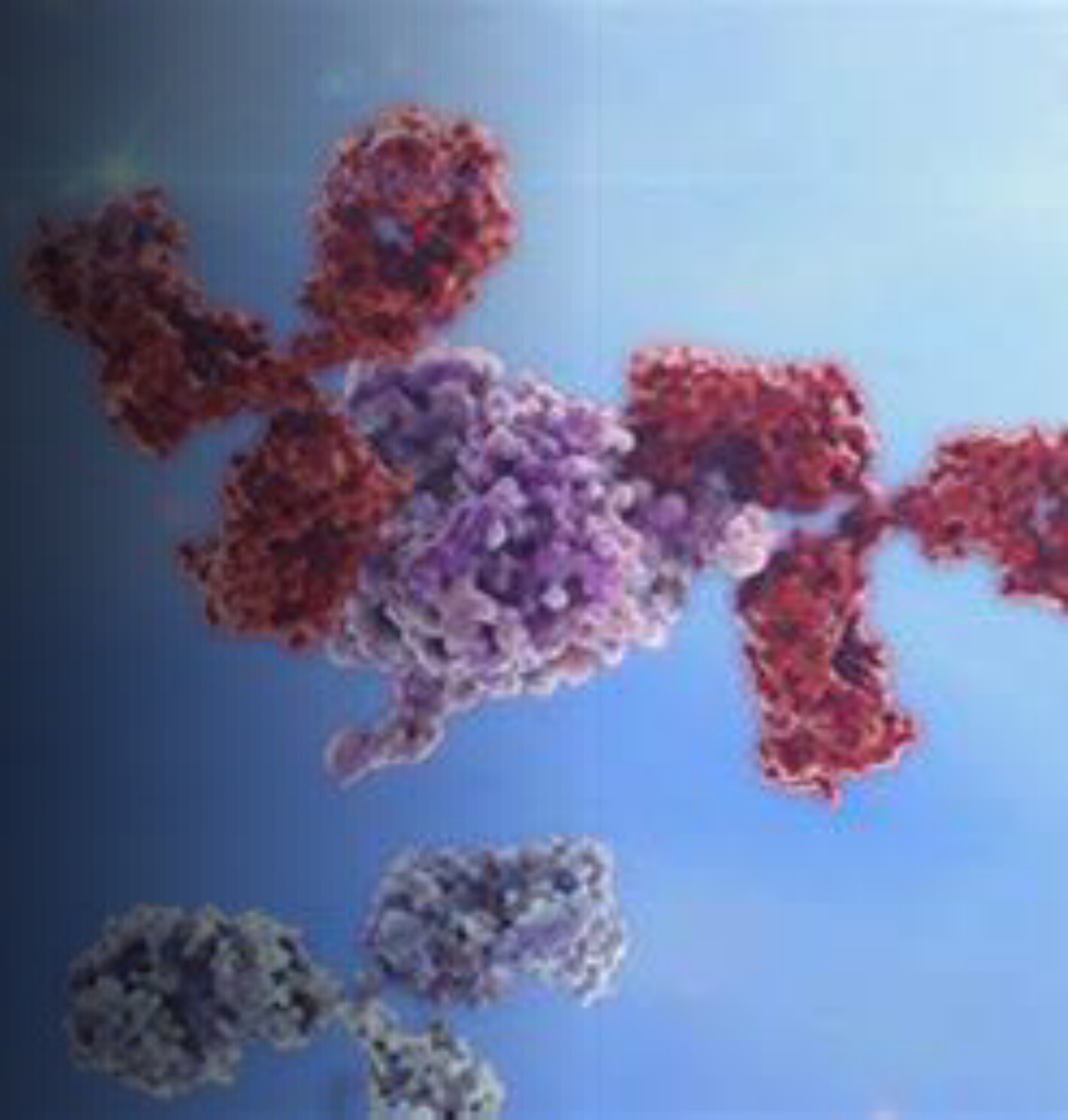
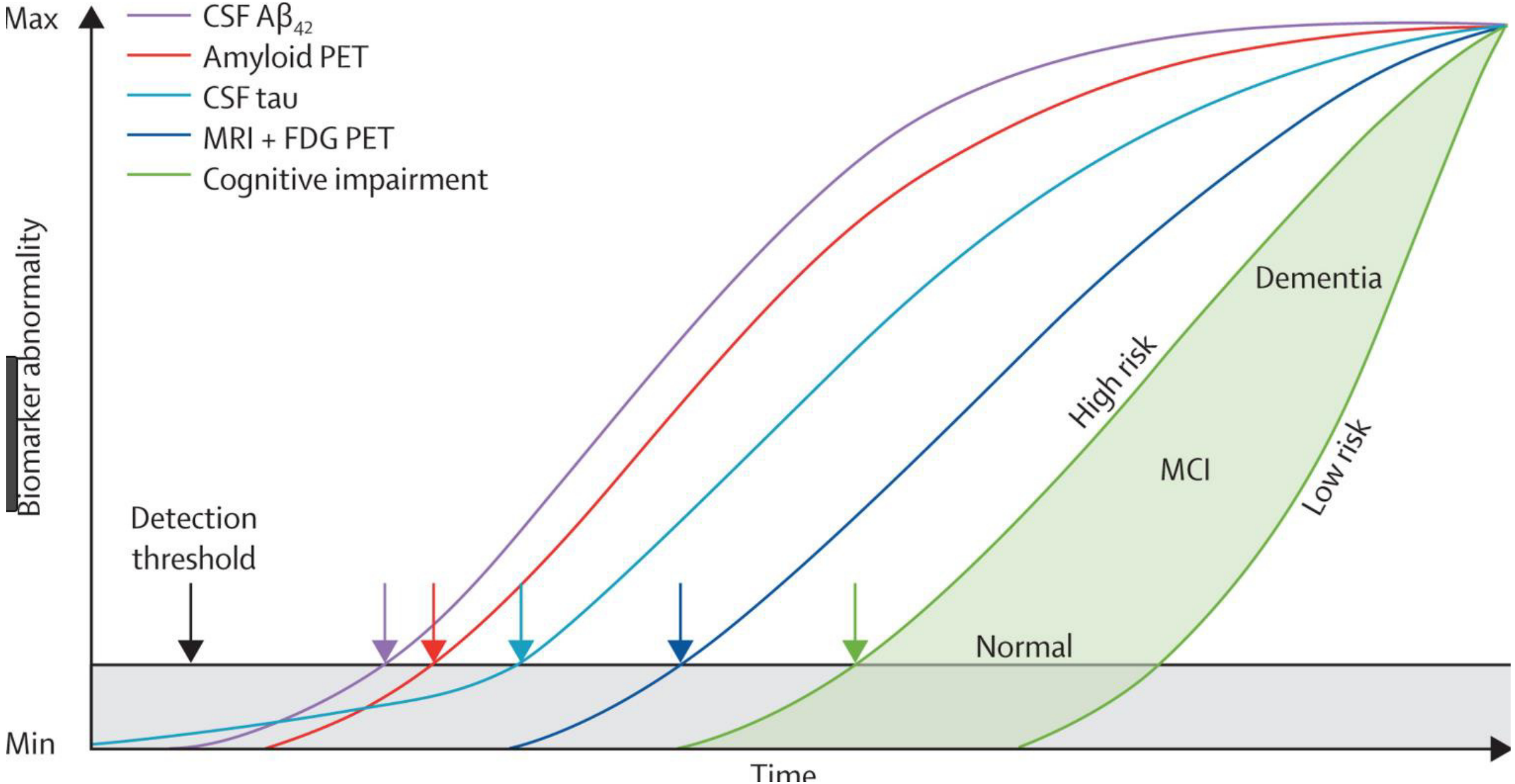
New Dementia Medications

Cari Levy, MD, PhD

Professor of Medicine

University of Colorado School of Medicine




Max
CSF Aβ42
Amyloid PET
CSF tau
MRI + FDG PET
Cognitive impairment
Biomarker abnormality
Detection threshold
Min
Time
Normal
MCI
Dementia
High risk
Low risk

Objectives

- Participants will:
  - Understand the effects of monoclonal antibodies approved for the treatment of dementia
  - Understand who is eligible for new dementia therapies
  - Understand burdens, risks and benefits of new treatments for dementia

Aducanumab

$56,000/yr

Aducanumab Controversy

- Skipping Phase 2 trials = poorly informed Phase 3
- Futility analysis = shutting down ENGAGE and EMERGE
- More data ->high dose in EMERGE better than placebo

- Am Neurological Assn
  - Clinical evidence does not support efficacy
- Former Biogen medical director
  - Should not have been approved
- FDA
  - Accelerated approval allowed for drugs without persuasive proof of benefit in serious disease with few treatment options if biomarker “reasonably likely to predict clinical benefit”

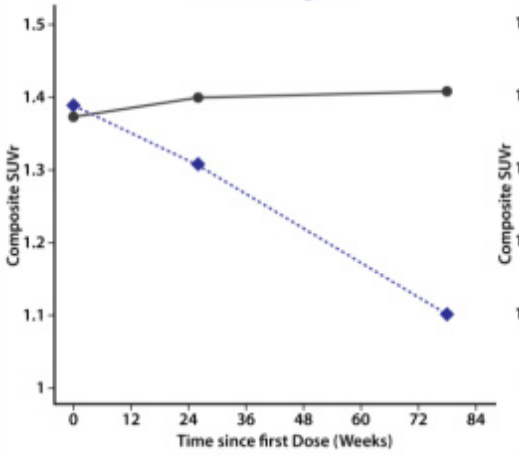
Aducanumab Controversy cont…

ENGAGE consistent with EMERGE in subset of patients with sufficient exposure to 10 mg/kg aducanumab

Corrected on October 28, 2019

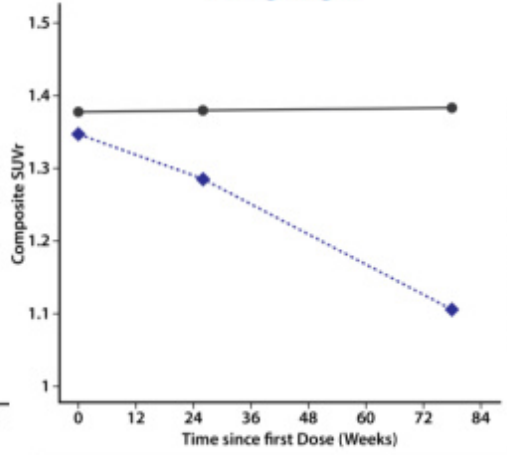
Amyloid PET

EMERGE



	Wk 0	Wk 26	Wk 78
PBO	157	128	90
ADU	55	46	43

ENGAGE



	Wk 0	Wk 26	Wk 78
PBO	203*	164*	121*
ADU	44*	39*	31*

PBO = placebo

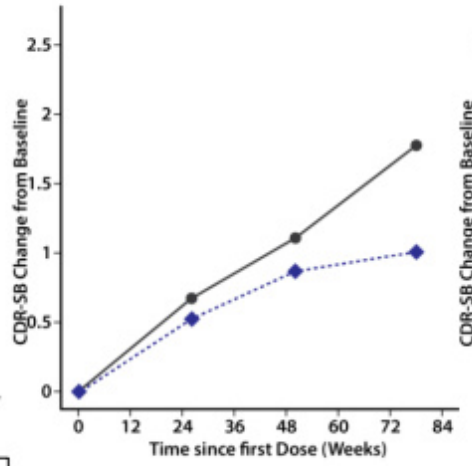
ADU = aducanumab

*Corrected numbers above vs. numbers below from original slide posted on October 22, 2019:

	Wk 0	Wk 26	Wk 78
	157	128	90
	55	46	43

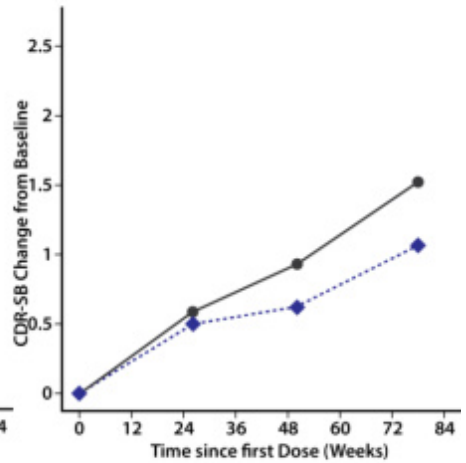
CDR-SB

EMERGE



	Wk 0	Wk 26	Wk 50	Wk 78
PBO	546	532	437	297
ADU	147	146	146	127

ENGAGE



	Wk 0	Wk 26	Wk 50	Wk 78
PBO	545	522	460	336
ADU	116	116	114	97

Placebo

≥ 10 uninterrupted 10 mg/kg dosing intervals at steady-state

Biogen

Evidence for Lecanemab

- Promising signs of effectiveness across almost all measures
- FDA approved January 6th 2023
- $26,500/yr

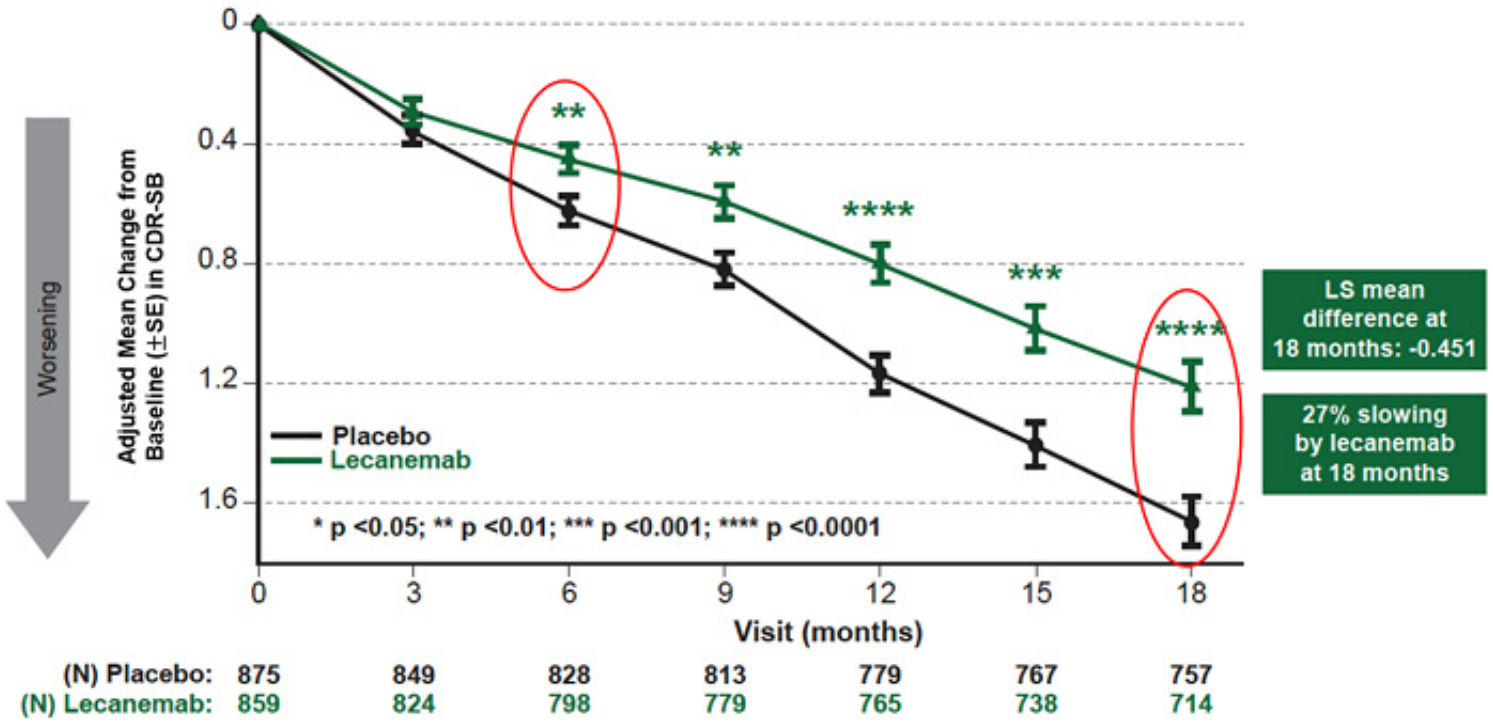
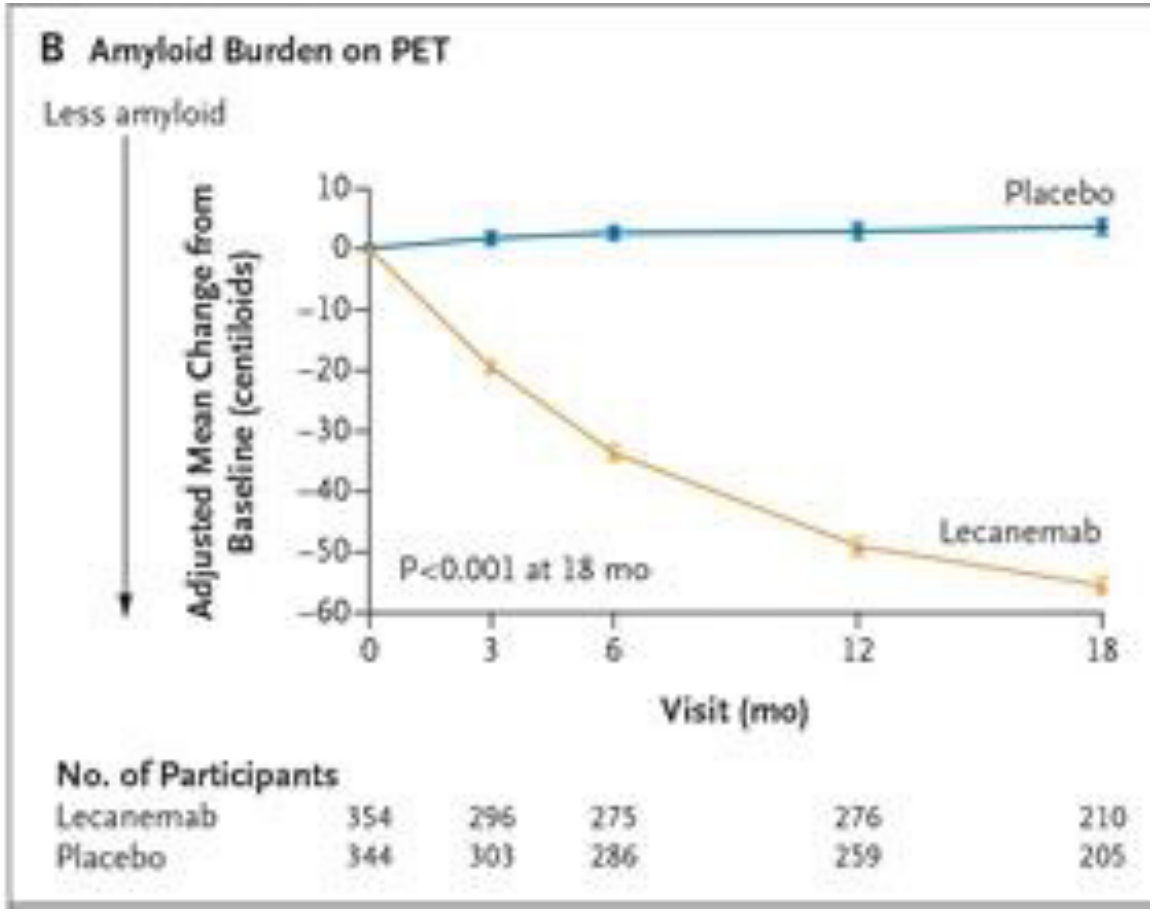
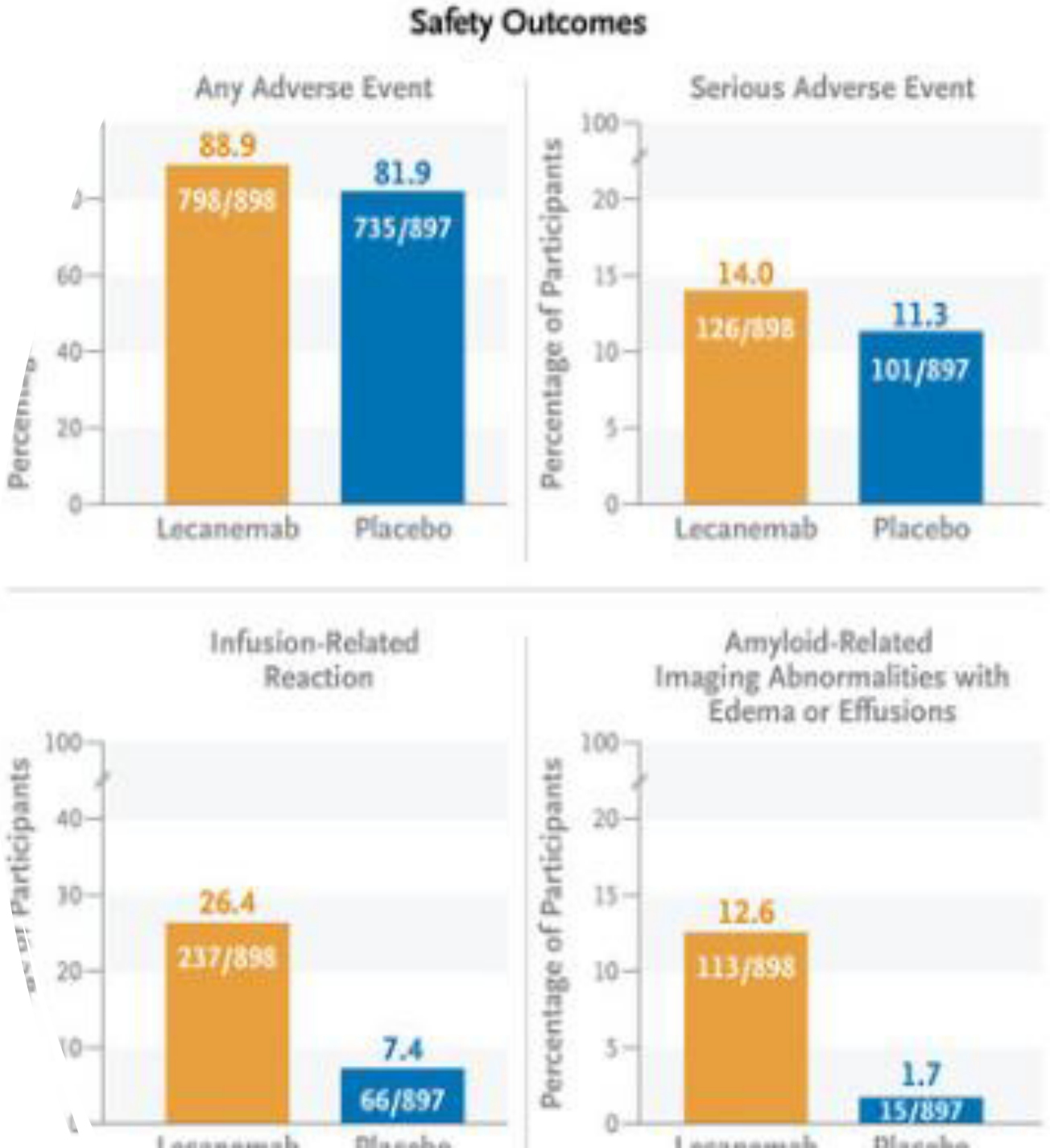


Figure1. CDR-SB as Primary endpoint change (18 months)

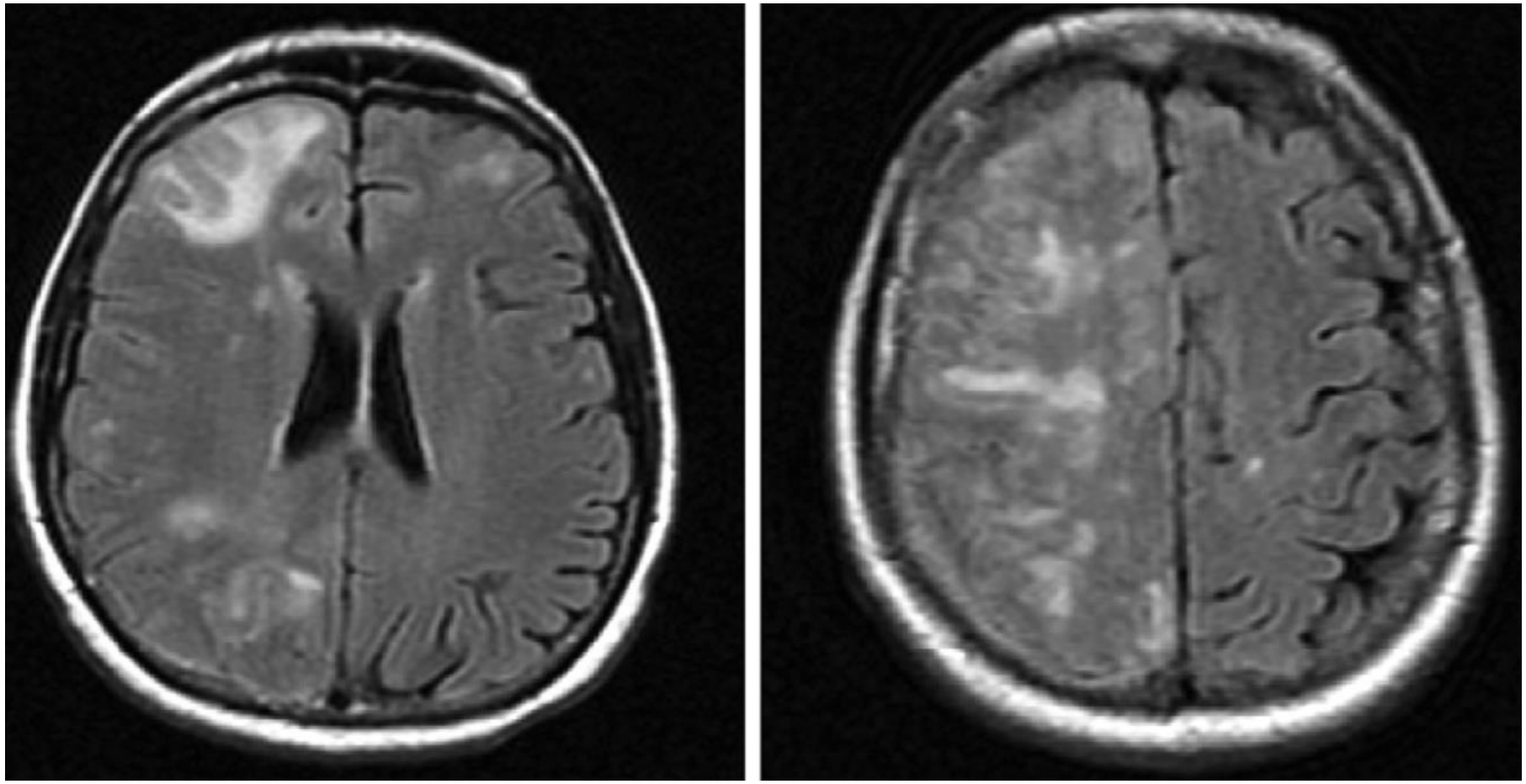


Dramatically Reduces Amyloid on PET

- **Serious Adverse Events**
  - Infusion reactions
  - ARIA-E
  - Atrial fibrillation
  - Syncope
  - Angina pectoris



ARIA - Amyloid Related Imaging Abnormality



Who is Eligible for Lecanemab?

Appropriate Use Recommendations

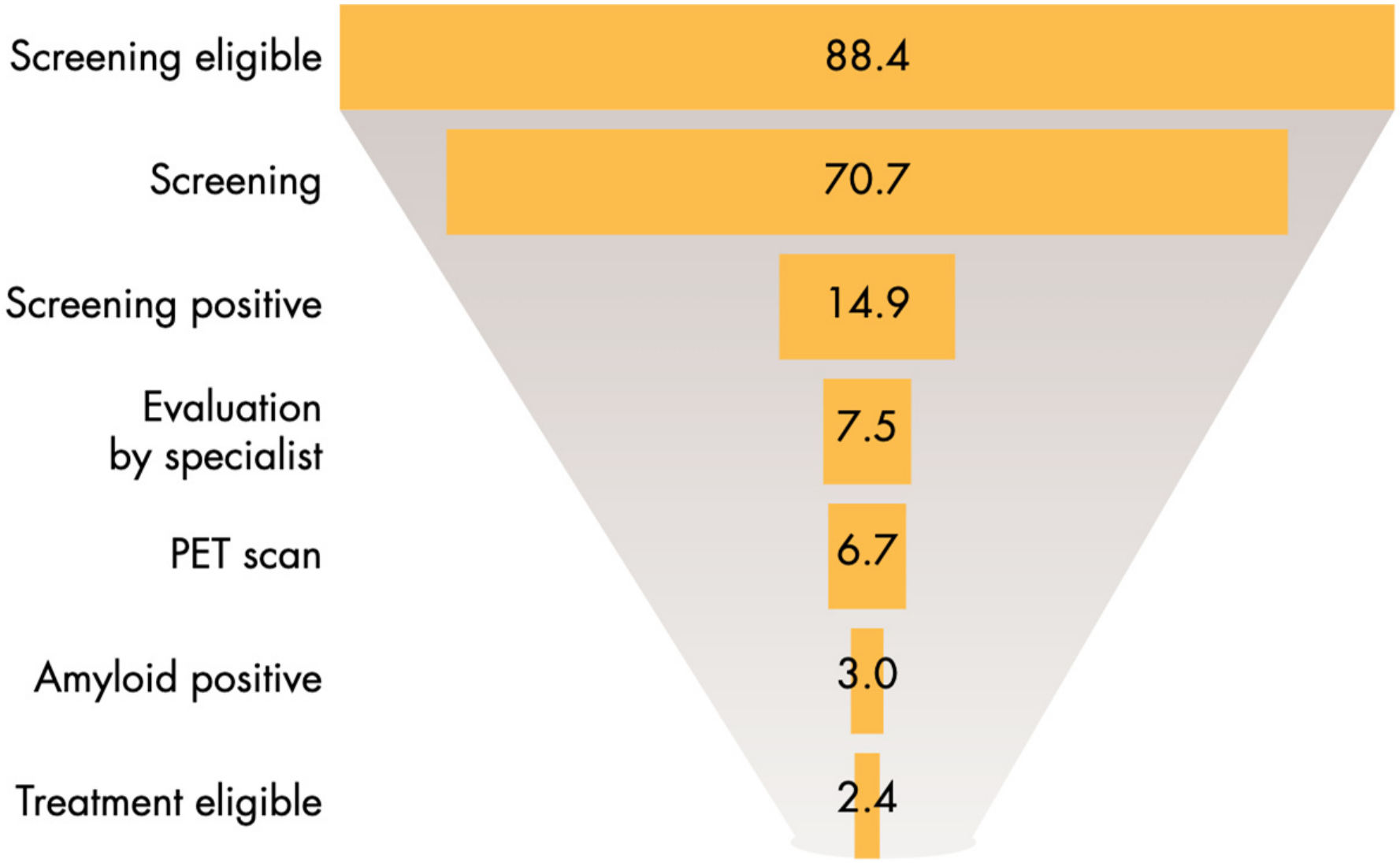
- MCI or mild AD
- Positive amyloid PET or CSF studies indicative of AD
- MMSE 22-30
- BMI >17 and <35
- Care partner available to support treatment

Cummings et al.
J Prevention of AD 2023

Who is Not Eligible for Lecanemab?

- MRI evidence of non-AD dementia
- TIA, CVA or seizure past 12 months
- Mental illness that interferes with treatment
- Major depression
- History of immunologic disease (SLE, RA, Crohn's)
- Anticoagulation (coumadin, apixaban etc.)
- Bleeding disorder (plts <50K, INR >=1.5)

Only a Small Fraction are Treatment Eligible



RAND *RR2272-2*

Treatment Schedule

- IV infusion every other week
- Dosing is weight-adjusted 10mg/kg
- Approximately 1 hour infusion
- Observation:
  - 1st infusion - 3 hours
  - 2nd infusion – 2 hours
  - 3rd and subsequent infusions - 30min

Monitoring

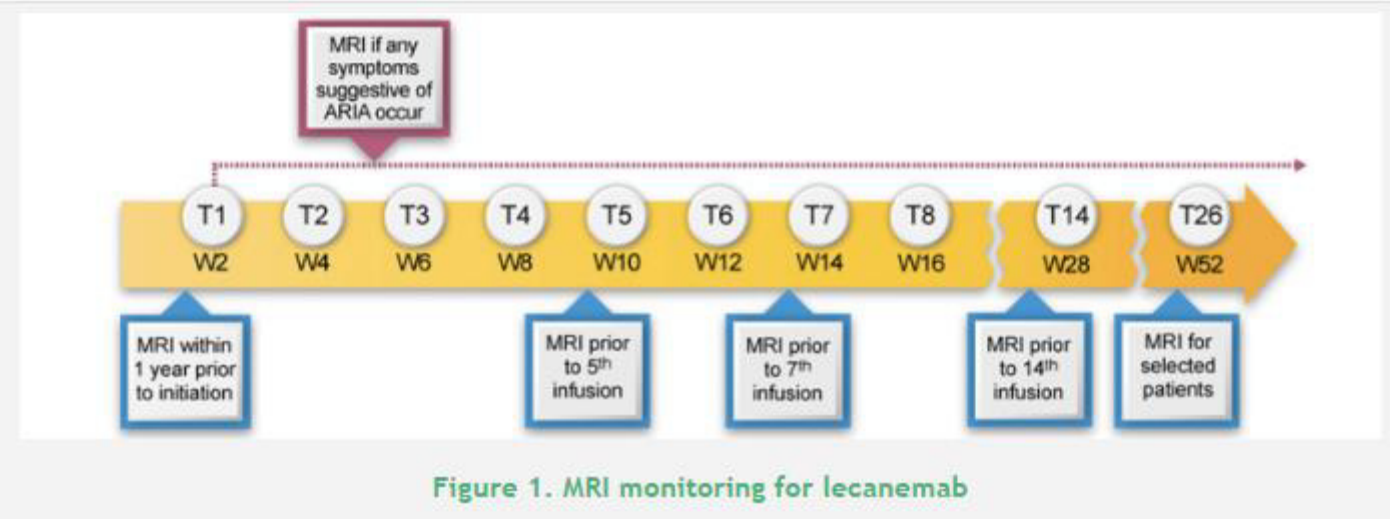


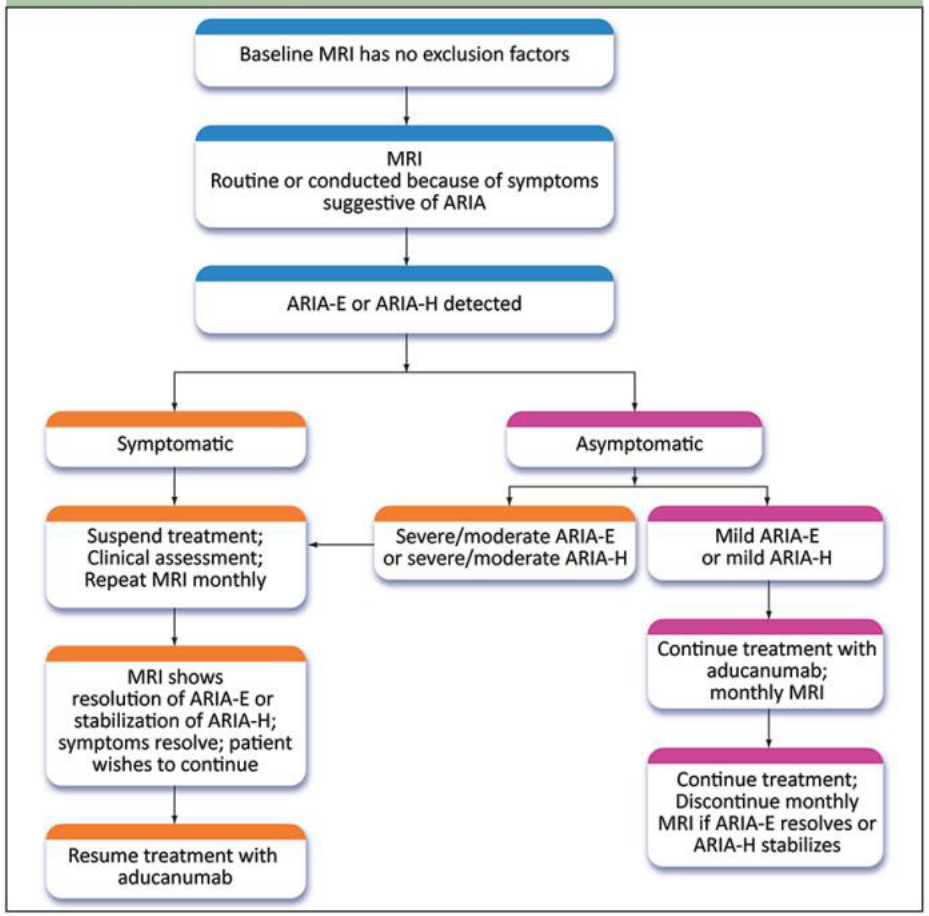
Figure 1. MRI monitoring for lecanemab

ARIA Symptoms:

Mild - Headache, confusion, visual changes, dizziness, nausea, gait changes

Serious – seizures, status epilepticus, encephalopathy, stupor, focal neurologic deficits

Figure 2. Management strategy for ARIA. Patients with severe symptomatic ARIA are not re-titrated and are not candidates for further treatment with aducanumab (Expert Panel recommendation; © J Cummings; illustrator M de la Flor, PhD)



Cummings et al 2022

Biomarkers

- Amyloid PET – $6,000, as of Oct 2023 covered by Medicare
- CSF – phosphorylated tau and low Ab42
- High-performing biomarkers include:
  - Ab42/Ab40, p-tau181, p-tau217, p-tau231, neurofilament light chain and glial fibrillary acidic protein
- Demonstrate prognostic and diagnostic utility to detect current and future disease

Balogen et al Curr Opin Psychiatry 2023, 36:112–118

Medicare Coverage Requirements

1. Enrolled in Medicare
2. Diagnosed with mild cognitive impairment or mild Alzheimer's disease dementia, with documented evidence of beta-amyloid plaque on the brain, and
3. Receive care from a physician who participates in a qualifying registry with an appropriate clinical team, follow-up care and data submission

New unbiased AT(N) Classification Scheme (Jack et al., 2018)

- A descriptive system for categorizing multidomain biomarker findings at the individuals person level in a format that is easy to understand and use

- **A Aggregated b-amyloid or associated pathophysiology**
    a. CSF Aβ42 or 42/40 ratio
    b. Amyloid PET

- **T Aggregated tau (neurofibrillary tangles) or associated pathophysiology**
    a. CSF p-tau
    b. Tau PET

- **(N) Neurodegeneration/neuronal injury**
    a. Anatomic MRI
    b. FDG PET
    c. CSF total tau

42 negative trials

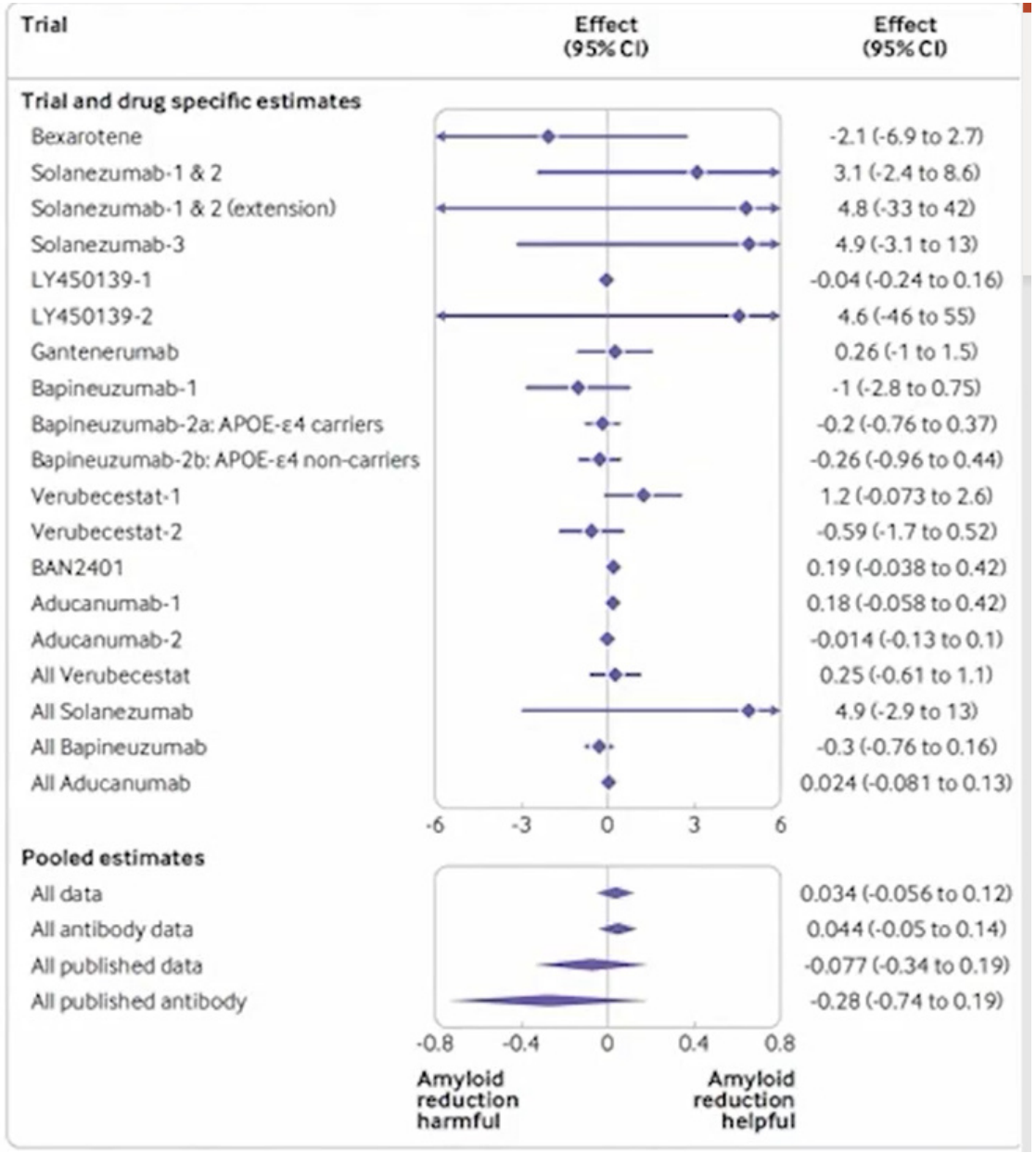
Was it too late in the disease?

- Mild-Moderate AD
  - Null = 56%
  - Worse = 44%
- Mild Cognitive Impairment
  - Null = 58%
  - Worse = 42%
- Preclinical
  - Null = 0%
  - Worse = 100%

Drug, Year	Mechanism	Phase	Amyloid	Outcome
Mild-moderate Alzheimer's disease				
Ponezumab, 2011	Anti-Aβ antibody	2		No change
Bapineuzumab, 2012	Anti-Aβ antibody	3		No change
Vanutide, 2013	Aβ antigen	2		No change
Immunoglobulin, 2013	Anti-Aβ antibody	3		No change
Begacestat, 2010	γ-Secretase inhibitor	2		No change, toxic
Tramiprosate, 2007	Aβ aggregation inhibitor	3	Reduced	No change
Crenezumab, 2014	Anti-Aβ antibody	2	Reduced	No change
Crenezumab, 2018	Anti-Aβ antibody	2	Reduced	No change
Solanezumab, 2013	Anti-Aβ antibody	3	Reduced	No change
LY2886721, 2013	β-Secretase inhibitor	2	Reduced	No change, toxic
AN-1792, 2002	Aβ antigen	2	Reduced	No change, toxic
Avagacestat, 2012	γ-Secretase inhibitor	2	Reduced	Worse cognition
Verubecestat, 2018	BACE inhibitor	3	Reduced	Worse cognition
Semagacestat, 2011	γ-Secretase inhibitor	3	Reduced	Worse cognition, toxic
Scyllo-inositol, 2009	Aβ aggregation inhibitor	2	Reduced	Increase mortality
Mild Alzheimer's disease				
Solanezumab, 2018	Anti-Aβ antibody	3		No change
Tarenflurbil, 2009	γ-Secretase modulator	3		Worse globally
Affitope AD02, 2014	Aβ antigen	2		Worse cognition
Solanezumab, 2016	Anti-Aβ antibody	3	Reduced	No change
Gantenerumab, 2014	Anti-Aβ antibody	2	Reduced	No change
Atabecestat, 2018	BACE inhibitor	3	Reduced	No change
Elenbecestat, 2019 (x3)	BACE inhibitor	3	Reduced	No change
Lanabecestat, 2019 (x2)	BACE inhibitor	3	Reduced	No change (2/2)
CAD106, 2014	Aβ antigen	2	Reduced	Worse cognition, atrophy
Lanabecestat, 2018	BACE inhibitor	3	Reduced	Worse cognition
Donanemab, 2021	Anti-Aβ antibody	2	Reduced	Worse atrophy
Aducanumab, 2019 (x2)	Anti-Aβ antibody	3	Reduced	Post-hoc benefit in 1/2 trials[1]
Lecanemab	Anti-Aβ antibody	3	Reduced	Benefit, increased brain atrophy

Pooled data shows amyloid reduction does not improve cognition

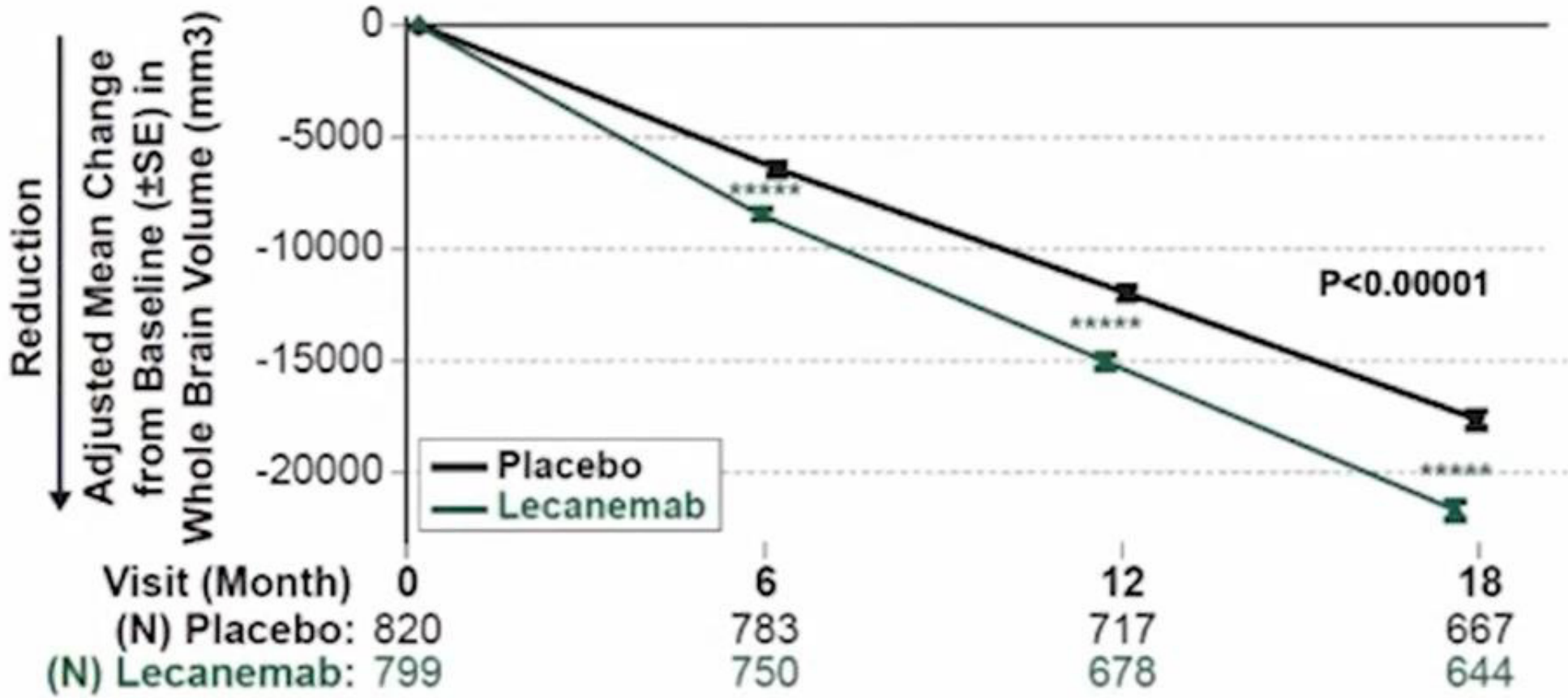
Ackley et al, BMJ 2021



Clinical Meaningfulness & Number Needed to Harm

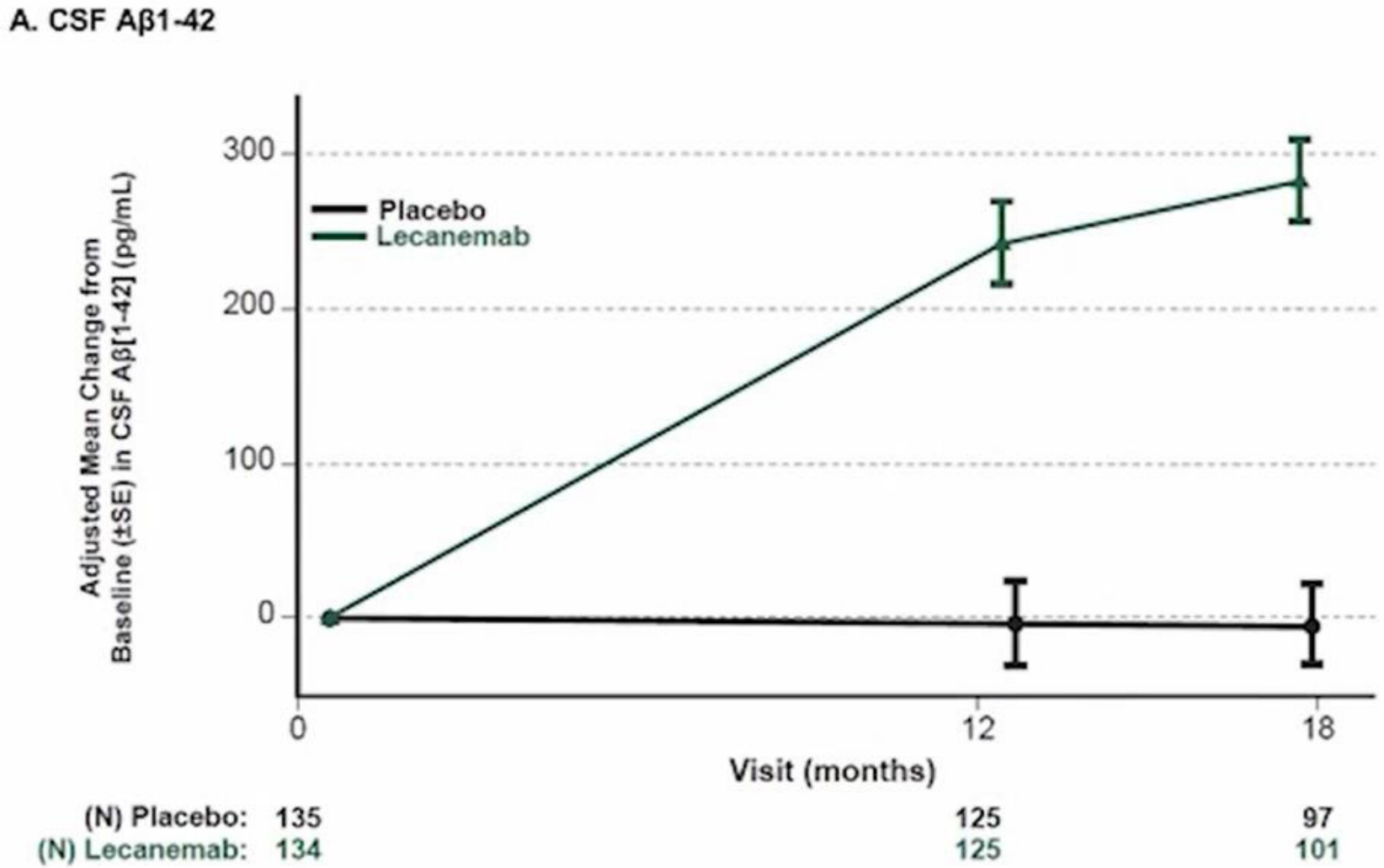
- 19 publications with 23,202 total participants evaluated 8 anti-amyloid antibodies
- Small improvements over placebo in the ADAS-Cog, MMSE, CDR-SB
- None of the changes for lecanemab, aducanumab, or donanemab, exceeded the Minimal clinically important difference (MCID)
- Harms included significantly increased risks of:
  - ARIA-edema (relative risk [RR] = 10.29; number needed to harm [NNH] = 9)
  - ARIA-hemorrhage (RR = 1.74; NNH = 13)
  - Symptomatic ARIA-edema (RR = 24.3; NNH = 86)

Whole brain volume



https://pbs.twimg.com/media/FiyAEaiXoAcfrl7?format=jpg&name=4096x4096

Lecanemab increases AB1-42



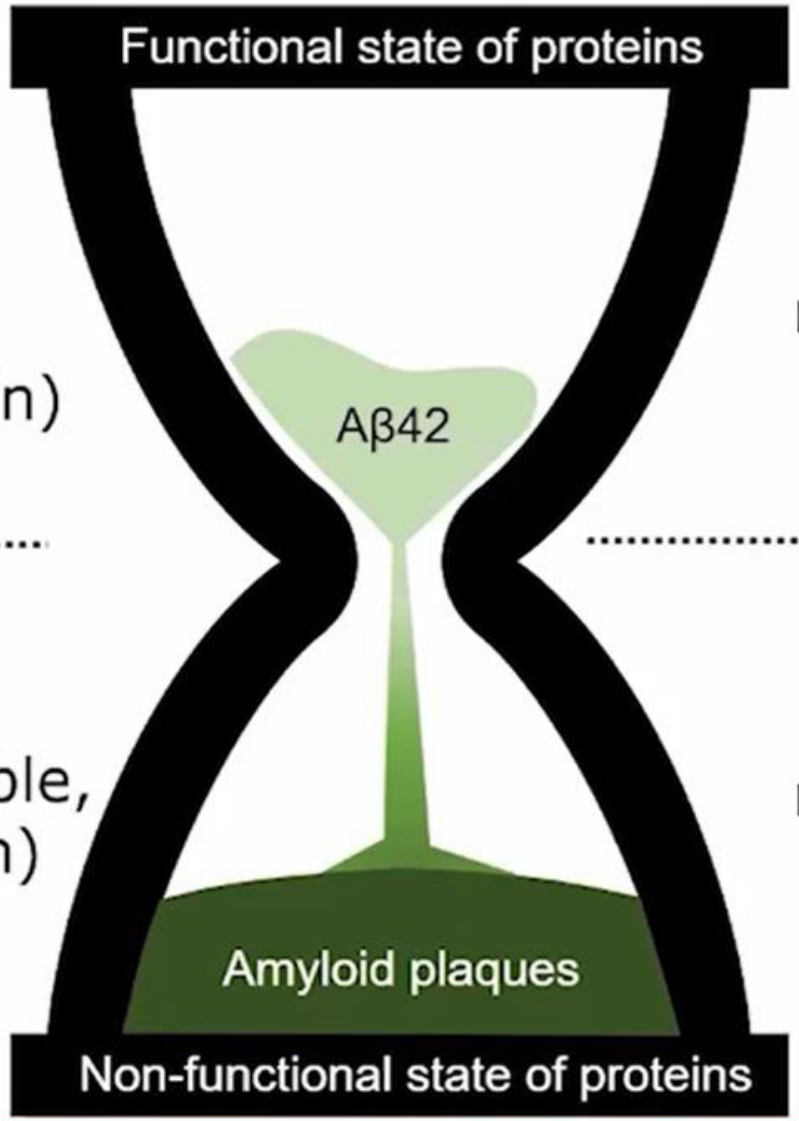
van Dyck et al. N Engl J Med 2023; 388:9-21

Precision medicine?

Proteinopenia
(loss of soluble, monomeric protein)

Proteinopathy
(accrual of insoluble, cross-beta protein)

Protein Aggregation Process



Therapeutic Pipeline

Espay and Okun, JAMA Neurology 2023

Objectives Revisited

- Participants will:
  - Understand effects of monoclonal antibodies approved and in development for the treatment of dementia
  - Identify who is eligible for new dementia therapies
  - Understand burdens, risks and benefits of new treatments for dementia