University of Washington Memory and Brain Wellness Center: Amyloid Monoclonal Antibodies

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UW MEDICINE MEMORY AND BRAIN WELLNESS CENTER

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Alzheimer's Disease Research Center

UW Medicine
MEMORY & BRAIN WELLNESS CENTER

Disclosures

Dr. Rosebloom is a consultant for Eisai. *All relevant financial relationships have been mitigated.*

Lecanemab:

The Newest Alzheimer's Treatment

tomorrow.bio

Lecture Outline

- Amyloid Cascade Hypothesis
- Available Biomarkers in Clinical Practice
- CLARITY-AD Trial (Lecanemab)
- TRAILBLAZER-ALZ2 Trial (Donanemab)
- Role of Primary Care in AD Management

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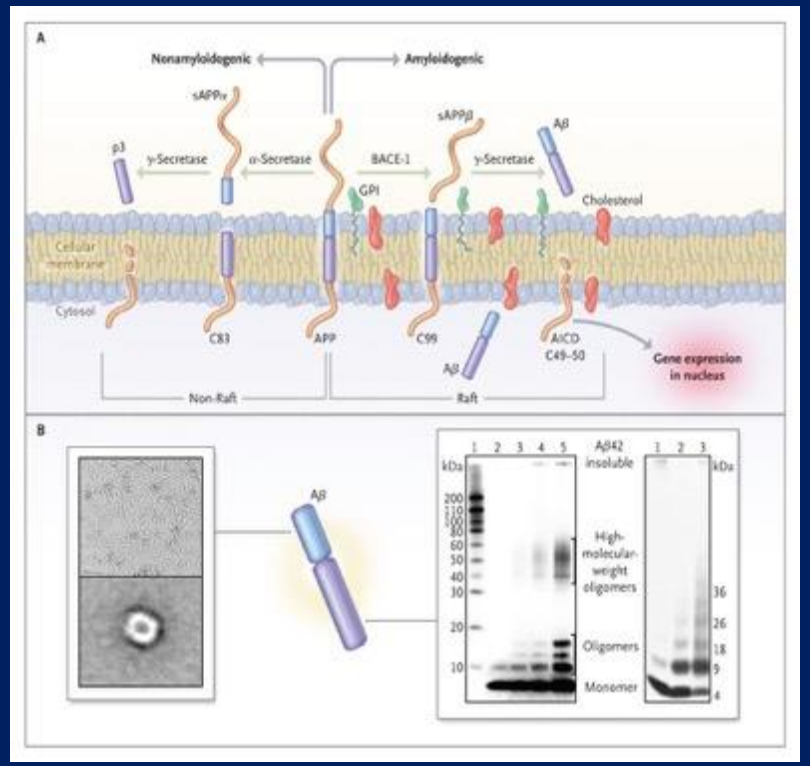
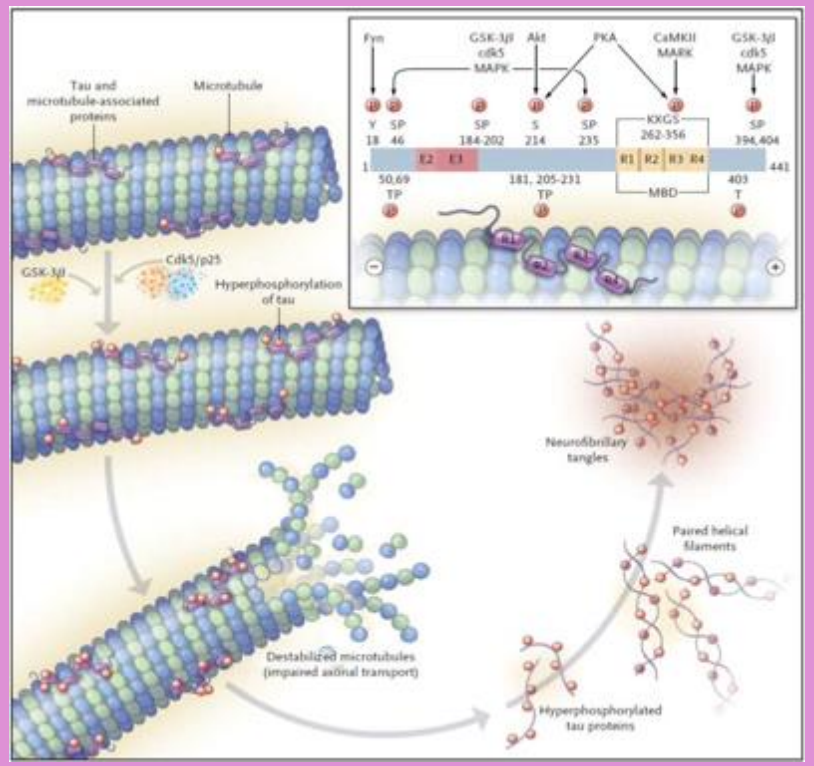
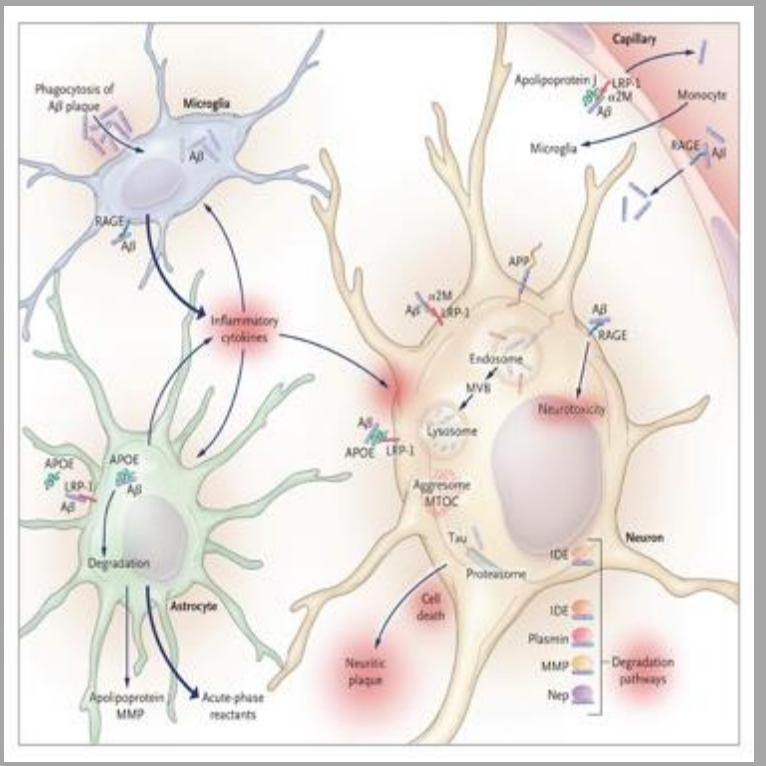
Amyloidosis

Tau Phosporylation

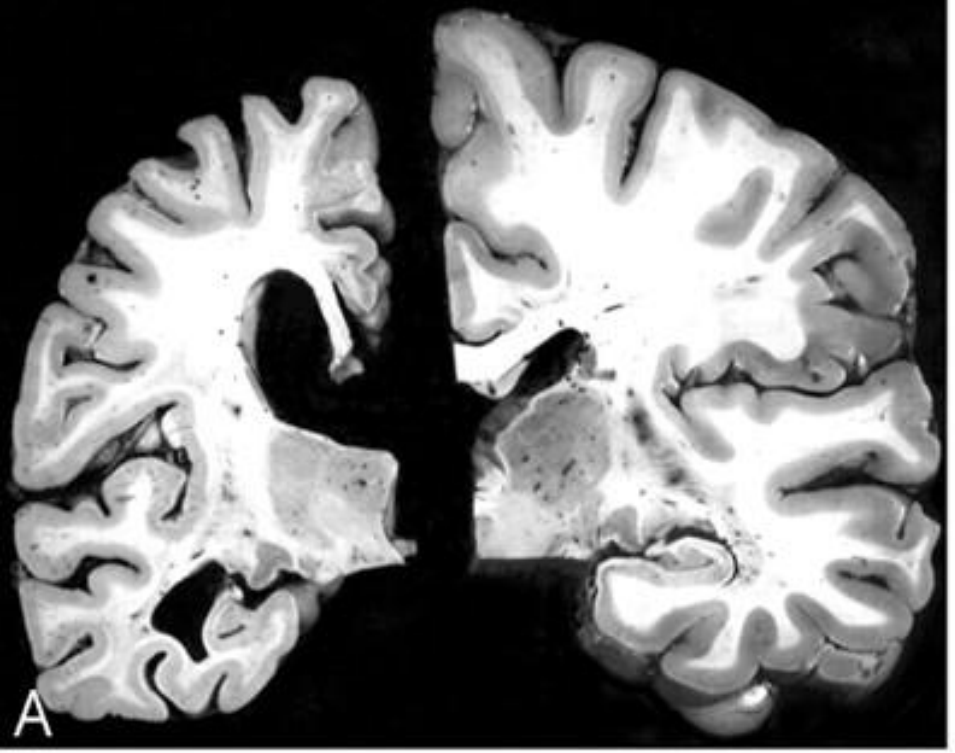
Downstream Neuroinflammation Oxidative Stress







Querforth NEJM 2010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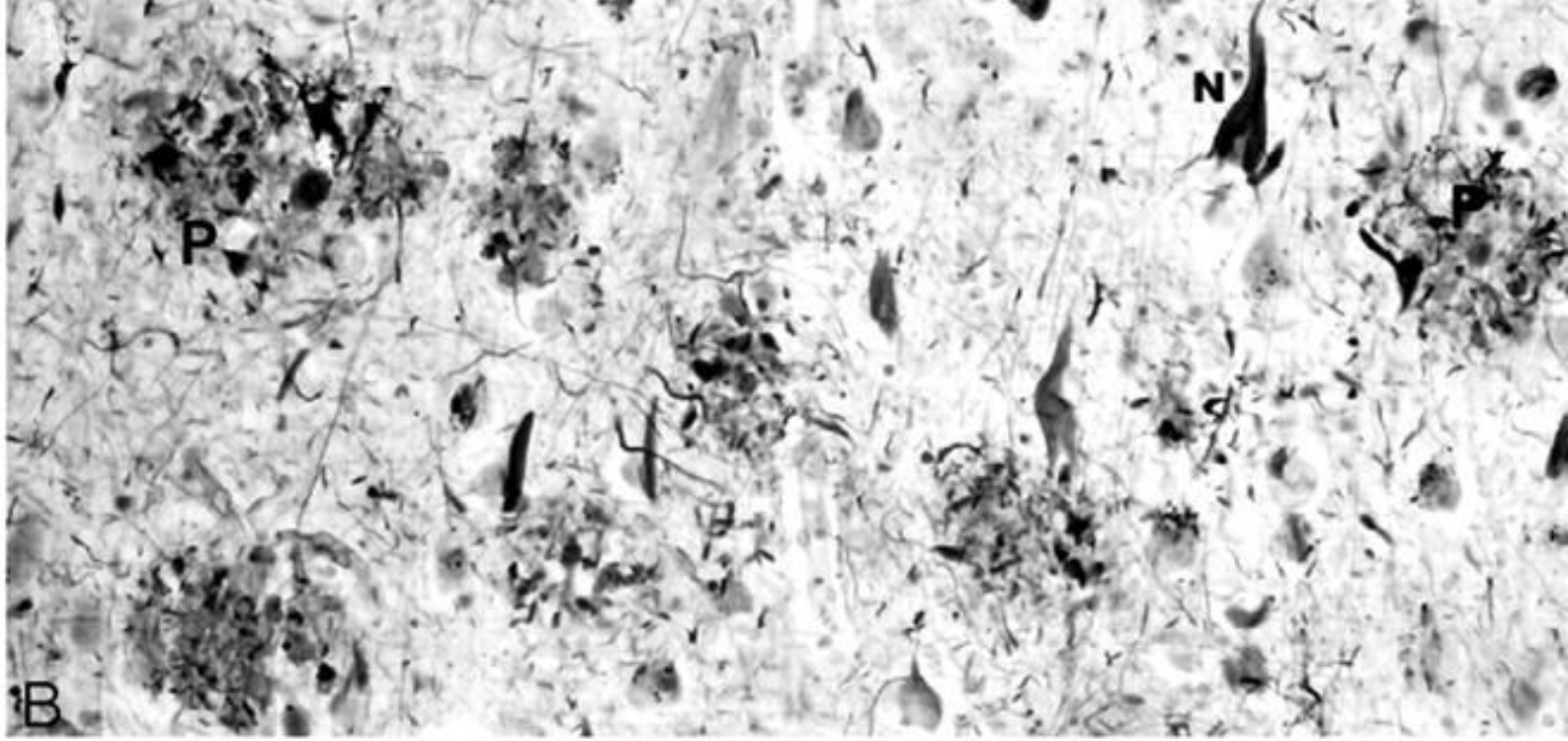
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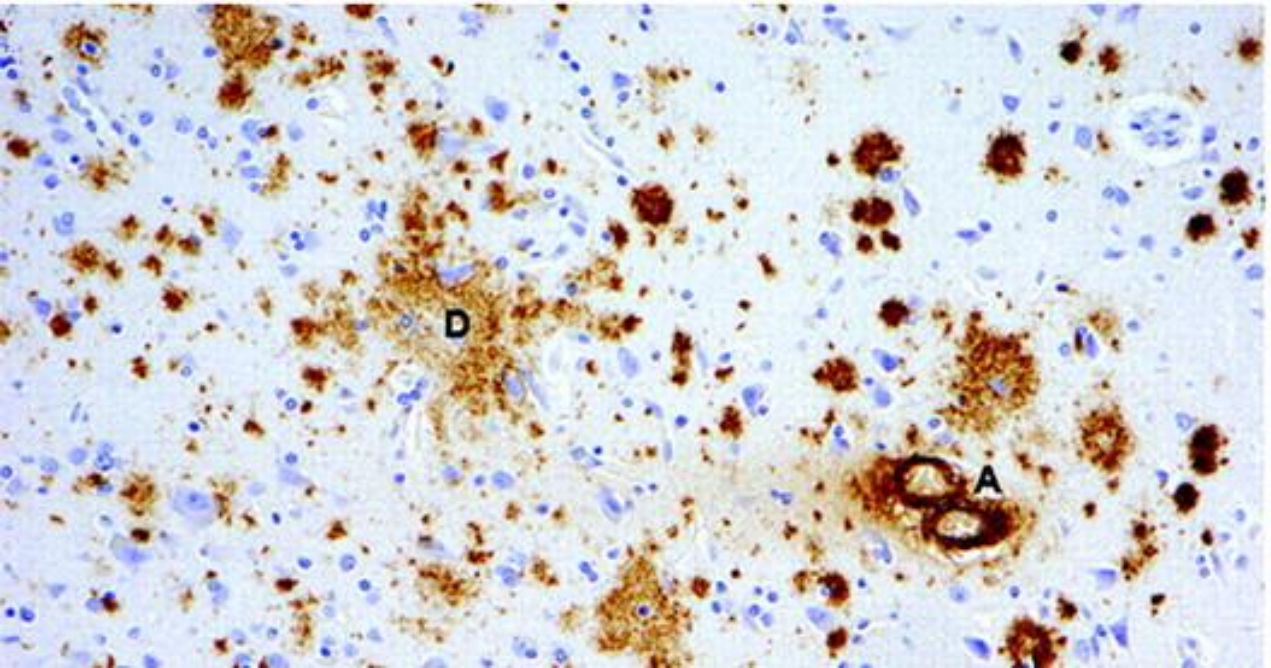
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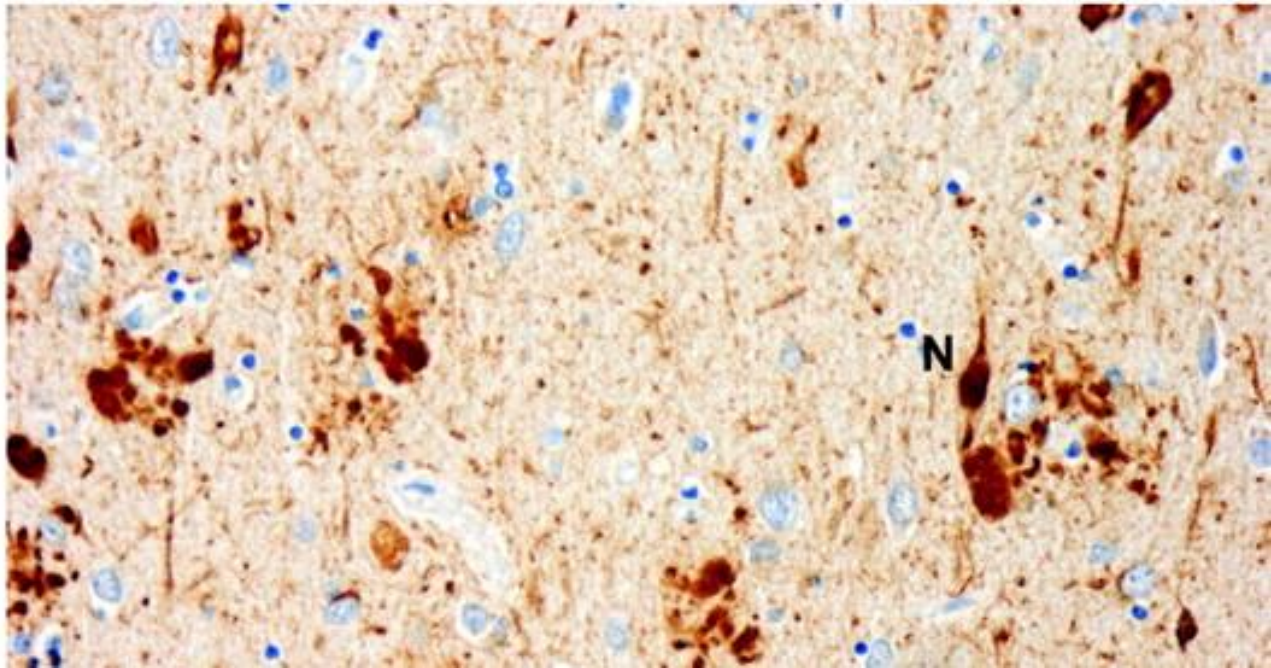
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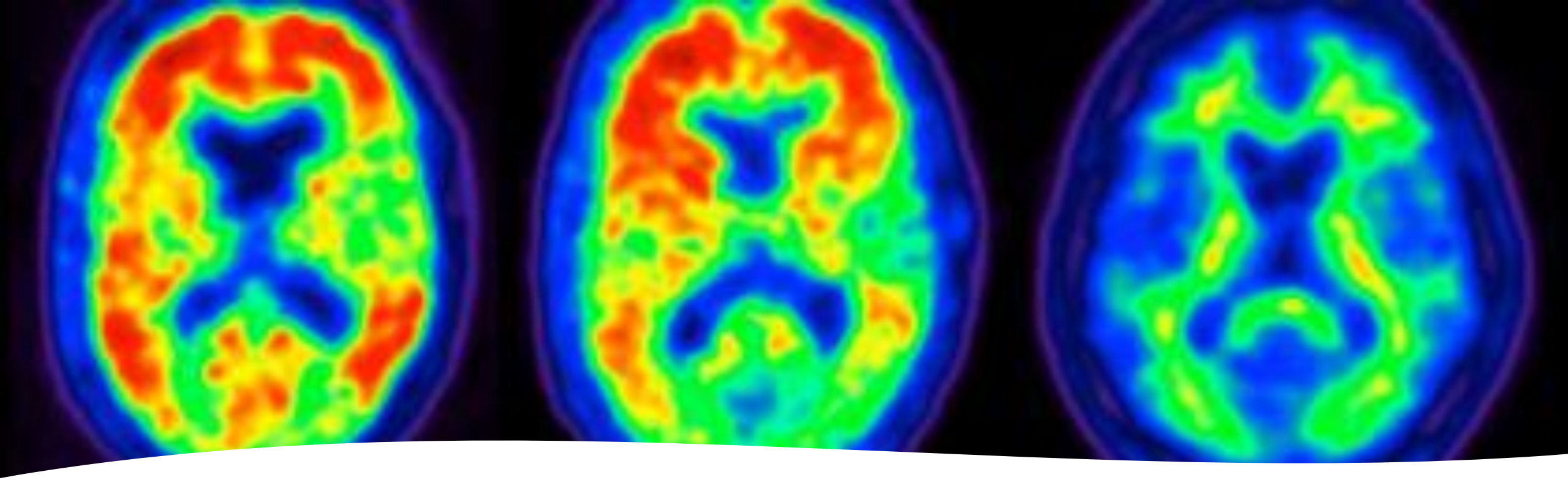
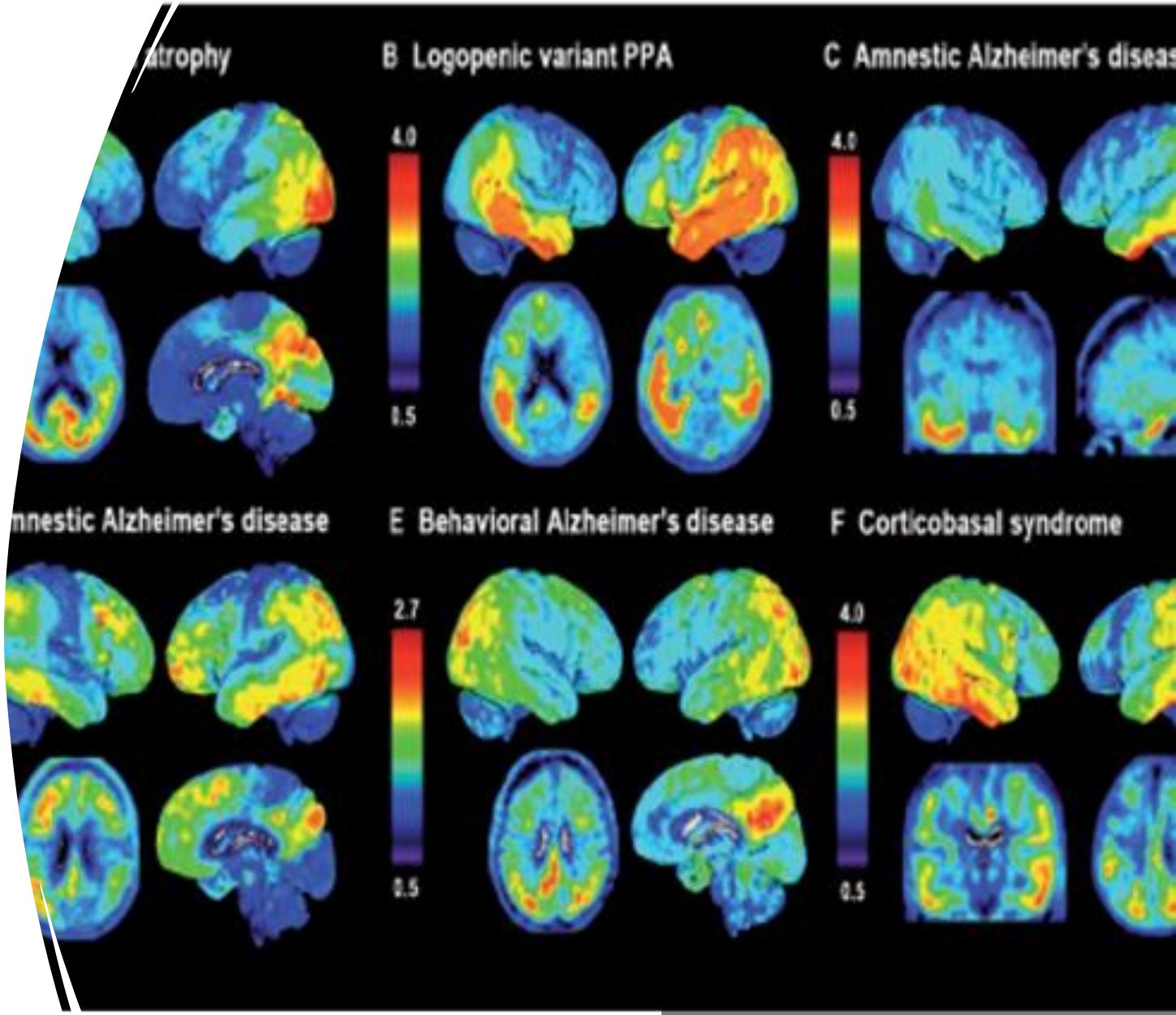


Amyloid Biomarkers

- Molecular PET Imaging
  - Amyloid PET (fibrillar amyloid)
  - Pittsburgh Compound B (C^{11})=20 min half life
  - Florbetapir, Flutemetamol, Florbetaben (F^{18})=2-hour half-life
- Cerebrospinal Fluid
  - CSF Aβ42 (APP biproduct reduced by 50%) in AD (Olsson Lancet Neur 2016)
  - Panel includes Phosphotau181 + total tau (Ptau181/Abeta 42 ratio>0.028 positive w/ Mayo Clinic assay)

Neurofibrillary Tangle Biomarkers

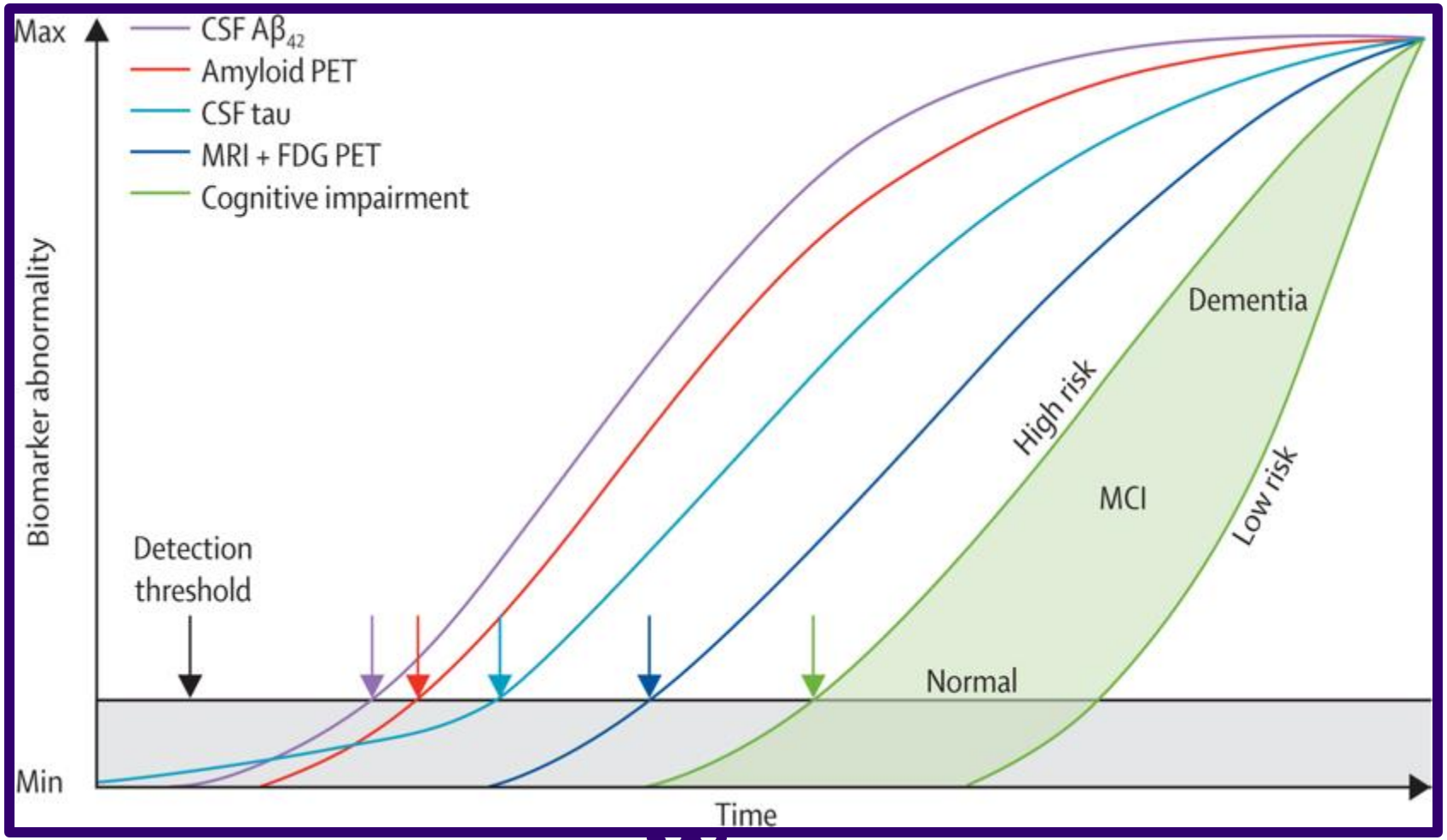
- Molecular Imaging
- Tau-PET
  - Flortaucipir (AV-1451)
  - Associated with + binding in inf temporal cortex/clinical symptoms
- Cerebrospinal Fluid
  - CSF P181/217 associated with NFT formation



Johnson KA Ann Neurol 2016

The Alzheimer's disease continuum

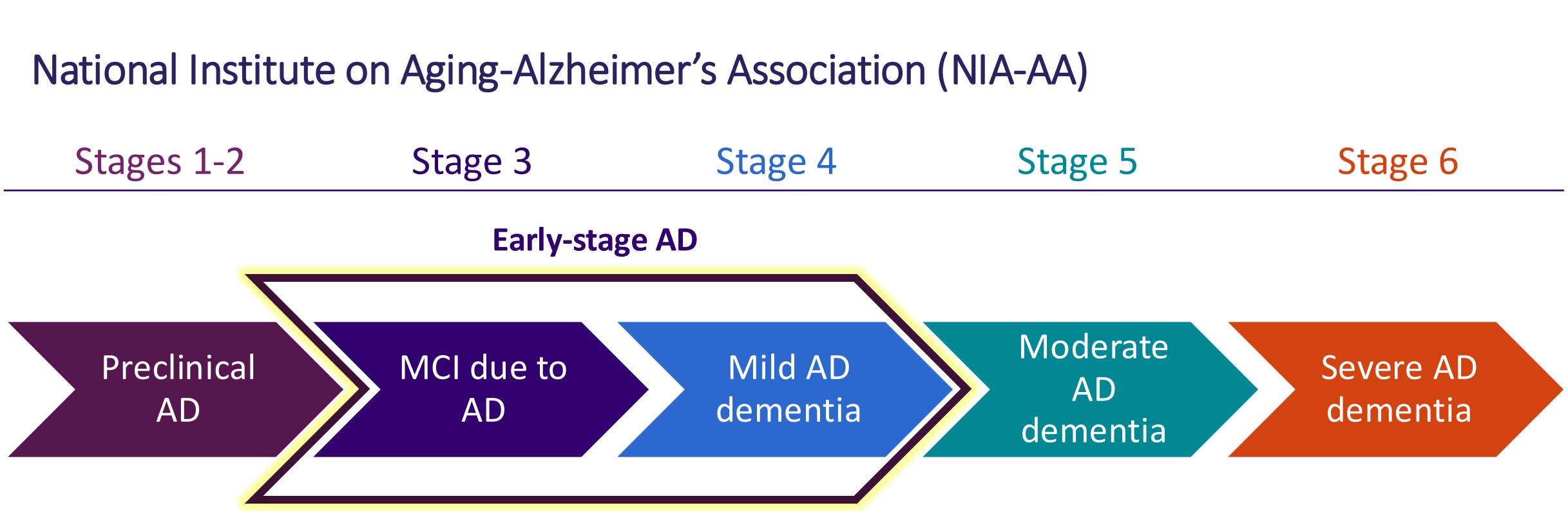
- Studies in autosomal dominant AD have shown that biomarker changes precede symptoms by 20-30 years (Jansen JAMA 2015)
- Amyloidosis represents earliest change in AD
- Progression to MCI/AD may be vary depending on *cognitive reserve* (Aisen Alz Res Ther 2017)

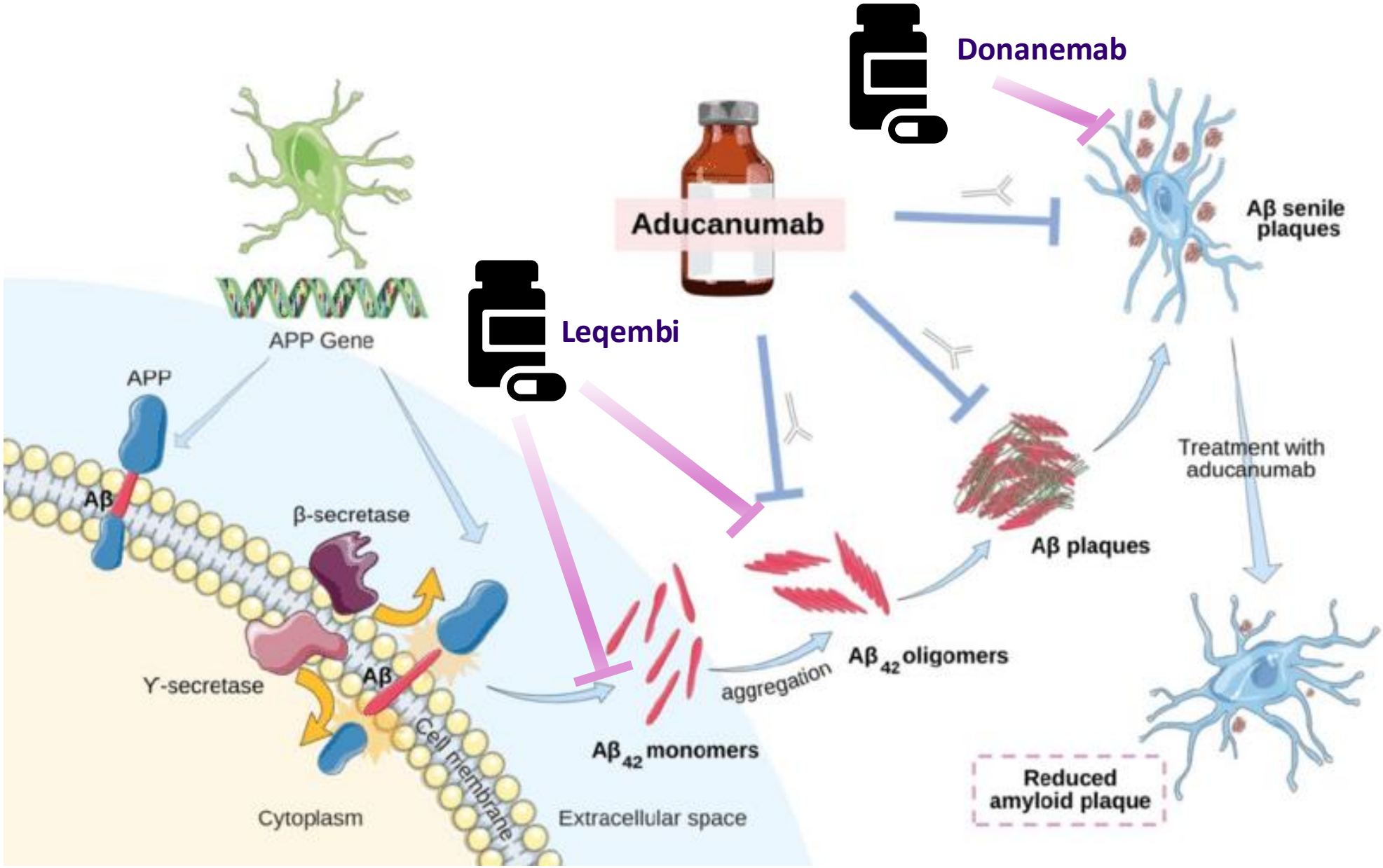


Jack et al Lancet 2013

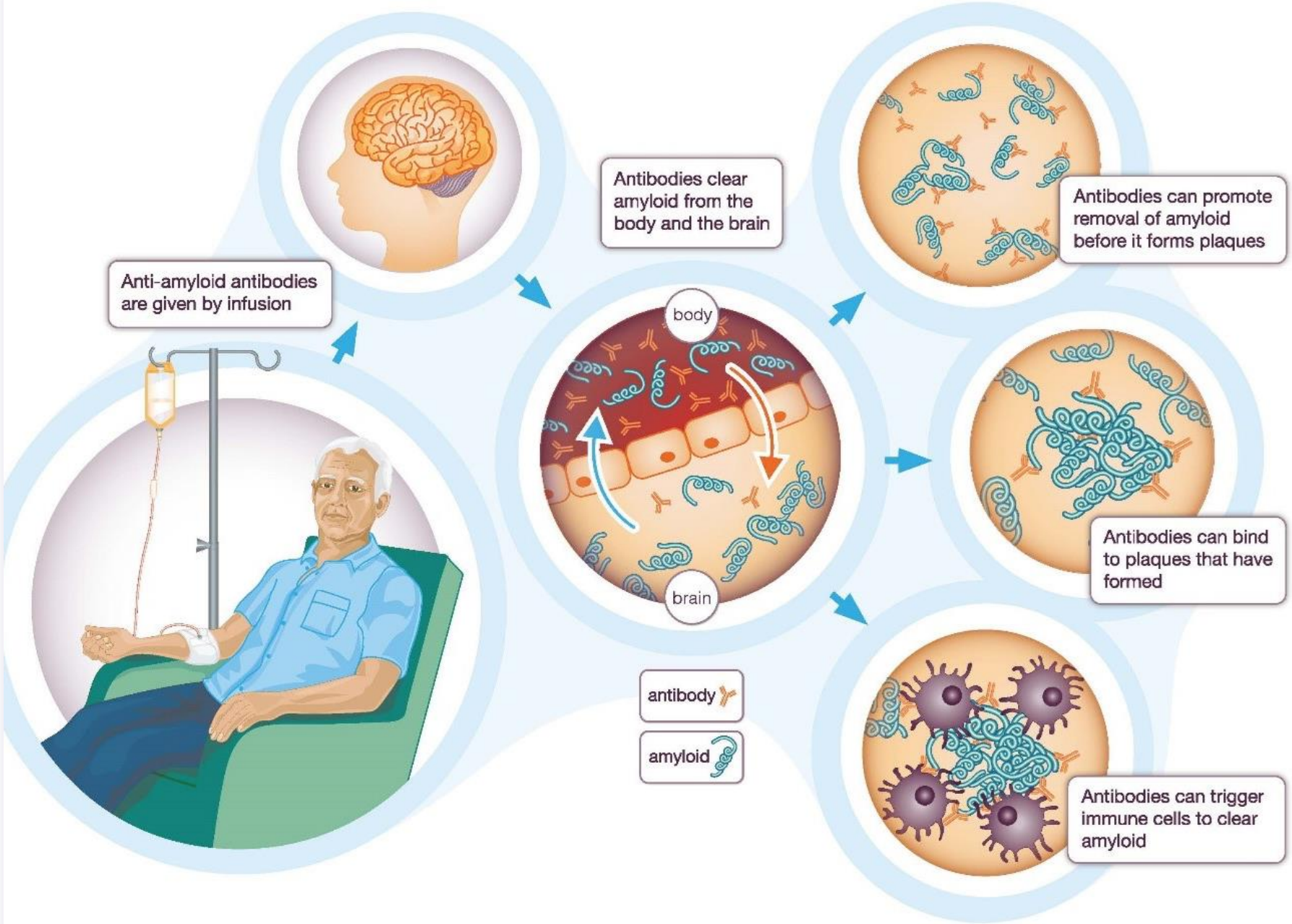
AD Continuum

National Institute on Aging-Alzheimer's Association (NIA-AA)




Donanemab
Aducanumab
Leqembi
Aβ senile plaques
APP Gene
APP
Aβ
β-secretase
Y-secretase
Aβ
Cell membrane
Cytoplasm
Extracellular space
Aβ42 monomers
aggregation
Aβ42 oligomers
Aβ plaques
Treatment with aducanumab
Reduced amyloid plaque

Alzheimer's Research UK



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

ABSTRACT

BACKGROUND

The accumulation of soluble and insoluble aggregated amyloid-beta (Aβ) may initiate or potentiate pathologic processes in Alzheimer's disease. Lecanemab, a humanized IgG1 monoclonal antibody that binds with high affinity to Aβ soluble protofibrils, is being tested in persons with early Alzheimer's disease.

METHODS

We conducted an 18-month, multicenter, double-blind, phase 3 trial involving persons 50 to 90 years of age with early Alzheimer's disease (mild cognitive impairment or mild dementia due to Alzheimer's disease) with evidence of amyloid on positron-emission tomography (PET) or by cerebrospinal fluid testing. Participants were randomly assigned in a 1:1 ratio to receive intravenous lecanemab (10 mg per kilogram of body weight every 2 weeks) or placebo. The primary end point was the change from baseline at 18 months in the score on the Clinical Dementia Rating–

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. van Dyck can be contacted at christopher.vandyck@yale.edu or at the Alzheimer's Disease Research Unit, Division of Aging and Geriatric Psychiatry, Yale School of Medicine, 1 Church St., 8th Fl., New Haven, CT 06510.

This article was published on November 29, 2022, at NEJM.org.

DOI: 10.1056/NEJMoa2212948

Clarity AD is an 18-month, global, double-blind, parallel-group randomized study[1]

Study population (N=1795)[2,3]

- Aged 50-90 years
- MCI due to AD or mild AD dementia
  - Global CDR score 0.5-1.0; CDR Memory Box score ≥0.5
  - MMSE score ≥22 to ≤30
  - WMS-IV LM II ≥1 SD below age-adjusted mean
- Amyloid pathology confirmed (no tau requirement)

Randomization stratified by[2]:

- Disease stage (MCI due to AD or mild AD dementia)
- Use of symptomatic AD medications
- ApoE ε4 carrier or noncarrier status
- Geographical region

R 1:1

Randomization phase[1]

LEQEMBI (n=898)
10 mg/kg biweekly IV infusion

Placebo (n=897)
Biweekly IV infusion

Primary endpoint[2]

Change from baseline at 18 months on: CDR-SB

Key secondary endpoints[2]

Change from baseline at 18 months on:
ADAS-Cog14; ADCS MCI-ADL; amyloid PET; ADCOMS

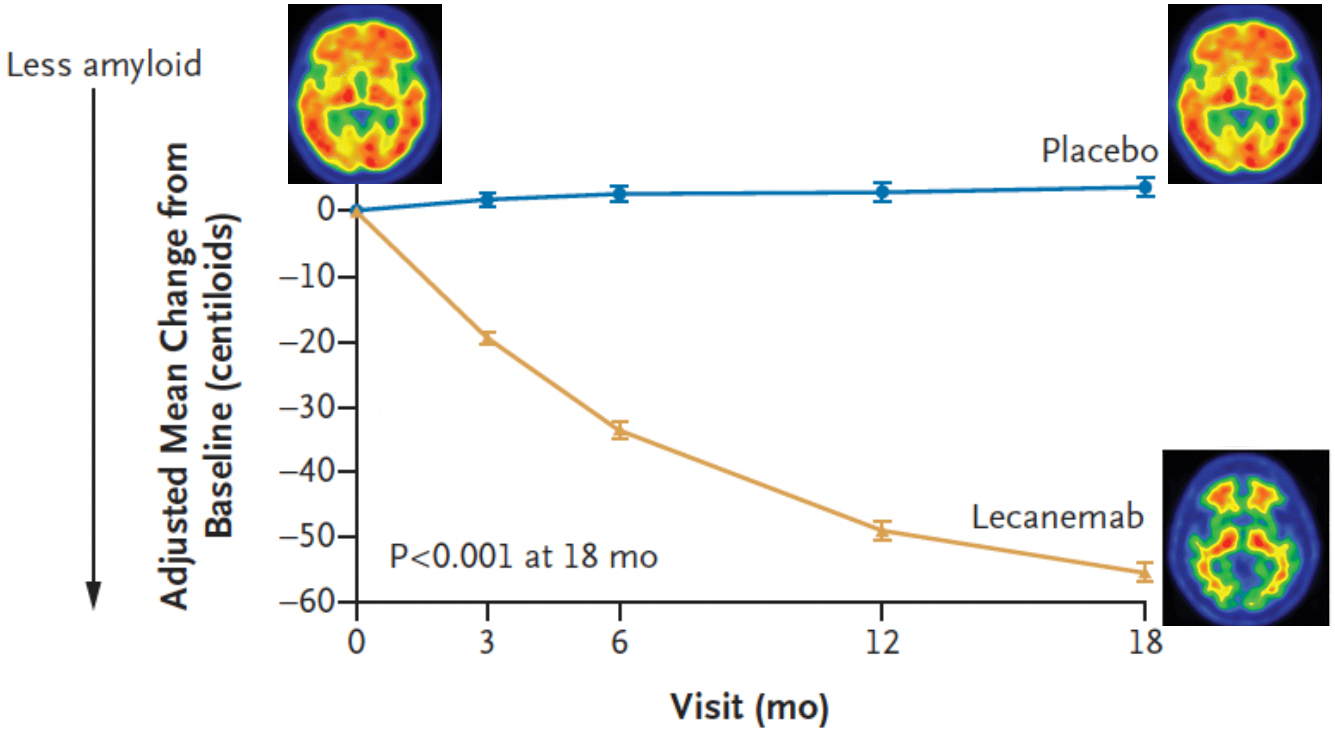
Prespecified exploratory analyses[4]

Measures of health-related QoL and caregiver burden; time to worsening of global CDR score

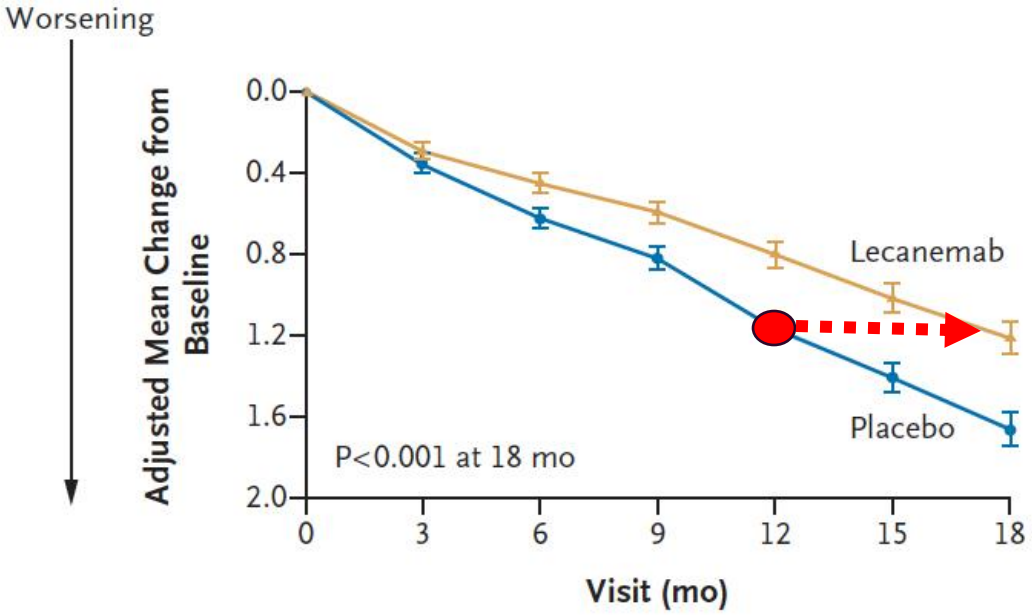
Primary Endpoint	Key Secondary Endpoints		
CDR-SB[1]	ADAS-Cog14[1]	ADCS MCI-ADL[1]	Brain amyloid (PET)[1,2]
Cognition and function[3]	Cognition[3]	Function[3]	Aβ (biomarker)[3]
27% slowing of cognitive and functional decline vs placebo	**26%** slowing of cognitive decline vs placebo	**37%** slowing of functional decline vs placebo	**~56 CL** reduction compared to placebo, achieving plaque clearance[a]
P<0.0001	*P*<0.001	*P*<0.0001	*P*<0.0001
✓ Endpoint met	✓ Endpoint met	✓ Endpoint met	✓ Endpoint met
LEQEMBI: N=859 Placebo: N=875	LEQEMBI: N=854 Placebo: N=872	LEQEMBI: N=783 Placebo: N=796	LEQEMBI: N=354 Placebo: N=344

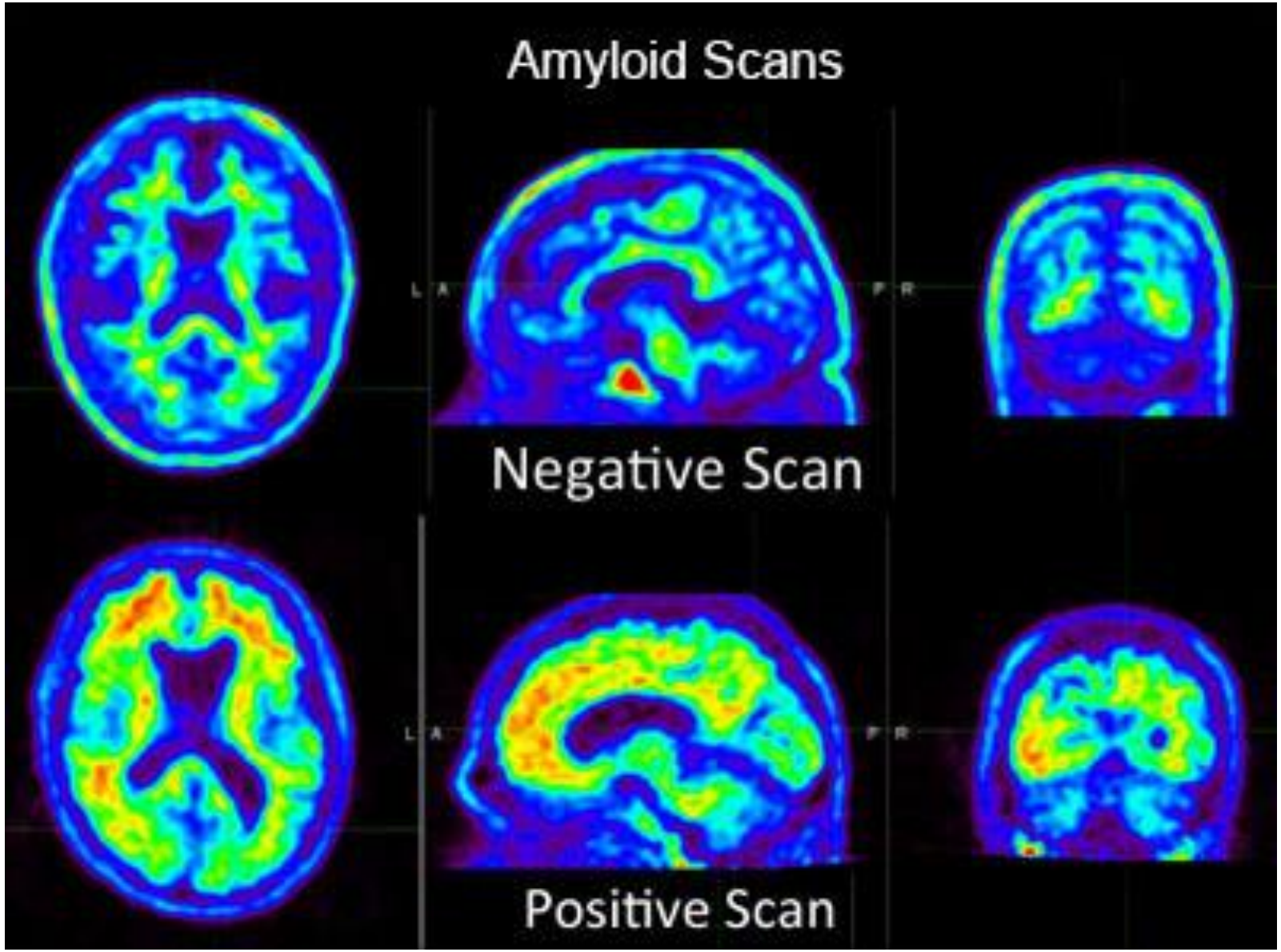
Leqembi Reduces Amyloid Burden and Slows Cognitive Decline

Big reduction in amyloid burden



Slower clinical decline





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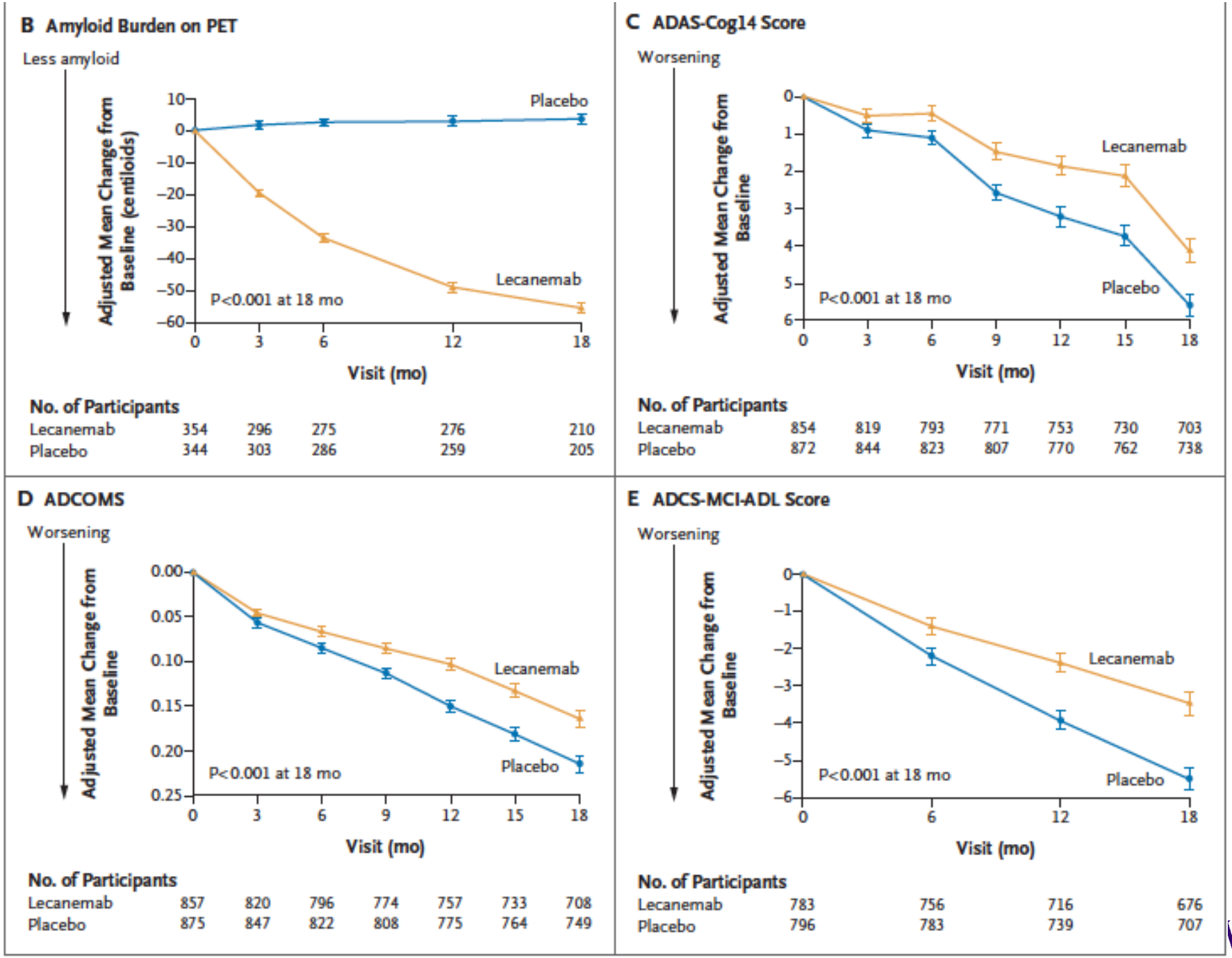
B Amyloid Burden on PET
Less amyloid
Adjusted Mean Change from Baseline (centiloids)
10
0
−10
−20
−30
−40
−50
−60
Placebo
Lecanemab
P<0.001 at 18 mo
0
3
6
12
18
Visit (mo)
No. of Participants
Lecanemab 354 296 275 276 210
Placebo 344 303 286 259 205
C ADAS-Cog14 Score
Worsening
Adjusted Mean Change from Baseline
0
1
2
3
4
5
6
Lecanemab
Placebo
P<0.001 at 18 mo
0
3
6
9
12
15
18
Visit (mo)
No. of Participants
Lecanemab 854 819 793 771 753 730 703
Placebo 872 844 823 807 770 762 738
D ADCOMS
Worsening
Adjusted Mean Change from Baseline
0.00
0.05
0.10
0.15
0.20
0.25
Lecanemab
Placebo
P<0.001 at 18 mo
0
3
6
9
12
15
18
Visit (mo)
No. of Participants
Lecanemab 857 820 796 774 757 733 708
Placebo 875 847 822 808 775 764 749
E ADCS-MCI-ADL Score
Worsening
Adjusted Mean Change from Baseline
0
−1
−2
−3
−4
−5
−6
Lecanemab
Placebo
P<0.001 at 18 mo
0
6
12
18
Visit (mo)
No. of Participants
Lecanemab 783 756 716 676
Placebo 796 783 739 707

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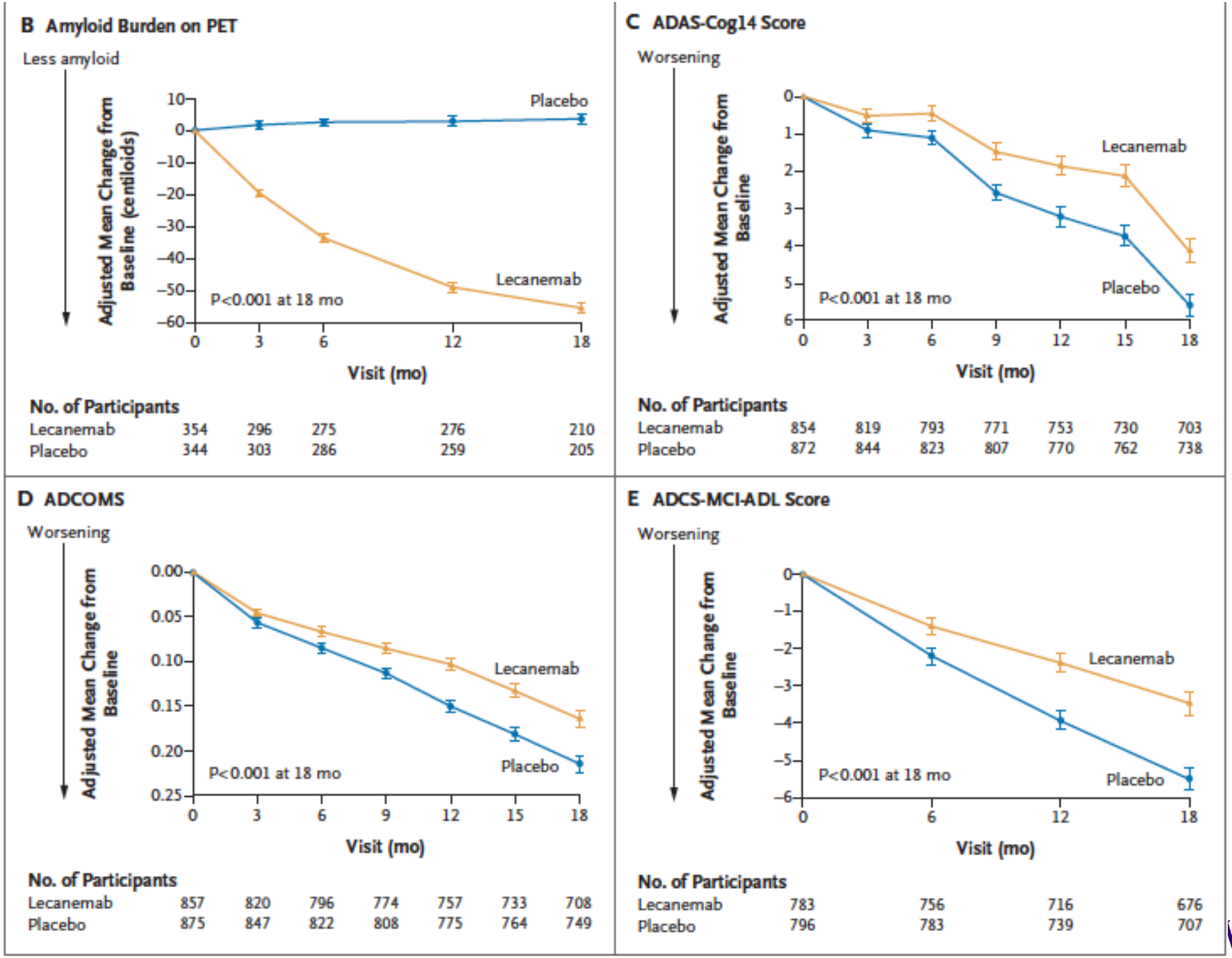
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0.10
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0.20
0.25
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P<0.001 at 18 mo
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Visit (mo)
No. of Participants
Lecanemab 857 820 796 774 757 733 708
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Worsening
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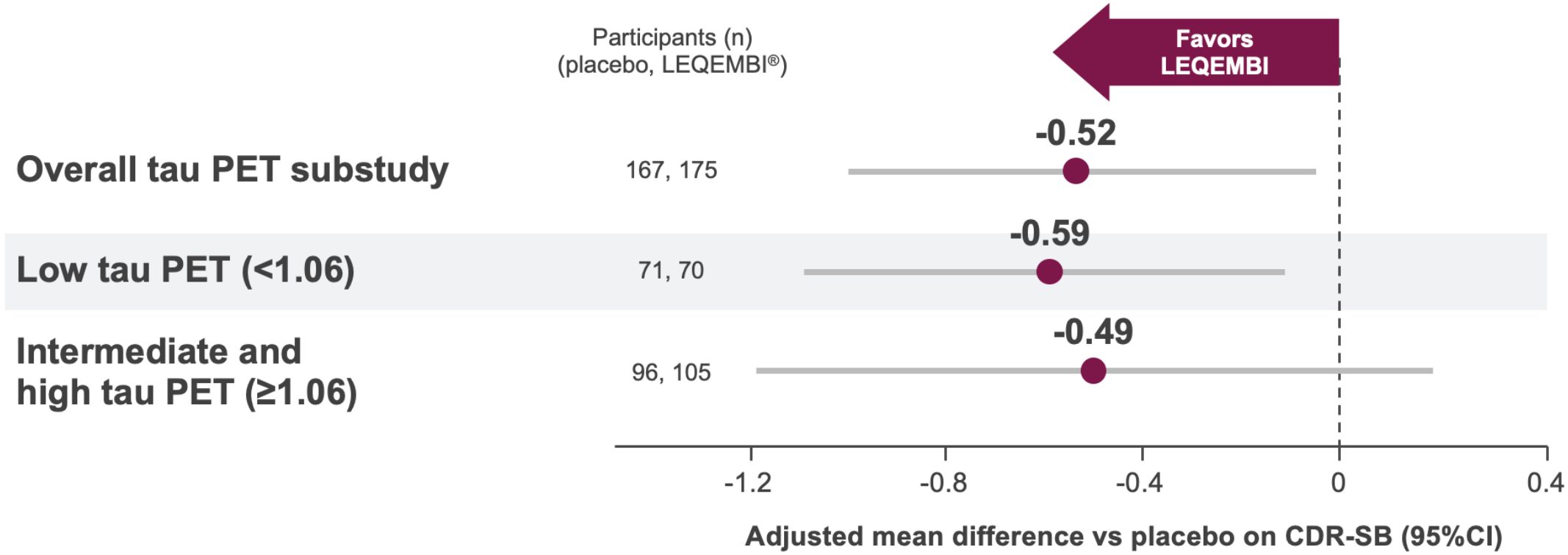
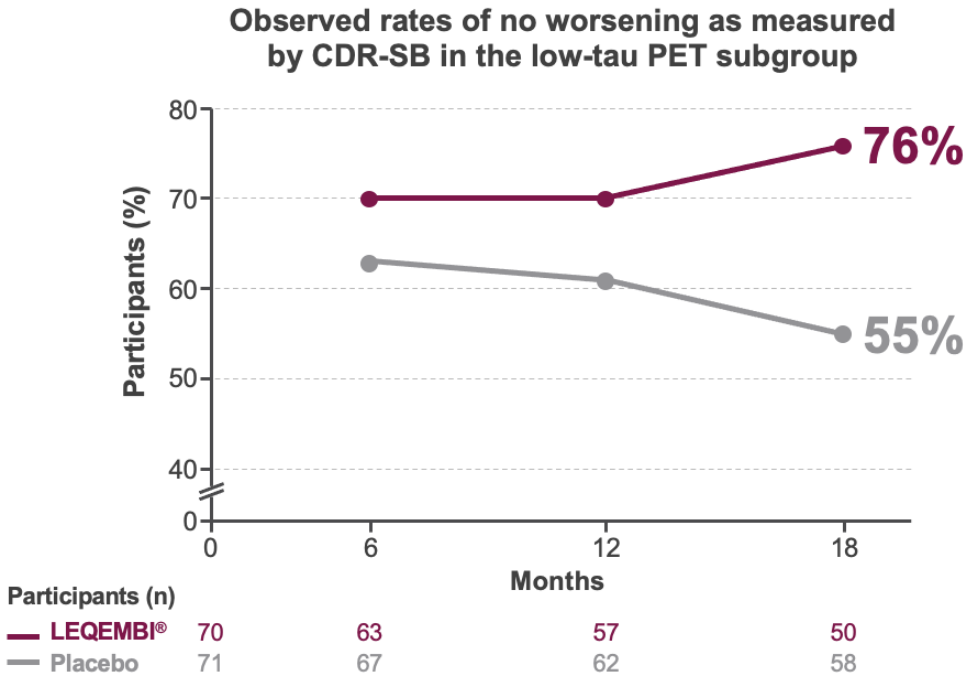
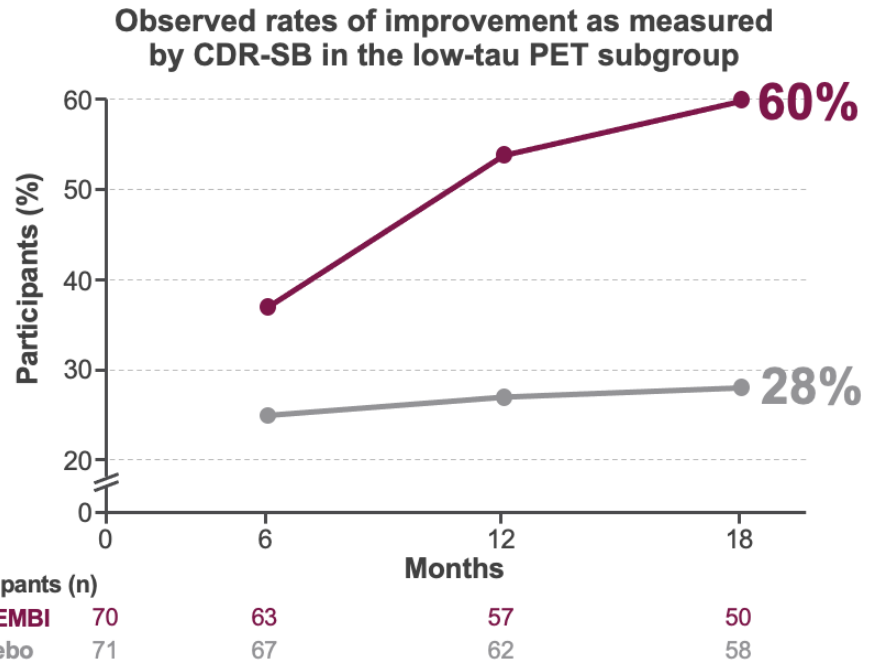


CDR-SB measures cognition and function. An increase in score=increased impairment, and a decrease in score=decreased impairment[1]

76% of participants with early AD and low tau showed no worsening in CDR-SB scores compared with baseline[2,3]



60% of participants with early AD and low tau showed an improvement as measured by the CDR-SB compared with baseline[2,3]



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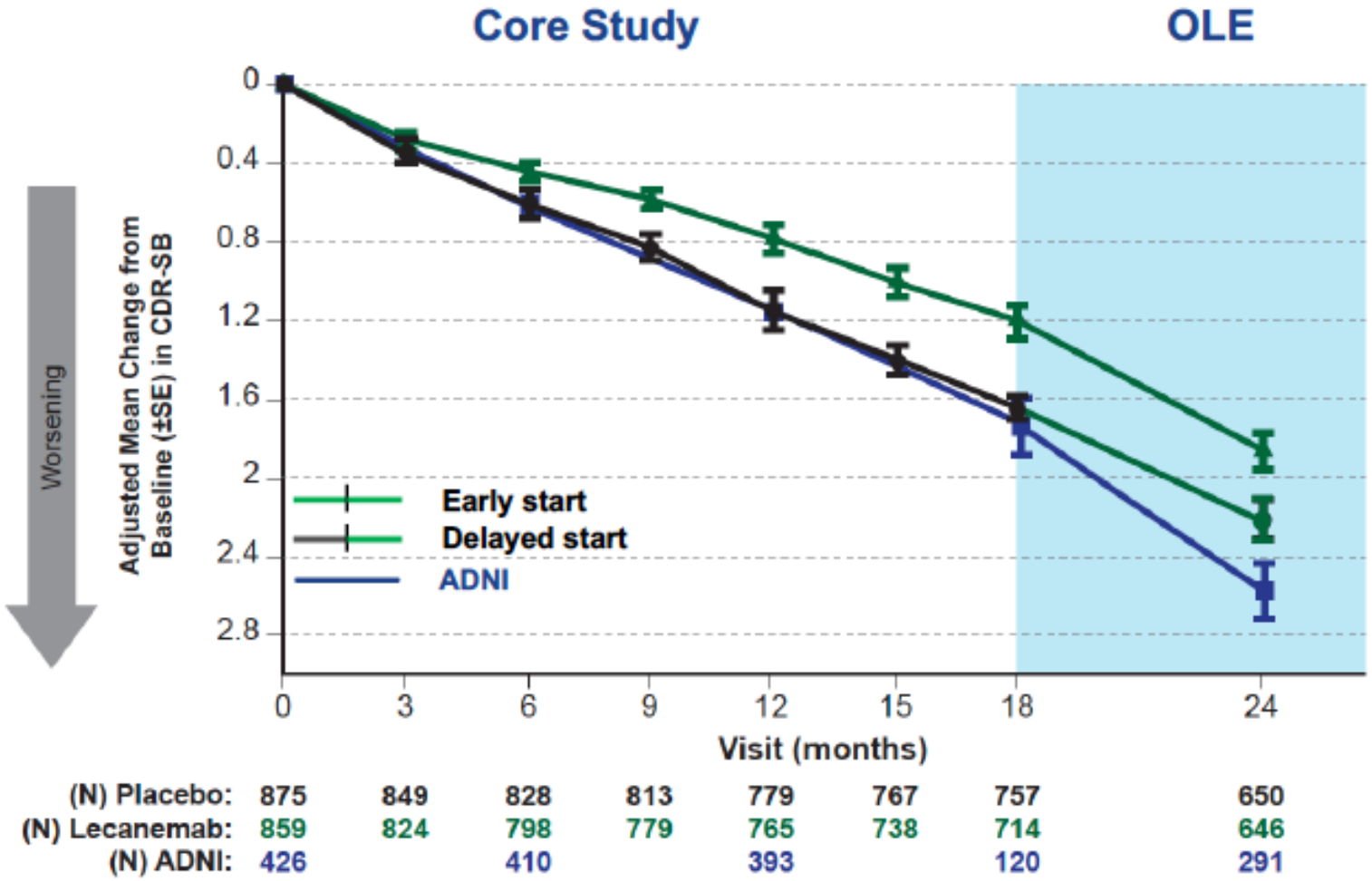
Clarity AD CDR-SB: OLE in Context of Observational Cohort

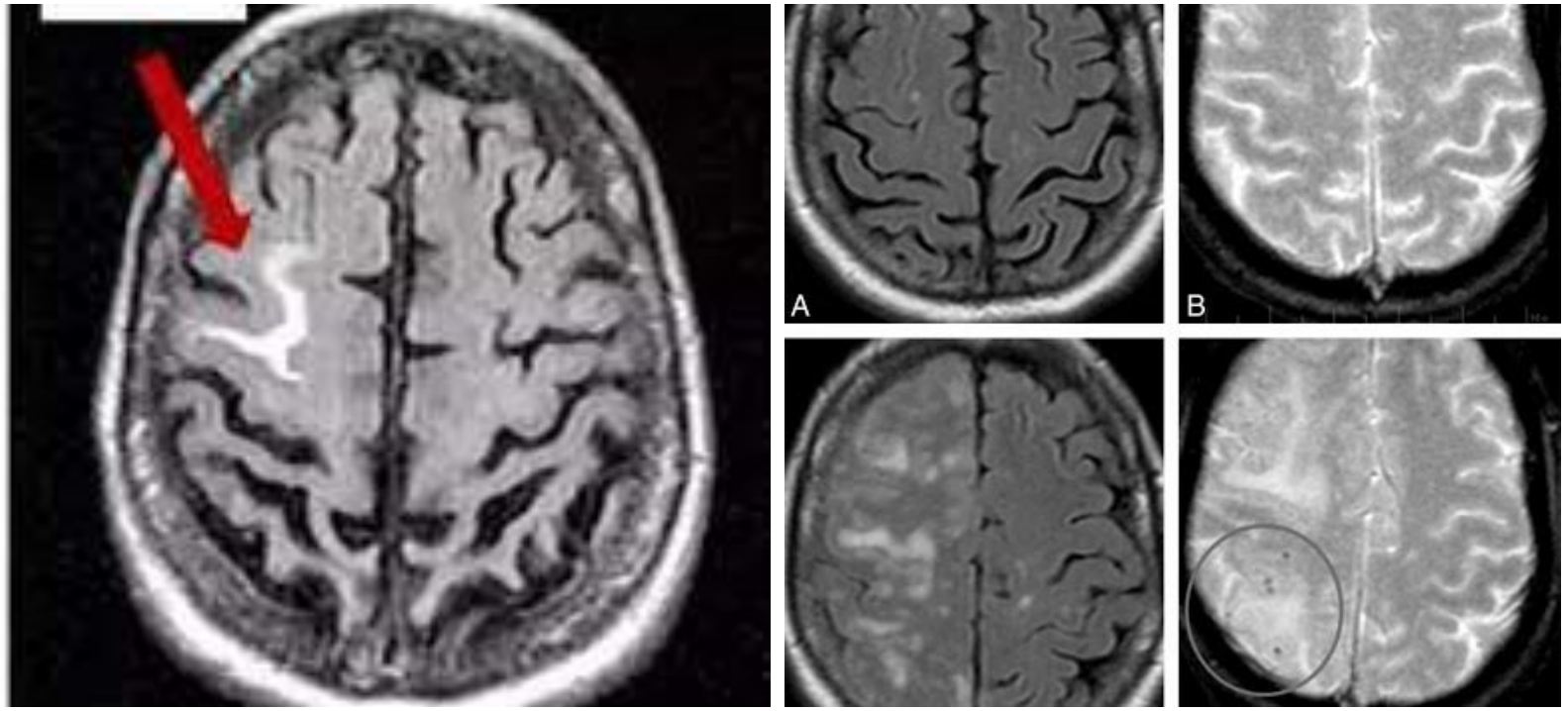
Lecanemab-Treated Participants Continued to Benefit Through 24 Months



- These ADNI participants selected to match with Clarity AD population
  - Baseline demographics and clinical characteristics including randomization strata
- Matched ADNI participants show similar degree of decline to placebo group out to 18 months
- Caveats
  - ADNI is an observational cohort;
  - Delayed start is Open-label; all participants know they are receiving lecanemab

CLARITY AD: ADVERSE EVENTS

- Infusion Reactions 26.4%
- ARIA-E 12.6% (vs. 1.7% placebo)
- ARIA-H- 17.3% (vs. 9.0% placebo)
- Most likely occurs within first 4 months (<8th infusion)
- 80% of cases asymptomatic
- <3% of individuals with symptomatic ARIA (van Dyck NEJM 2022)
- + FDA Box warning



ARIA-E according to ApoE ε4 genotype — no./total no. (%)		
ApoE ε4 noncarrier	15/278 (5.4)	1/286 (0.3)
ApoE ε4 carrier	98/620 (15.8)	14/611 (2.3)
ApoE ε4 heterozygote	52/479 (10.9)	9/478 (1.9)
ApoE ε4 homozygote	46/141 (32.6)	5/133 (3.8)
ARIA-H according to ApoE ε4 genotype — no./total no. (%)		
ApoE ε4 noncarrier	33/278 (11.9)	12/286 (4.2)
ApoE ε4 carrier	122/620 (19.7)	69/611 (11.3)
ApoE ε4 heterozygote	67/479 (14.0)	41/478 (8.6)
ApoE ε4 homozygote	55/141 (39.0)	28/133 (21.1)

CNS Drugs
https://doi.org/10.1007/s40263-024-01097-w

THERAPY IN PRACTICE

A Framework for the Administration of Anti-amyloid Monoclonal Antibody Treatments in Early-Stage Alzheimer's Disease

Michael H. Rosenbloom[1,6,9] · Tricia O'Donohue[2] · Domi Zhou-Clark[3] · Deepashni Mala[4] · Andrew Frazier[4] · Michael Tarrant[4] · Michelle Modrijan[4] · Melora Riveira[5] · Darla Chapman[1] · Yvonne Griffin[1] · Lauren Shakalis[8] · Thomas J. Grabowski[1,6,7]

Accepted: 13 May 2024

Abstract

The US Food and Drug Administration (FDA) approval of lecanemab for early-stage Alzheimer's disease (AD) represents an exciting new chapter in the management of neurodegenerative disease, but likewise presents numerous clinical, technical, and financial logistical challenges for both academic and non-academic medical institutions hoping to administer this drug. Minimal resources exist that provide guidance for establishing and maintaining a lecanemab treatment program at the institutional level. The current report aims to provide healthcare institutions a framework for the planning, onboarding, and longitudinal treatment of AD with anti-amyloid monoclonal antibody treatments. We present an implementation study involving three stages: (1) feasibility assessment, (2) operations and going live, and (3) monitoring assessment. We found that implementation of lecanemab in clinical practice was feasible due to the assignment of an enterprise-wide project manager to facilitate the planning phase, a cost analysis showing that lecanemab was financially sustainable, and the development of electronic medical record tools to support operational efficiency.

Key Points

Both academic and non-academic healthcare institutions face numerous clinical, technical, and financial logistical challenges when starting an anti-amyloid monoclonal antibody (AMA) program.

We provide a framework for the institution of AMAs within a healthcare system.

Our experience has shown that the process was facilitated by having an enterprise-wide project manager, performing a financial analysis prior to starting, and leveraging electronic-medical-record-based tools.

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6 Department of Neurology, University of Washington, Seattle,


Benefit
Risk

Appropriate Use Criteria-Cummings et al J Prev Alz Dis 2023

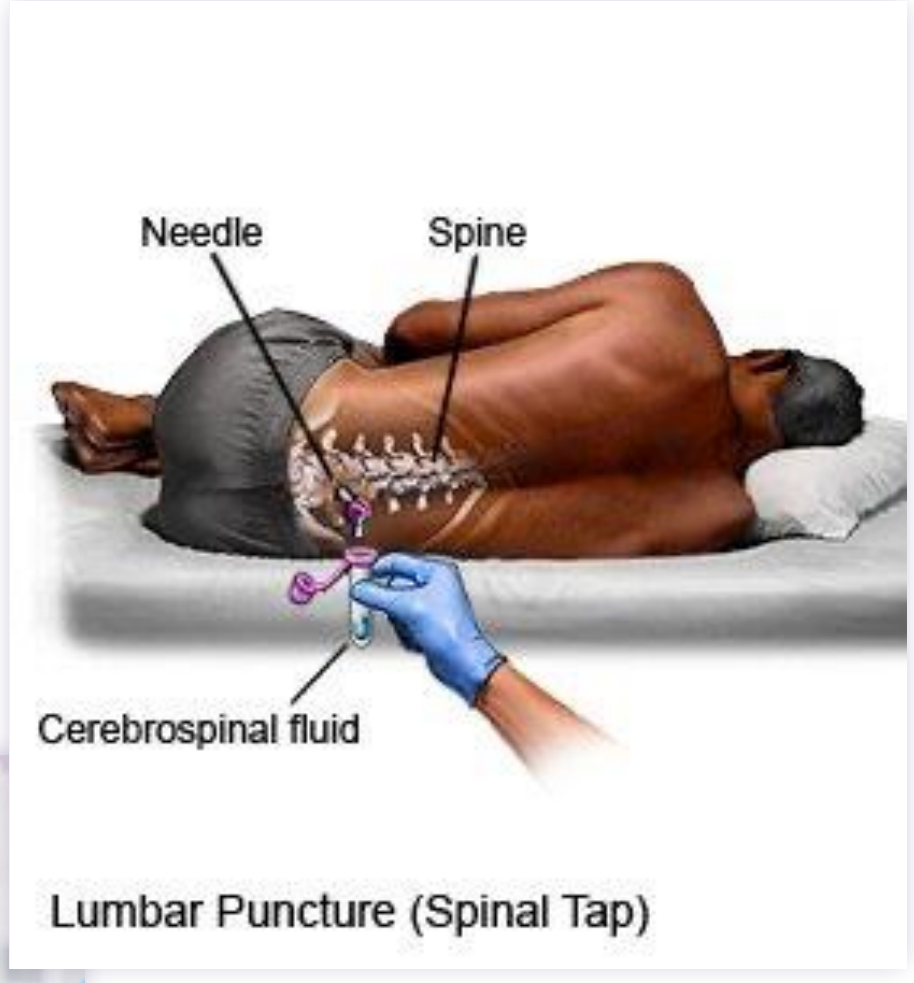
Inclusion Criteria	Exclusion Criteria
Clinical Diagnosis of MCI/AD	Any medical, neurologic, or psychiatric condition contributing ton non-AD MCI or dementia
Positive amyloid PET or CSF studies	1)> than 4 microhemorrhages on SWI 2) single macrohemorrhage>10 mm in diameter 3) superficial siderosis, 4) vasogenic edema,5)multiple lacunar strokes, 6) large vessel infarction, and 7) severe CVD
Age 50-90	Recent history (12 mo) of stroke or TIA
MMSE 22-30 or MOCA 17-30	Mental illness that interferes with compression
Care partner or family member involved	Any hx of immunologic dx or systemic treatment with immunosuppressants
Must understand risks/benefits of treatment	Bleeding disorder, low platelets, INR>1.5
	Anticoagulation use (”tPA should not be administered to individuals on lecanemab”)
	Unstable conditions that may be affected by lecanemab therapy
	Any history of seizures

Recommended Labs Prior to Starting Leqembi Infusion Therapy

Spinal fluid biomarkers for Abeta 42, p-tau, t-tau vs. amyloid PET

PT/INR/PTT (bleeding disorder, AC)

ApoE4 (risk of ARIA)

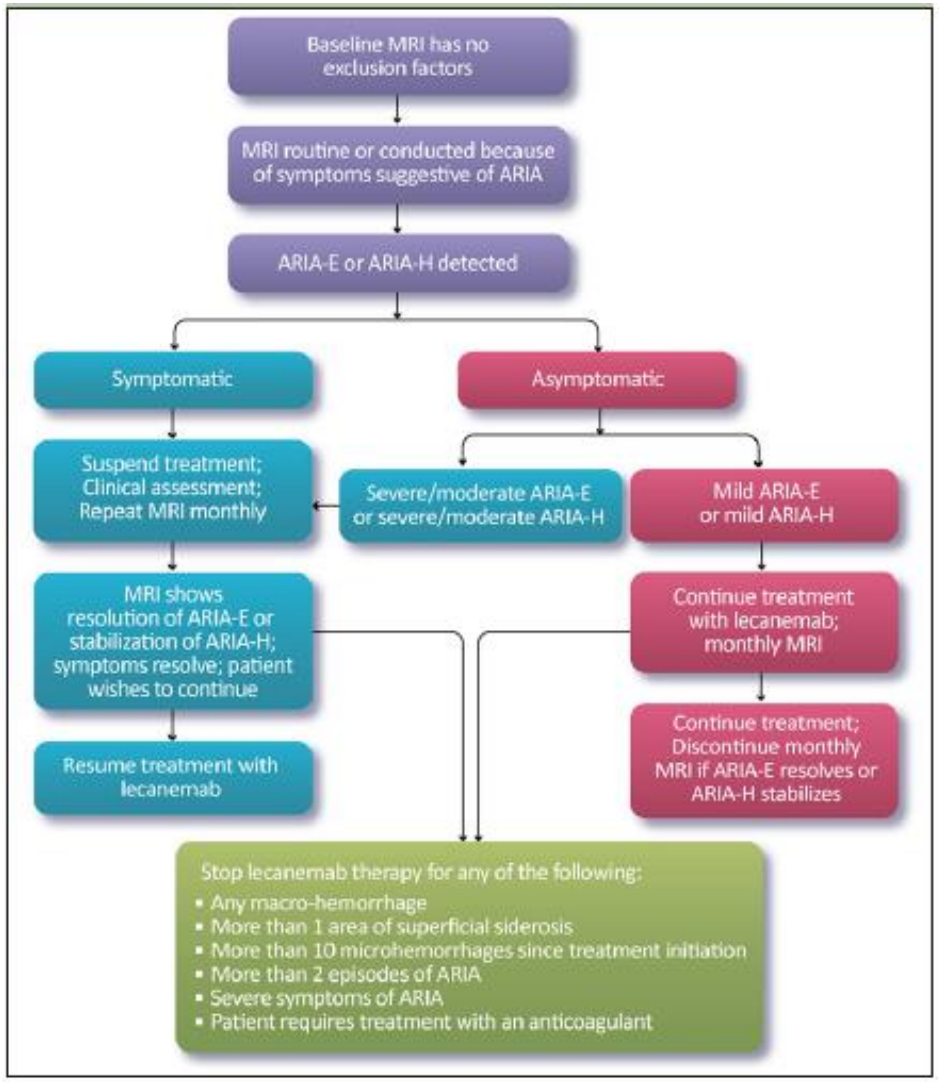


Lumbar Puncture (Spinal Tap)

ARIA Protocol (Cummings et al J Prev Alz Dis 2023)

Table 2: ARIA MRI Classification Criteria

ARIA Type	Radiographic Severity		
	Mild	Moderate	Severe
ARIA-E	FLAIR hyperintensity confined to sulcus and or cortex/subcortical white matter in one location < 5 cm	FLAIR hyperintensity 5 to 10 cm, or more than 1 site of involvement, each measuring < 10 cm	FLAIR hyperintensity measuring > 10 cm, often with significant subcortical white matter and/or sulcal involvement. One or more separate 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 focal areas of superficial siderosis



NY Times
10 June 2024

- Baseline amyloid PET necessary for confirming AD diagnosis and possibly again as early as 6 months to confirm amyloid removal/cessation of treatment (induction therapy approach)
- Baseline tau PET unnecessary for predicting potential response to donanemab based on low/medium versus high tau

Advisory Panel of Experts Endorses F.D.A. Approval of New Alzheimer's Drug

The modest benefits of the treatment, donanemab, made by Eli Lilly, outweigh the risks, the panel concluded unanimously.

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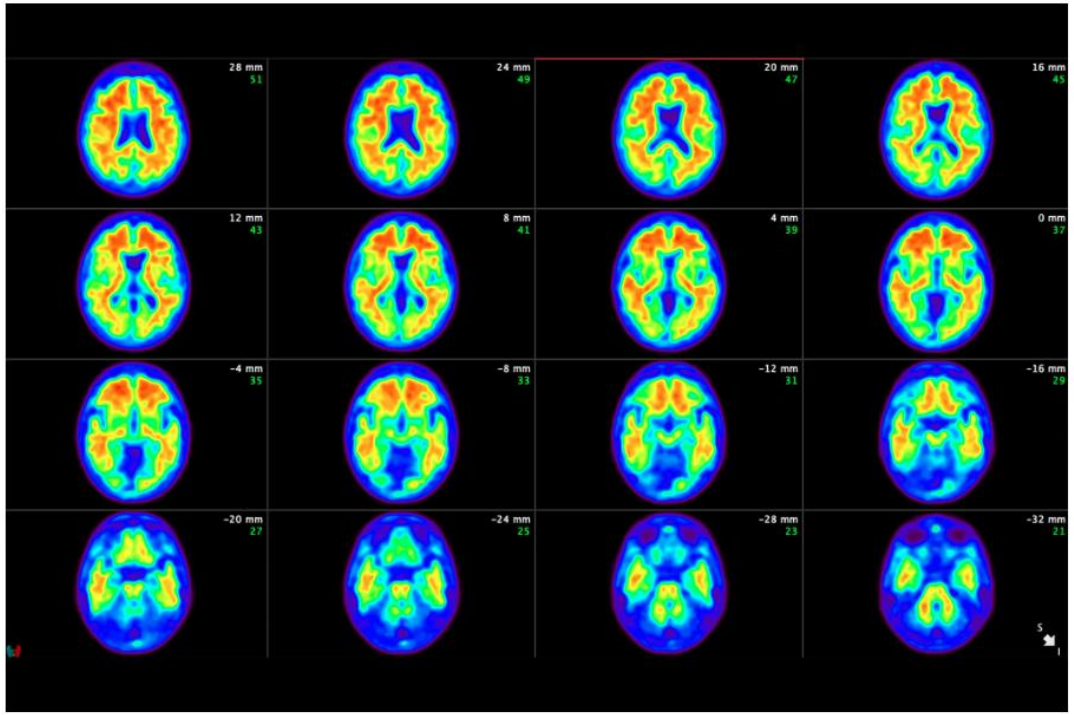

Brain scans from a patient in the clinical trials of donanemab showed amyloid plaque being removed from the patient's brain. Eli Lilly

JAMA | Original Investigation

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

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IMPORTANCE There are limited efficacious treatments for Alzheimer disease.

OBJECTIVE To assess efficacy and adverse events of donanemab, an antibody designed to clear brain amyloid plaque.

DESIGN, SETTING, AND PARTICIPANTS Multicenter (277 medical research centers/hospitals in 8 countries), randomized, double-blind, placebo-controlled, 18-month phase 3 trial that enrolled 1736 participants with early symptomatic Alzheimer disease (mild cognitive impairment/mild dementia) with amyloid and low/medium or high tau pathology based on positron emission tomography imaging from June 2020 to November 2021 (last patient visit for primary outcome in April 2023).

INTERVENTIONS Participants were randomized in a 1:1 ratio to receive donanemab (n = 860) or placebo (n = 876) intravenously every 4 weeks for 72 weeks. Participants in the donanemab group were switched to receive placebo in a blinded manner if dose completion criteria were met.

MAIN OUTCOMES AND MEASURES The primary outcome was change in Integrated Alzheimer Disease Rating Scale (IADRS) score from baseline to 76 weeks (range, 0-144; lower scores indicate greater impairment). There were 24 gated outcomes (primary, secondary, and exploratory), including the secondary outcome of change in the sum of boxes of the Clinical

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QUESTION Does donanemab, a monoclonal antibody designed to clear brain amyloid plaque, provide clinical benefit in early symptomatic Alzheimer disease?

CONCLUSION Among patients with early symptomatic Alzheimer disease and amyloid and tau pathology, donanemab significantly slowed clinical progression at 76 weeks in low/medium tau and combined low/medium and high tau pathology populations.

POPULATION

996 Women
740 Men

Adults aged 60-85 years with symptomatic Alzheimer disease and amyloid and tau pathology

Mean age: **73** years

LOCATIONS

277
Medical sites in 8 countries

INTERVENTION

1736 Patients randomized
1599 Patients analyzed

860
Donanemab
Administered intravenously every 4 weeks for up to 72 weeks

876
Placebo
Administered intravenously every 4 weeks for up to 72 weeks

PRIMARY OUTCOME

Least-squares mean change in integrated Alzheimer Disease Rating Scale (iADRS) score (range, 0-144; lower scores indicate greater impairment) from baseline to 76 weeks

FINDINGS

Least-squares mean change in iADRS

Donanemab

Low/medium tau population: **−6.02**

Combined population: **−10.19**

Placebo

Low/medium tau population: **−9.27**

Combined population: **−13.11**

Differences were statistically significant:

Low/medium tau: 3.25 (95% CI, 1.88-4.62); *P* < .001

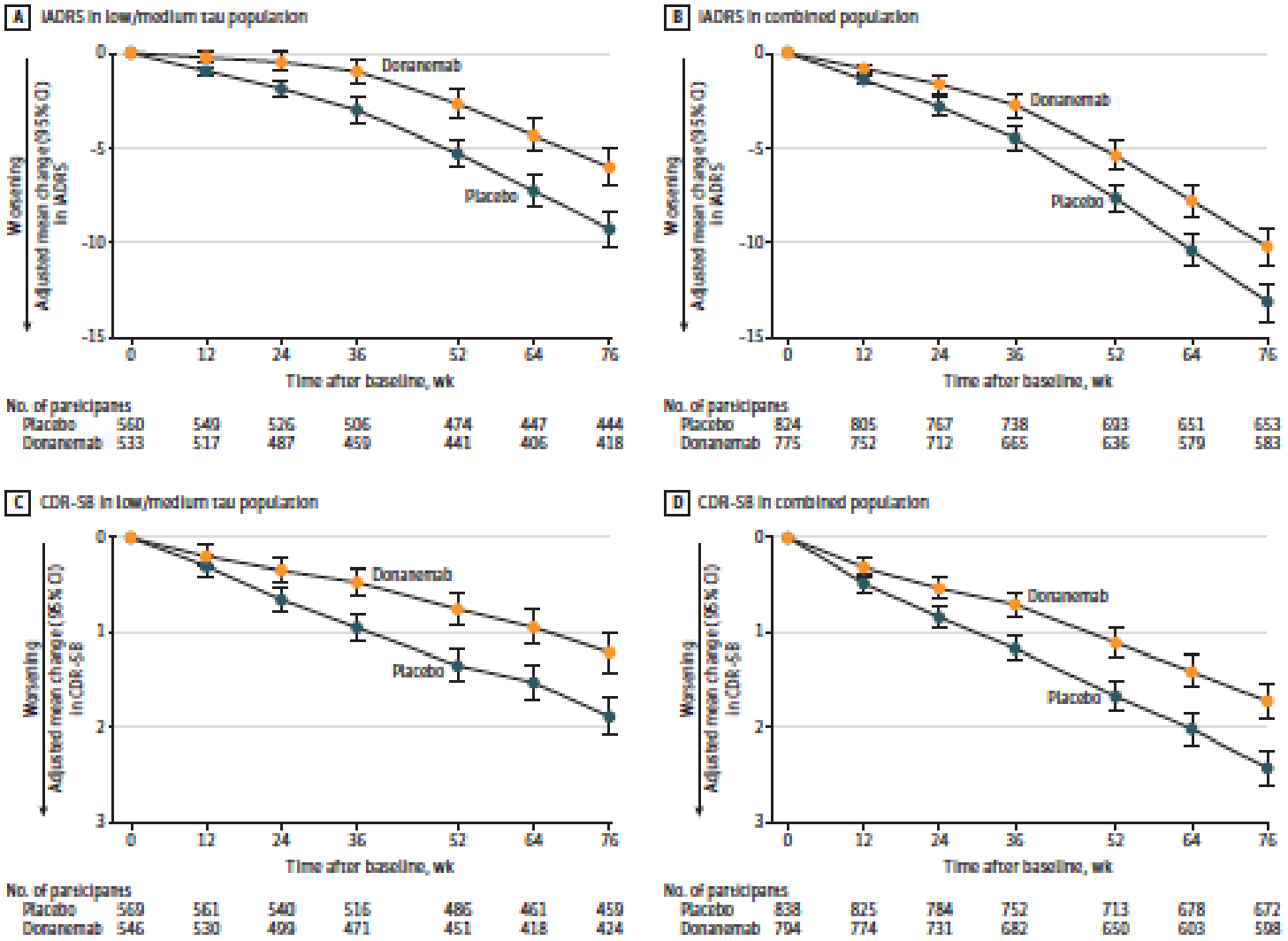
Combined: 2.92 (95% CI, 1.51-4.33); *P* < .001

Sims JR, Zimmer JA, Evans CD, et al; TRAILBLAZER-ALZ 2 Investigators. Donanemab in early symptomatic Alzheimer disease: the TRAILBLAZER-ALZ 2 randomized clinical trial. *JAMA*. Published online July 17, 2023. doi:10.1001/jama.2023.13239

TRAILBLAZER-ALZ 2

- Randomized double-blinded, placebo-controlled, 18 months (76 weeks) phase 3 trial
- A total of 1736 early stage-AD participants randomized (mean age 73.0 years)
  - 68.1% with low/medium tau pathology (Tau PET scan)
  - 31.8% with high tau pathology
- Subjects with a single amyloid PET scan <11 centiloids or 2 consecutive PET scans between 11 and 25 centiloids. (wk 24 +52) were switched from IP to placebo
- Primary outcome iADRS (ADAS-Cog13+ ADCS-iADL)
  - Meaningful within patient changes=5 in MCI and 9 in mild AD

Figure 2. Integrated Alzheimer Disease Rating Scale (iADRS) and Sum of Boxes of the Clinical Dementia Rating Scale (CDR-SB) From Baseline to 76 Weeks



iADRS@76 weeks:
35.1% slowing in the low/medium tau (22.3% combined)

CDR SOB@76 weeks
36.0% slowing in low/medium tau (28.9% combined)

Progression
47% of low/med tau group showed NO change in CDR-SOB vs. 29% of Placebo

Based on scales: Delay by 4.5-7.5 months over 1.5 years

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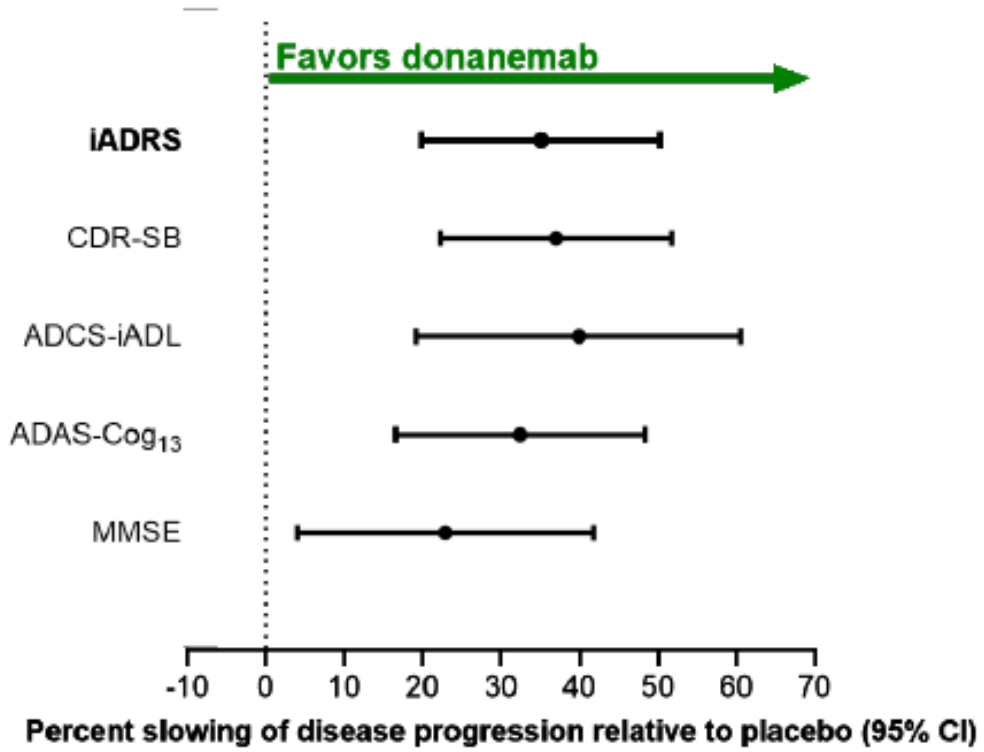
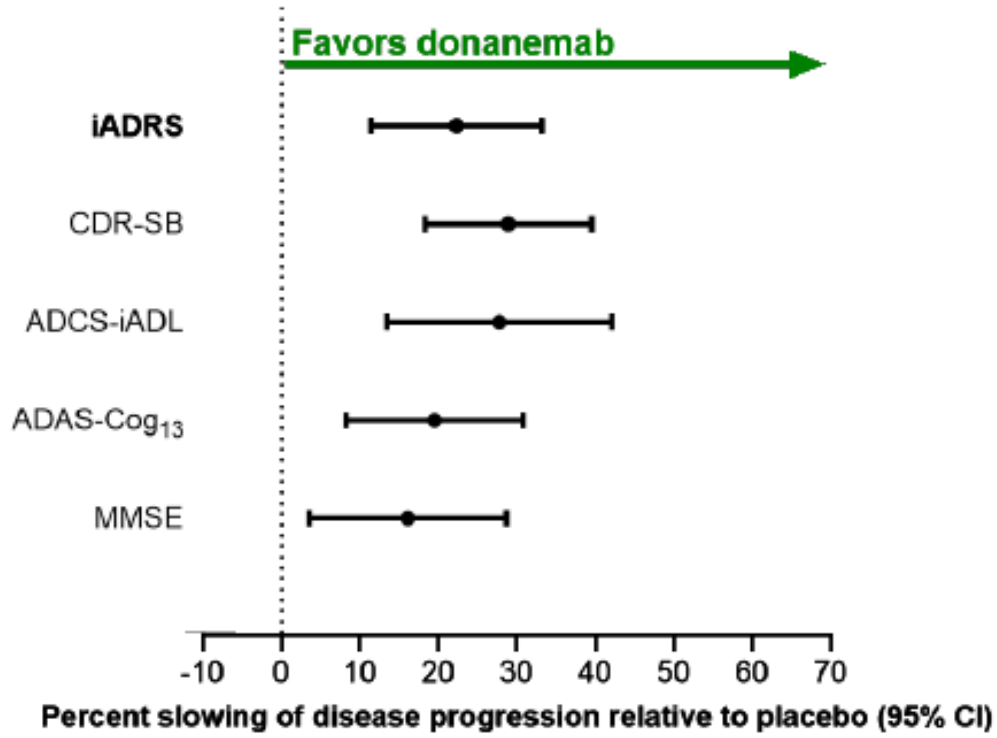
Low-medium Tau Population



Combined Tau Population



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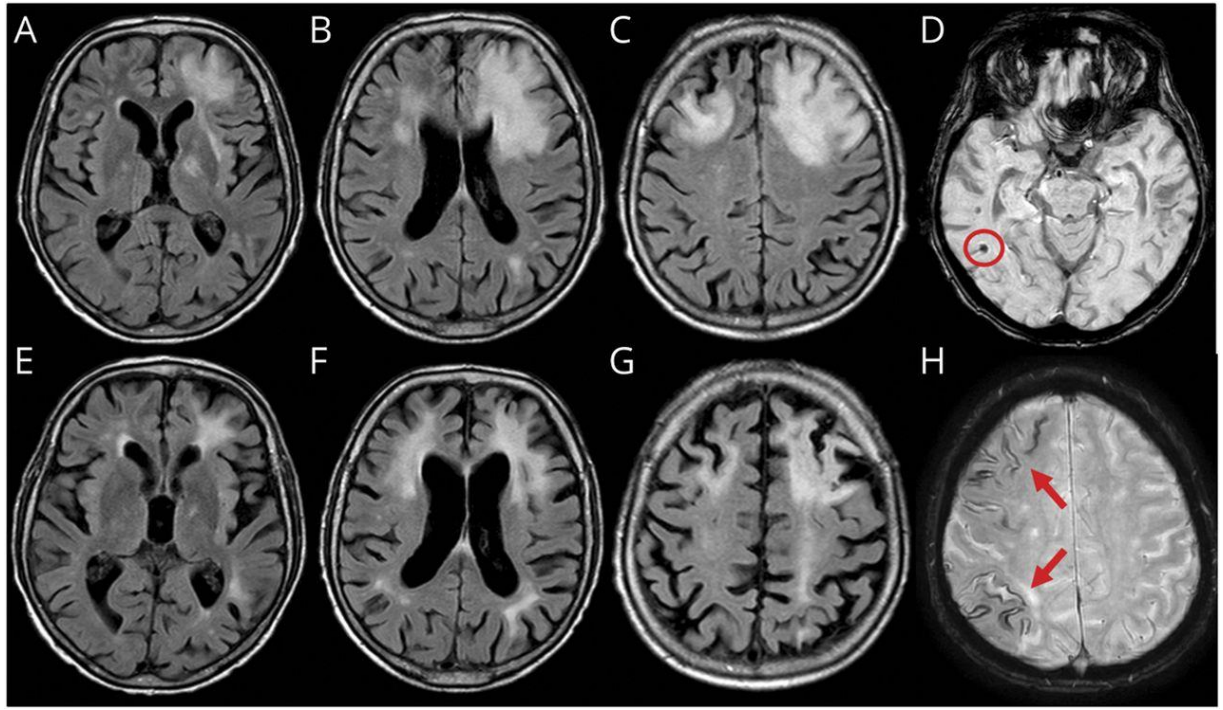
TRAILBLAZER2-ALZ ADVERSE EVENTS

- Incidence ARIA-E or H: 36.8% (14.9% placebo)
- ARIA-H: 31.4% (13.6% placebo)
- ARIA E: 24.0% (2.0% placebo); 6.1% symptomatic; 1.5% serious
  - 15% no E4/E4; E4 heterozygous 23%; 40% E4 homozygous
- Three cases of severe ARIA resulting in death (2/3 ApoE4/E4)
- 57.9% of ARIA developed with first 3 infusions and 98% resolved in 72.5 days
- Infusion reactions 8.7% (0.5% placebo)



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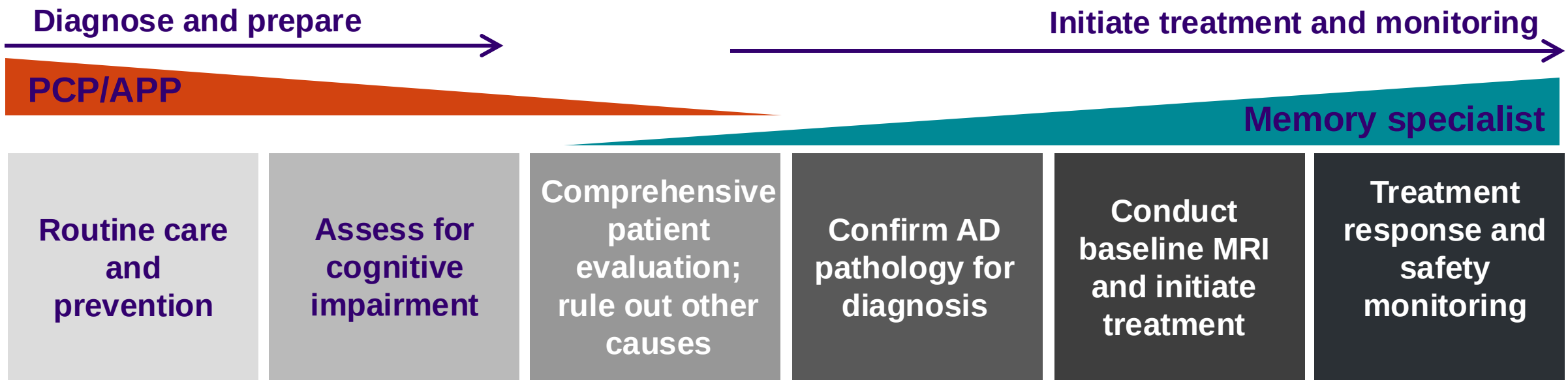
Key Lessons from CLARITY-AD and TRAILBLAZER2 Trials

- Amyloid monoclonal AB-treated patients with low tau values on Tau-PET had better outcomes than patients with high tau values
  - Therefore, identification of low tau pathology in patients may help enrich for those individuals most likely to respond best to treatment
- Amyloid PET imaging may be necessary as outcome measure to decide whether AMA treatment needs to be continued
  - Importance of centiloid units
- Patients who receive delayed amyloid monoclonal antibody treatment fail to experience the same benefit as those treated immediately
  - Therefore, early diagnosis and initiation of treatment without delay is the ultimate goal

Optimizing collaboration along the clinical care pathway[1-4]



While patients are waiting to see a specialist[3-4]:

Rule out other causes
- Cognitive and functional assessments
- Behavioral and neuropsychiatric examination
- Dementia labs and imaging

Discuss potential treatment(s)
- Symptomatic treatment
- Non-pharmacological treatment

Order diagnostic confirmation tests
- PET, CSF

Provide resources
- Patient and care partner education
- Counsel on expectations with emerging treatments

AD, Alzheimer's disease; APP, advanced practice provider; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; PET, positron emission tomography.

1. Hampel H, et al. *Nat Aging*. 2022;2:692-703; 2. Reis AB, et al. *AIMS Public Health*. 2022;9(4):661-689. 3. Liss J L, et al. *J Int Ern Med*. 2021;290(2):310-334; 4. Panos C, Gamble S. *BMC Palliat Care* 2019;18(1):6.

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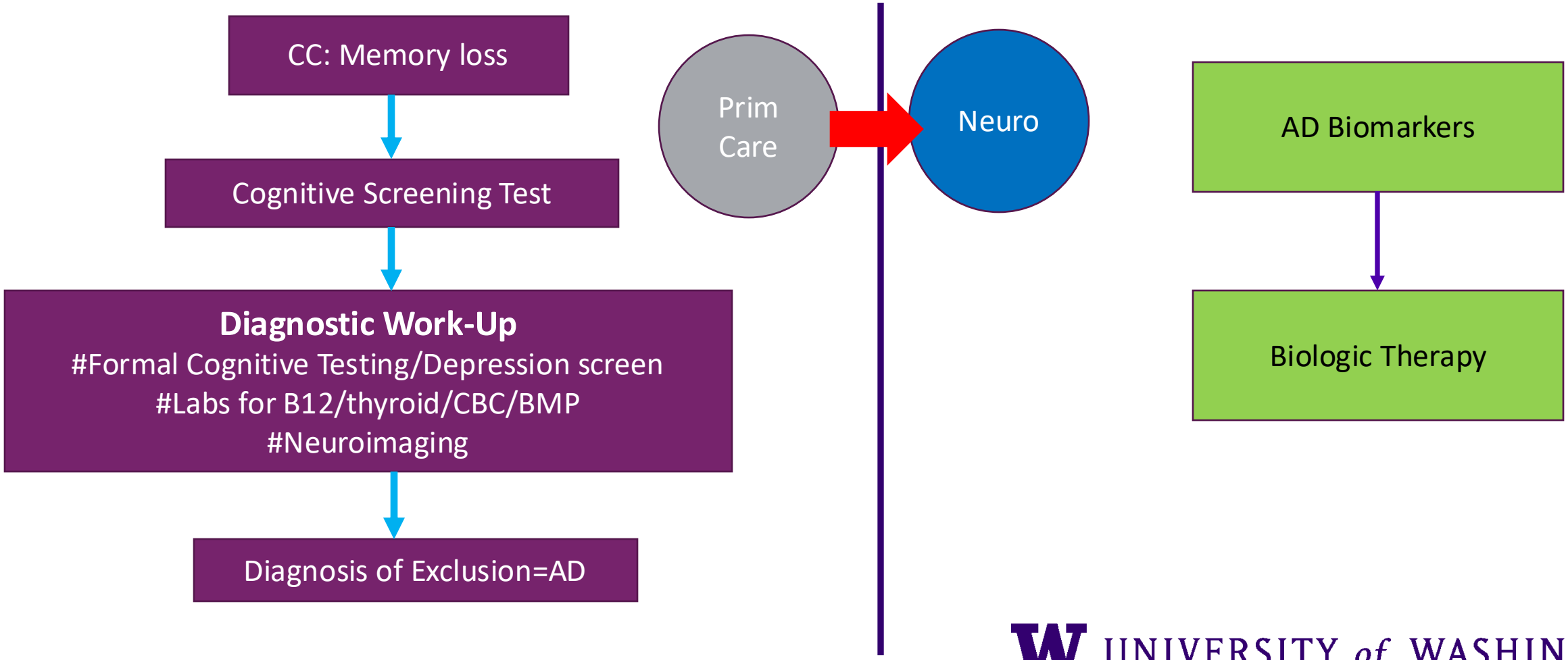
Standardized cognitive screening is needed in primary care[1]

	Advantages	Disadvantages	Cutoff to test for AD
MMSE[1-3]	• Widely used • Validated • Can monitor AD over time	• Copyright issues • Potential adjustments (age, education) • Not ideal to detect mild impairment	<24/25 (<23 if less than high school education)
SLUMS[3-5]	Higher sensitivity for detecting cognitive problems in earlier AD	• Not as widely used as other screening tests (e.g., MMSE) • Lack of research in different populations	<25.5 (<23.5 if less than high school education)
MoCA[1,6,7]	• Assesses many important cognition areas • Useful in patients with mild dementia or MCI	• Possible bias against limited education • Cutoffs not validated	<26
Mini-Cog[1,5]	• High sensitivity to predict dementia status • Visible performance indicator	Clock-drawing test is vulnerable to interpretation	Recall ≤3 and abnormal clock

AAPA, American Academy of Physician Associates; AD, Alzheimer's disease; Mini-Cog, Mini Cognitive Assessment Instrument; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; SLUMS, Saint Louis University Mental Status Examination.

1. Jin R, et al. *J Clin Med.* 2020;9(10):3287; 2. Stoner CR, et al. *J Clin Pharm Ther.* 2020;45(4):874-880; 3. Fernández Montenegro JM, et al. *Sensors (Basel).* 2021;21(24):7291; 4. Yang YR, et al. *Gerontology.* 2021;67(2):152-159; 5. Wang J, Dong B. *Clin Geriatr Med.* 2018;34(4):515-536; 6. Fasnacht JS, et al. *J Am Geriatr Soc.* 2023;71(3):869-879; 7. Davis DH, et al. *Cochrane Database Syst Rev.* 2021;7(7):CD010775.

A Potential Future Model of Care?



Thank You for Your Time

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