Hot Topics in Medicine

The new era of disease modifying therapies (DMT) for Alzheimer's disease (AD)

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UC San Diego Health

UC San Diego
SCHOOL OF MEDICINE

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Disclosures

I have no relevant disclosures
Although I do have some acknowledgements:

It takes a village. This lecture is in part a product of a group effort here at UCSD with Dr Douglas Galasko, and later with the San Diego Alzheimer's Project Clinical Roundtable, with contributions from:

- Dr Michael Lobatz, neurologist
- Dr Ian Neel, geriatrician
- Dr Daniel Sewell, geriatric psychiatrist

CHAMPIONS for HEALTH
PHYSICIANS IMPROVING HEALTH CHANGING LIVES

With special thanks to Barabara Mandel (who kept everybody organized)

Objectives

Understand the biomarker-based diagnosis of AD

Be aware of the new DMTs for AD, including their:

- Mechanism of action
- Expected benefits
- Potential complications

How to prepare patients for referral to memory disorders clinic to consider DMT

Auguste Deter

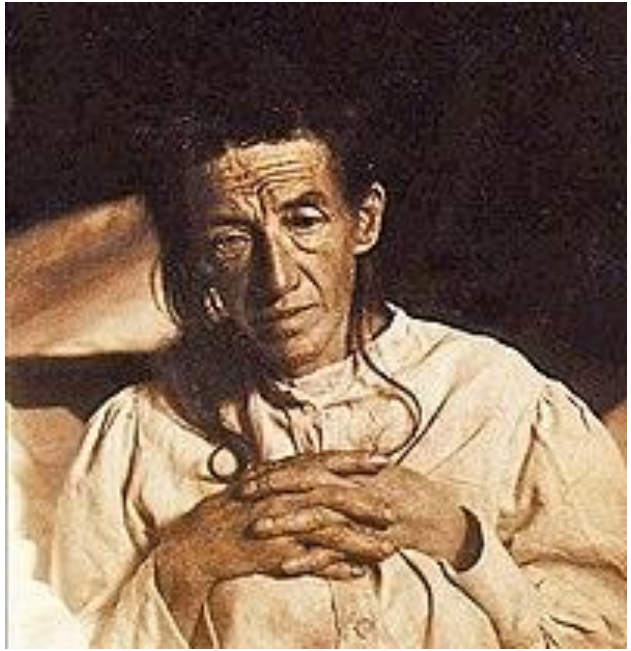
Born Auguste Hochmann, May 5,1850, in Kassel Germany

Schooled till age 14 (high education) & became a seamstress

Married railway clerk Carl Deter at age 23 and moved to Frankfurt. They had one daughter and lived a "happy and harmonious" life

At age 50, she developed insomnia, memory loss, delusions of infidelity, paranoia, and became unable to continue being a home maker.

Carl was unable to take care of her. She was ultimately moved to the *Institute for the mentally Ill and epileptic* in Nov 1901 (at age 51).



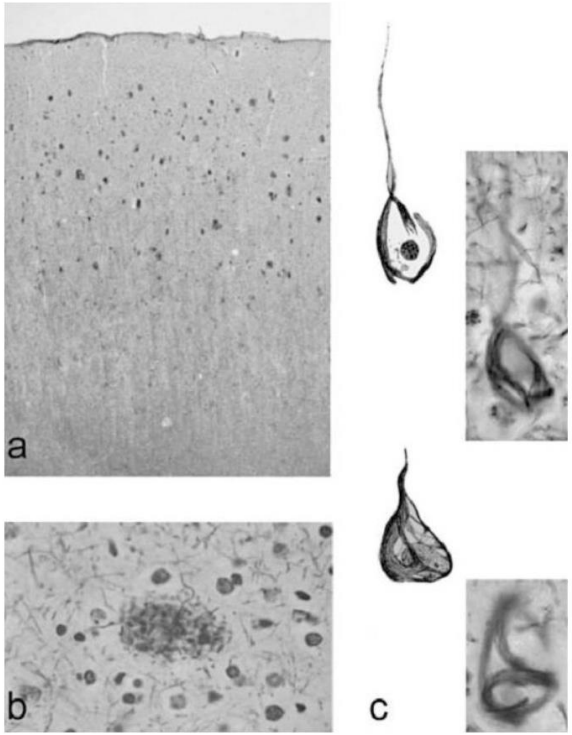
Auguste Deter

There she was under the care of a physician, who was struck by her decline and younger age. He would follow her until his move to Munich in March 1903.

It's said that Carl was struggling to afford the care that Auguste needed so the physician arranged for her to get free care in exchange for permission to examine her brain when she passed.

Auguste passed on April 8, 1906. Her physician was able to examine her brain shortly after, using specialized silver staining techniques that he had developed.

Auguste Deter and her doctor, Alois Alzheimer



Alois Alzheimer

Auguste Deter

Maurer K, Volk S, Gerbaldo H. Auguste D and Alzheimer's disease. *Lancet*. 1997;349(9064):1546-1549.

Alzheimer A, Stelzmann RA, Schnitzlein HN, Murtagh FR. *An English Translation of Alzheimer's 1907 Paper, "Uber Eine Eigenartige Erkankung Der Hirnrinde"*. Vol 8. Wiley Subscription Services, Inc., A Wiley Company; 1995:429-431.

Perry, George. (2013). Molecular Pathology of Alzheimer's Disease.

The Long Wait: More than half a century

1970s: Research into treatments for AD began, National Institute on Aging (NIA) was established

Mid-1970s: Studies provided early support for the ***cholinergic hypothesis*** *of AD* by showing abnormally low levels of the enzyme choline acetyltransferase (ChAT) in the neocortex

1984: Glenner & Wong discovered that the ***amyloid β protein (Aβ)*** is the central component of extracellular amyloid plaques in AD

1986: Researchers identify tau protein as a key component of tangles, a pathological hallmark of AD

Glenner GG, Wong CW. Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein. Biochem Biophys Res Commun. 1984 May 16;120(3):885-90. doi: 10.1016/s0006-291x(84)80190-4. PMID: 6375662.

The Long Wait – symptomatic therapies

1987: Alzheimer's Association, NIA and Warner-Lambert Pharmaceutical Company launched the first clinical trial for a drug to treat cholinergic based AD symptoms: tacrine

Acetylcholinesterase inhibitors (FDA approval date):

- Cognex® (Park-Davis) / tacrine (***1993***, discontinued in 2013)
- Aricept® (Eisai/Pfizer) / donepezil (1996)
- Exelon® (Novartis) / rivastigmine (1997)
- Reminyl® / Razadyne® (Jenssen) / galantamine (2001)

The partial NMDA channel blocker Namenda® / memantine was approved for moderate and late-stage AD in 2003

The Long Wait – symptomatic therapies

Both acetylcholinesterase inhibitors and memantine are modestly helpful, and both can be associated with non-negligible side effects in about one third of patients.

The Long Wait – addressing the disease process

1989: Research shows that amyloid may play a central role in the brain changes that lead to AD

1990s: The amyloid hypothesis of AD gains traction, focusing on abnormal processing of the amyloid precursor protein (APP)

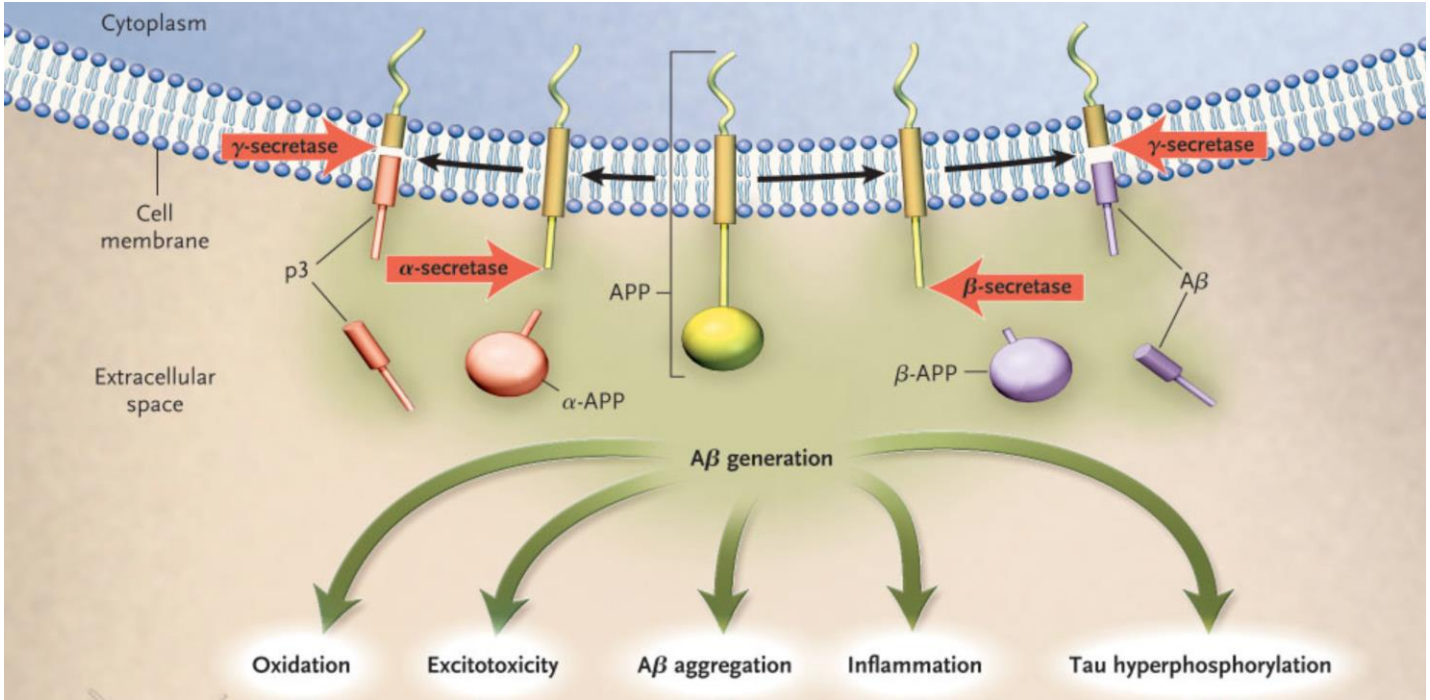
30 years to finally address amyloid

Approval of immunotherapies for AD, to treat the “root cause”

- 2023 (July): FDA approved Leqembi® / lecanemab (Eisai & Biogen)
- 2024 (July): FDA approved Kisunla® / donanemab (Eli Lilly)

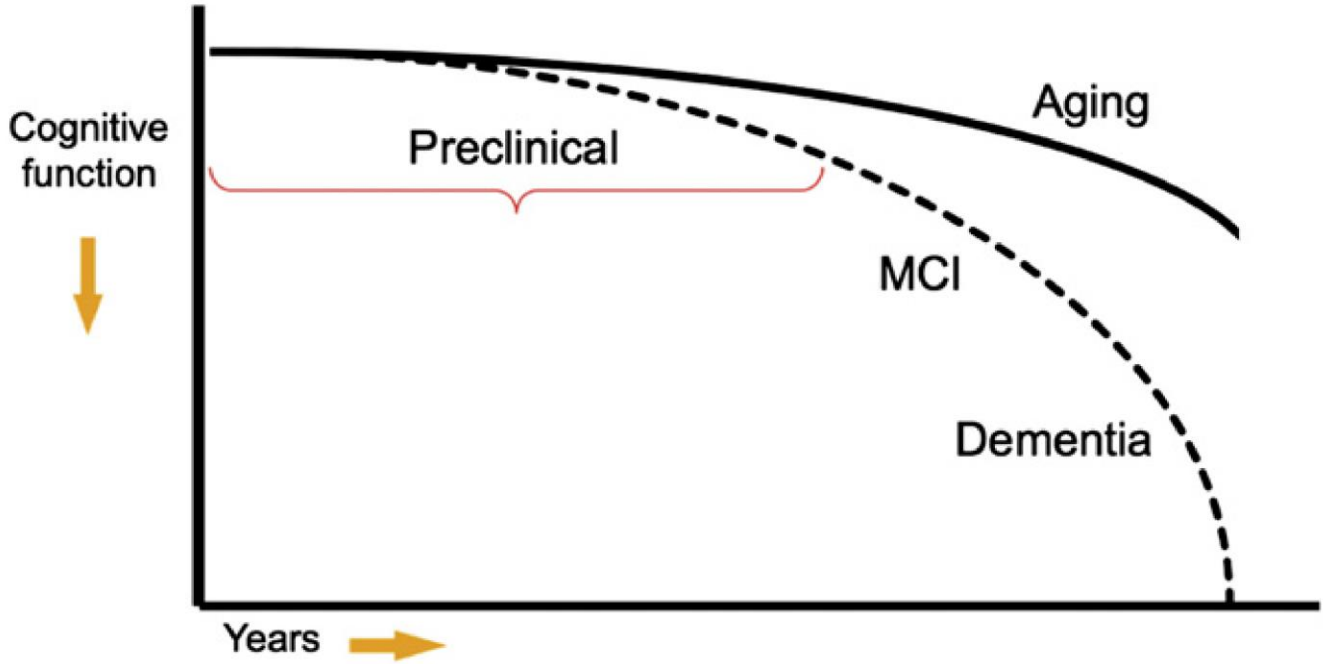
“The Amyloid Hypothesis”

Cummings, J.L., 2004. Alzheimer's disease. *The New England journal of medicine*, 351(1), pp.56–67.

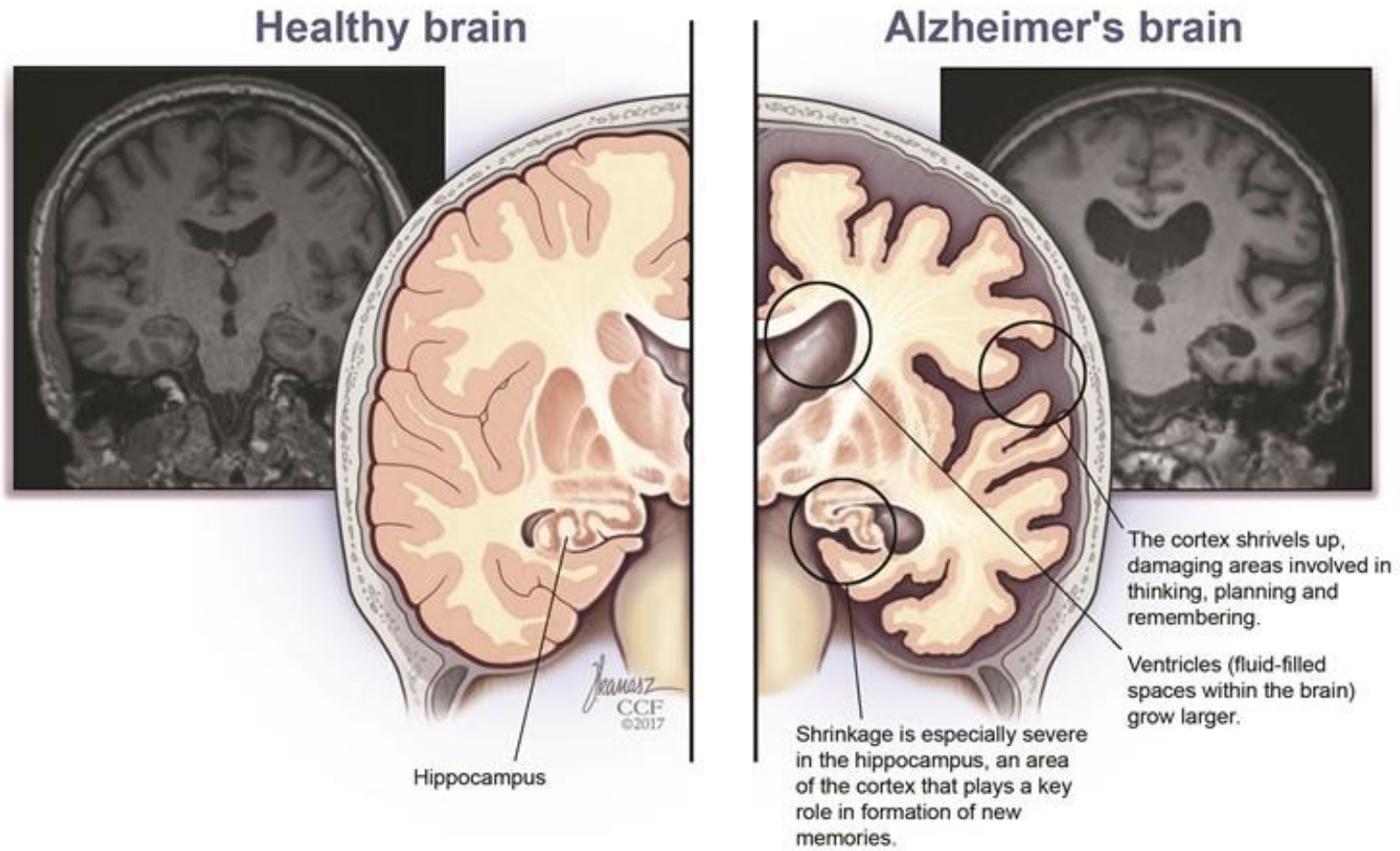


Oxidation
Excitotoxicity
Aβ aggregation
Inflammation
Tau hyperphosphorylation
Neuron
Senile plaque with microglial activation
Neurofibrillary tangles
Cell death
Neuro-transmitter deficit
Cognitive and behavioral abnormalities
Target of Current therapies

The Continuum of Alzheimer's Disease

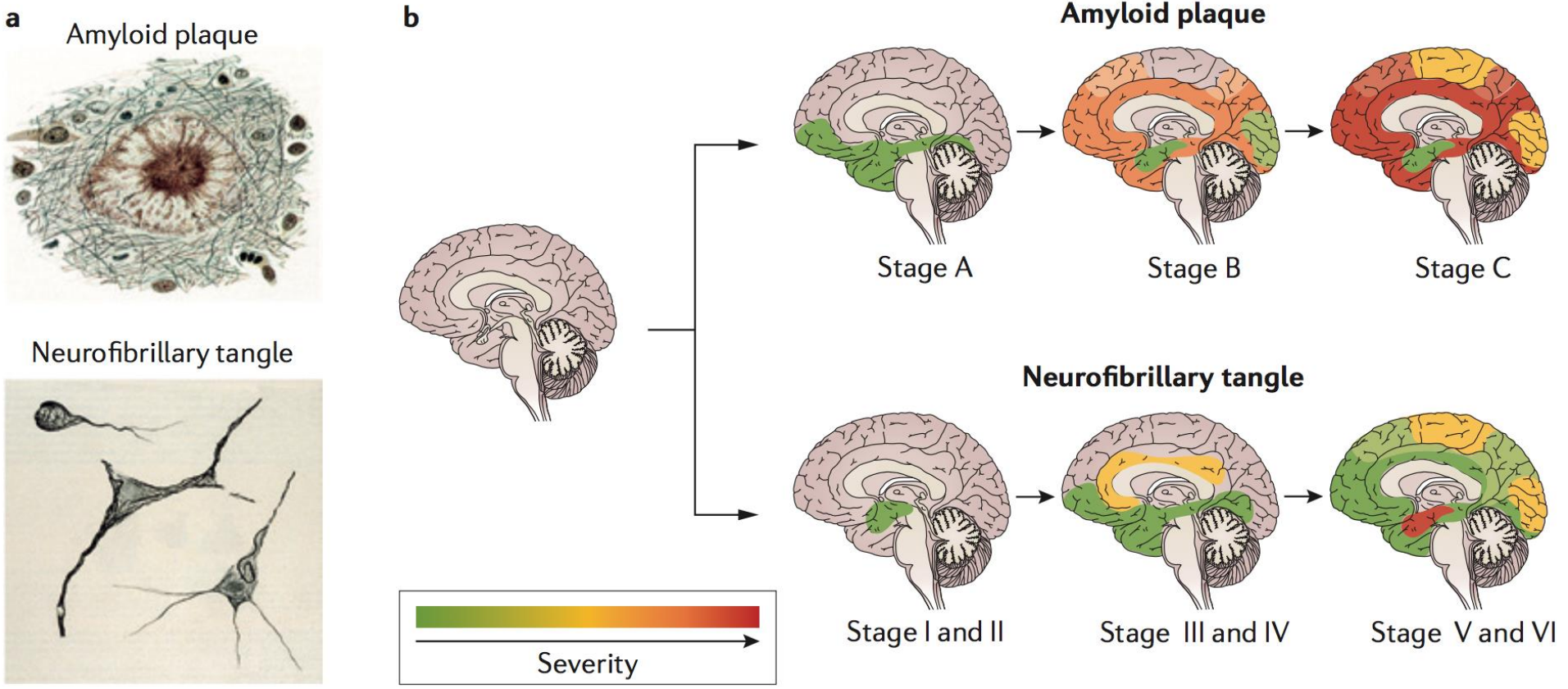


Sperling, R.A. et al., 2011. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer"s & dementia : the journal of the Alzheimer"s Association*, 7(3), pp.280–292.



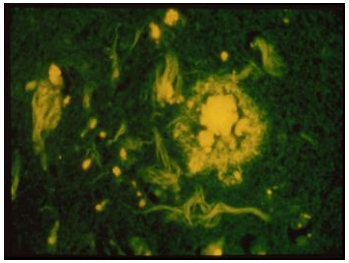
MRI scans (gray) and illustrations (color) show the differences between a brain affected by Alzheimer's disease and a normal brain.

https://www.keepmemoryalive.org/brain-science/alzheimers-brain

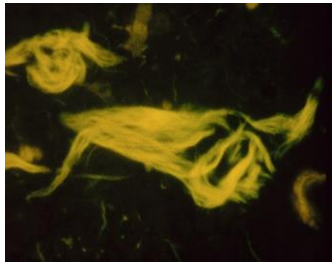


Masters, C.L. et al., 2015. Alzheimer's disease. *Nature reviews. Disease primers*, 1, p.15056.

Biomarkers can now detect and map A,T and N



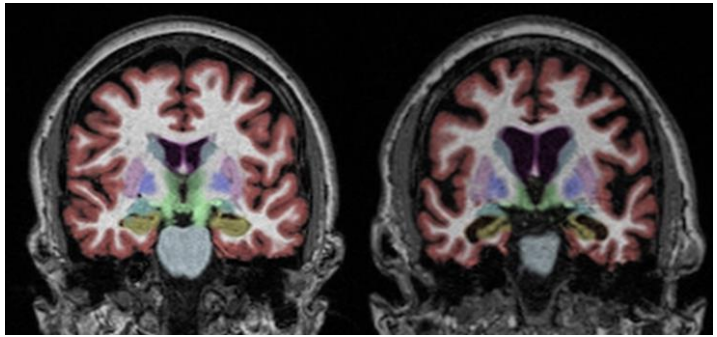
Amyloid plaques



Neurofibrillary tangles

A Amyloid PET, CSF or plasma Aβ42/40

T Tau PET, CSF or plasma P-tau



Brain atrophy and neuron loss

N Neurodegeneration

Anatomy:

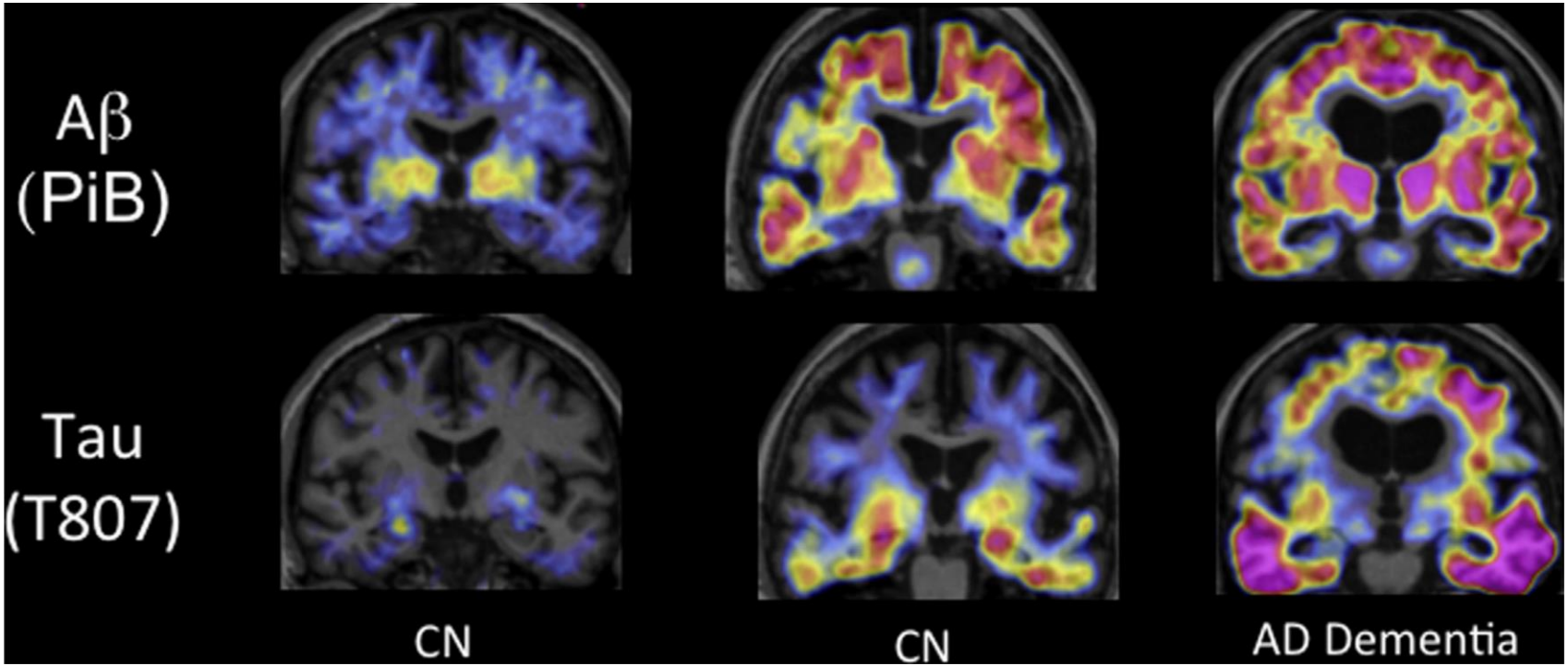
MRI - atrophy, pathways

PET - glucose use

Biochemistry:

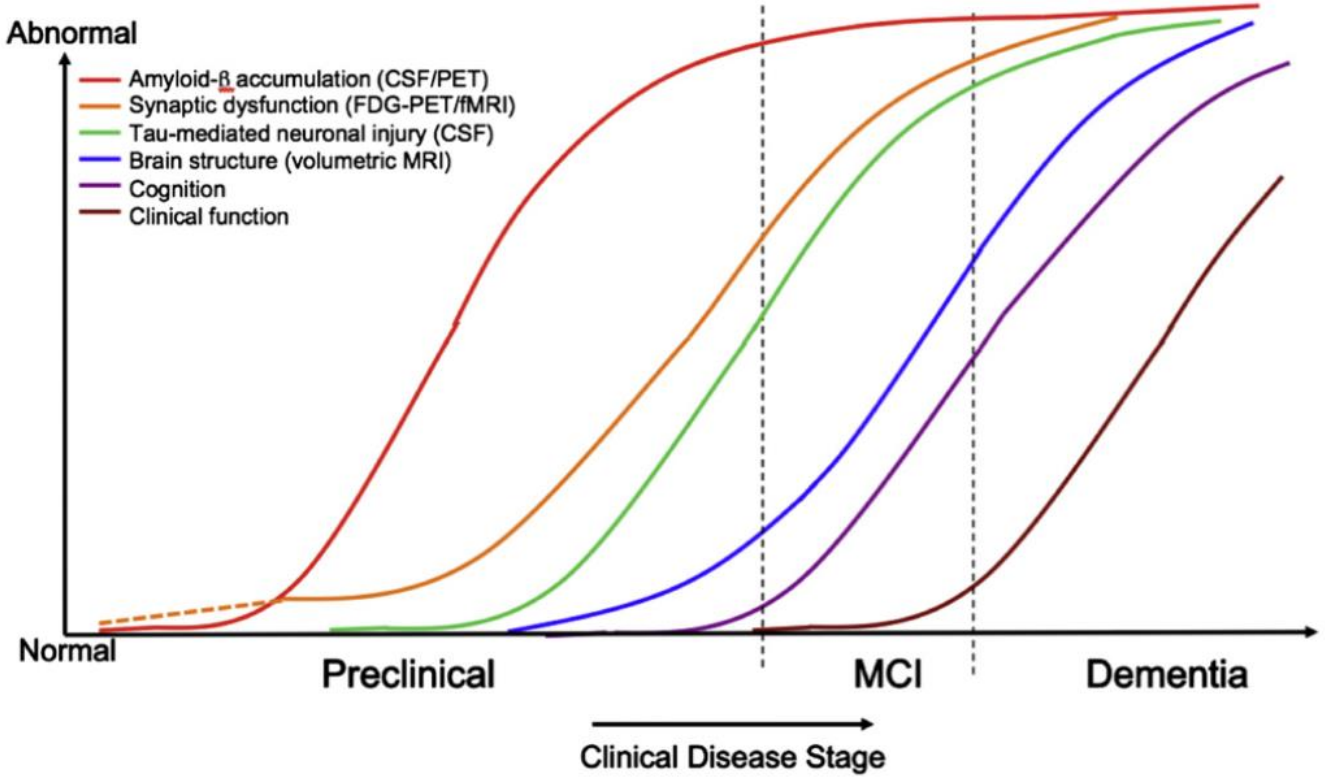
CSF or plasma - tau, NfL, others

The Continuum of Alzheimer's Disease



Sperling, R., Mormino, E. & Johnson, K. The evolution of preclinical Alzheimer's disease: implications for prevention trials. Neuron 84, 608–622 (2014).

The Continuum of Alzheimer's Disease



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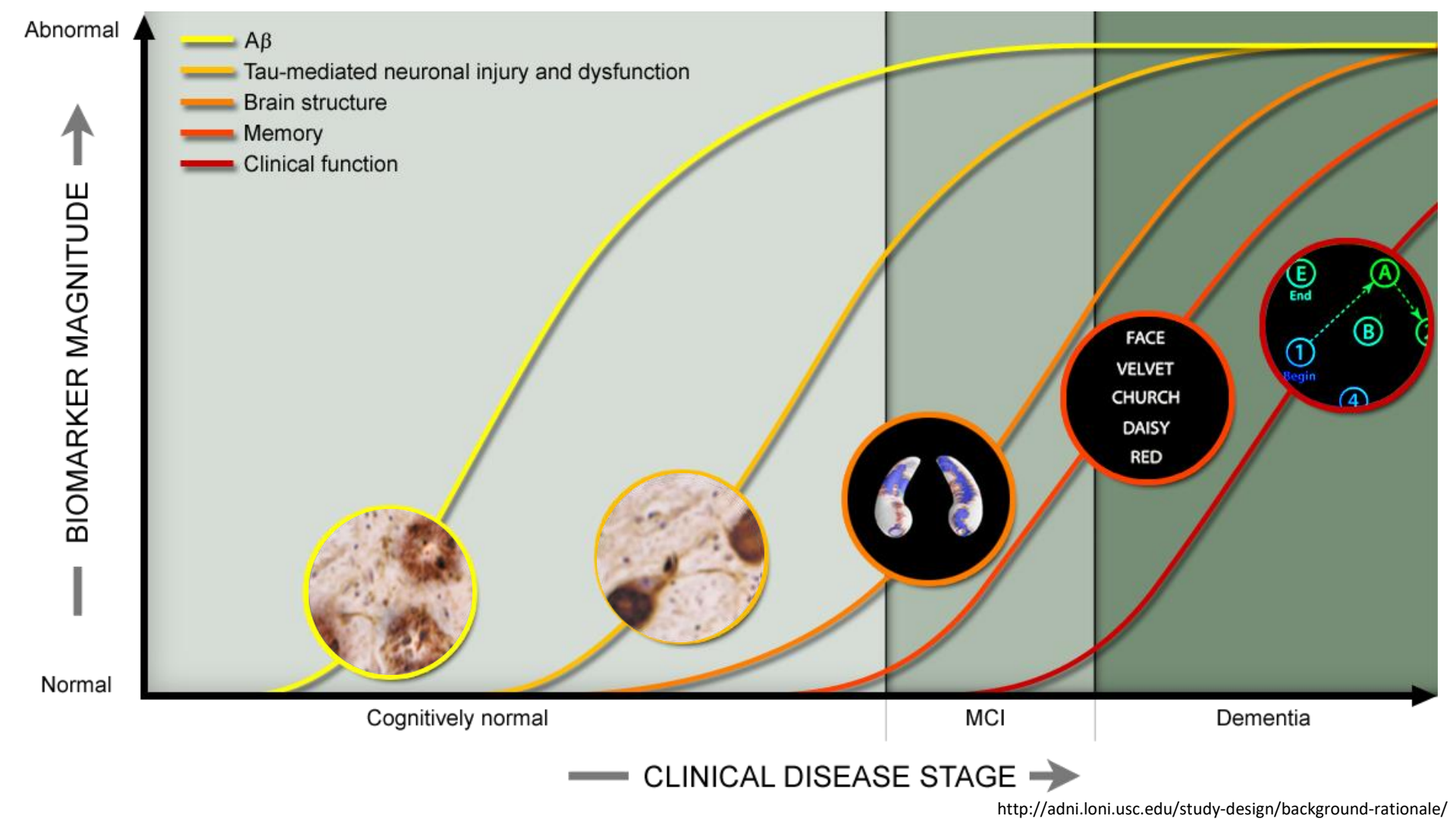
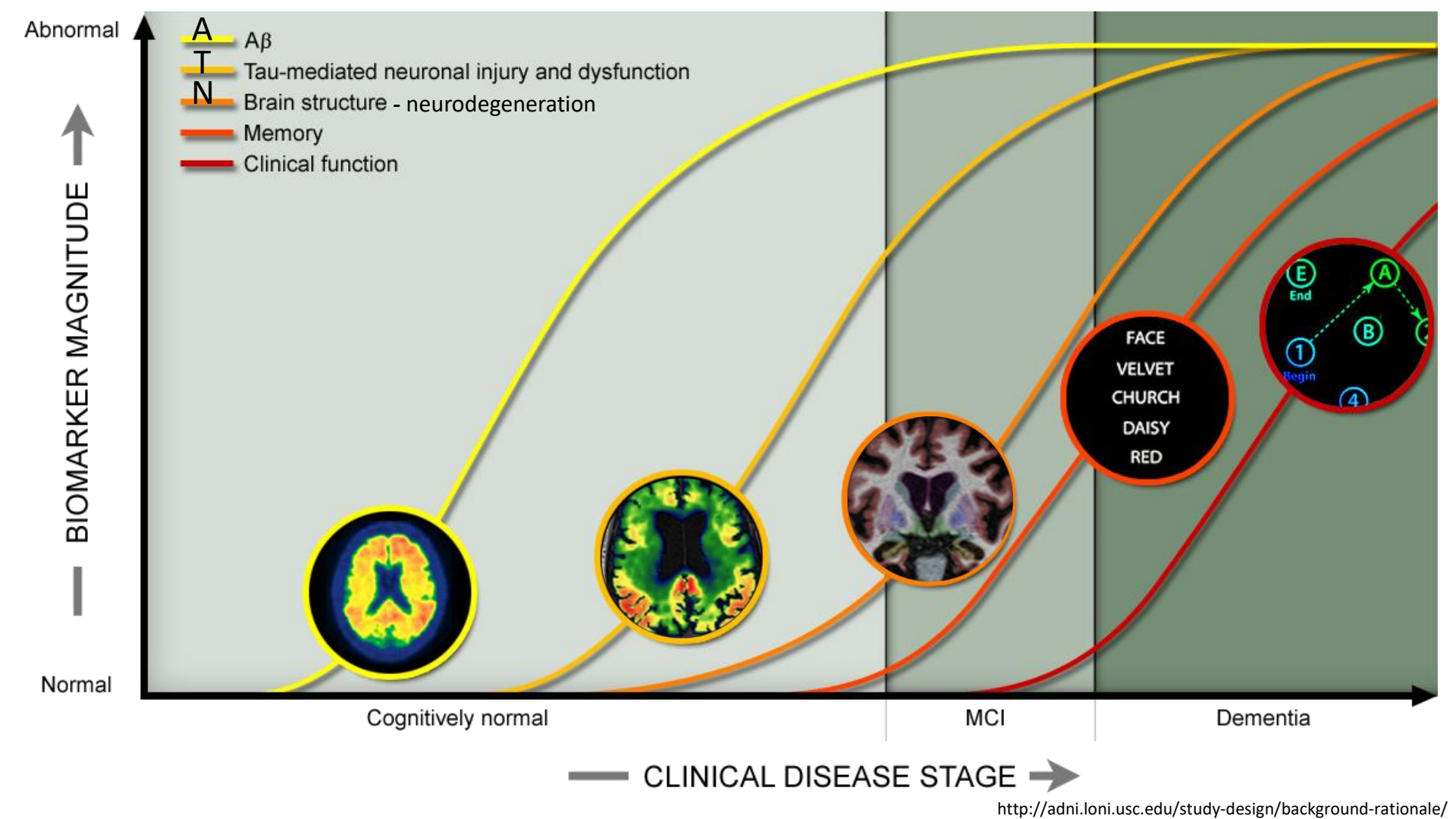


http://adni.loni.usc.edu/study-design/background-rationale/



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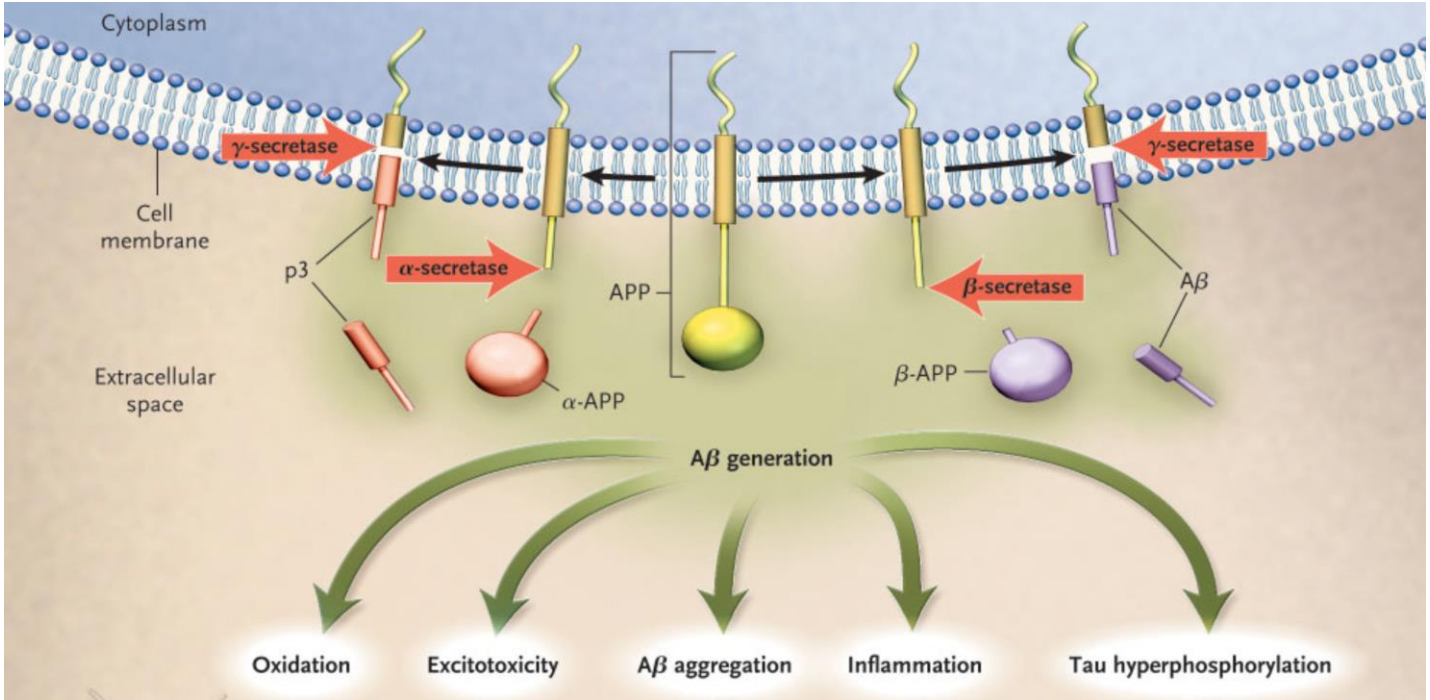

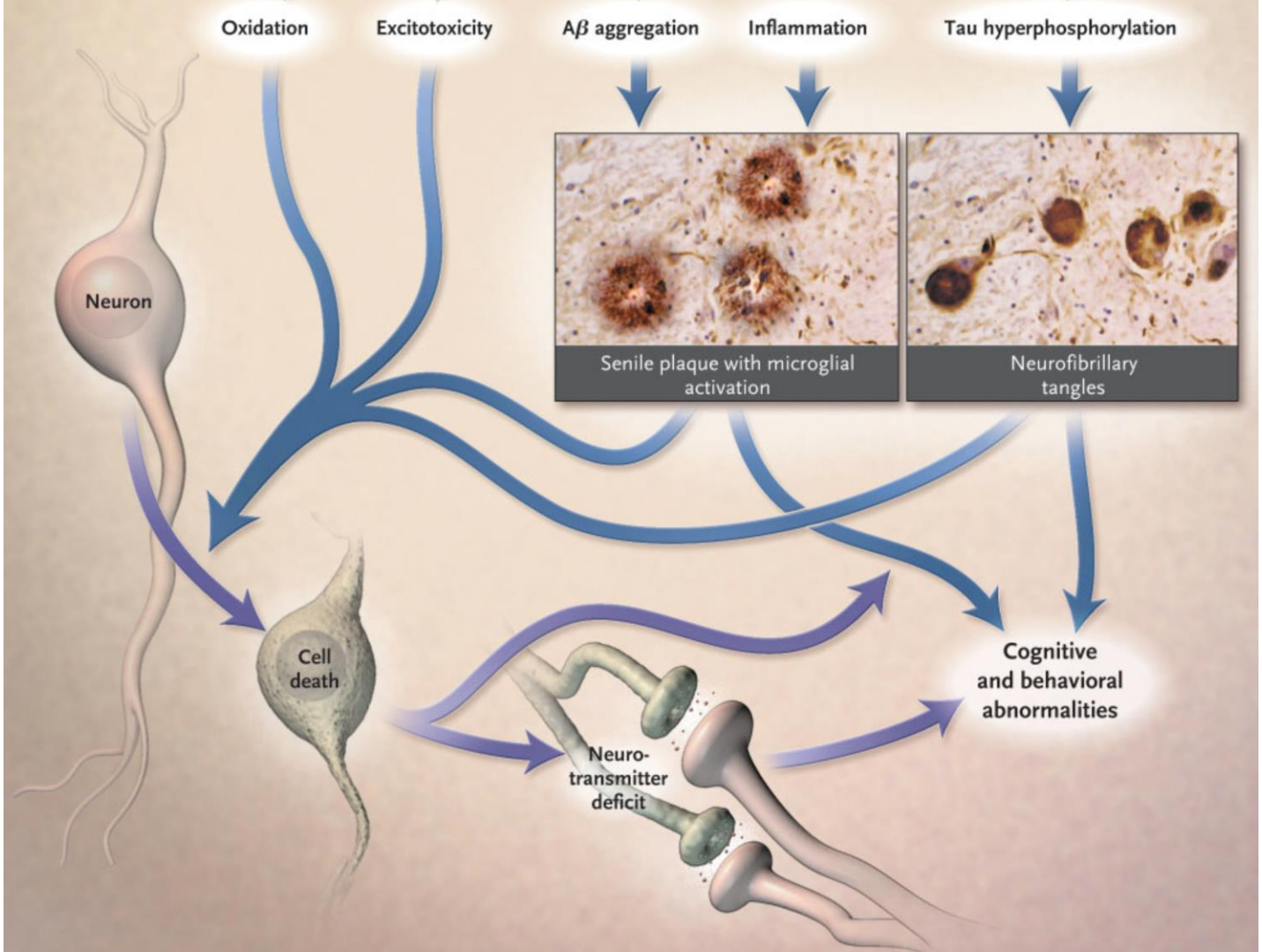
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Excitotoxicity
Aβ aggregation
Inflammation
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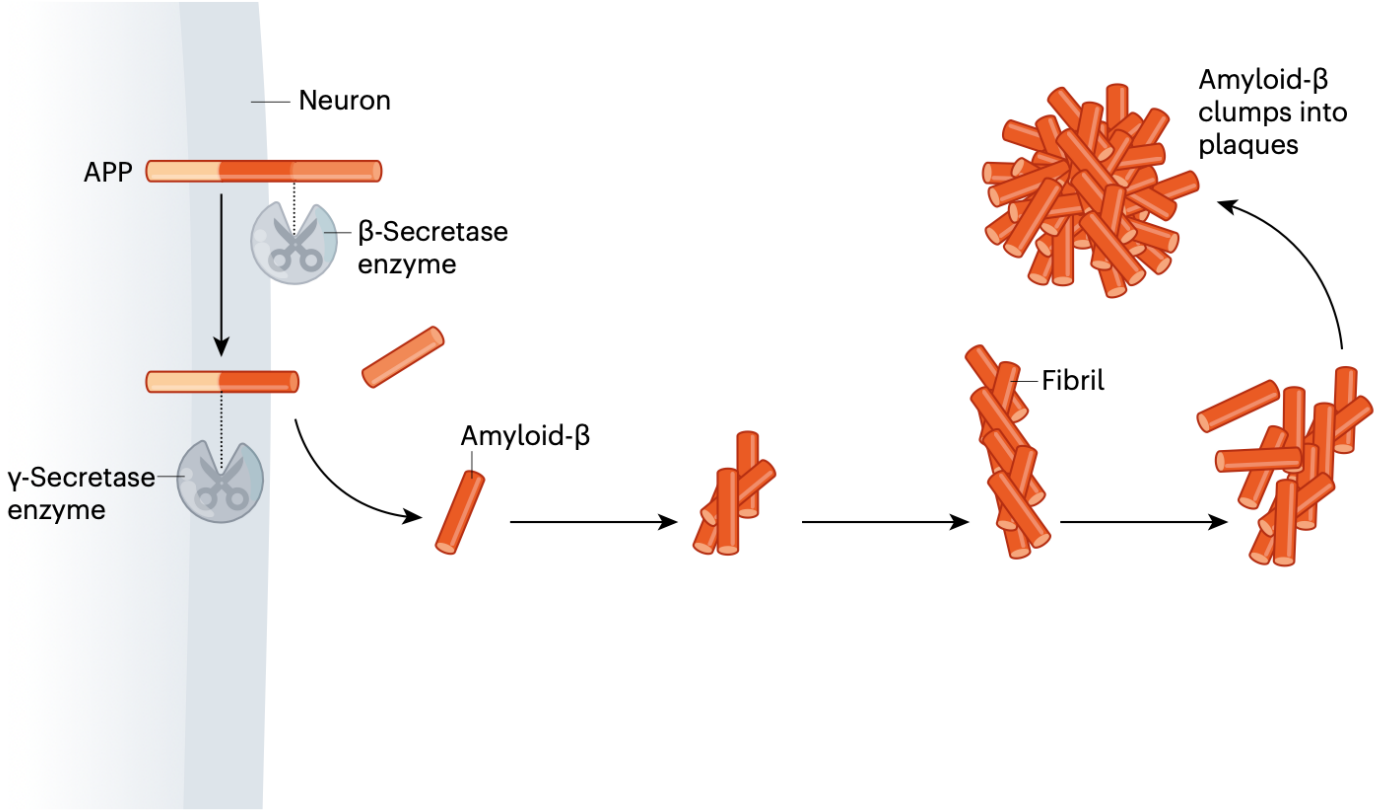
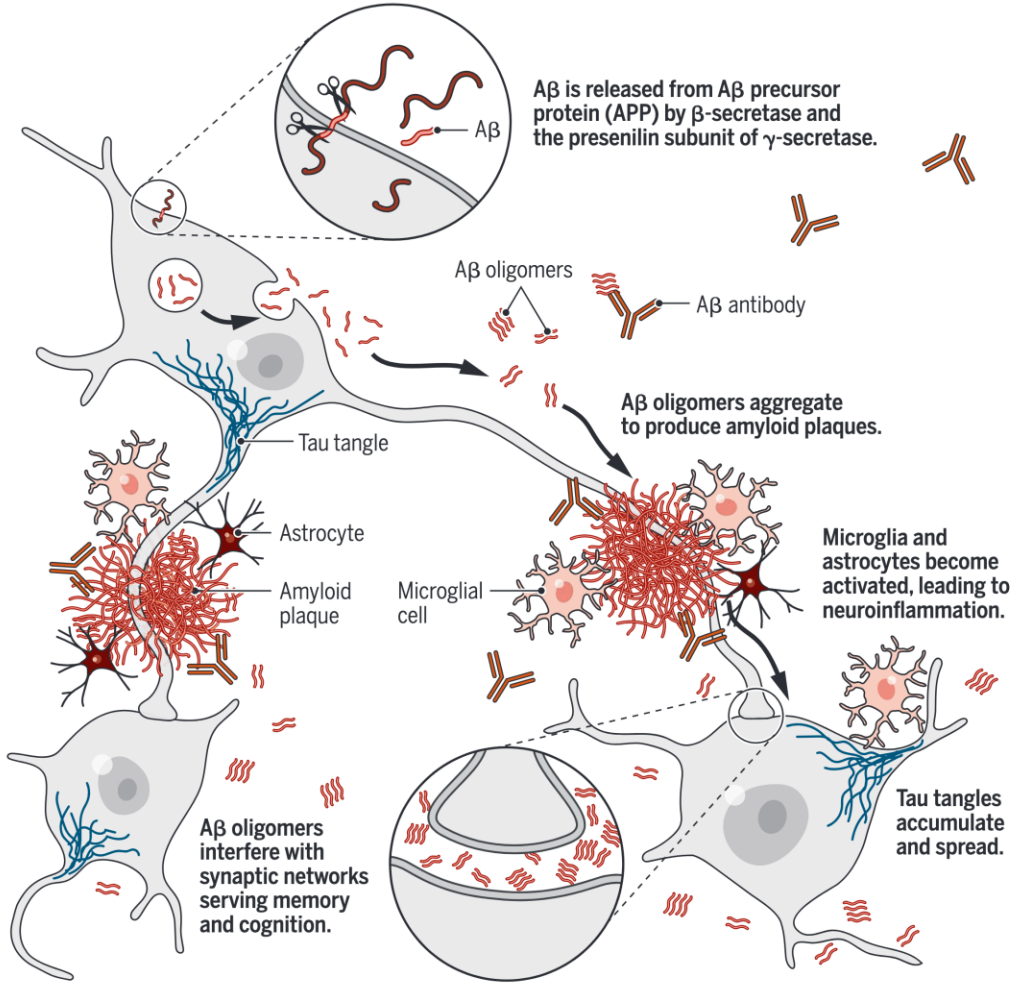
Senile plaque with microglial activation
Neurofibrillary tangles
Cell death
Neuro-transmitter deficit
Cognitive and behavioral abnormalities

Anti-amyloid therapy removes brain amyloid

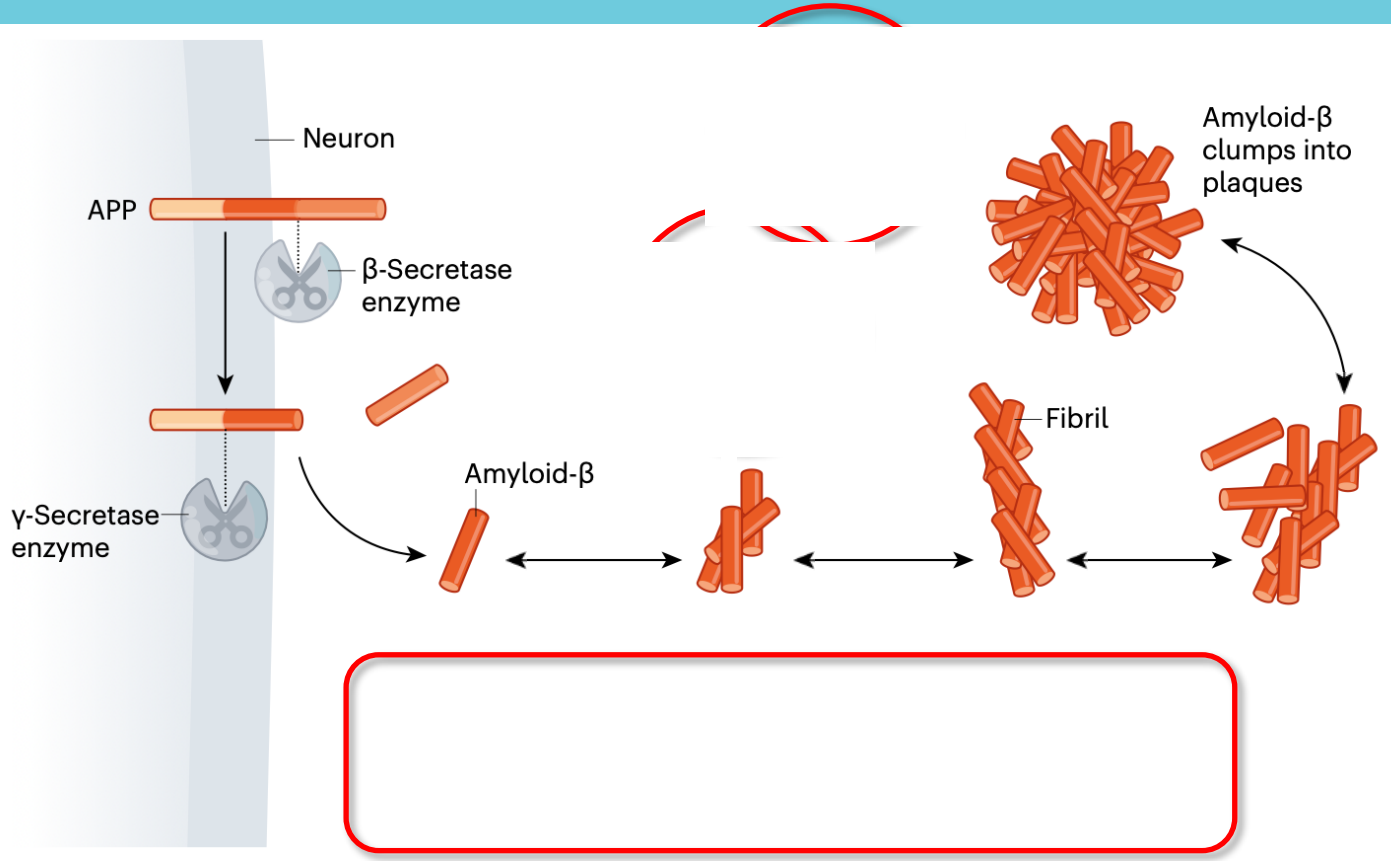


Abbott, A. Could drugs prevent Alzheimer's? These trials aim to find out. *Nature* **603**, 216–219 (2022).



Selkoe, D. J. Treatments for Alzheimer's disease emerge. Science 373, 624–626 (2021).

Anti-amyloid therapy removes brain amyloid



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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 5, 2023 VOL. 388 NO. 1

Lecanemab in Early Alzheimer's Disease

C.H. van Dyck, C.J. Swanson, P. Aisen, R.J. Bateman, C. Chen, M. Gee, M. Kanekiyo, D. Li, L. Reyderman, S. Cohen, L. Froelich, S. Katayama, M. Sabbagh, B. Vellas, D. Watson, S. Dhadda, M. Irizarry, L.D. Kramer, and T. Iwatsubo

JAMA | Original Investigation

Donanemab in Early Symptomatic Alzheimer Disease
The TRAILBLAZER-ALZ 2 Randomized Clinical Trial

John R. Sims, MD; Jennifer A. Zimmer, MD; Cynthia D. Evans, PhD; Ming Lu, MD, MS, MPH; Paul Ardayfio, PhD; JonDavid Sparks, PhD; Alette M. Wessels, PhD; Sergey Shcherbinin, PhD; Hong Wang, PhD; Emel Serap Monkul Nery, MD; Emily C. Collins, PhD; Paul Solomon, PhD; Stephen Salloway, MD; Liana G. Apostolova, MD; Oskar Hansson, MD, PhD; Craig Ritchie, MD, PhD; Dawn A. Brooks, PhD; Mark Mintun, MD; Daniel M. Skovronsky, MD, PhD; for the TRAILBLAZER-ALZ 2 Investigators

JAMA. 2023;330(6):512-527. doi:10.1001/jama.2023.13239
Published online July 17, 2023.

Anti-amyloid immunotherapy

Lecanemab (Leqembi®):

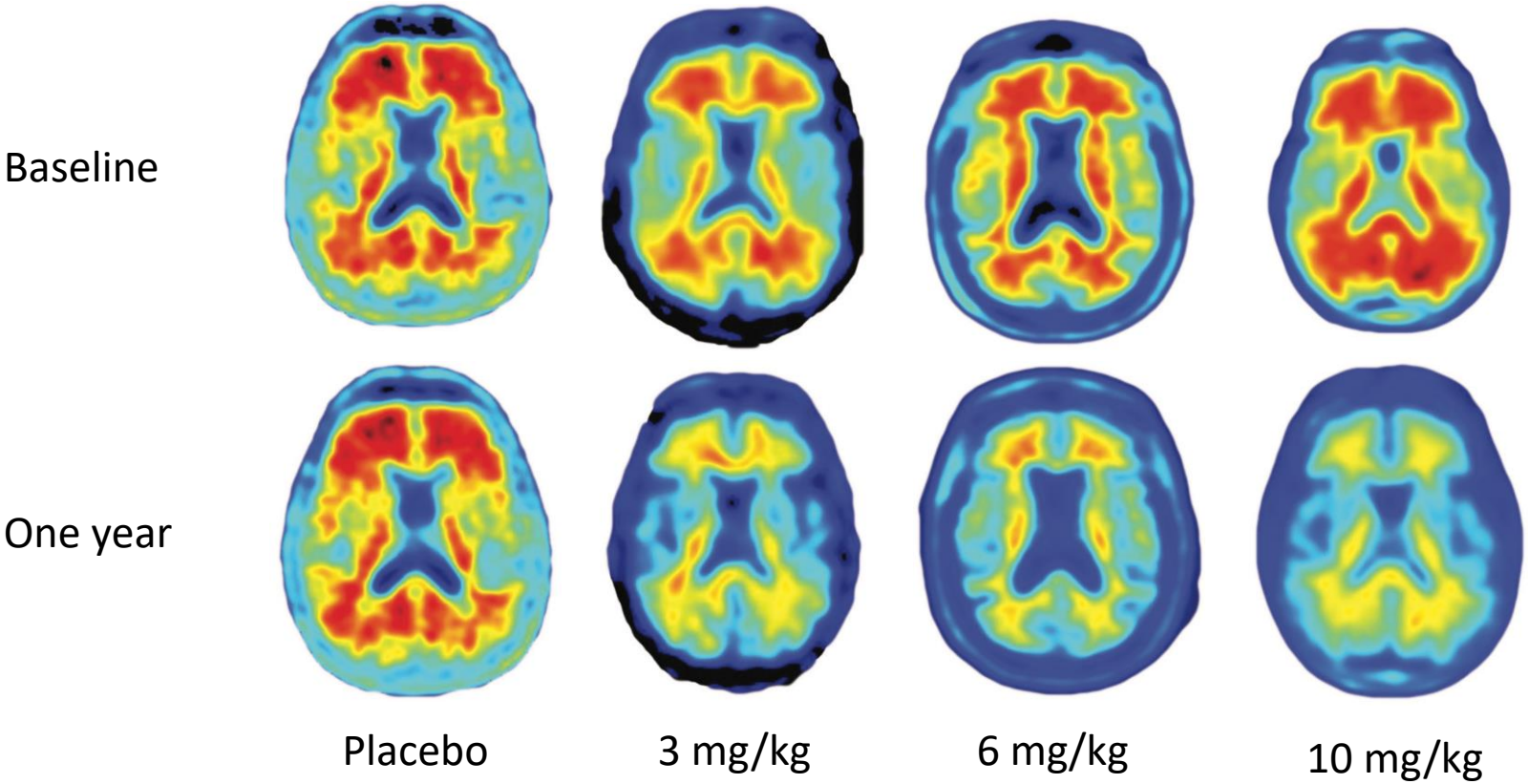
- Binds to *soluble protofibrils* of amyloid and clears plaques.
- Positive phase 2 and phase 3 trials.
- FDA approval in July 2023; covered by CMS.

Donanemab (Kisunla®):

- binds to *insoluble amyloid* in plaques and helps clear them.
- Positive phase 2 and phase 3 trials.
- FDA approval in July 2024; also covered by CMS.

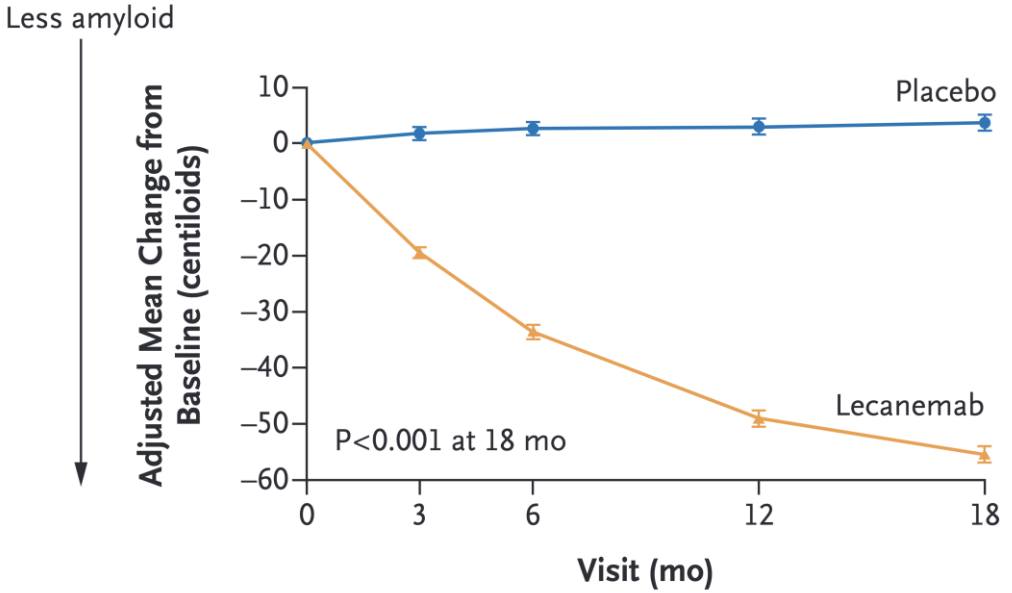
Both antibodies *slowed clinical progression*.
Both were associated with adverse events, especially "ARIA" (which resulted in a black box warning from the FDA).

Anti-amyloid therapy removes brain amyloid



Sevigny, J. *et al.* The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. *Nature* **537**, 50–56 (2016).

Anti-amyloid therapy removes brain amyloid



No. of Participants

Lecanemab	354	296	275	276	210
Placebo	344	303	286	259	205

Dyck, C. H. van *et al.* Lecanemab in Early Alzheimer's Disease. *New Engl J Med* **388**, 9–21 (2022).

Lecanemab & Donanemab lower amyloid and results in clinical slowing

Lecanemab (Leqembi®)

- Phase 3, RCT, 18 months
- (CLARITY AD trial)
- 50-90 years
- MCI or early AD
- 897 placebo : 898 Lecanamab
- IV infusions every 2 weeks
- Overall, 24-37 % reduction in progression
- (patients *still* progress)
- Infusion related reactions in 26.4%
- Overall, ARIA in 12.6% (with 22% Sx)
- Deaths 0.8% *vs* 0.7%

Donanemab (Kisunla®)

- Phase 3, RCT, 18 months
- (TRAILBLAZER-ALZ 2 trial)
- 60-85 years
- MCI or early AD
- 876 placebo : 860 Donanemab
- IV infusions every 4 weeks
- Overall, 20-40 % reduction in progression
- (patients *still* progress)
- Infusion related reactions in 8.7%
- Overall, ARIA in 24% (with 25% Sx)
- Deaths 1.1% *vs* 1.9%

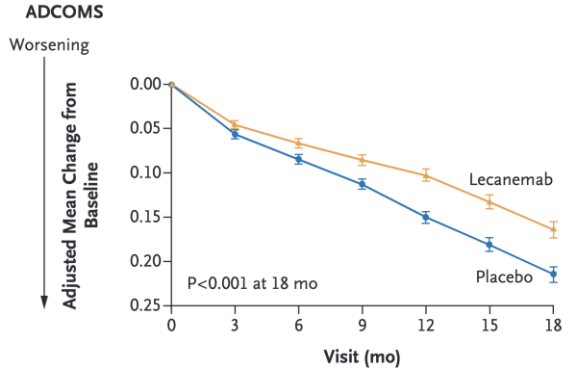
Dyck, C. H. van *et al.* Lecanemab in Early Alzheimer's Disease. *New Engl J Med* **388**, 9–21 (2022).
Sims, J. R. *et al.* Donanemab in Early Symptomatic Alzheimer Disease. *JAMA* **330**, 512–527 (2023).

What does slowing of progression mean?

Source: Kennedy GJ. Primary Psychiatry. Vol 14, No 11 2007

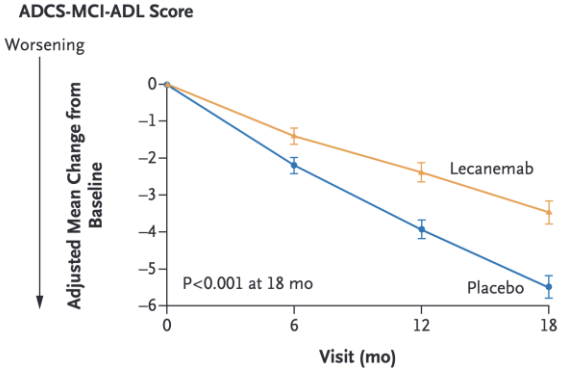
Lecanemab & Donanemab lower amyloid and results in clinical slowing

Lecanemab



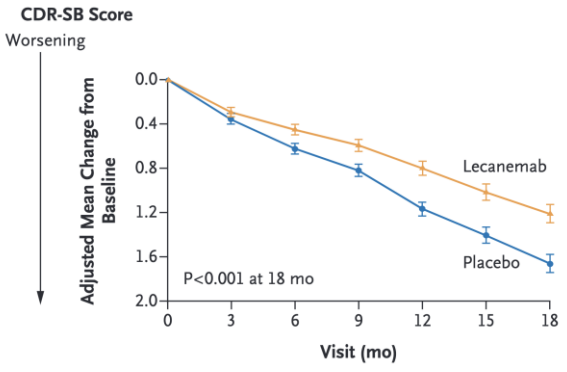
No. of Participants

Lecanemab	857	820	796	774	757	733	708
Placebo	875	847	822	808	775	764	749



No. of Participants

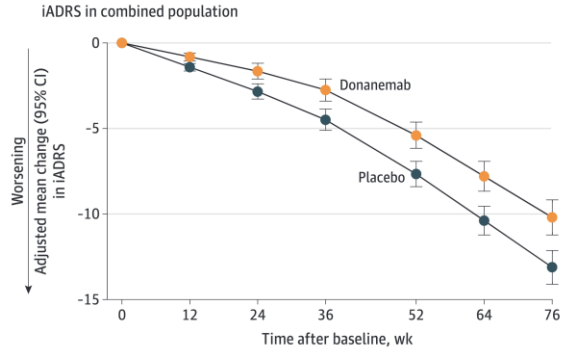
Lecanemab	783	756	716	676
Placebo	796	783	739	707



No. of Participants

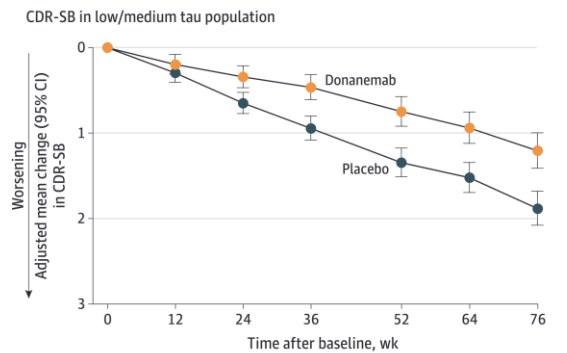
Lecanemab	859	824	798	779	765	738	714
Placebo	875	849	828	813	779	767	757

Donanemab



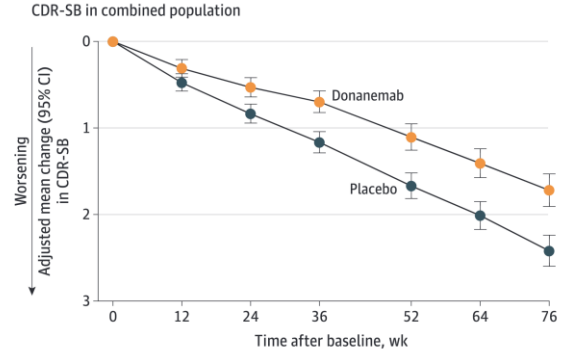
No. of participants

Placebo	824	805	767	738	693	651	653
Donanemab	775	752	712	665	636	579	583



No. of participants

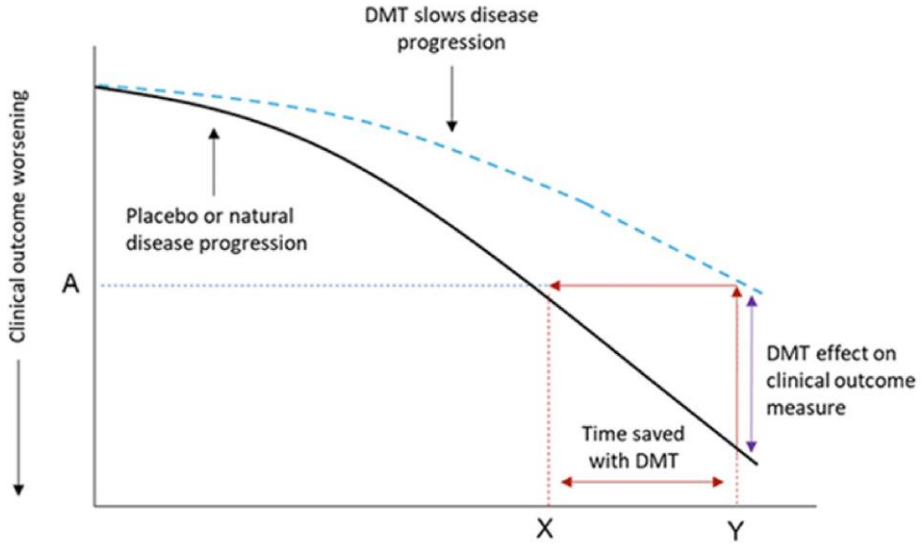
Placebo	569	561	540	516	486	461	459
Donanemab	546	530	499	471	451	418	424



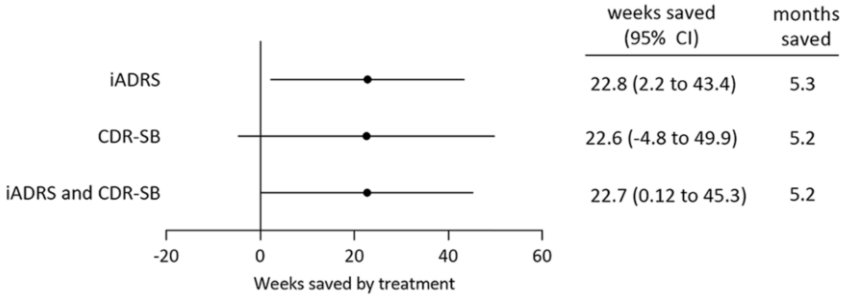
No. of participants

Placebo	838	825	784	752	713	678	672
Donanemab	794	774	731	682	650	603	598

What does slowing of progression mean?

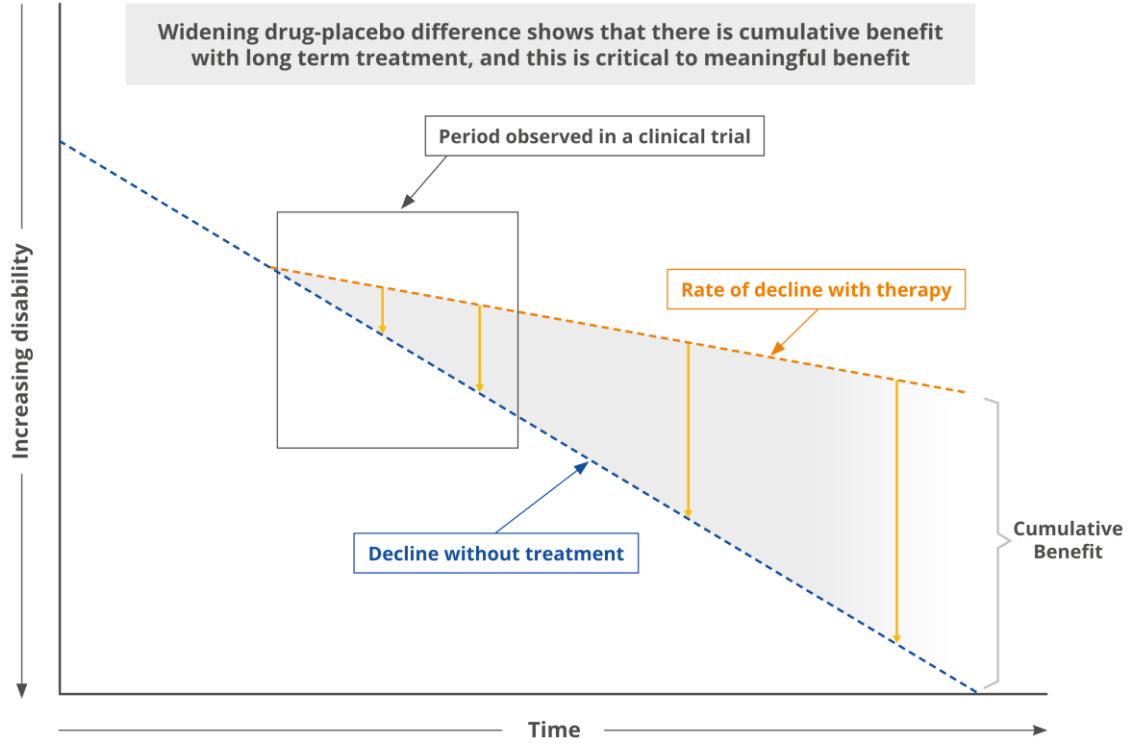


Time saved over 18 months



Dickson, S. P. *et al.* 'Time Saved' As a Demonstration of Clinical Meaningfulness and Illustrated Using the Donanemab TRAILBLAZER-ALZ Study Findings. *J. Prev. Alzheimer's Dis.* **10**, 595–599 (2023).

What does slowing of progression mean?



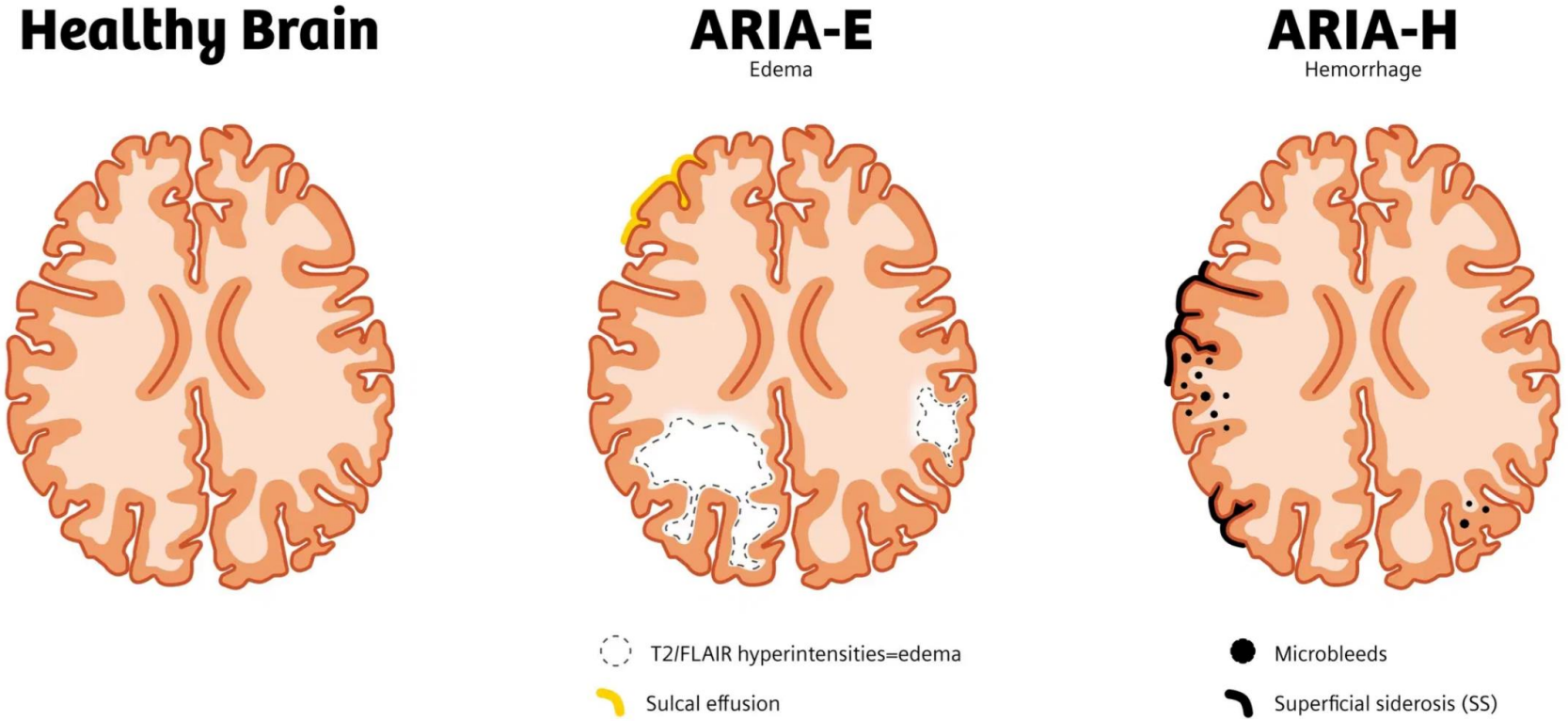
Assunção, S. S. *et al.* Meaningful benefits: a framework to assess disease-modifying therapies in preclinical and early Alzheimer's disease. *Alzheimer's Res. Ther.* **14**, 54 (2022).

Benefit – At what cost?

- Actual monetary cost
- Time spent in the infusion center

- Complications:
  - Infusion reactions
  - ARIA
  - No anti-coagulants or tPA (if patient suffers from MI or stroke)

ARIA – Amyloid Related Imaging Abnormality



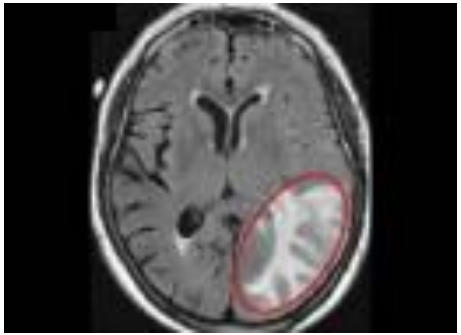
https://www.siemens-healthineers.com/en-us/magnetic-resonance-imaging/clinical-specialities/neuro-mr-imaging/alzheimers

ARIA – Amyloid Related Imaging Abnormality

Most ARIA episodes are ***asymptomatic*** but can be seen on MRI

However, symptoms may occur:

- headache, nausea, confusion, dizziness
- rarely stroke or seizures

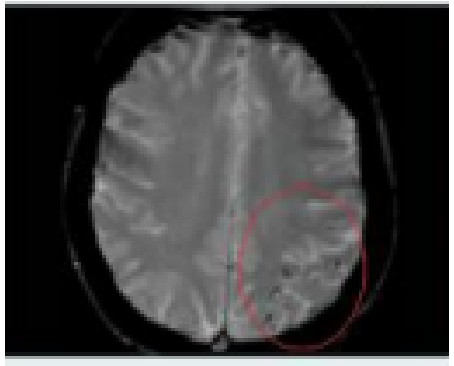


ARIA-E
(FLAIR MRI)

Mitigate

Baseline MRI: exclude people with >4 microhemorrhages

Monitor - especially early in treatment and in ApoE ε4 carriers with safety MRIs at multiple time points, and if/when symptoms emerge



ARIA-H
(SWI MRI)

Appropriate Use Recommendations (AURs)

J Prev Alz Dis 2023;3(10):362-377
Published online March 27, 2023, http://dx.doi.org/10.14283/jpad.2023.30

Review

Lecanemab: Appropriate Use Recommendations

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Special Article

Donanemab: Appropriate use recommendations

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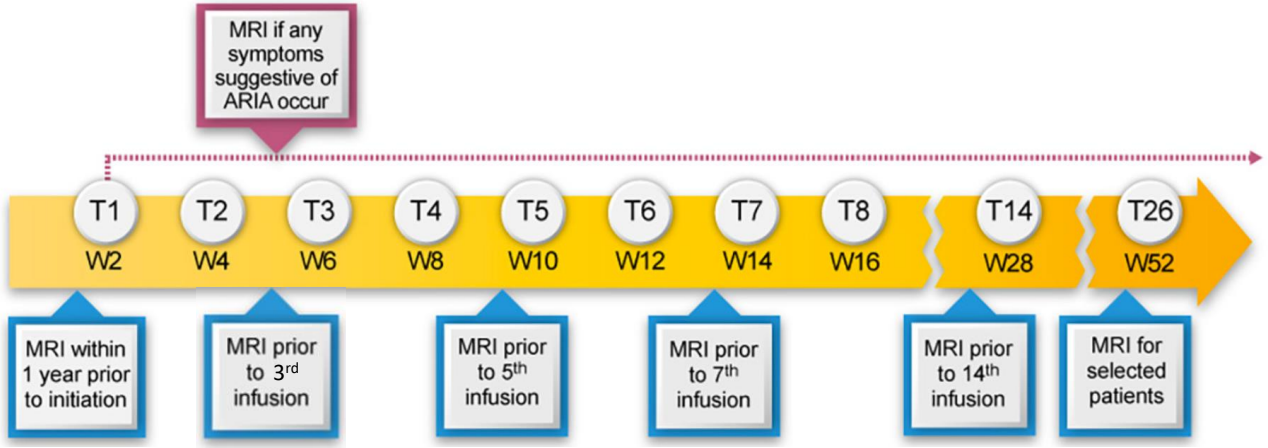
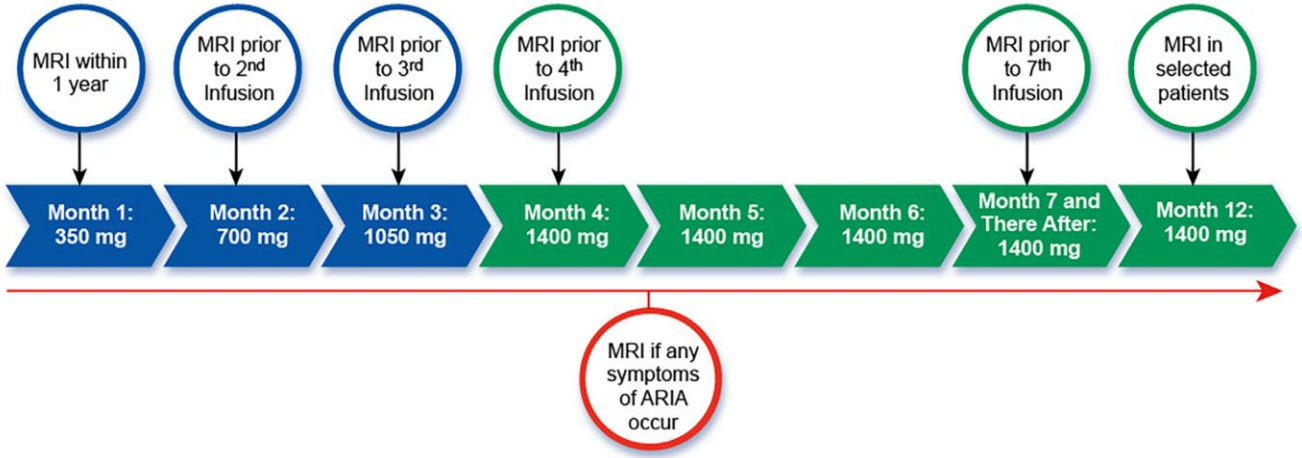
Lecanemab



Donanemab



ARIA – Amyloid Related Imaging Abnormality

ARIA risk higher in APOE ε4 carriers				
ApoE status	**Lecanemab (E & H)**	**Sx**	**Donanemab (E & H)**	**Sx**
ε2-3/2-3	5.4 & 11.1%	22%	15 & 18%	25%
ε2-3/4	10.9 & 14%		22 & 32%	
ε4/4	32.6 & 39%		40 & 50%	

Dyck, C. H. van *et al.* Lecanemab in Early Alzheimer's Disease. *New Engl J Med* **388**, 9–21 (2022).
Sims, J. R. *et al.* Donanemab in Early Symptomatic Alzheimer Disease. *JAMA* **330**, 512–527 (2023).

Category, n (%)	Standard (*N* = 207)	Modified titration (*N* = 212)
ARIA-E[a,b]	49 (23.7)	29 (13.7)
Asymptomatic[a,b]	39 (18.8)	23 (10.8)
Symptomatic[a,b]	10 (4.8)	6 (2.8)
ARIA-H[a,c]	52 (25.1)	43 (20.3)
Asymptomatic[a,c]	52 (25.1)	42 (19.8)
Symptomatic[a,c,d]	0 (0)	1 (0.5)
Microhemorrhage[e]	41 (19.8)	36 (17.0)
Cortical superficial siderosis[e]	26 (12.6)	14 (6.6)

Wang, H. *et al.* Modified titration of donanemab reduces ARIA risk and maintains amyloid reduction. *Alzheimer's Dement.* **21**, e70062 (2025)

Possibly associated SSx (in 1:4 or 1:5 patients)

Symptoms observed in patients who develop symptomatic ARIA.

- Headache
- Confusion
- Visual changes
- Dizziness
- Nausea
- Gait difficulty

Easily reversible

- Serious ARIA
  - Seizures, including status epilepticus
  - Encephalopathy
  - Focal neurological deficits
  - Death

Rabinovici, G. D. *et al.* Donanemab: Appropriate use recommendations. *J. Prev. Alzheimer's Dis.* **12**, 100150 (2025).

Management of ARIA depends on severities

Figure 2. Monitoring and management of ARIA

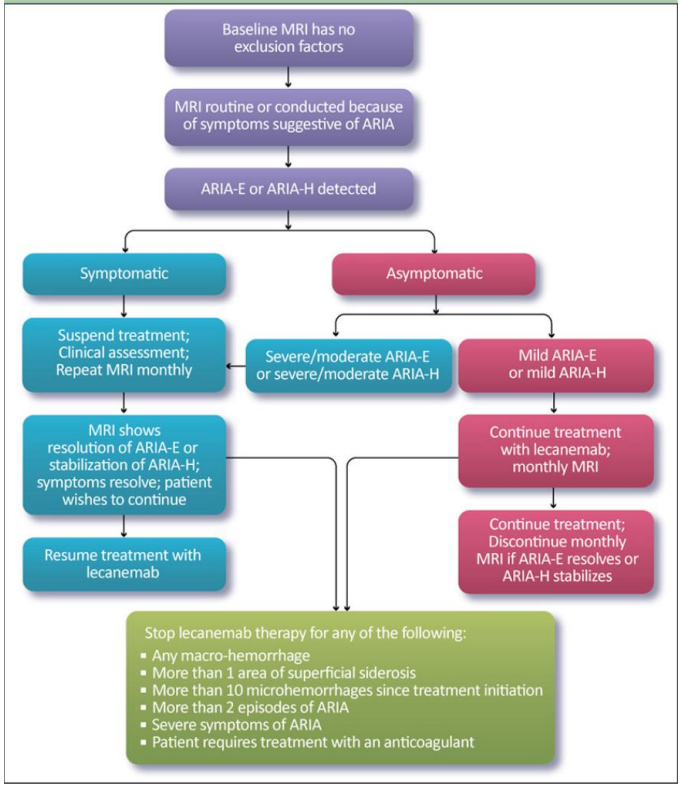


Table 7. Description of mild, moderate, and severe radiographic ARIA (from the Prescribing Information)

	Radiographic Severity		
ARIA Type	**Mild**	**Moderate**	**Severe**
ARIA-E	FLAIR hyperintensity confined to sulcus and/or cortex/subcortex white matter in one location <5 cm	FLAIR hyperintensity 5 to 10 cm in single greatest dimension, or more than 1 site of involvement, each measuring <10 cm	FLAIR hyperintensity >10 cm with associated gyral swelling and sulcal effacement. One or more separate/independent sites of involvement may be noted
ARIA-H Microhemorrhage	≤ 4 new incident microhemorrhages	5 to 9 new incident microhemorrhages	10 or more new incident microhemorrhages
ARIA-H Superficial Siderosis	1 focal area of superficial siderosis	2 focal areas of superficial siderosis	> 2 areas of superficial siderosis

Table 8. Management of ARIA depending on the severity of symptoms and the severity of the radiographic ARIA-E or ARIA-H on MRI

	Symptom Description			
	No Symptoms	**Mild Symptoms**	**Moderate Symptoms**	**Severe Symptoms**
Severity of Changes Observed on MRI	None	Discomfort noted; no disruption of daily activity	Discomfort sufficient to reduce or affect normal daily activity	Incapacitating, with inability to work or to perform normal daily activity
ARIA-E on MRI				
Mild	Continue dosing	Suspend dosing	Suspend dosing	Discontinue dosing
Moderate	Suspend dosing	Suspend dosing	Suspend dosing	Discontinue dosing
Severe	Discontinue dosing	Discontinue dosing	Discontinue dosing	Discontinue dosing
ARIA-H on MRI				
Mild	Continue dosing	Suspend dosing	Suspend dosing	Discontinue dosing
Moderate	Suspend dosing	Suspend dosing	Suspend dosing	Discontinue dosing
Severe	Discontinue dosing	Discontinue dosing	Discontinue dosing	Discontinue dosing

Cummings, J. *et al.* Lecanemab: Appropriate Use Recommendations. *J. Prev. Alzheimer's Dis.* **10**, 362–377 (2023)

Implications for practice

To prescribe anti-amyloid therapies, we need to:

- detect MCI or mild dementia (*i.e.* Early symptomatic disease)
- determine if Alzheimer's is the cause of cognitive decline

  (requires the use of biomarker tests to confirm diagnosis)
- explain risks and benefits of anti-amyloid immunotherapy

  (to promote informed consent)
- refer appropriate patients for therapy consideration

Work-up

Screen for MCI or Mild Alzheimer's

History: mild *memory loss*, most *complex ADLs intact* or needs only a little assistance

Cognitive testing: consider anti-amyloid therapy if

- MoCA: usually > 18 or Mini-Mental State Exam: > 21
- Other causes of dementia ruled out
- Minimal or mild impact on iADLs

General good health. **Not on anticoagulants**.

Able to have safety MRIs.

If an MRI is ordered for diagnosis, important to include SWI (susceptibility weighted) sequences (to assess ARIA risk), and obtain volumetric MRI analysis if possible

Discussion with patient

Diagnosis of MCI or Mild dementia *due to AD*

Underlying etiology must be biomarker confirmed

- CSF or amyl
- Blood tests

ApoE genotypir

Treatment: 1-2

Likely costs:

Treatment costs ~ $26,000 per year (x at least 18 months)

Covered by Medicare, but watch out for copays

Diagnostic tests, PET scan, and the safety MRIs

Examples of Chemotherapy Costs:

- **Breast cancer:** $34,979 per year (average)
- **Lung cancer:** $134,682 per year (stage 4)
- **Colon cancer:** $70,000 per year (average)
- **Lymphoma:** $50,000 to $100,000 per year

What we typically do in Memory Clinic

Review the workup

Repeat components as needed

Review inclusion/exclusion criteria

Obtain AD biomarker (CSF or amyloid PET or plasma)

Obtain MRI with SWI sequences to assess microbleeds

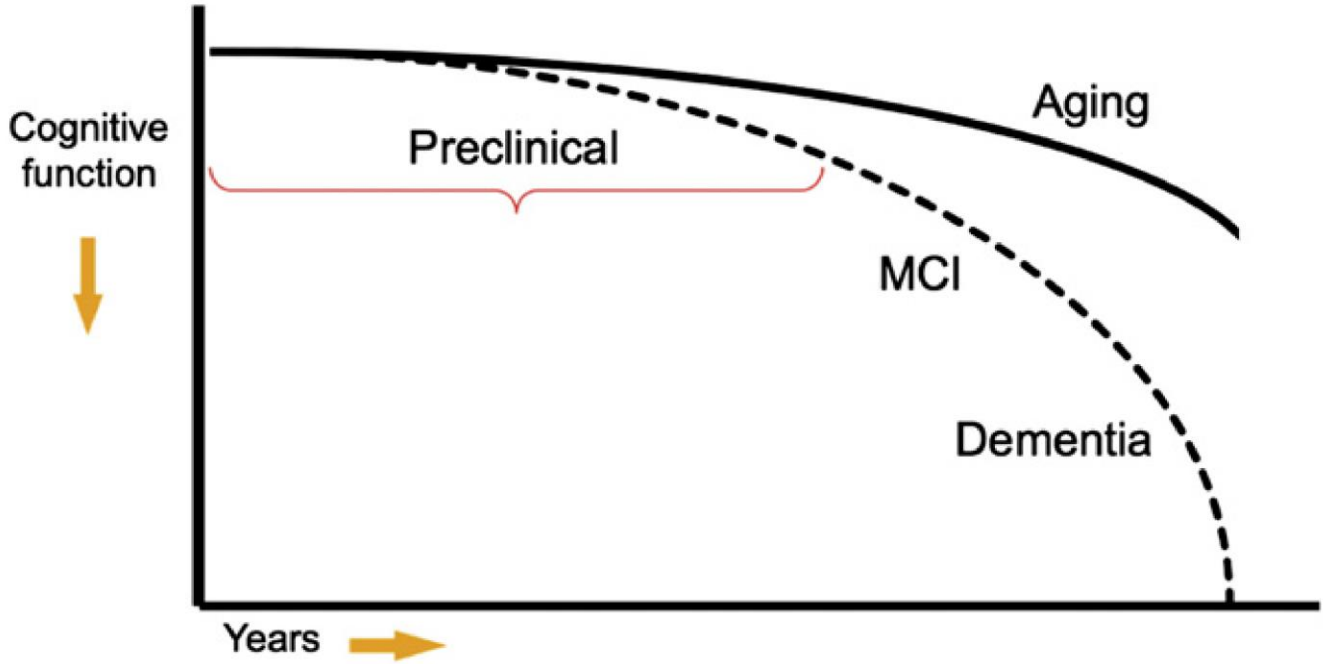
Obtain ApoE genotyping to evaluate ARIA risk

Discuss treatment plan with patient and family

Monitoring while on anti-amyloid Rx

- General health and cognition
- Infusion Center manages infusion reactions (from 10 to 26% of patients)
- Symptoms that might be ARIA -> may need to go to ED, get MRI
- Safety MRIs:
  - Lecanemab: weeks 4, 8, 12 and 26
  - Donanemab: weeks 4, 8, 12, and 28
  - If significant or symptomatic ARIA –> hold or d/c treatment
- New need for ***anticoagulation*** or ***IV tPA***? Treatment carries **major risk of intracranial hemorrhage** – if necessary, should stop anti-amyloid treatment

The Continuum of Alzheimer's Disease



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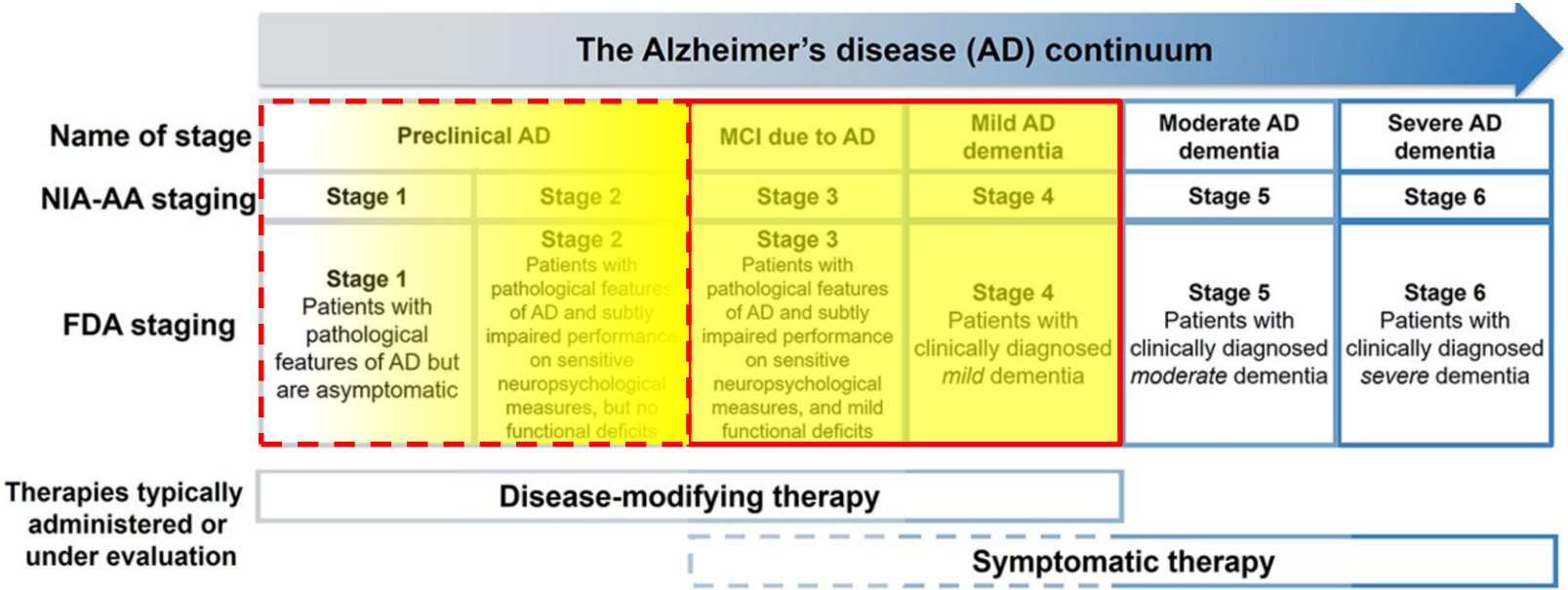
The Continuum of Alzheimer's Disease



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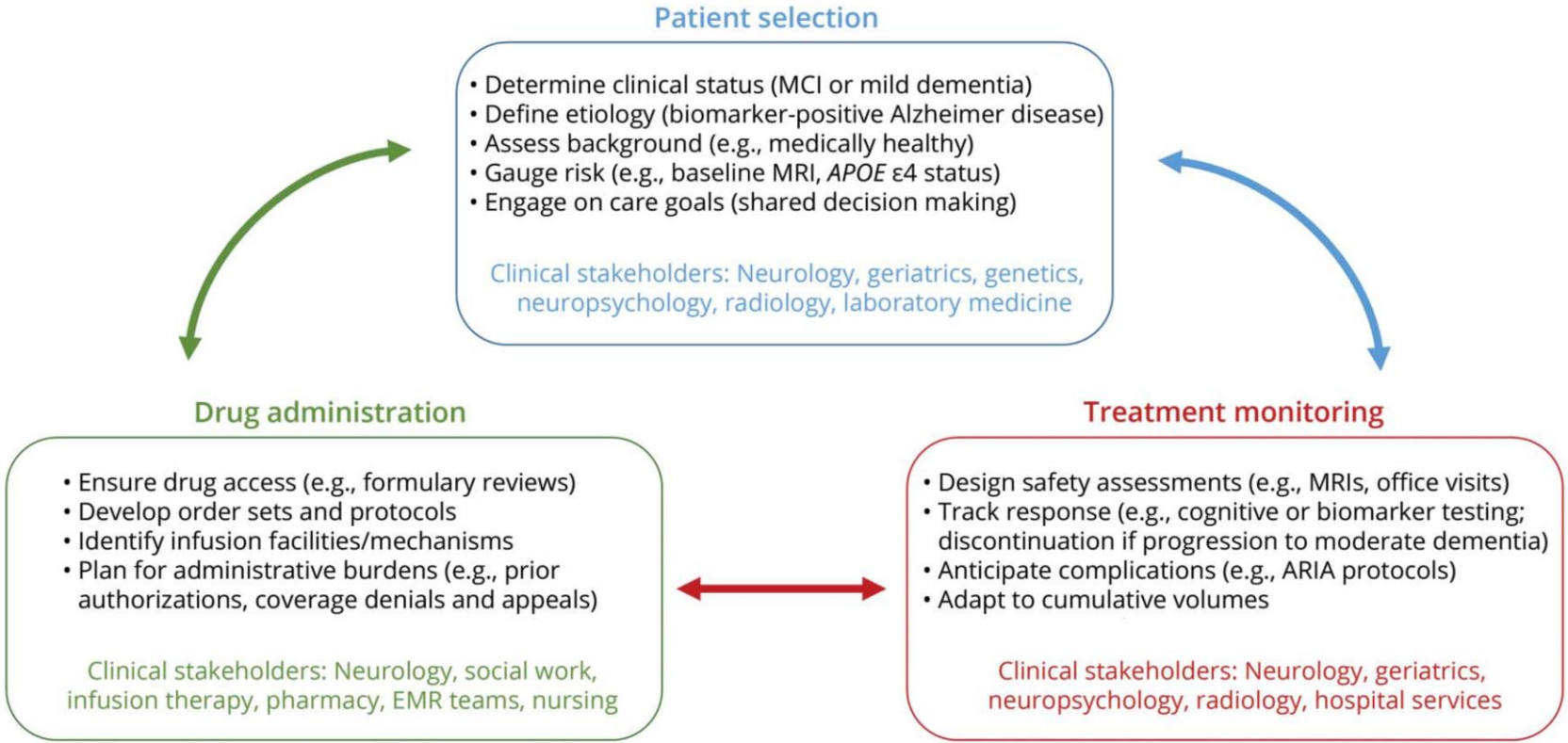
The overall plan:



Ramanan, V. K. et al. Antiamyloid Monoclonal Antibody Therapy for Alzheimer Disease. Neurology 101, 842–852 (2023).

Managing Expectations

Discussing treatment with lecanemab or donanemab will require a significant amount of time and may best occur during an appointment scheduled exclusively for this purpose

Appropriated discussions with patients and care partners:

- Cummings, J. *et al.* Lecanemab: Appropriate Use Recommendations. *J. Prev. Alzheimer's Dis.* **10**, 362–377 (2023)
- Rabinovici, G. D. *et al.* Donanemab: Appropriate use recommendations. *J. Prev. Alzheimer's Dis.* 100150 (2025)

Are these new medications game changers?

The Numbers

About 5-7 million individuals in the US are estimated to have MCI

About 6.9 million individuals in the US have AD

Among those with AD

- 50% have mild disease
- 30% have moderate disease
- 17% have severe disease

Who is eligible?

- About 1 in 10 MCI or mild AD will be eligible for treatment with anti-amyloid agents
- About 47% (2.7 million) currently living with AD are not eligible based severity of disease

2024 Alzheimer's disease facts and figures. *Alzheimer's Dement.* **20**, 3708–3821 (2024).
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