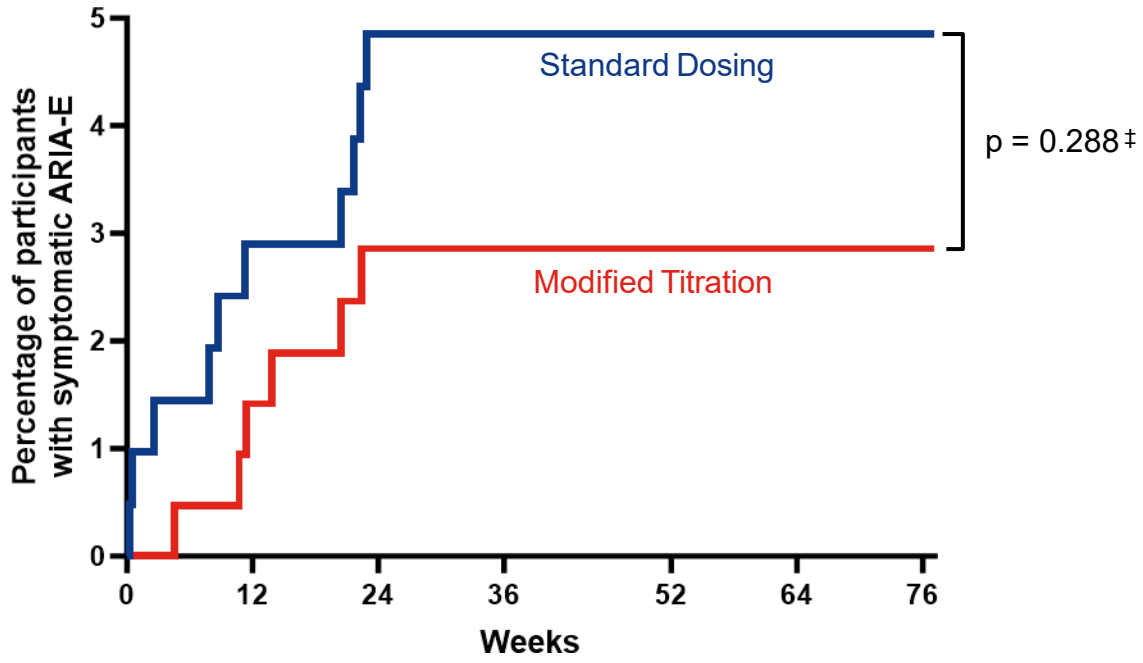
ARIA-E: After 76 weeks, modified titration arm had a significantly lower percentage of participants with ARIA-E. No new ARIA-E events detected after 52 weeks.

Hazard Ratio (95% CI) = 0.624 (0.401, 0.970) p=0.036†



Symptomatic ARIA-E: At 76 weeks, modified titration arm had numerically lower symptomatic ARIA-E. All initial symptomatic ARIA-E occurred within the first 24 weeks.

Hazard Ratio (95% CI) = 0.584 (0.212, 1.610) p=0.299†



Data from Wang H, et al. JPAD. 2025.

†Event analyzed using Cox proportional hazards model with dosing regimens, *APOE* e4 genotype (heterozygote, homozygote, non-carrier), presence of microhemorrhage at baseline, presence of superficial siderosis at baseline, and baseline amyloid terciles fitted as explanatory variables.

‡Log-rank unstratified p-value (2-sided)

Abbreviations: ARIA-E=amyloid-related imaging abnormalities with edema/effusion.

CLARITY AD RESULTS

Met Primary Endpoint, Showing Highly Statistically Significant Reduction of Clinical Decline

Primary Endpoint

Reduced clinical decline on CDR-SB, compared with placebo at 18 months from baseline

27% (P=0.00005)

Key Secondary Endpoints

All key secondary endpoints also met, demonstrating highly statistically significant results (P<0.01)

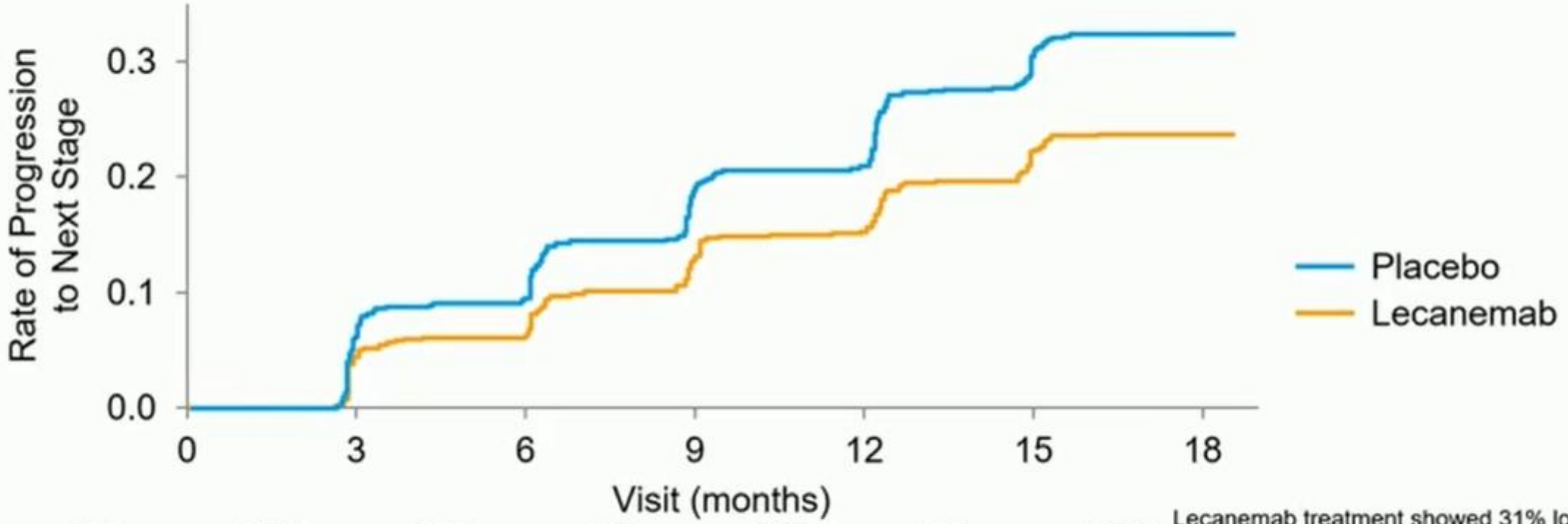
Safety

ARIA-E: 12.5% (symptomatic: 2.8%)
ARIA-H: 17.0% (symptomatic: 0.7%)

Dyck CH et al. N Engl J Med. 2023 Jan 5; 388(1):9-21

Alzheimer's disease progressed more slowly in people on lecanemab, delaying arrival of the next disease stage

Time to Worsening of Global CDR Scores



(N) Placebo	875	792	757	649	603	524	265*
(N) Lecanemab	859	801	765	677	642	554	299*

Lecanemab treatment showed 31% lower risk of converting to next stage of disease by Global CDR assessment (Hazard Ratio: 0.69).

ALZHEIMER'S ASSOCIATION | ALZPro

AAIC 25 FOR ALL

Dyck CH et al. N Engl J Med. 2023 Jan 5; 388(1):9-21

Clarity AD OLE: CDR-SB Efficacy Through 48 Months

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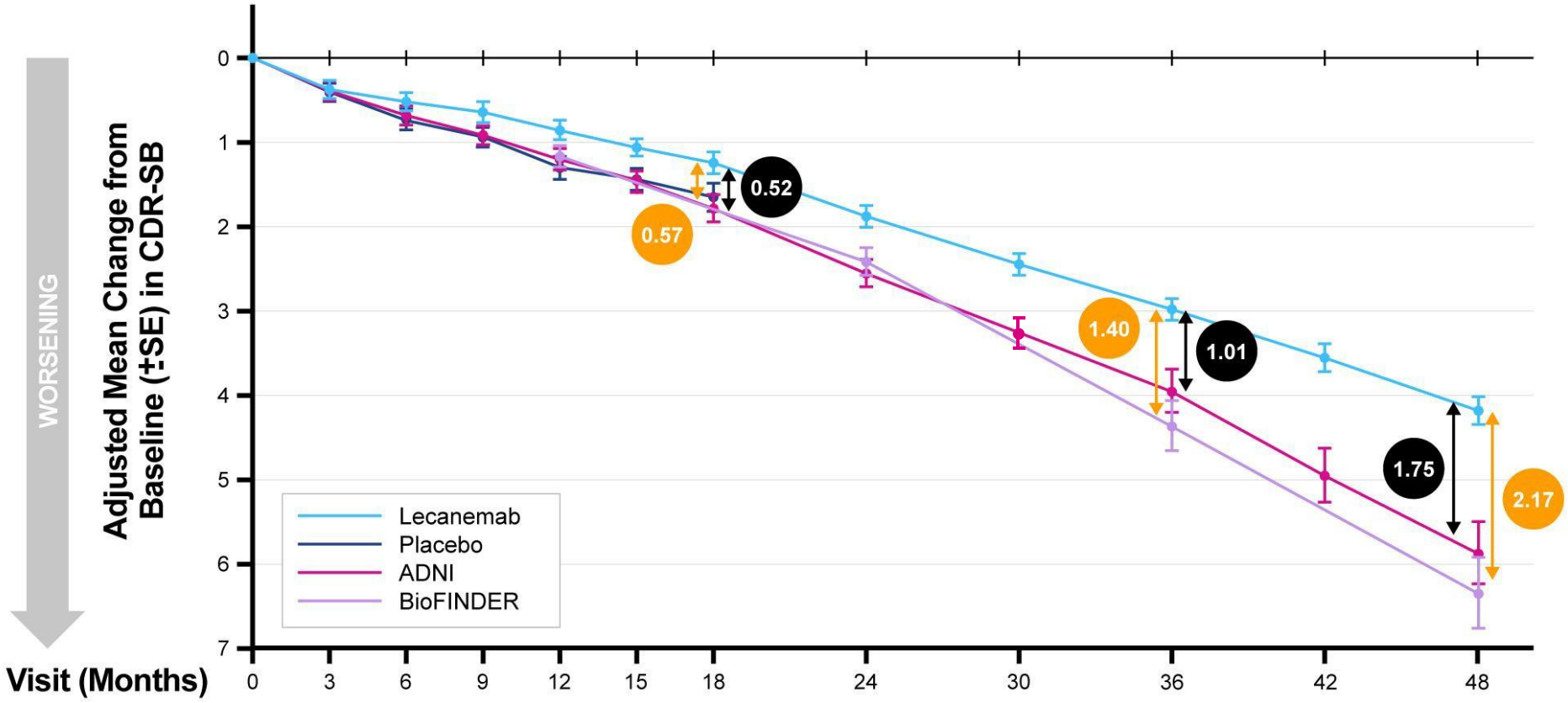


N (Placebo)	875	849	828	813	779	767	757					
N (Lecanemab)	859	824	798	779	765	738	714	659	613	573	527	478
N (ADNI)	436		410		401		121	301	173	173	98	98
N (BioFINDER)	147				139			137		117		112

Note: OLE includes those participants on subcutaneous and intravenous formulations. BioFINDER data are from BioFINDER 1.

Based on modified intention-to-treat analysis population. Adjusted mean change from baseline, SE and p-value are derived using mixed model repeat measures (MMRM) with treatment group, visit, treatment group by visit interaction, clinical subgroup, use of Alzheimer's disease symptomatic medication at baseline, ApoE4 carrier status, region, baseline value by visit interaction as fixed effects, and baseline value as covariate.

ADNI, Alzheimer's Disease Neuroimaging Initiative. CDR-SB, Clinical Dementia Rating-sum of boxes. OLE, open-label extension. SE, standard error.

Are there subgroups that benefit more?

- On donanemab, people with fewer tangles benefited the most
- On lecanemab, people with the fewest tangles improved most on CDR-SB
- Overall, 76 percent of low-tau participants on lecanemab, and 55 percent on placebo, held their ground on the CDR-SB over 18 months

Clinical Trials on Alzheimer's Disease (CTAD) 2023

Trontinemab “Brain Shuttle”

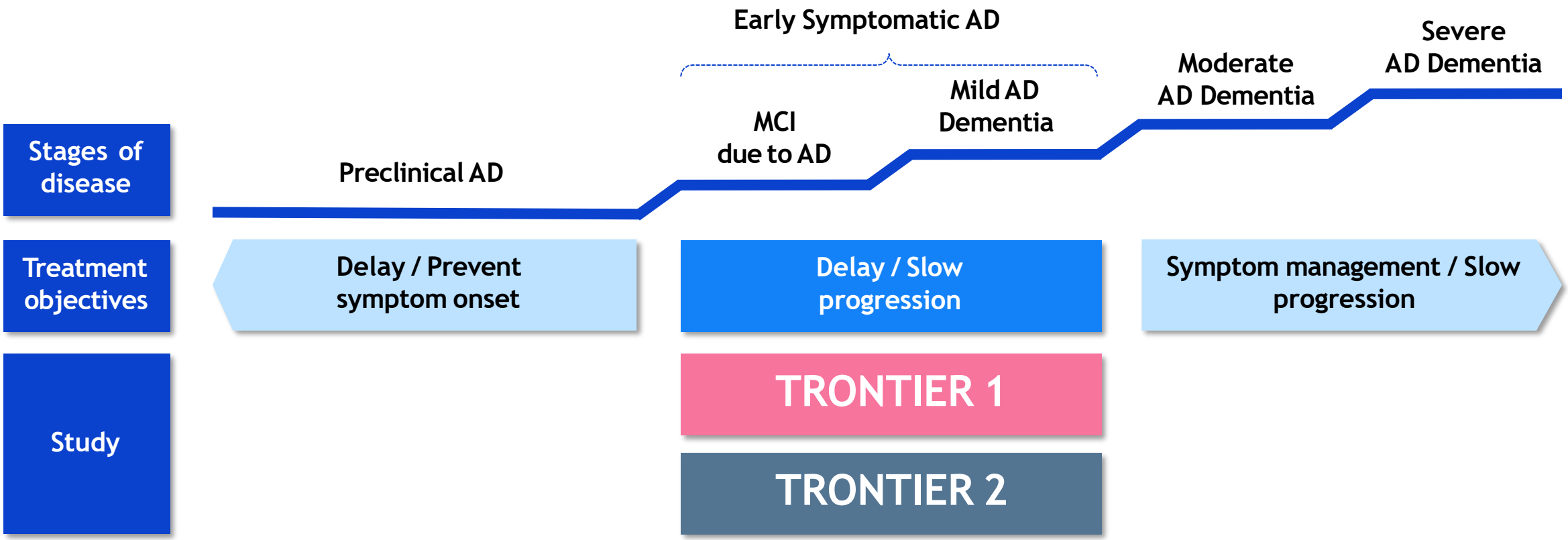
- **Innovation**: New version of **gantenerumab** engineered for enhanced **blood-brain barrier crossing** using **"brain shuttle“**
  - Binds the transferrin receptor on the endothelial cells (blood-brain barrier) leading to its endocytosis and release into the brain parenchyma

- **Key Findings**:
- **8x higher CNS exposure** than standard gantenerumab.
- **2023+2024 (CTAD)**:**Rapid plaque removal** with **few mild ARIA cases**

- **Safety Data**:
- **1 death** in a participant with **superficial siderosis & probable cerebral amyloid angiopathy**

Targeting populations most likely to benefit from treatment with DMTs[1-3]

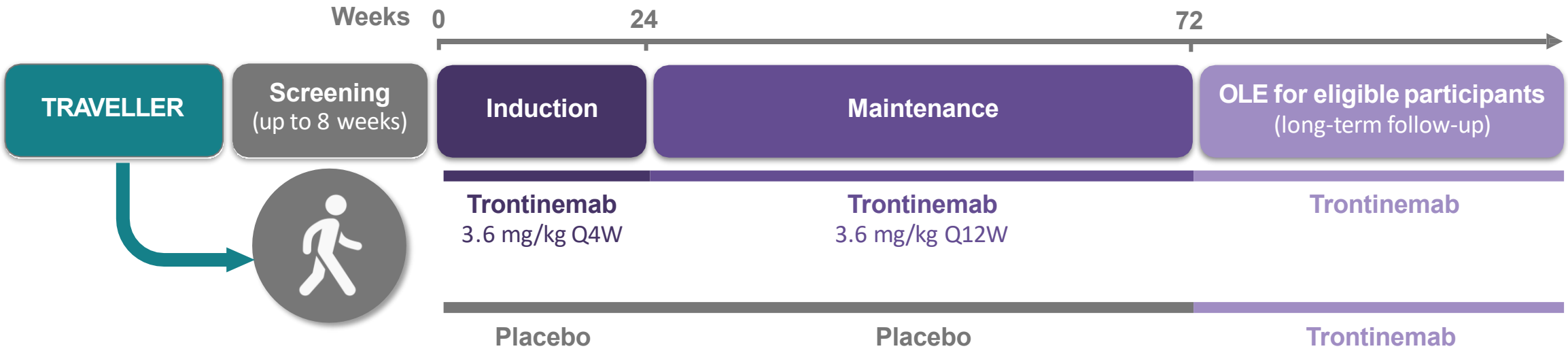
Delaying disease progression for as long as possible



Trontinemab is an investigational product not approved for use in any market.
AD, Alzheimer's disease; DMT, disease-modifying treatments; MCI = mild cognitive impairment, also referred to as prodromal Alzheimer's disease.
1. Hampel H, et al. Mol Psychiatry 2021;26:5481–5503; 2. Alzheimer's Association. 2024 Alzheimer's Disease Facts and Figures. Alzheimers Dement 2024;20:3708–3821.

TRONTIER 1 & 2: Dosing regimen enables and maintains low amyloid status

Two global, identically designed, 18-month, randomized, double-blind, placebo-controlled studies



✓ Induction

- Rapid and robust amyloid removal

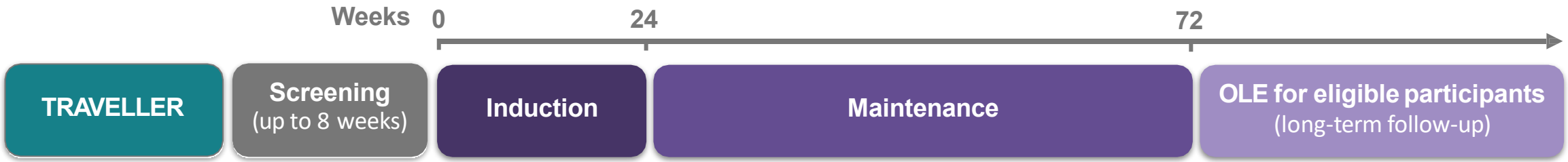
✓ Maintenance

- Simplified dosing regime with reduced participant burden
- Further clearance and control of AD pathology

Trontinemab is an investigational product not approved for use in any market.
AD, Alzheimer's disease; OLE, open-label extension.

TRONTIER 1 & 2: Key criteria to enroll early symptomatic AD population

Two global, identically designed, 18-month, randomized, double-blind, placebo-controlled studies



Key Inclusion Criteria

- Age 50–90 inclusive
- Evidence of amyloid pathology
- Clinical stage 3 (MCI-AD) or 4 (mild AD dementia)[1]
- MMSE ≥ 22
- CDR-GS 0.5 or 1

Key Exclusion Criteria

- Other condition/disease that could impact cognition
- >4 microhemorrhages
- Any macrohemorrhage
- Severe white matter disease

Trontinemab is an investigational product not approved for use in any market.
AD, Alzheimer's disease; CDR-GS, Clinical Dementia Rating Global Score; MCI-AD, Mild Cognitive Impairment-Alzheimer's Disease; MMSE, Mini-Mental State Examination; OLE, open-label extension.
1. Jack Jr CR, et al. Alzheimers Dement 2024;20:5143–5169.

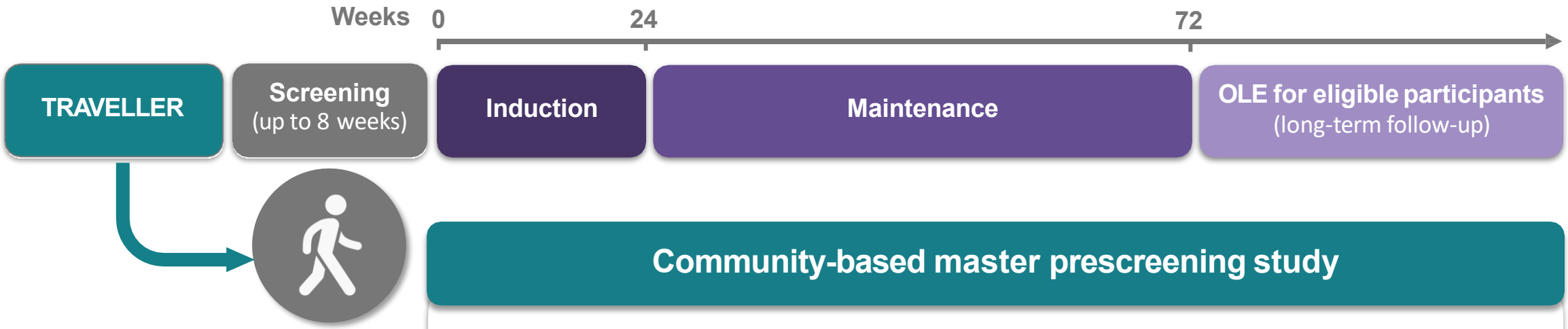
TRONTIER 1 & 2: A global footprint advancing outcomes for all

1,600 participants (800 per study) across 18 countries; ~155 TRONTIER 1 sites, ~152 TRONTIER 2 sites

Trontinemab is an investigational product not approved for use in any market.
Countries for TRONTIER 1: Argentina, Brazil, Canada, China, France, Germany, Italy, Japan, Poland, Spain, Taiwan, United Kingdom, USA.
Countries for TRONTIER 2: Argentina, Australia, Brazil, Canada, Denmark, France, Germany, Italy, Japan, Korea, Netherlands, Poland, Spain, Switzerland, United Kingdom, USA.

TRAVELLER: Prescreener study to optimise recruitment in TRONTIER 1 & 2

Now recruiting at US and Canadian sites; more countries will open for recruitment soon



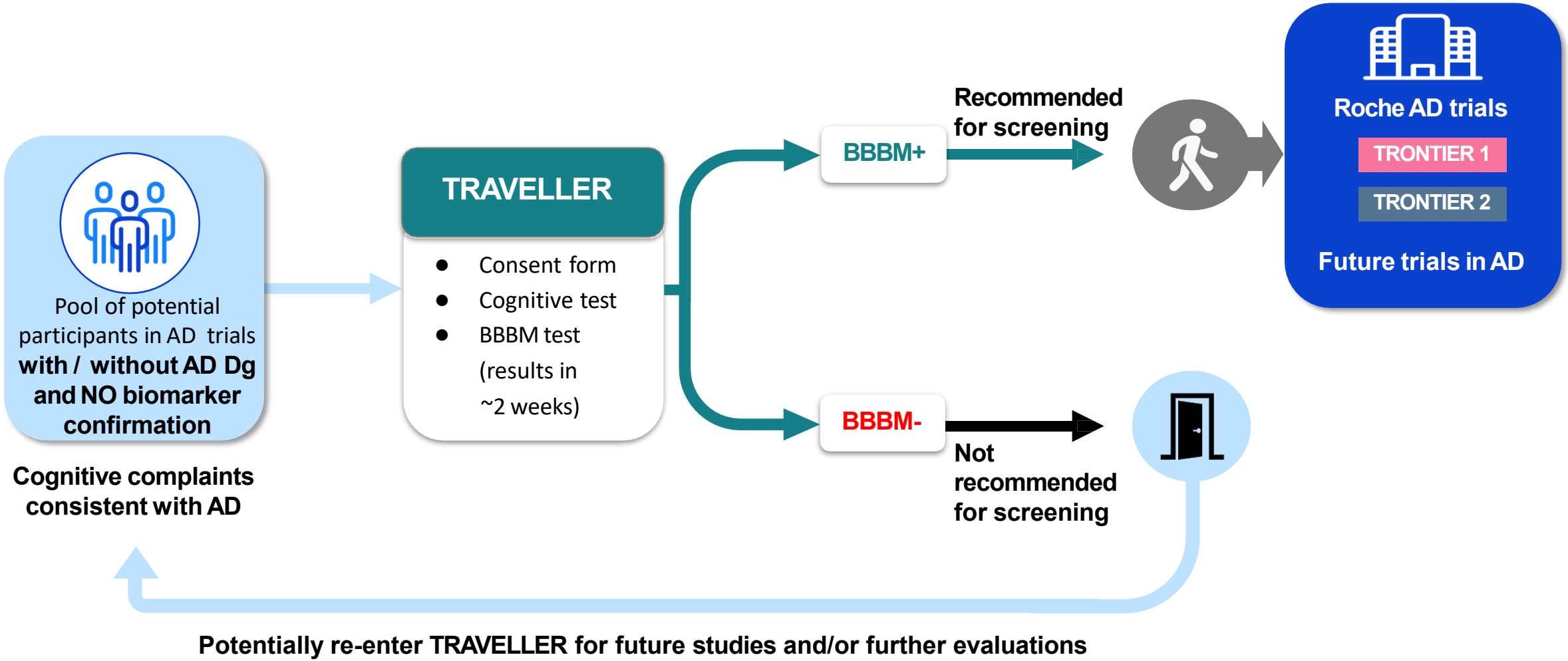
Community-based master prescreening study

- Increase access to research to optimize health outcomes for all
- Enable sites to engage broader communities and increase reach for trial participation
- Reduce high screen failure rates in AD trials
- Opportunity to reduce burden for trial participants, families and sites
- More effectively identify eligible target populations for clinical trial participation
- Identify potential participants for future trials if not eligible at first prescreen
- Ability to include community-based memory service and build disease education

Trontinemab is an investigational product not approved for use in any market.
AD, Alzheimer's disease; OLE, open-label extension.

TRAVELLER: Master prescreening study deployed across AD clinical trials

Decreasing participant burden and improving efficiencies for trial sites



AD, Alzheimer's disease; BBBM, blood–based biomarker; Dx, diagnosis.

Tau Therapeutics are Making Progress

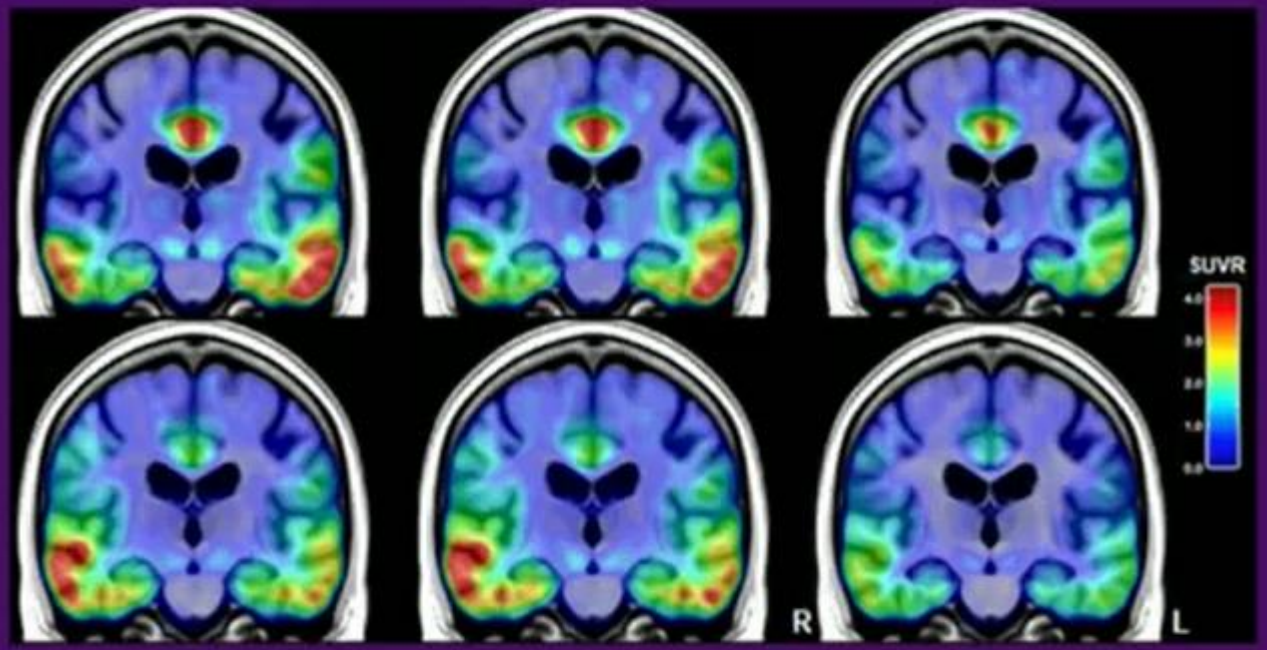


Figure from: AlzForum.April,2023

- Tau protein is encoded by the microtubule associated protein tau (MAPT) gene
- BIIB080 is an antisense oligonucleotide reducing MAPT messenger RNA
- BIIB080 markedly reduces CSF and PET tau in AD
- Phase 2 trial testing two doses and two injection regimens against placebo in MCI/mild dementia due to AD (2026)

Mummery C, et al. Nat Med 2023; doi.org/10.1038/s41591-023-02326-3

- Terapie disturbi comportamentali e terapie non farmacologiche

First-line therapy: non-pharmacological options

Interventions for carers: [1]

Training for carers, support for carers, links to external
organisations and services

Elimination of stress factors:[2]

Separating patients from stimuli and environments that intensify or exacerbate symptoms, evaluating the effects of medication.

Improvement of sensory perception/relaxation:[1,3]

Hand massages, individualised music or art, sensory modulation, multisensory environments, light therapy, supportive interactions, orienting stimuli

Improvement of the **environment:**[2,4]

temperature control, facilitation and simplification of activities, reduction of environmental noise

Targeted activity: [1]

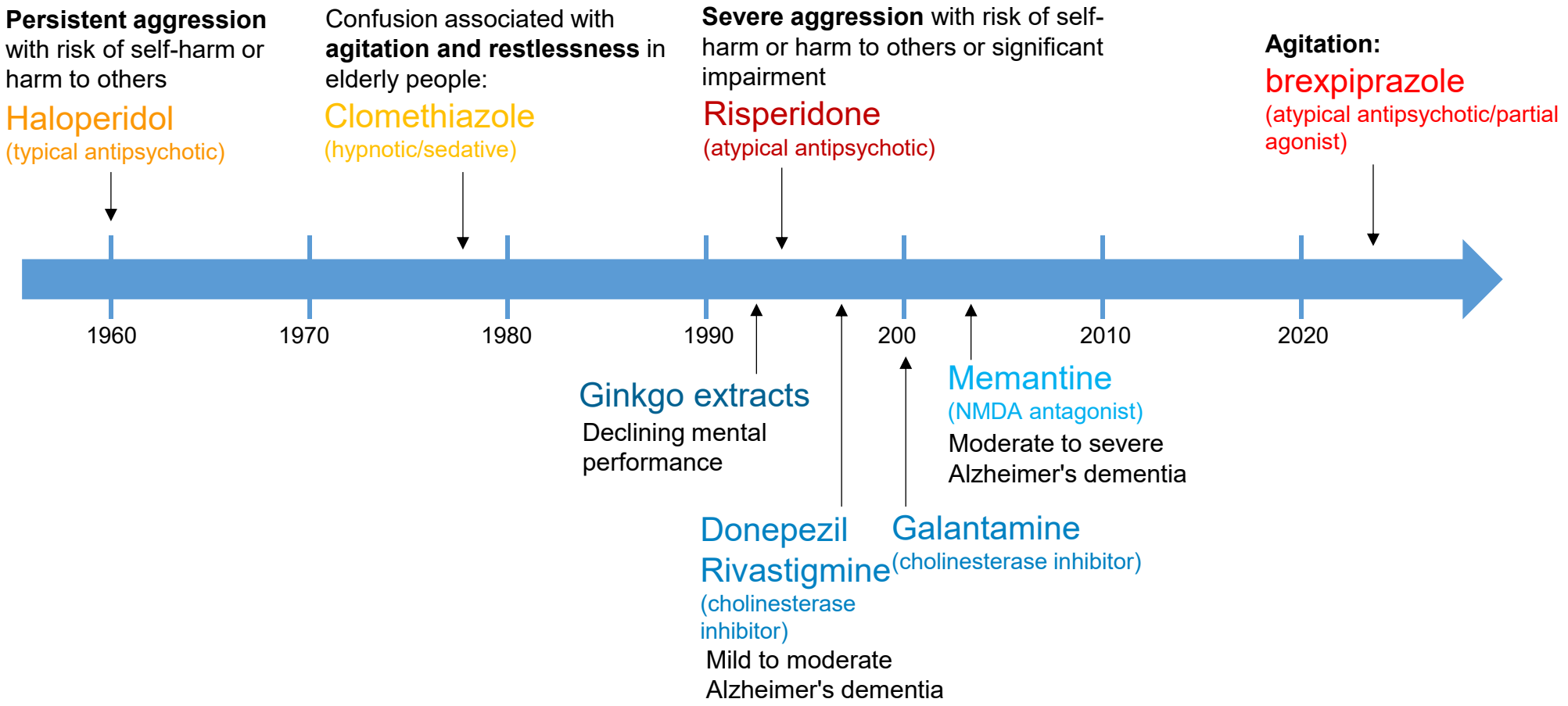
Supportive tasks/volunteer work,
Inclusion in group activity programmes,
Access to the outdoors, physical activity

Social contacts:[1]

Animal therapy, individual visits, gentle touch

1. Davies et al. J Psychopharmacol 2018;32(5):509-523; 2. Desai and Grossberg. Prim Care Companion J Clin Psychiatry 2001;3(3):93-109;
3. Cohen-Mansfield et al. J Am Geriatr Soc 2010;58(8):1459-1464; 4. Hall et al. J Gerontol Nurs 1995;21(1):37-47

What is currently approved for the treatment of patients with Alzheimer's dementia and agitation?



Details on the individual substances can be found in the respective product information at www.swissmedicinfo.ch

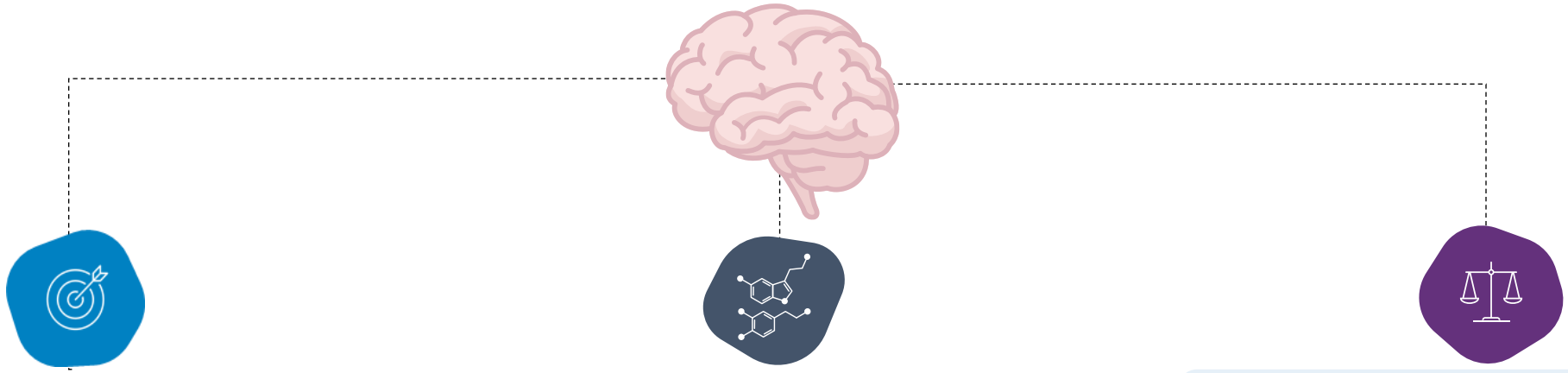
Pharmacological treatments for agitation in Alzheimer's dementia can be associated with adverse events

Guidelines recommend avoiding receptor antagonists (anticholinergics, antihistamines, dopamine antagonists) whenever possible[5].

[a]Some family caregivers of patients with Alzheimer's disease and other forms of dementia find sedative effects distressing and unhelpful[4]

1. Schneider, L. S., Dagerman, K., & Insel, P. S. (2006). Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized, placebo-controlled trials. *American Journal of Geriatric Psychiatry*, 14(3), 191-210. doi:10.1097/01.JGP.0000200589.01396.6d. 2. Caraci, F., Santagati, M., Caruso, G., Cannavò, D., Leggio, G. M., Salomone, S., & Drago, F. (2020). New antipsychotic drugs for the treatment of agitation and psychosis in Alzheimer's disease: focus on brexpiprazole and pimavanserin. *F1000Research*, 9. doi:10.12688/f1000research.22662.1. 3. Marcinkowska, M., Śniecikowska, J., Fajkis, N., Paśko, P., Franczyk, W., & Kołaczkowski, M. (2020). Management of Dementia-Related Psychosis, Agitation and Aggression: A Review of the Pharmacology and Clinical Effects of Potential Drug Candidates. *CNS drugs*, *34*(3), 243–268. https://doi.org/10.1007/s40263-020-00707-7. 4. Harding, R., & Peel, E. (2012). 'He was like a zombie': Off-label prescription of antipsychotic drugs in dementia. *Medical Law Review*, 21(2), 243-277. doi:10.1093/medlaw/fws029. 5. Guidelines recommend avoiding receptor antagonists (anticholinergics, antihistamines, dopamine antagonists) whenever possible5.

Investigation of brexpiprazole for the treatment of agitation in Alzheimer's dementia



An important goal of pharmacotherapy is to reduce agitation without causing sedation.[1]

Brexpiprazole* is a modulator of serotonin-dopamine activity that acts as a

- partial agonist at serotonin 5-HT_{1A} , and dopamine D_2 receptors.
- Antagonist of serotonin 5-HT_{2A} e and noradrenaline α_{1B} /α_{2C} receptors[2]

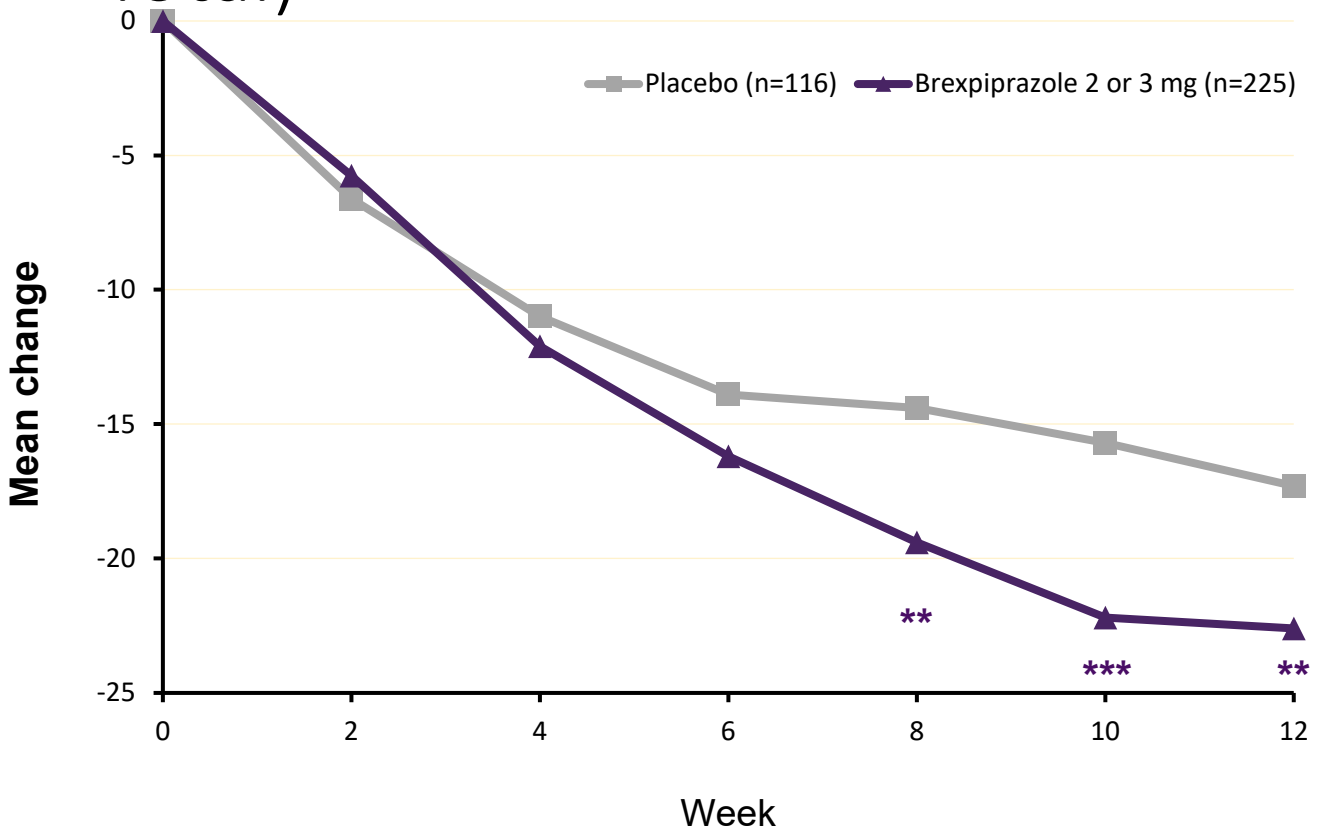
Brexpiprazole

- is considered neither activating nor sedative in schizophrenia;[3] has been studied in four trials for the treatment of agitation in Alzheimer's dementia[4-6]
- Brexpiprazole has been approved by the US FDA and Health Canada for the treatment of agitation associated with dementia due to Alzheimer's disease[7,8]

5-HT = serotonin; D = dopamine;

1. Casey. P&T 2015;40(4):284–287; 2. Maeda et al. J Pharmacol Exp Ther 2014;350(3):589–604; 3. Citrome L. J Clin Psychopharmacol. 2017;37(2):138-147; 4. Grossberg et al. Am J Geriatr Psychiatry 2020;28(4):383–400; 5. Lee D et al. JAMA Neurol. 2023:e233810; 6. Grossberg et al. Am J Geriatr Psychiatry 2020;28(4):383–400. 6. Grossberg et al. Oral presentation at American Society of Clinical Psychopharmacology (ASCP) Annual Meeting, 30 May – 2 June 2023; Miami Beach, Florida, USA; 7. FDA. Rexulti approval letter 10 May 2023. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2023/205422Orig1s009ltr. 8. Health Canada Product information: https://health-products.canada.ca/dpd-bdpp/info?lang=eng&code=94955

High-Dose-Study: Primary endpoint – effects of brexpiprazole on symptoms of agitation (CMAI Total)



	Placebo (n=116)	Brexpiprazole 2 or 3 mg (n=225)
CMAI Total score at baseline (mean, SD)	79.2 (17.5)	80.6 (16.7)
Mean change in CMAI Total score at Week 12 (LS mean, SE)	-17.3 (1.44)	-22.6 (1.08)
Treatment difference at Week 12 (95% CI)	-5.32 (-8.77, -1.87) p=0.0026	

Baseline CMAI Total score: placebo, 79.17 (n=116); brexpiprazole 2 or 3 mg, 80.55 (n=225)

*p<0.05, **p<0.01, ***p<0.001 versus placebo; MMRM

CI=confidence interval; CMAI=Cohen–Mansfield Agitation Inventory; MMRM=mixed model for repeated measures; SE=standard error; SD=standard deviation

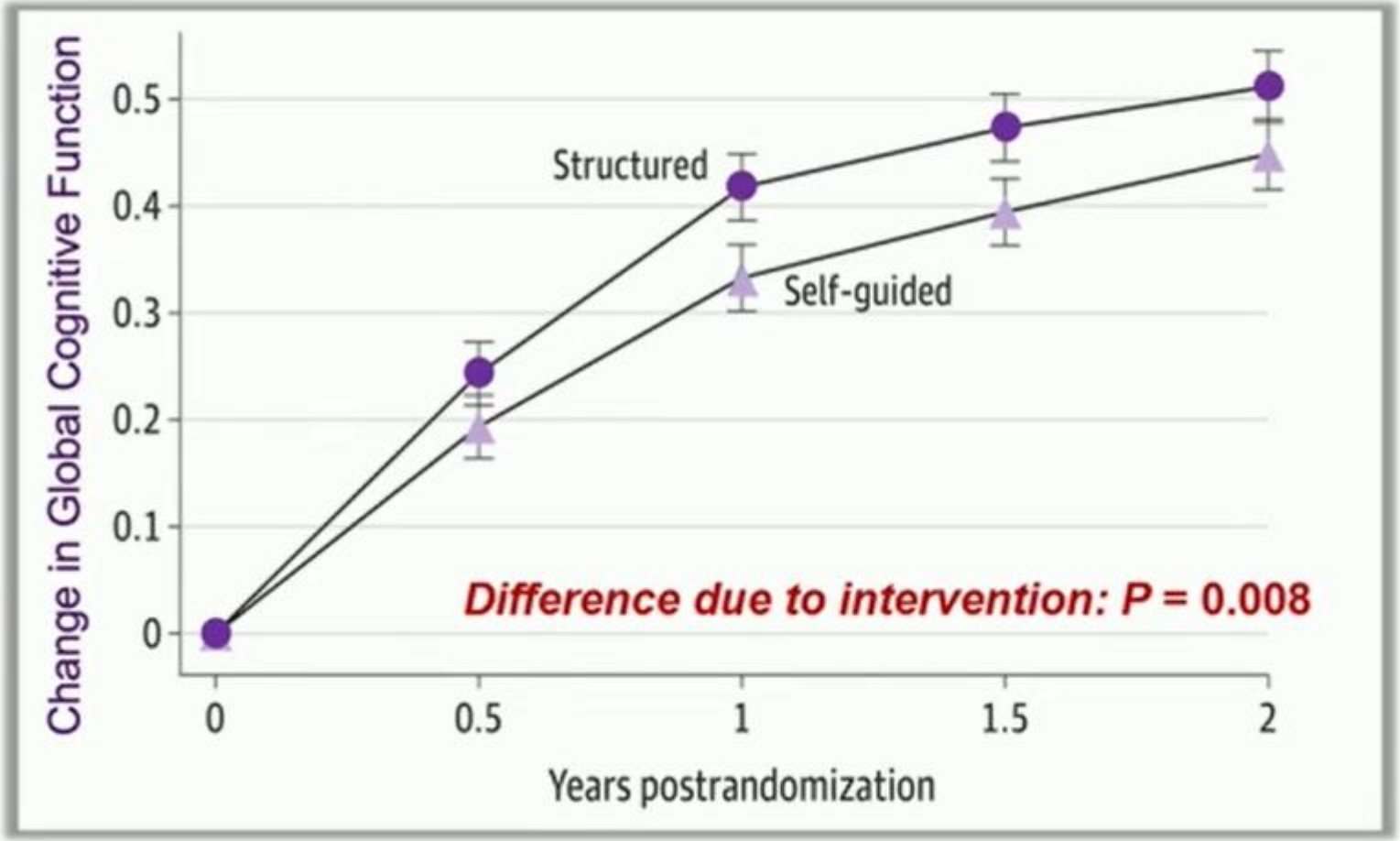
Lee D et al. JAMA Neurol. 2023 Nov 6:e233810

U.S.POINTER ALZHEIMER'S ASSOCIATION

KEY TAKEAWAYS

1. Global cognitive function improved over time for BOTH groups

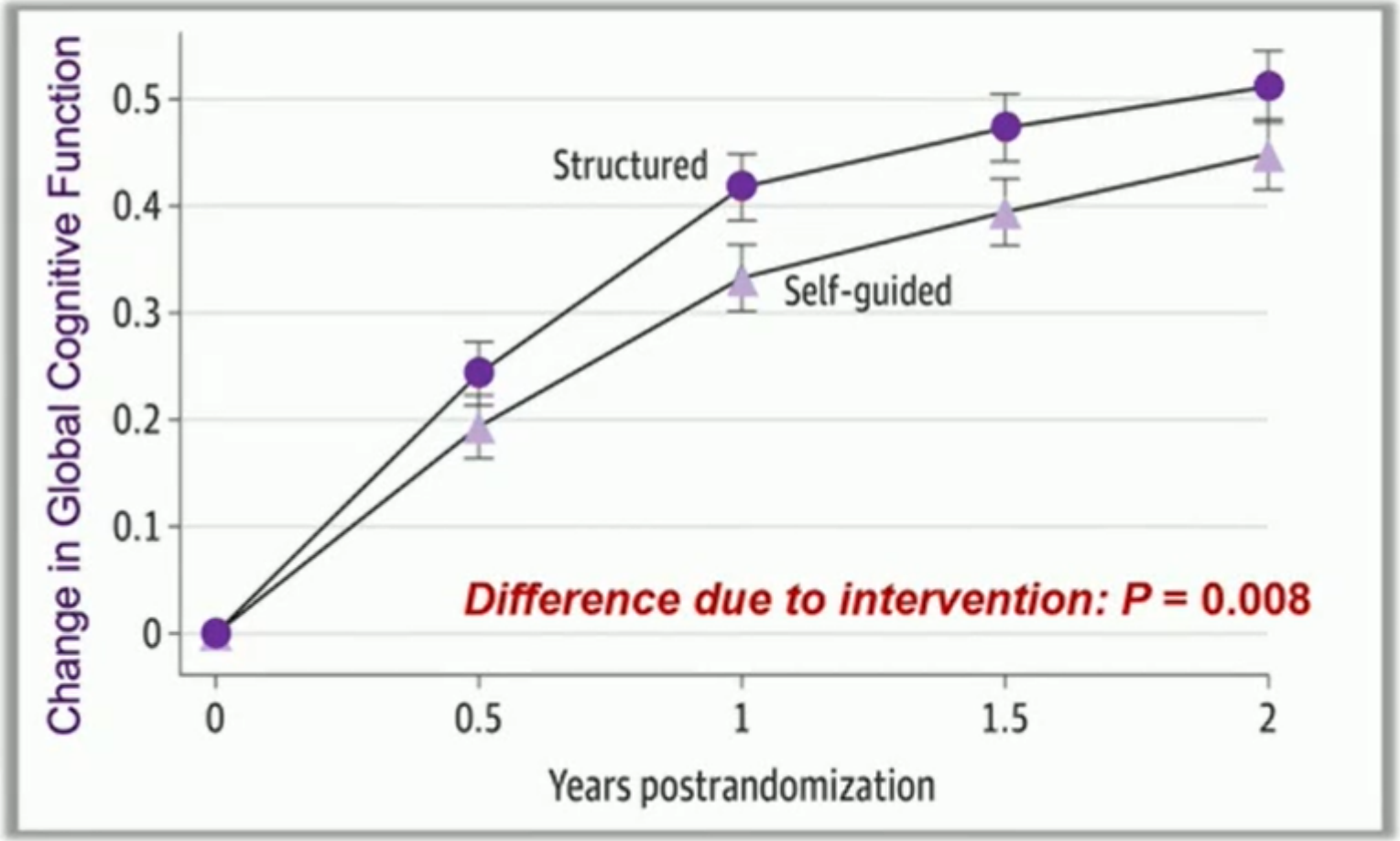
2. **The Structured intervention had a significantly greater benefit**



U.S.POINTER ALZHEIMER'S ASSOCIATION

KEY TAKEAWAYS

The Structured group performed at a level comparable to adults who are **1 to 2 years younger** — an effect that could increase resilience against cognitive decline



Overview of U.S. POINTER

Primary Objective

Compare the effects of two multidomain lifestyle interventions on global cognitive function in 2000 older adults at risk for cognitive decline and dementia

Study Design, Participants & Interventions

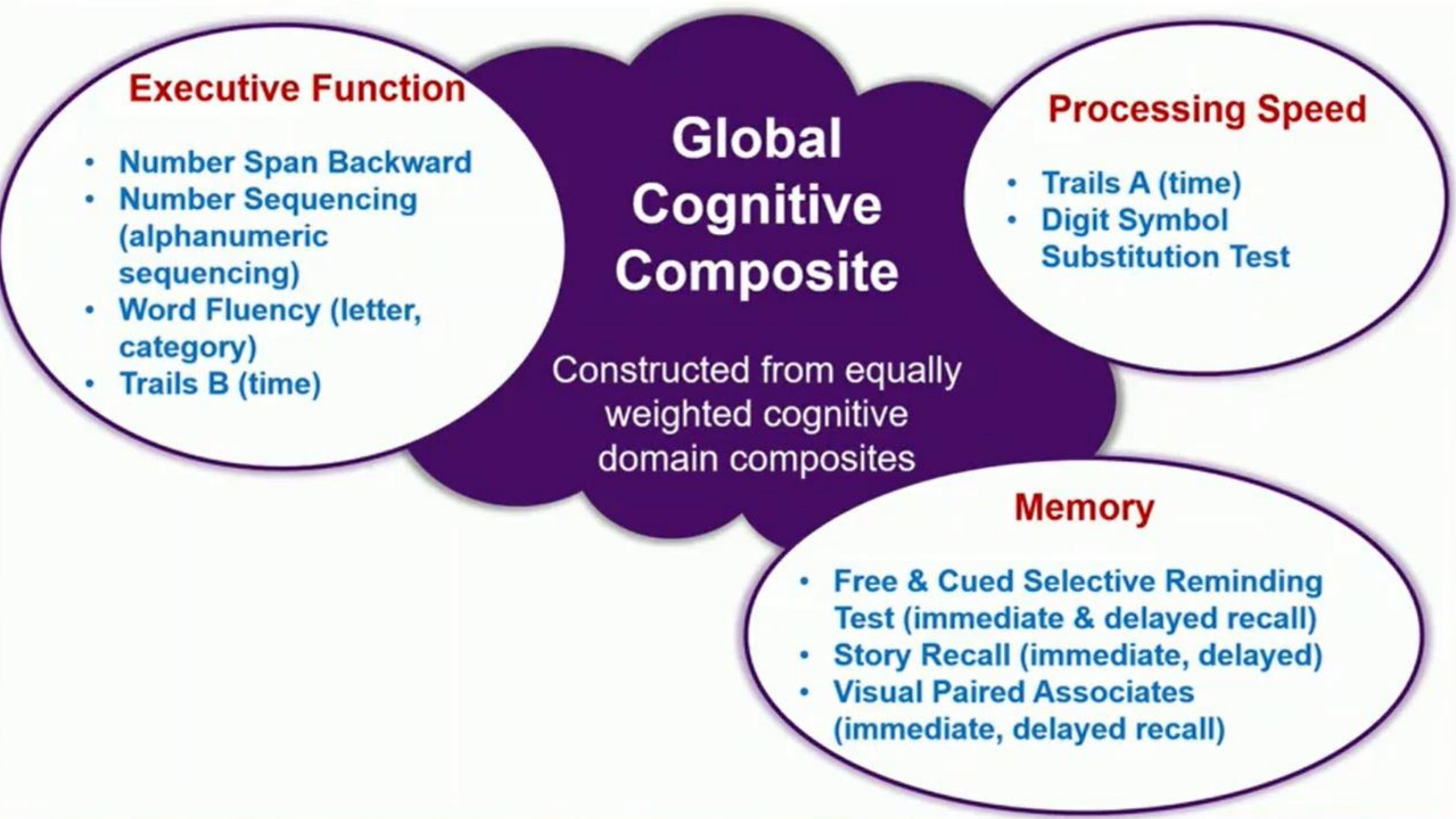
2-year RCT; enrolled diverse cohort of 2,111 cognitively healthy older adults at risk for cognitive decline due to lifestyle, health, and demographic factors; clinic assessments at baseline and every 6 mos; randomized to one of two interventions

STR — 38 peer team meetings over 2 years with study Navigator and Interventionist for goal-setting, accountability and support

- **Physical Exercise**: Aerobic, resistance, and stretching & balance exercise
- **Nutrition**: MIND diet
- **Cognitive and Social Challenge**: Computer cognitive training and participation in other challenging social & intellectual activities
- **Guideline-Based Health Coaching**

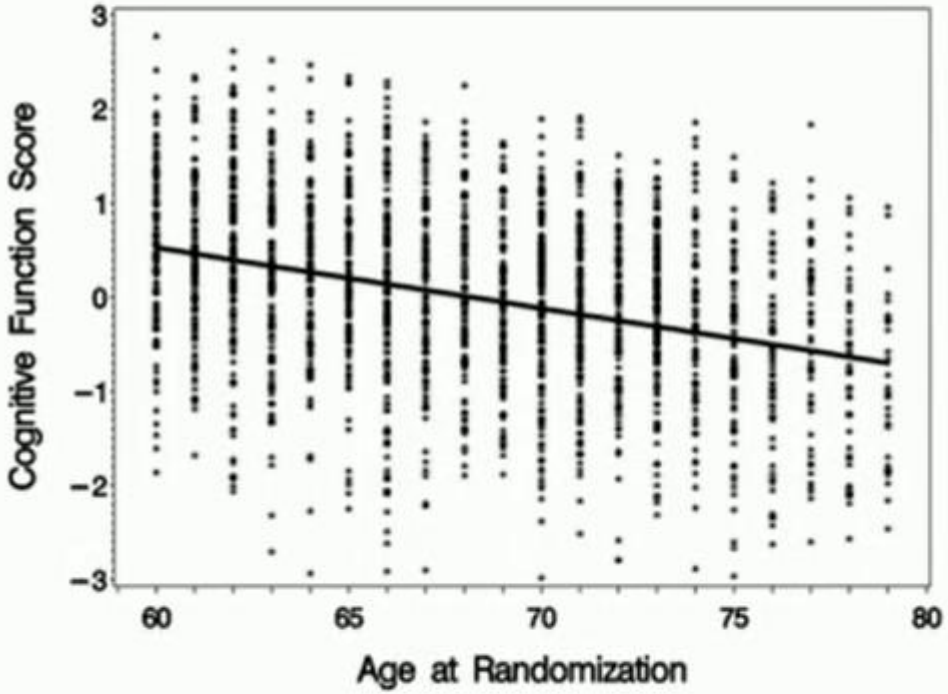
SG — 6 peer team meetings over 2 years with study Navigator

- **Education & General Support**
  - Health education
  - Tools to support self-guided plans
  - General encouragement
- **Health Monitoring**

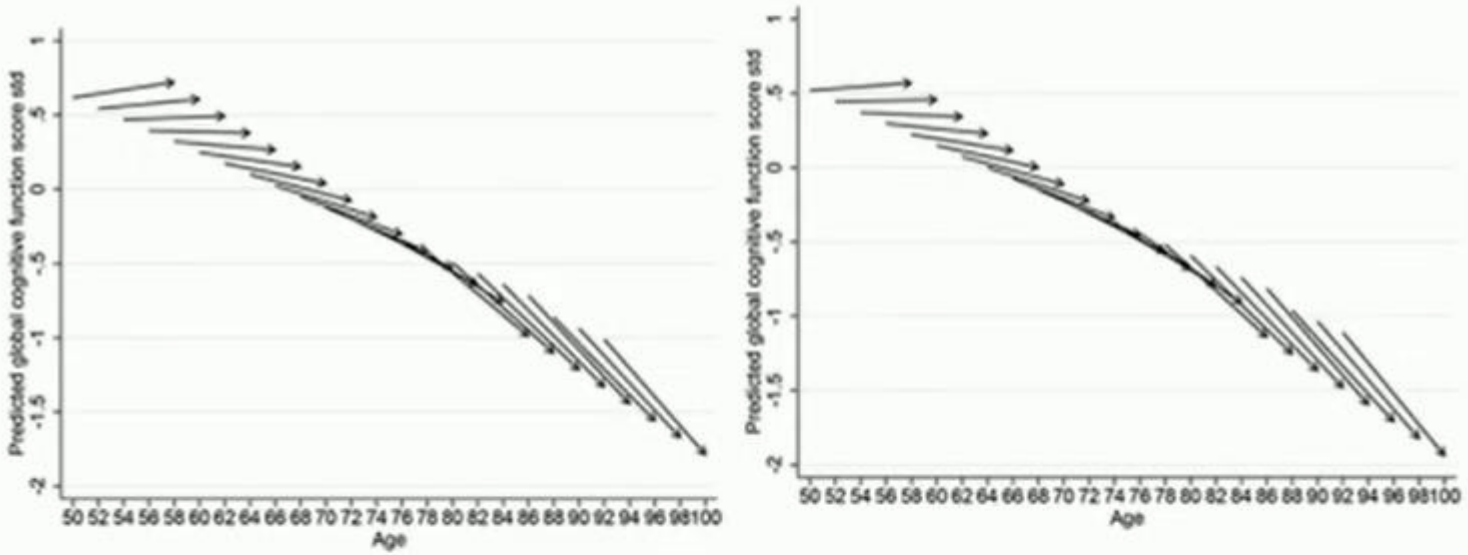

Executive Function
• Number Span Backward
• Number Sequencing (alphanumeric sequencing)
• Word Fluency (letter, category)
• Trails B (time)
Global Cognitive Composite
Constructed from equally weighted cognitive domain composites
Processing Speed
• Trails A (time)
• Digit Symbol Substitution Test
Memory
• Free & Cued Selective Reminding Test (immediate & delayed recall)
• Story Recall (immediate, delayed)
• Visual Paired Associates (immediate, delayed recall)

Assessing Clinical Relevance

How does global cognitive function decline with age when there is no lifestyle intervention?



U.S. POINTER at Baseline: -0.064 SD per year (cross-sectional)



Females

Males

English Longitudinal Study of Aging: -0.037 SD per year

Paola Zaninotto et al. J Epidemiol Community Health 2018;72:685-694

- Grazie per l’attenzione