X(Twitter): @TheDrAtri

Translating the Latest Research Advances Into Routine Care for Alzheimer's Disease

Preparing Dementia Specialists With the Latest Strategies to Support Early Diagnosis and Comprehensive Care

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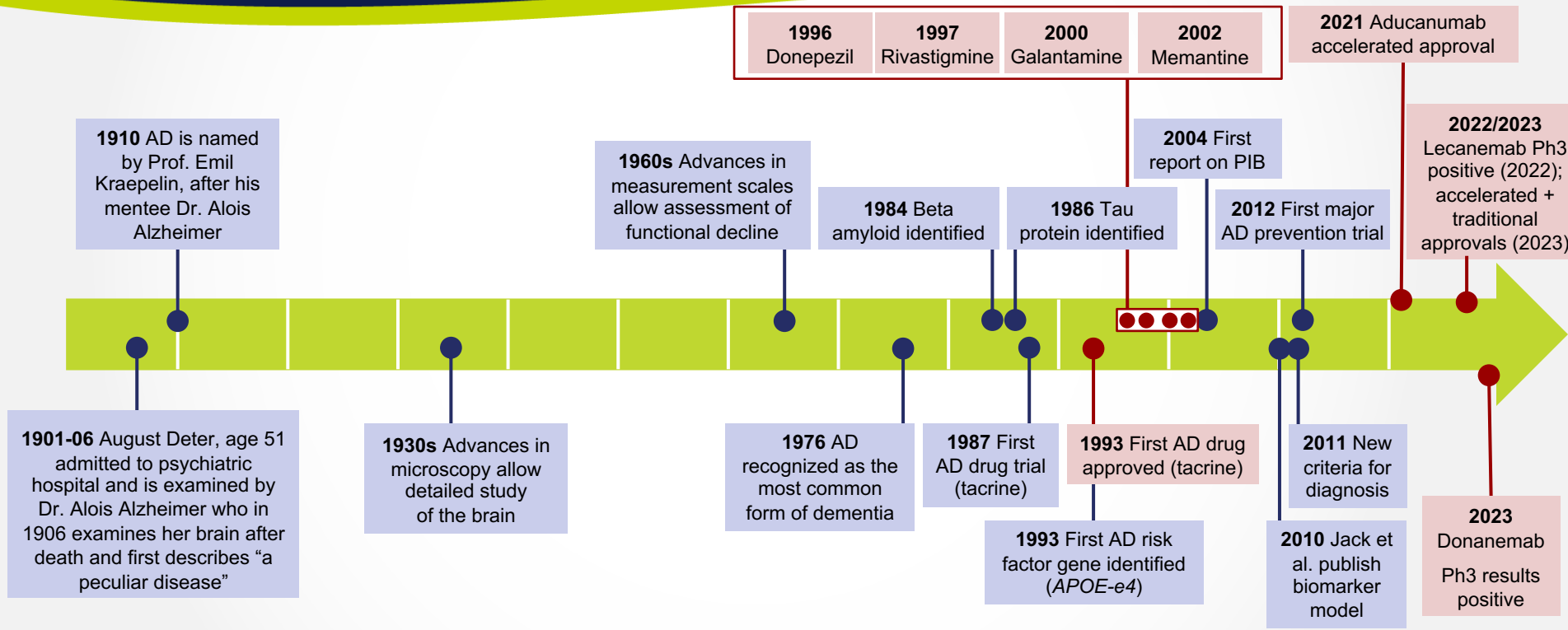
120 years of Alzheimer's disease (AD)

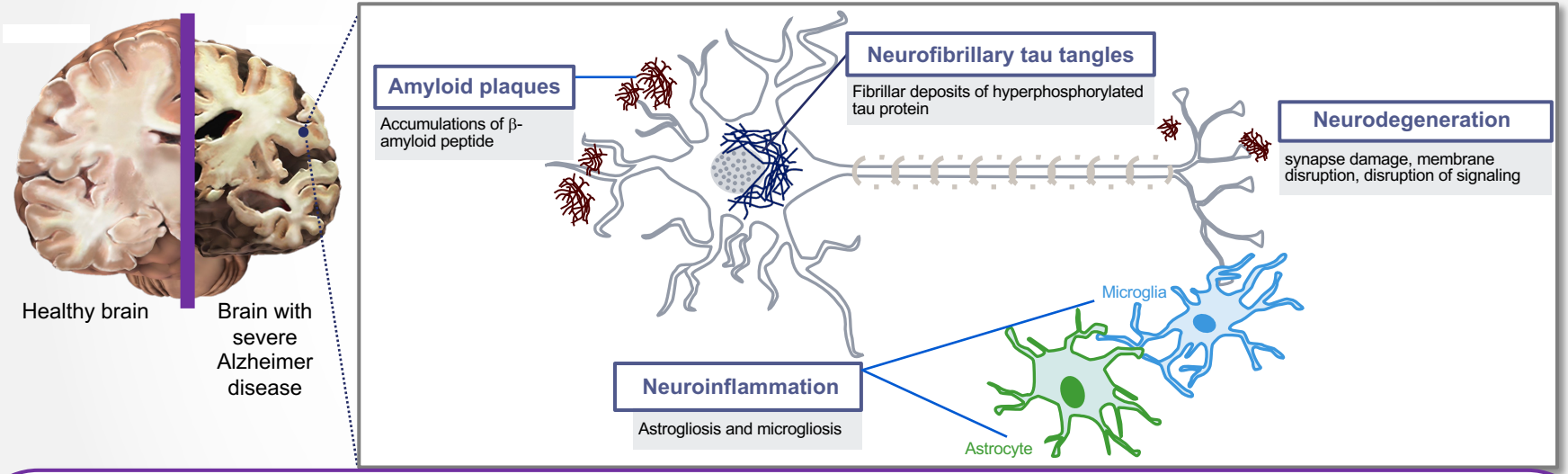


Courtesy of Alireza Atri, MD, PhD

de Castro AKA, et al. *Intl J Comput Intell Sys*. 2011; https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf;
Kinney JW, et al. *Alzheimers Dement (N Y)*. 2018; Atri A, et al. *Med Clin North Am*. 2019.

What Is Our Current Understanding of AD?

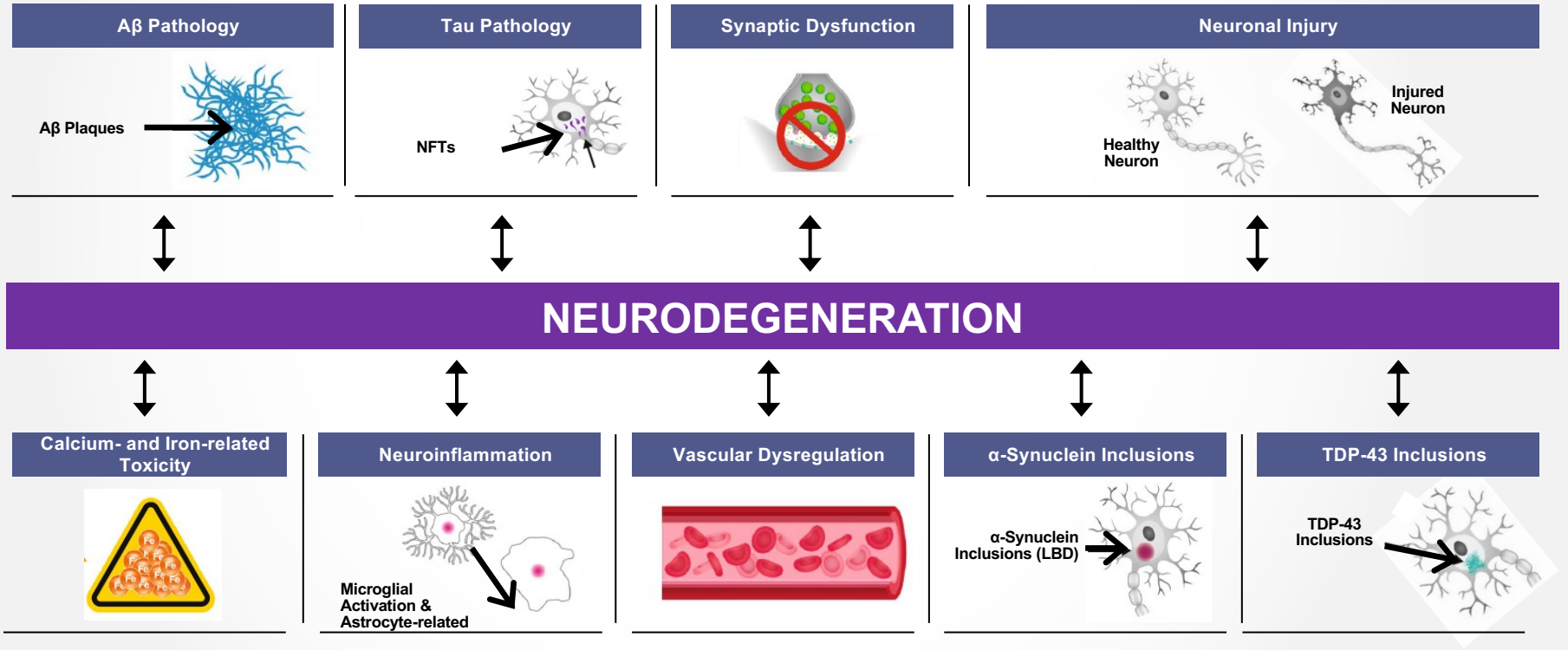
Pathologically defined by amyloid plaques and neurofibrillary tangles—but impacts much more in the brain.



- AD has preclinical, pathobiological disease stages (span 20–25 years)
- The disease phases includes abnormal amyloid-beta plaque deposits in the brain, neuronal and synaptic injury, tau tangle deposits, neuroinflammation, damage to brain blood vessels and more.

- AD has clinical illness stages (span 5–20 years)
- In the illness (clinical) phase, there is usually slowly recognized symptoms and progressive impairments in cognition and function.

Multiple Mechanisms Implicated in AD and ADRD Pathobiology and Co-pathobiology



Hampel H, et al. *Nat Rev Drug Discov*. 2010; Molinuevo JL, et al. *Acta Neuropathologica*. 2018.

Optimizing the Early Detection and Diagnosis of AD With Validated and Emerging Biomarkers

PeerView
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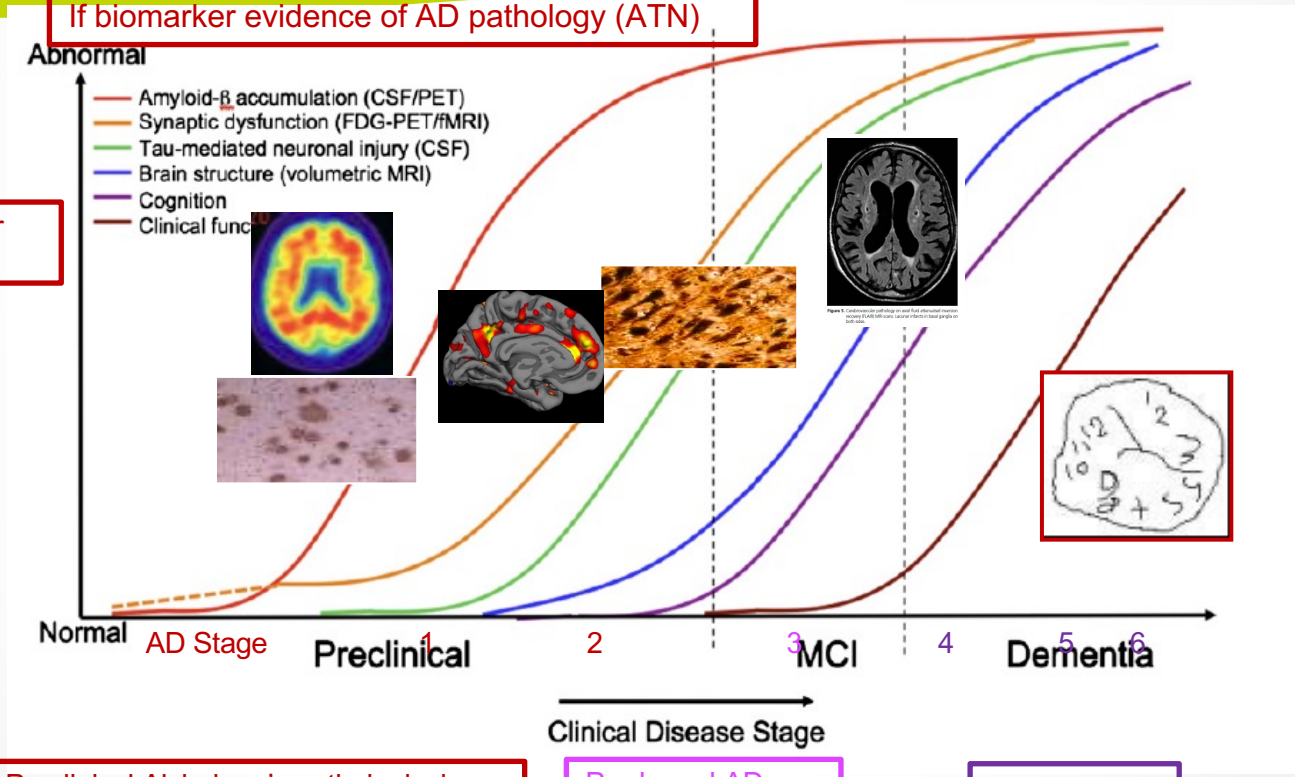
Stages and "Pathobio-clinical" Abnormalities in the Alzheimer's Disease Spectrum

If biomarker evidence of AD pathology (ATN)



AD biomarker (ATN)

Preclinical Alzheimer's pathological change (A+T-) or preclinical AD (A+T+)

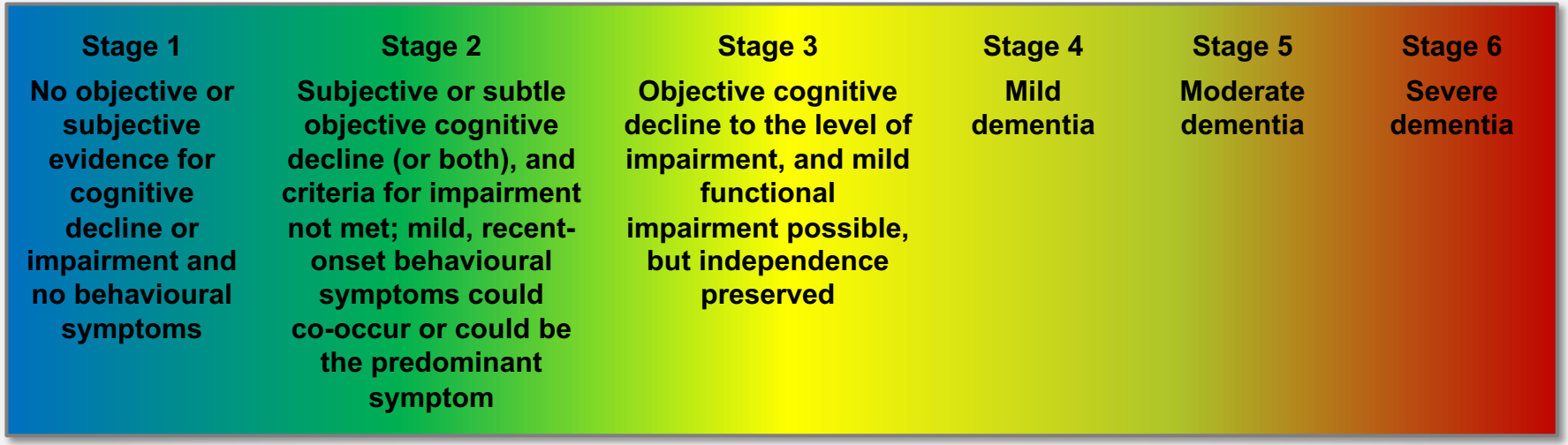
Prodromal AD or MCI due to AD

AD dementia

Jack CR, et al. *Lancet Neurol*. 2010.

Symptomatic Stages of AD According to the NIA-AA Research Framework

Symptomatic stages of Alzheimer's disease according to the NIA-AA research framework.

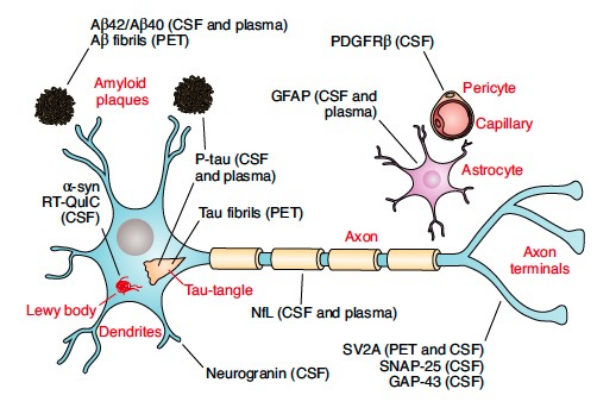


The stages apply only to individuals who are in the Alzheimer's disease continuum, which is defined by biomarker evidence of amyloid pathology with or without tau pathology, and is irrespective of the status of neurodegeneration; the colour scheme indicates the continuous progression of cognitive impairment in an individual, from no objective cognitive impairment (blue) to severe objective cognitive impairment (red).

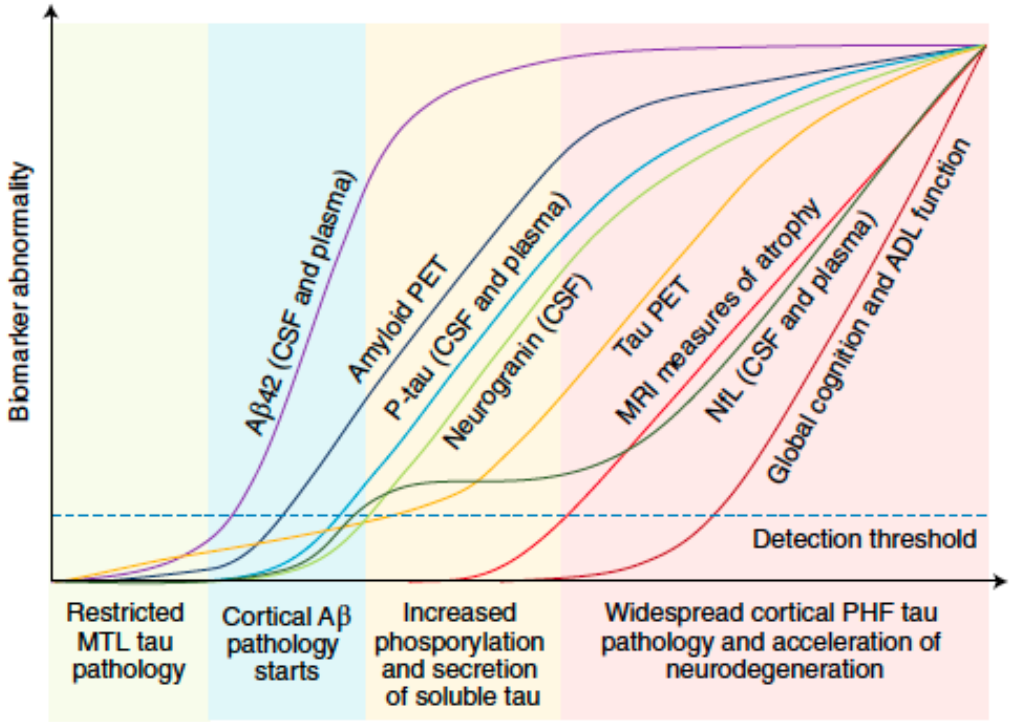
NIA-AA, National Institute on Aging and Alzheimer's Association.

Jessen F, et al. *Lancet Neurol.* 2020; Jack CR, et al. *Alzheimers Dement.* 2018.

Types of Biomarkers in Neurodegenerative Diseases and Trajectories of Biomarkers in AD



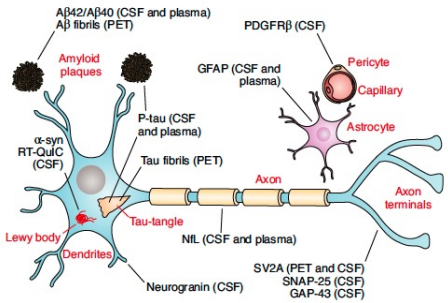
AT(N) Profiles	Biomarker Category	
A-T-(N)-	Normal AD biomarkers	
A+T-(N)-	Alzheimer's pathologic change	Alzheimer's continuum
A+T+(N)-	Alzheimer's disease	
A+T+(N)+		
A+T-(N)+	Alzheimer's and concomitant suspected non-Alzheimer's pathologic change	
A-T+(N)-	Non-AD pathologic change	
A-T-(N)+		
A-T+(N)+		



Hansson O, Biomarkers for Neurodegenerative Diseases, Nat Med 2021

ATX(N) – Proposed NIA-AA Revised Criteria for AD

Jack et al. AAIC July 2023



X = 3 new biomarker categories proposed
  I = Inflammatory/Immune mechanisms
Non-AD Co-pathologies
  V = Vascular Brain Injury
  S = Synucleinopathy

Table 1. Biomarker Categorization

Biomarker category	fluid	imaging
Core Biomarkers		
A (Ab proteinopathy)	Ab42/40	Amyloid PET
T (AD tau proteinopathy)	ptau 181, 217	Tau PET
Non - specific biomarkers of tissue reaction involved in AD pathophysiology		
N (injury, dysfunction, or degeneration of neuropil)	NfL	Anatomic MR, FDG PET
I (inflammation) Astrocytic activation	GFAP	
Biomarkers of non-AD co-pathology		
V vascular brain injury		Anatomic infarction, WMH, abundant dilated perivascular spaces
S α-synuclein	αSyn-SAA*	

If a fluid biomarker is informative only when measured in CSF this is denoted by (*), if informative with plasma or CSF then no specific notation added.

Table 2. Use cases

Use Cases	fluid	imaging
Diagnosis		
A (Ab proteinopathy)	Ab42/40	Amyloid PET
T (AD tau proteinopathy)	ptau 181, 217	Tau PET
Staging, prognosis, as an indicator of biological treatment effect		
A (Ab proteinopathy)	Ab42/40	Amyloid PET
T (AD tau proteinopathy)	ptau 181, 217	Tau PET
N (injury to or degeneration of neuropil)	NfL	Anatomic MR, FDG PET
I (inflammation) Astrocytic activation	GFAP	
Identification of co-pathology		
N (injury, dysfunction, or degeneration of neuropil)	NfL	Anatomic MR, FDG PET
V vascular brain injury		Anatomic infarction, WMH, abundant dilated perivascular spaces
S α-synuclein	αSyn-SAA *	

https://aaic.alz.org/downloads2023/NIA-AA-Revised-Clinical-Criteria-Figures-and-Tables-AAIC-2023.pdf

Amyloid PET Scans—Shades of Gray on Trees

Amyloid PET Tracers

(11)C-PiB—requires cyclotron

florbetapir F18

florbetaben F18

flutemetamol F18

(18)F-NAV4694

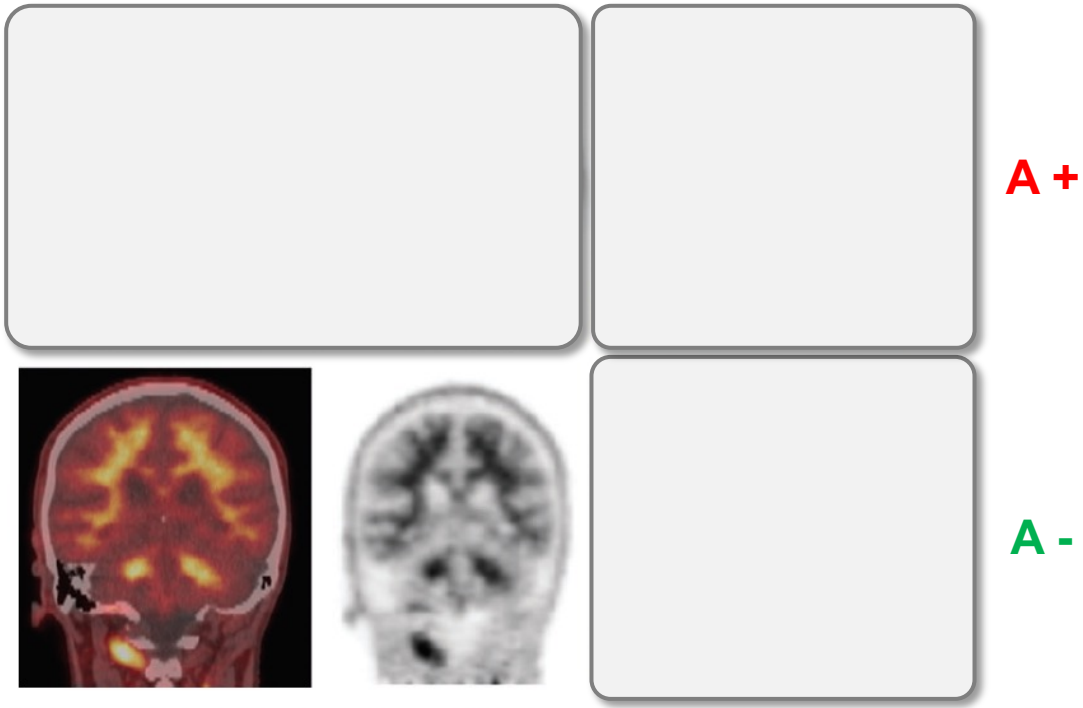
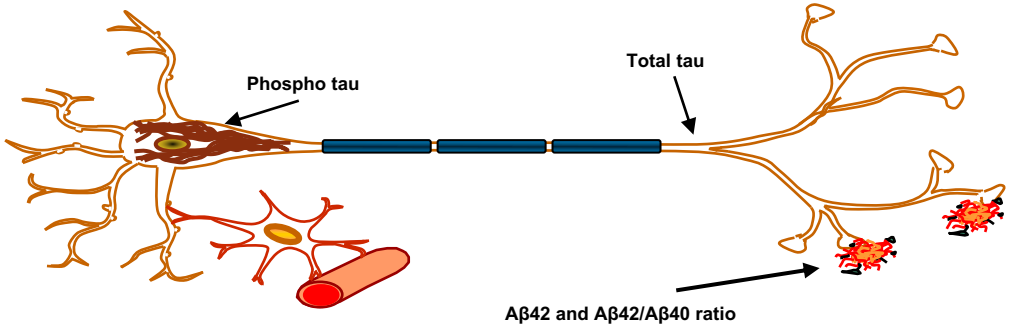


Figure 1 Amyloid PET interpretation (adapted from Dumba *et al*[24]). (A) 'Tree-in-bloom' sign with loss of cerebral grey–white matter differentiation indicating a positive scan. (B) 'Branching tree' sign with good grey–white matter differentiation indicating a negative scan. PET, positron emission tomography. With permission, Dr Zarni Win.

AD Core CSF Biomarkers Reflect Key Pathogenic Events and Are Highly Clinically Validated[1-3]



CSF t-tau	CSF Aβ42	CSF p-tau181
Intensity of neurodegeneration • Increase to 250% of controls	Brain amyloid deposition • Reduction to 55% of controls	Phosphorylation state of tau and grade of tau pathology • Increase to 190% of controls
• 238 studies • 27,500 AD patients and controls	• 210 studies • 24,900 AD patients and controls	• 153 studies • 19,600 AD patients and controls

Note: CSF ratio biomarkers (eg, Aβ42/Aβ40; p-tau181/Aβ42) consistently demonstrate superior concordance with amyloid PET compared with individual biomarkers

1. https://www.alzforum.org/alzbiomarker. 2. Olsson B et al. *Lancet Neurol.* 2016;15:673-684. 3. Van Harten AC et al. *Alzheimers Dement.* 2022;18:635-644.

Comparing Relative Strengths and Limitations of AD Biomarker Modalities

https://doi.org/10.1038/s43587-023-00400-6

The role of cerebrospinal fluid and other biomarker modalities in the Alzheimer's disease diagnostic revolution

Suzanne E. Schindler & Alireza Atri

nature aging

Volume 3 | May 2023 | 460–462 | 462

Table 1 | Relative strengths and weaknesses of AD biomarker modalities

	Molecular imaging	CSF biomarkers	BBBMs
Scientific aspects			
Diagnostic performance	✓	✓	–
Strength of validation	✓	✓	–
Reflects spatial distribution of pathology	✓	×	×
Reflects amount of pathology	✓	–	–
Enables evaluation of multiple pathologies	×	✓	–
Practical aspects			
Cost of test	×	–	–
Cost to individual (reimbursed)	×	✓	×
Availability	×	–	–
Acceptability	–	–	✓

Tick denotes a strength; dash denotes neither a strength or weakness; and cross denotes a weakness.

- There are currently several FDA-approved amyloid PET tracers (eg, flortaucipir, florbetapir, florbetaben), and 1 FDA-approved tau tracer (flortaucipir)
- There are 2 FDA-approved CSF tests: Fujirebio Aβ42/40 and Elecsys p-tau181/Aβ42

Schindler & Atri. Nat Aging 2023

Tier 1 Brain Imaging to Detect "N" and "V" and Assess for Other Conditions

(e.g., stigmata of vascular ischemic brain injury)

MRI >CT (if no contraindication) and Can Significantly Change Management

- MRI is better at detecting
  - Atrophy (e.g., hippocampal atrophy, ventricular enlargement)
  - Cerebrovascular disease burden: leukoaraiosis (white matter microangiopathic changes) and micro/lacunar infarcts
  - Microhemorrhages (non-acute)
  - Hydrocephalus

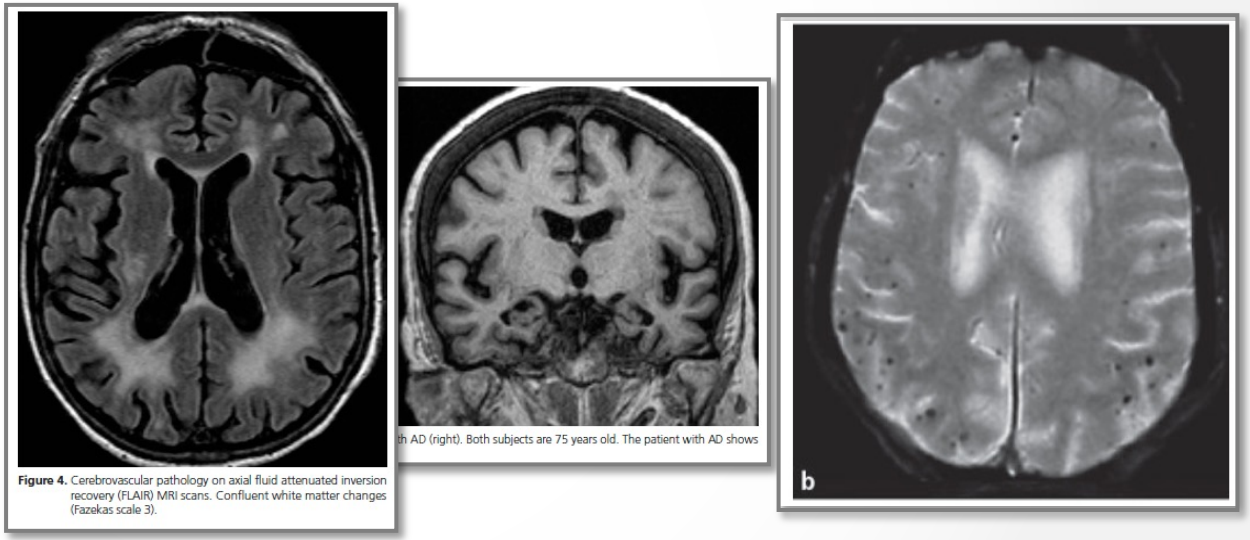


Figure 4. Cerebrovascular pathology on axial fluid attenuated inversion recovery (FLAIR) MRI scans. Confluent white matter changes (Fazekas scale 3).

Dickerson BC, Atri A. *Dementia: Comprehensive Principles and Practice.* 2014; Atri A. *Med Clin North Am*. 2019; Atri A. *Semin Neurol*. 2019.

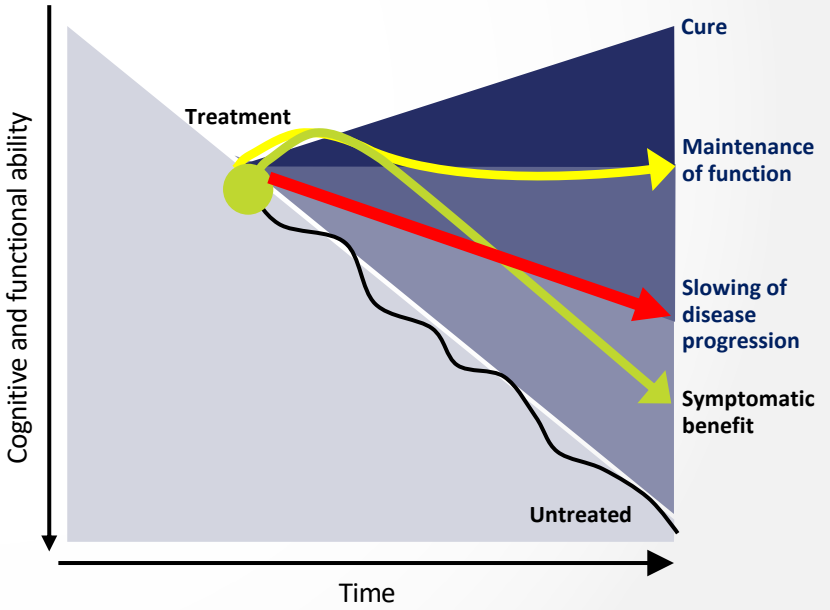
Adapting Practice Amidst an Evolving AD Management Paradigm and Preparing to Deliver Disease-Modifying Treatment in the Clinic

PeerView Live

Symptomatic and Disease-modifying Treatments
- Differences and Expectations for Benefit on Clinical Course

- A **symptomatic treatment** provides benefits to shift clinical trajectory (course), but does not impact the underlying disease processes and ultimately the rate of "clinical" decline – progression of symptoms and difficulties ability to function in daily life – will be unchanged[3,4]
- A **disease-modifying treatment** impacts one or more underlying disease processes and would translate to slowing of progression of symptoms and accumulating disability – the rate of clinical decline will be slowed[3,4]
- A **cure** for AD would reverse the disease progress and restore the patient to their original level of functioning[4]

Theoretical Ways in Which a Treatment Could Affect the Clinical Course of AD[4]



[1]Winblad B, et al. *Lancet Neurol.* 2016; [2]Cummings J, et al. *Alzheimers Res Ther.* 2021; [3]Cummings J, Fox N. *J Prev Alzheimers Dis.* 2017; [4]Adapted from Van Dam D, De Deyn PP. *Nat Rev Drug Discov.* 2006.

Anti-Amyloid Plaque-Lowering Monoclonal Antibodies

- appear to be disease modifying, when given at sufficiently high doses and for sufficient durations in appropriately selected and monitored patients with clinically early-stage AD

- **Impact AD pathobiology:**
  - Can lower amyloid plaques substantially; and make many patients “amyloid negative” within 12-18 months of treatment
  - Consistent signals of impact on other AD biomarkers such as on some biomarkers of abnormal tau, neuroinflammation, and possibly neurodegeneration

- **Impact on slowing of clinical decline:**
  - Consistent evidence for moderate group-level efficacy (*slowing of clinical decline for the “average” patient*) when amyloid plaques are sufficiently lowered in the right patients (clinically early-stage AD: mild cognitive impairment and mild dementia stages of AD)
  - Treatments provide, ”on average”, the equivalent ”savings” to about 5-7 months of expected decline compared to “placebo” over 18 months
  - Not a cure – no expectation of “getter better”

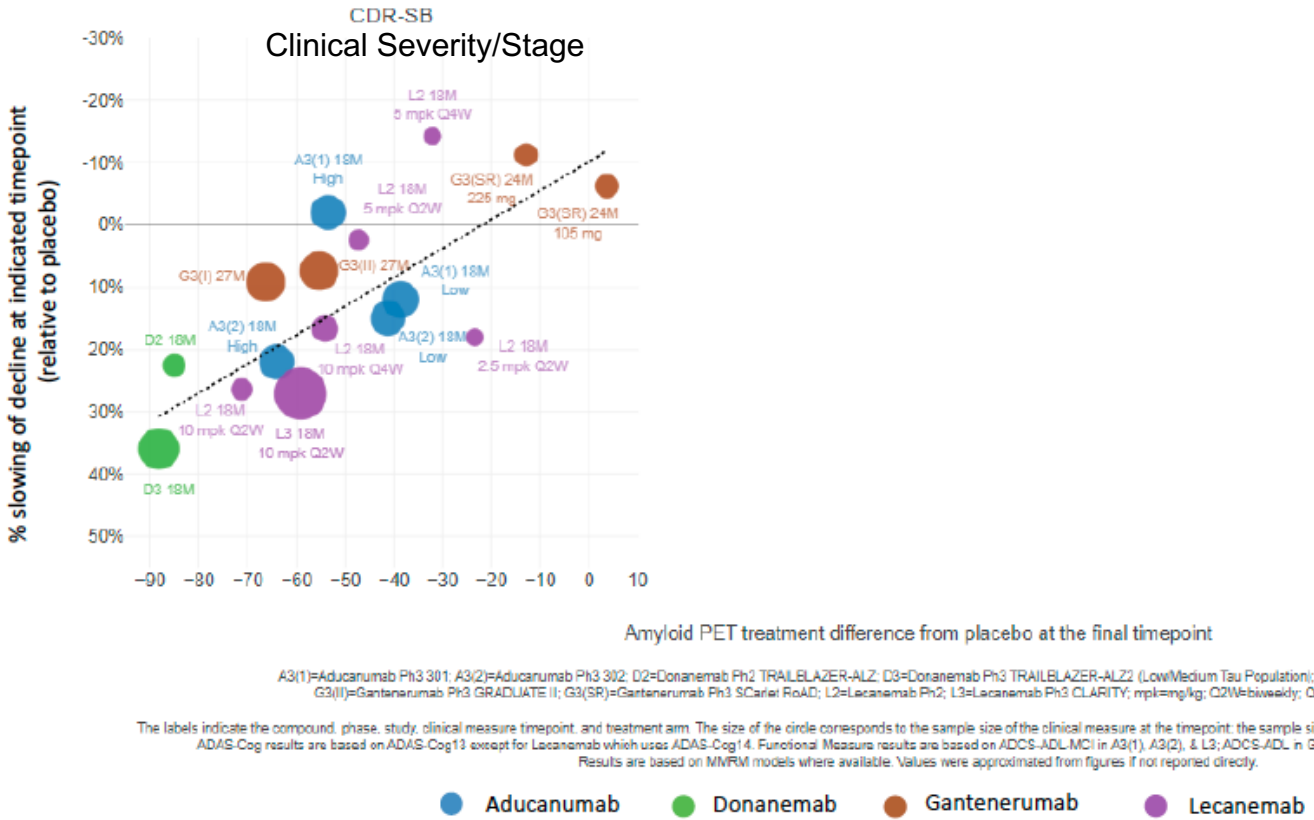
Atri A. *Semin Neurol.* 2019:39:227-240. Cummings J, et al. *Alzheimers Res Ther.* 2021;13:98. Aducanumab (Aduhelm®) PI 2022 (www.biogencdn.com/us/aduhelm-pi.pdf). Eisai news release 1/7/2023 (www.eisai.com/news/2023/ pdf/enews202301pdf.pdf). Lecanemab (Leqembi®) PI 2023 (https://www.leqembi.com/-/media/Files/Leqembi/Prescribing-Information.pdf?hash=3d7bf1a2-5db2-4990-8388-81086f415676). Salloway S, et al. *J Prev Alzheimers Dis.* 2022;9(suppl 1): S41-S42; Abstract LB3. Doody RS, et al. *N Engl J Med.* 2014;370:311-321. Roche news release 11/14/2022 (www.roche.com/investors/updates/inv-update-2022-11-14c). URLs accessed 2/9/2023.; van Dyck et al NEJM 2023; Sims JR, AAIC 2023; Sims et al NEJM 2023

Anti-Amyloid Plaque-Lowering Monoclonal Antibodies -- A completely new paradigm of AD diagnosis and care

- **Limitations, Burden and Safety Considerations:**
  - Infusions
  - Costly
  - Currently limited access due to healthcare providers and systems readiness, ramp up and coverage considerations (CMS requires entry into a patient registry)
  - Not an option or good fit for all persons with AD – selected population (clinically early-stage) require amyloid confirmation; no MRI evidence of substantial brain blood vessel leakages/bleeds (CAA: Cerebral Amyloid Angiopathy) and dysfunction; genetic considerations impact risk of side effects (APOE-e4 carrier status)
  - Serial safety MRI monitoring required for detection and mitigation of an important potential treatment side-effect: **Amyloid-related Imaging Abnormalities, ARIA (brain inflammation or bleeding)**
  - **With appropriate detection and management, ARIA is mostly short-lived and not symptomatic or serious, but could uncommonly can result in hospitalization; and rarely in disability or death**

Atri A. *Semin Neurol.* 2019:39:227-240. Cummings J, et al. *Alzheimers Res Ther.* 2021;13:98. Aducanumab (Aduhelm®) PI 2022 (www.biogencdn.com/us/aduhelm-pi.pdf). Eisai news release 1/7/2023 (www.eisai.com/news/2023/ pdf/enews202301pdf.pdf). Lecanemab (Leqembi®) PI 2023 (https://www.leqembi.com/-/media/Files/Leqembi/Prescribing-Information.pdf?hash=3d7bf1a2-5db2-4990-8388-81086f415676). Salloway S, et al. *J Prev Alzheimers Dis.* 2022;9(suppl 1): S41-S42; Abstract LB3. Doody RS, et al. *N Engl J Med.* 2014;370:311-321. Roche news release 11/14/2022 (www.roche.com/investors/updates/inv-update-2022-11-14c). URLs accessed 2/9/2023.; van Dyck et al NEJM 2023; Sims JR, AAIC 2023; Sims et al NEJM 2023

Associations between Amyloid-Plaque Lowering Treatments and Average Benefits to Slow Clinical Progression -- Overall, substantial plaque lowering = more benefits



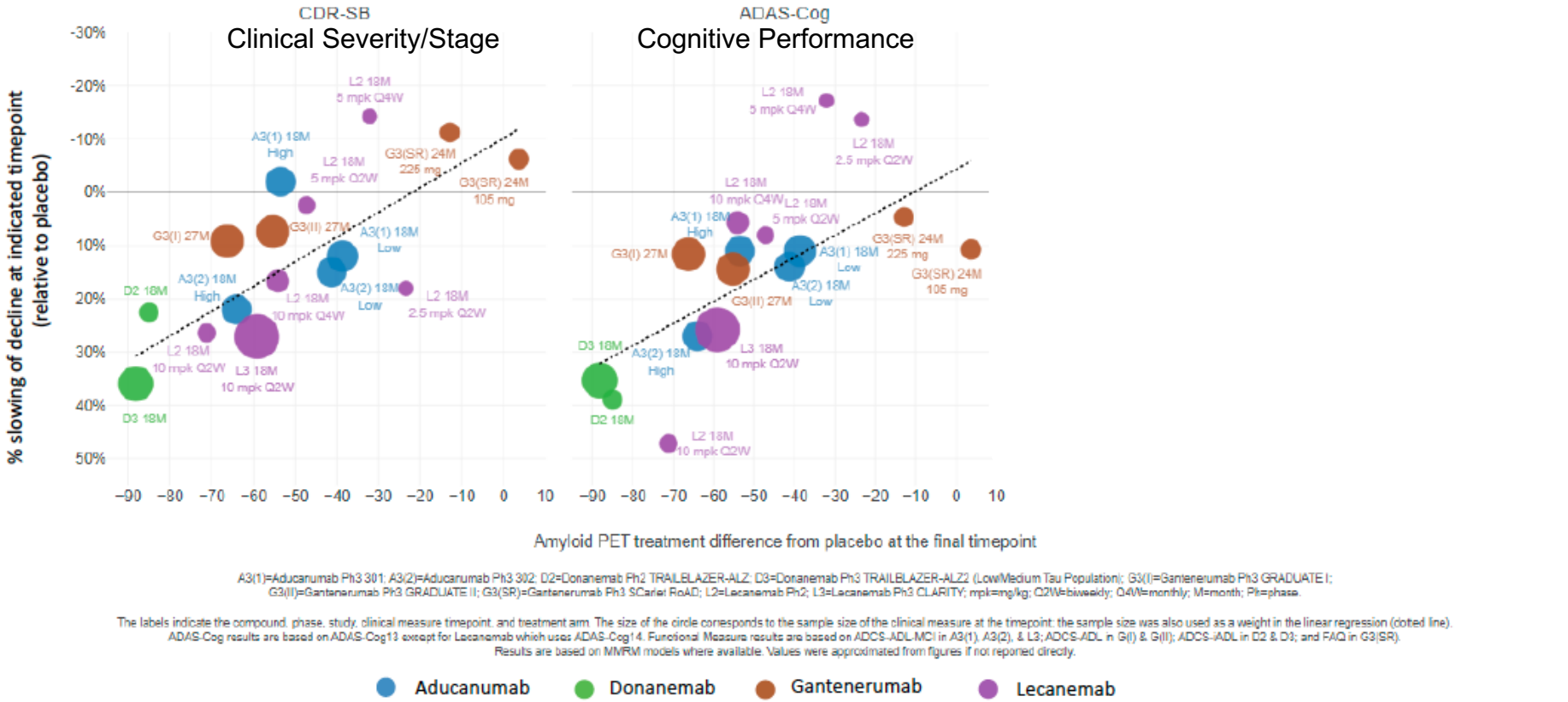
A3(1)=Aducanumab Ph3 301; A3(2)=Aducanumab Ph3 302; D2=Donanemab Ph2 TRAILBLAZER-ALZ; D3=Donanemab Ph3 TRAILBLAZER-ALZ2 (Low/Medium Tau Population); G3(I)=Gantenerumab Ph3 GRADUATE I; G3(II)=Gantenerumab Ph3 GRADUATE II; G3(SR)=Gantenerumab Ph3 SCarlet RoAD; L2=Lecanemab Ph2; L3=Lecanemab Ph3 CLARITY; mpk=mg/kg; Q2W=biweekly; Q4W=monthly; M=month; Ph=phase.

The labels indicate the compound, phase, study, clinical measure timepoint, and treatment arm. The size of the circle corresponds to the sample size of the clinical measure at the timepoint; the sample size was also used as a weight in the linear regression (dotted line). ADAS-Cog results are based on ADAS-Cog13 except for Lecanemab which uses ADAS-Cog14. Functional Measure results are based on ADCS-ADL-MCI in A3(1), A3(2), & L3; ADCS-ADL in G(I) & G(II); ADCS-iADL in D2 & D3; and FAQ in G3(SR). Results are based on MMRM models where available. Values were approximated from figures if not reported directly.

Aducanumab Donanemab Gantenerumab Lecanemab

Sims JR, Amyloid Reduction: Donanemab Perspective, AAIC Amsterdam July 2023

Associations between Amyloid-Plaque Lowering Treatments and Average Benefits to Slow Clinical Progression -- Overall, substantial plaque lowering = more benefits



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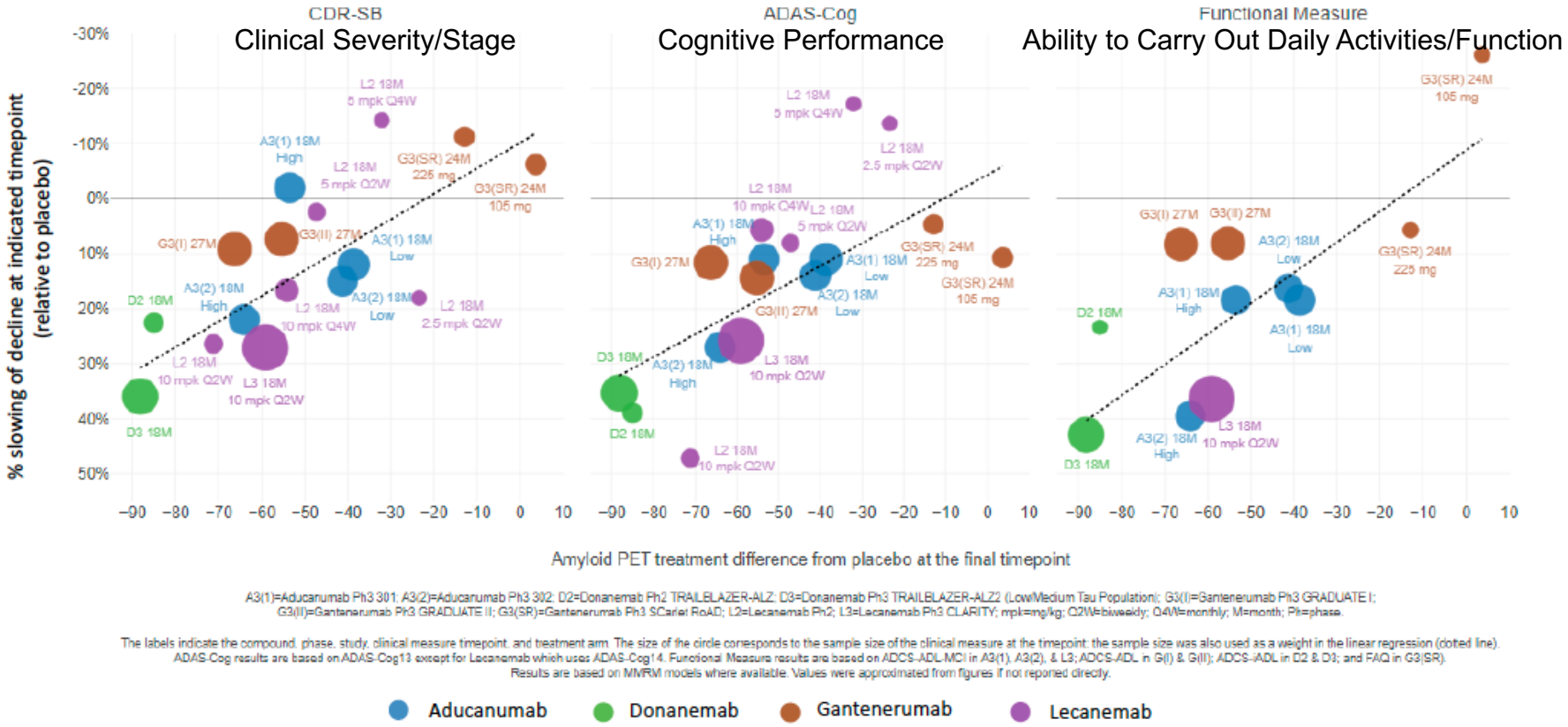

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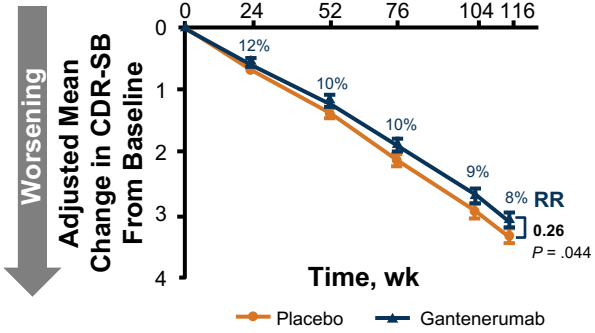
Aducanumab Donanemab Gantenerumab Lecanemab

Sims JR, Amyloid Reduction: Donanemab Perspective, AAIC Amsterdam July 2023

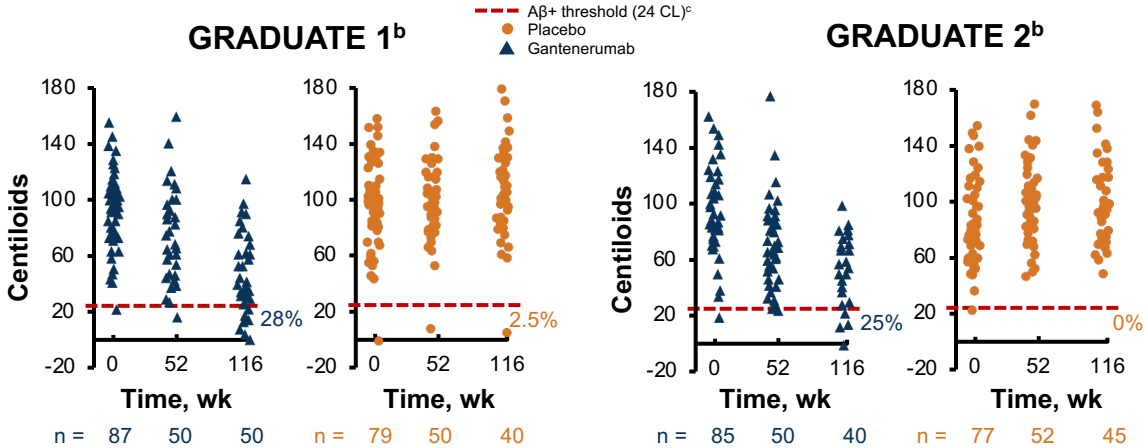
Gantenerumab Did Not Meet Its Prespecified Endpoints[1]

Pooled CDR-SB Showed Nominally Significant Effect in Favor of Gantenerumab



Gantenerumab Reduced Amyloid Plaque Levels Below Amyloid-Positivity Threshold in Fewer Participants Than Expected

The percentage of participants below positivity threshold in prior OLE studies was 26% at week 52 and 50% at week 104[a]



- All gantenerumab studies in early symptomatic AD and in secondary AD prevention were discontinued, including GRADUATION, Open RoAD, POSTGRADUATE, and SKYLINE[2]

[a] Based on data from Marguerite RoAD OLE non-pretreated population. [b] Clinical cutoff date: September 26, 2022. [c] 24 CL is the amyloid-positivity threshold.

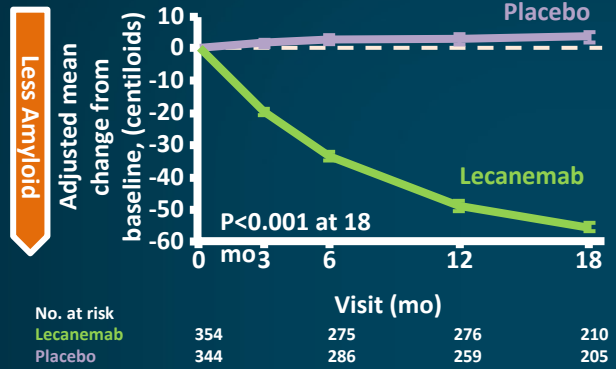
1. Bateman R. CTAD 2022. Oral presentation. 2. clinicaltrials.gov.

van Dyck CH, et al. *N Engl J Med*. 2023;388(1):9-21.

Lecanemab: CLARITY-AD Study

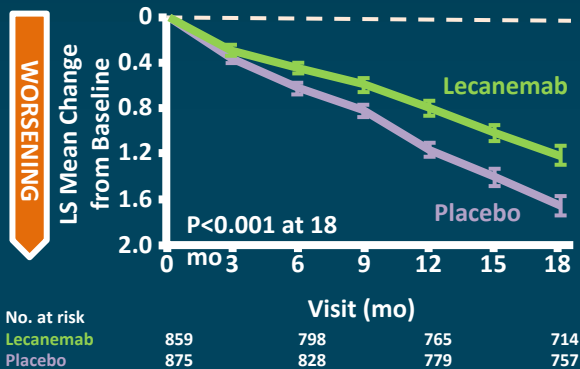
Lowered brain amyloid fibrillar plaques and demonstrated associated clinical benefits (in 20-40% range for slowing clinical decline) over ~18 months

Amyloid Burden on PET



No. at risk				
Lecanemab	354	275	276	210
Placebo	344	286	259	205

CDR-SB Score



No. at risk				
Lecanemab	859	798	765	714
Placebo	875	828	779	757

Primary:
CDR-sb -0.45 (-27%)

Secondary:
Amyloid PET -59 CL

81% Amyloid Neg

ARIA-E (brain inflammation - fluid build up) 12.6% (1.7% PBO)

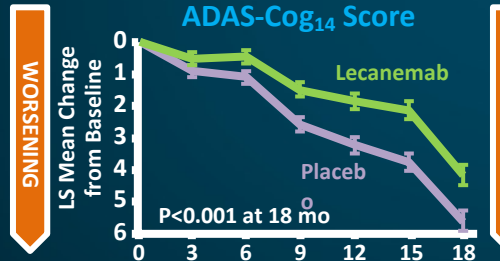
ARIA-H (brain bleeding) 17.3% (PBO 9.0%)

- 18 month study
- N = 1795 patients
- Early symptomatic AD with Amyloid +
- 1:1 randomization to placebo or lecanemab IV infusion 10 mg/kg q2weeks
- MRIs at ~0,2,3,6,12,18 months

Characteristics (mean):

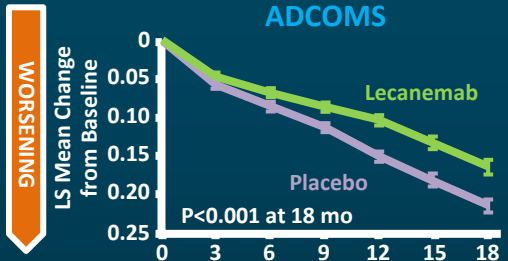
- Age ~71 yrs
- ~52% F
- MMSE ~25.5
- ~81% MCI due to AD
- CDR-sb ~3.2
- Amyloid PET ~76 CL
- 68% e4+ (53% e4+/15% e4++)

ADAS-Cog$_{14}$ Score



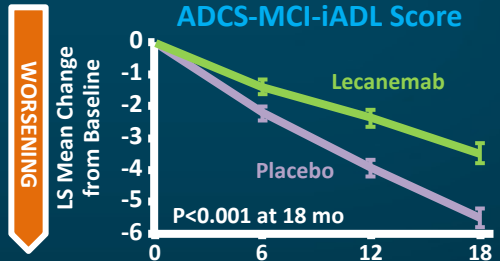
No. at risk				
Lecanemab	854	793	753	703
Placebo	872	823	770	738

ADCOMS



No. at risk				
Lecanemab	857	796	757	708
Placebo	875	822	775	749

ADCS-MCI-iADL Score

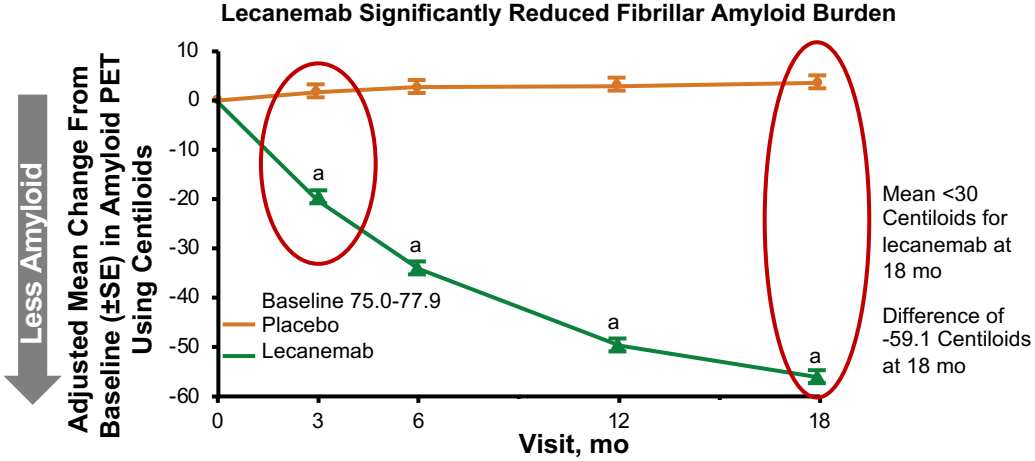


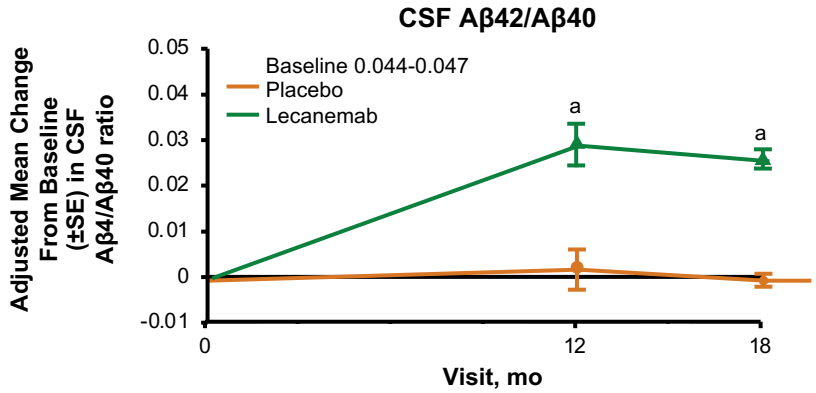
No. at risk				
Lecanemab	783	756	716	676
Placebo	796	783	739	707

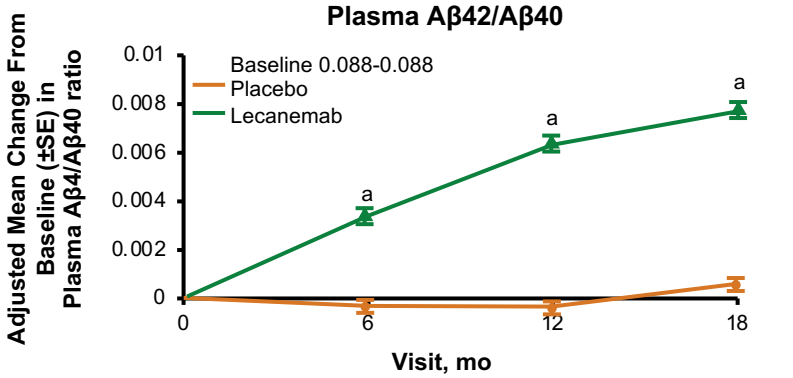
~1/3rd less chance of progressing to next major clinical stage over 18 months

CDR-SB = Clinical Dementia Rating-Sum of Boxes; ADCOMS = AD Composite Score; ADCS = AD Assessment Scale; ADCS MCI-iADL = AD Cooperative Study-Activities of Daily Living scale for MCI.

Lecanemab Improved Amyloid Biomarkers[1]



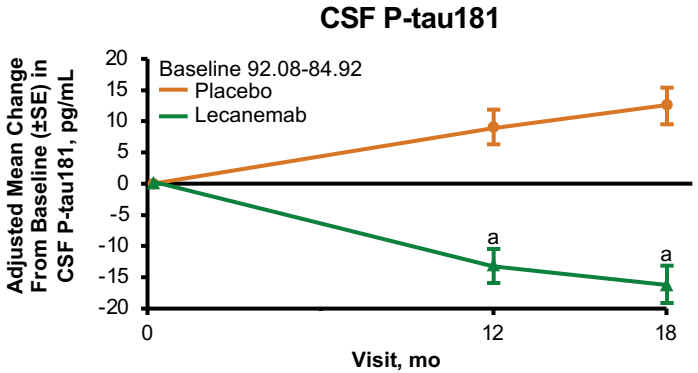


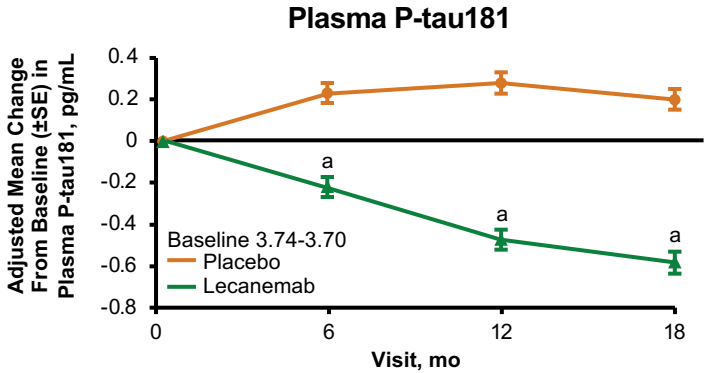


[a] *P* < .0001.

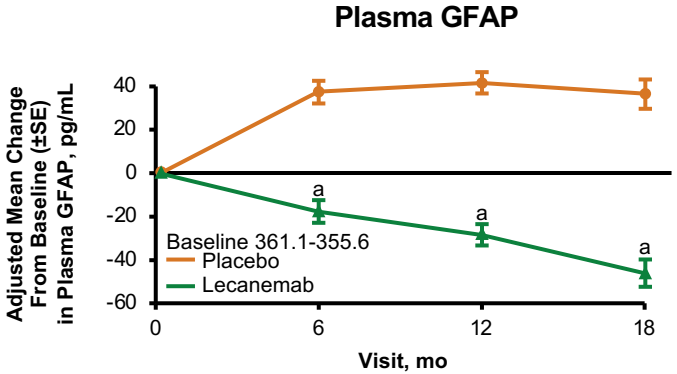
1. Van Dyck CH et al. *New Engl J Med*. 2023;388:9-21.

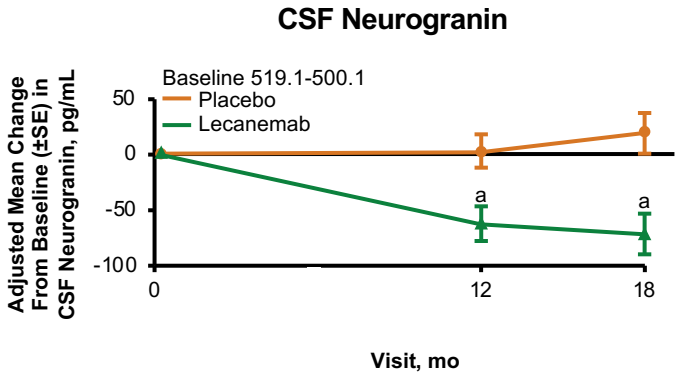
Lecanemab Improved Tau and Neurodegeneration Biomarkers[1,2]





In July 2023, lecanemab received full FDA approval for the treatment of MCI due to AD and mild AD dementia

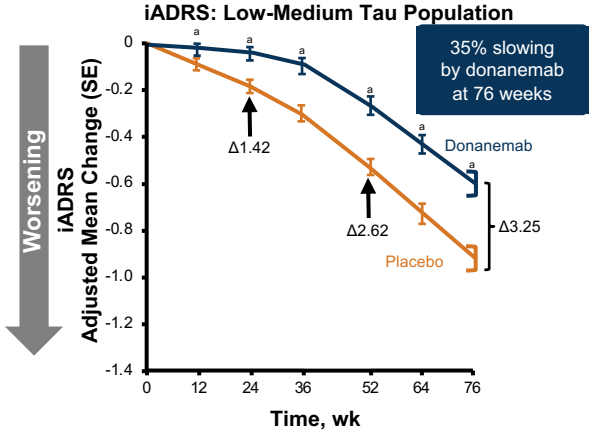


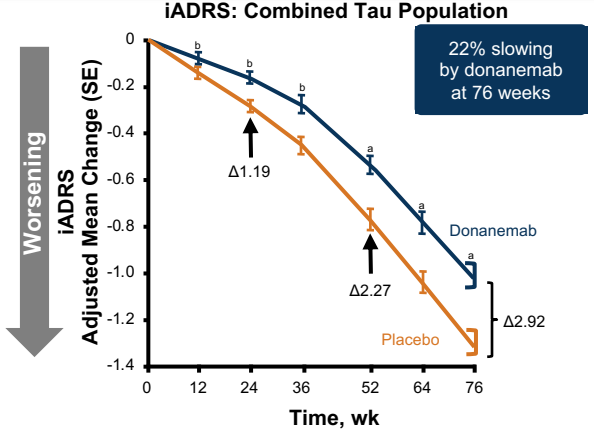


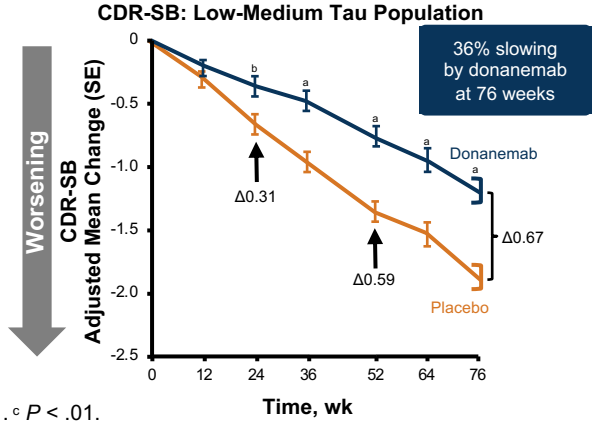
[a] *P* < .0001.

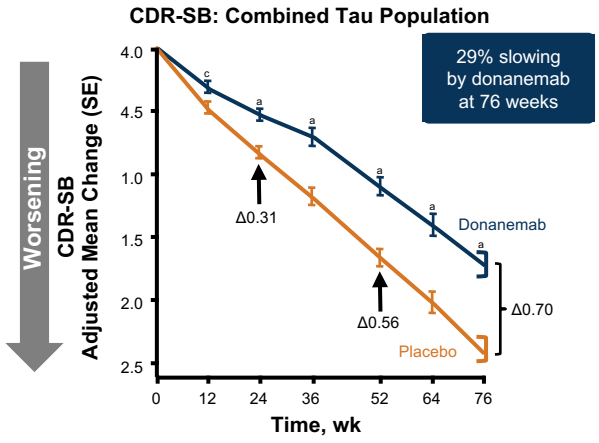
1. Van Dyck CH et al. *New Engl J Med*. 2023;388:9-21. 2. Leqembi (lecanemab) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761269Orig1s000lbl.pdf.

Donanemab Met Its Primary and Secondary Clinical Endpoints[1]





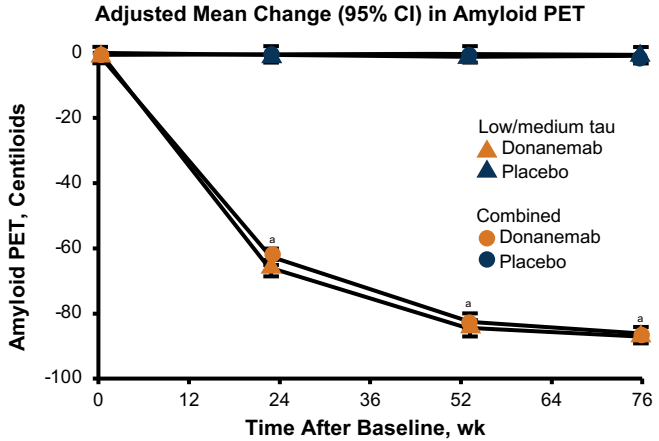


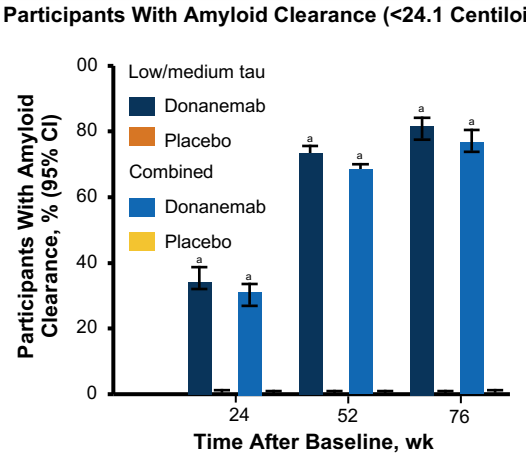


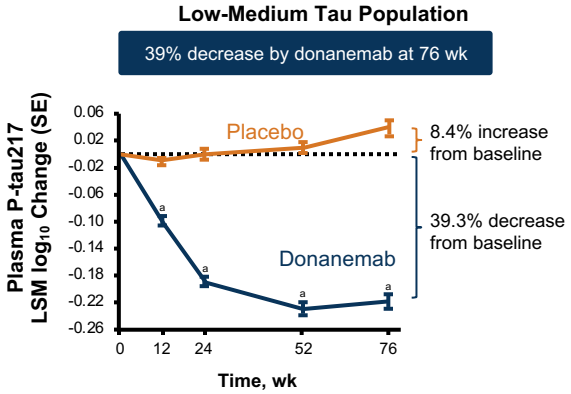
[a] $P < .0001$. [b] $P < .001$. [c] $P < .01$.

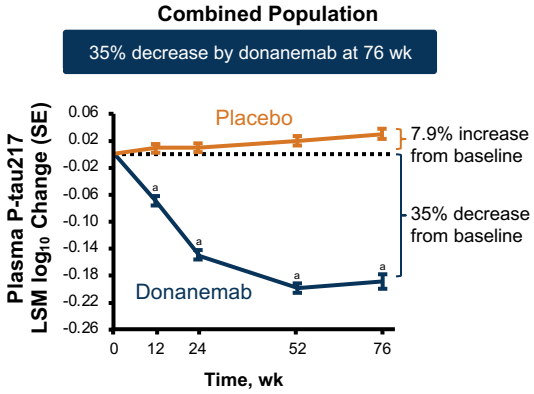
1. Sims JR et al. *JAMA*. 2023;330:512-527.

Donanemab Significantly Reduced Amyloid and Tau Biomarkers[1]







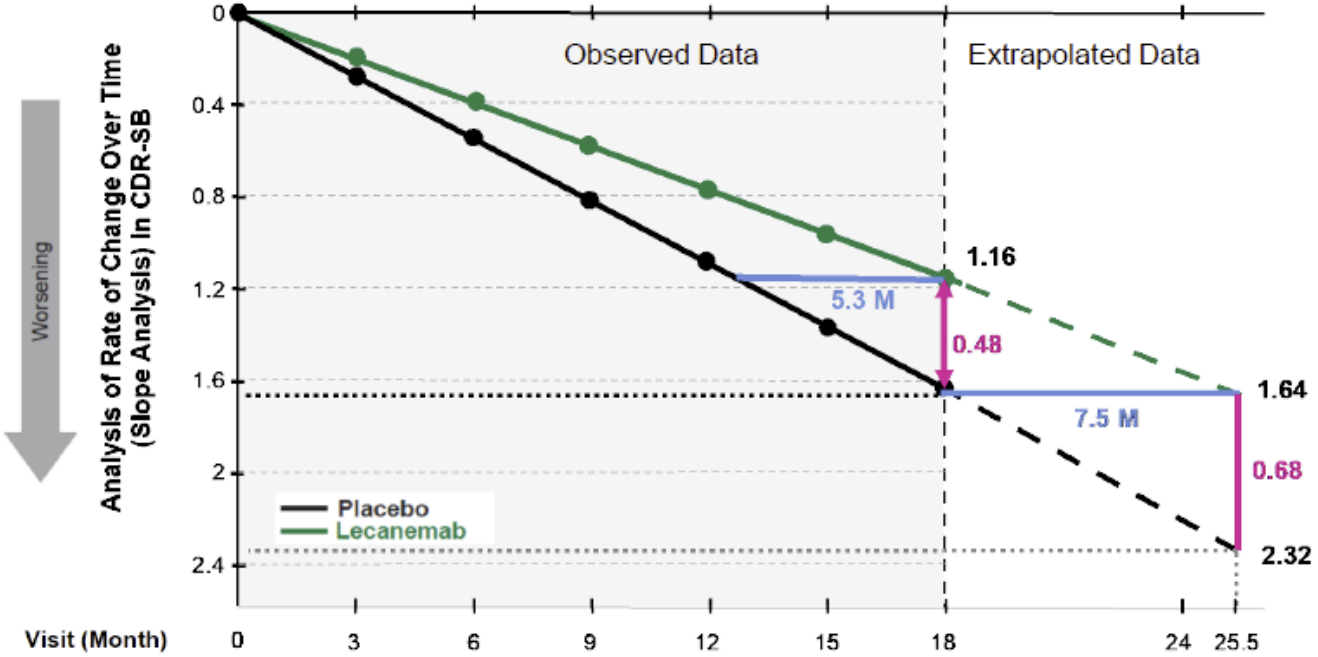


[a] $P < .001$.

1. Sims JR et al. *JAMA*. 2023;330:512-527.

Increasing separation over time between lecanemab and placebo – about 32% slowing of slope annually

- 32% slowing of slope annually [(95%CI: 18% to 46%), p=0.00001] on lecanemab vs. placebo
  - Projected treatment difference at 25.5 months based on slope showed -0.68 treatment difference
- Increasing separation over time between lecanemab & placebo



- Lecanemab takes 25.5 months to reach same level as placebo at 18 months

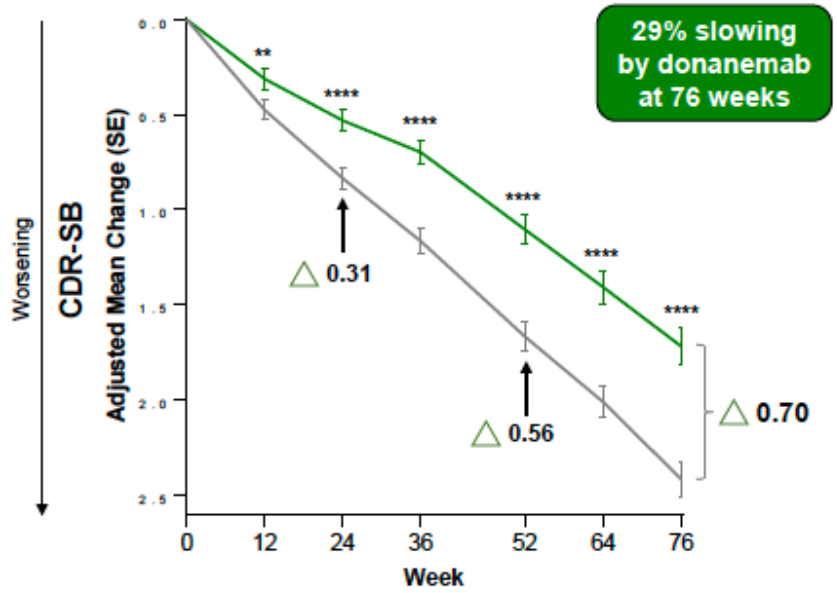
*note predicted Placebo decline in CDR-sb is ~1.6 in 18 months

Note: Rate of change over time (mean slope) based on change from baseline in the CDR-SB was analyzed using linear mixed effects (LME) model. LME model included time, treatment by assessment time as covariate with random intercept and slope. CDR-SB, Clinical Dementia Rating-Sum-of-Boxes.

Van Dyck et al. NEJM 2023; Cohen et al. CTAD2022

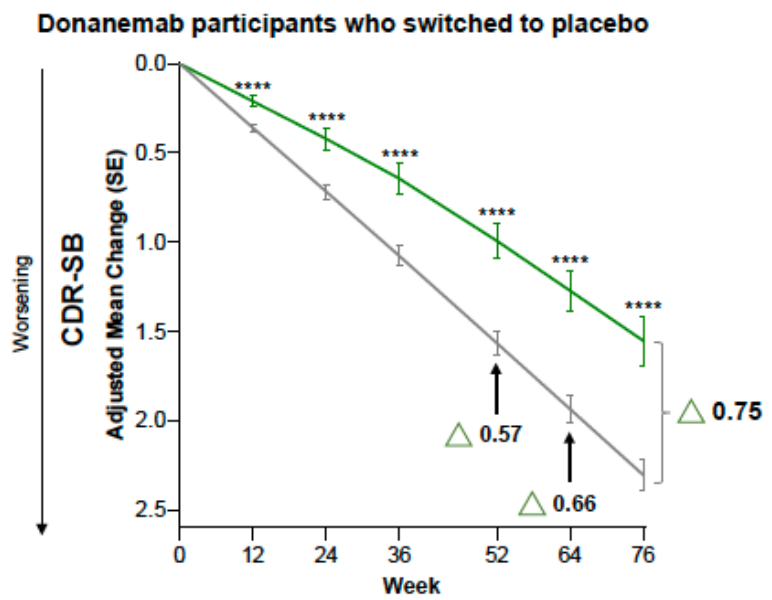
Increasing separation over time between donanemab and placebo – even after patients who became amyloid negative (after 6 or 12 months of donanemab treatment) were switched over to placebo infusions

CDR-SB: Combined Tau Population



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

CDR-SB: Combined Tau Population



Placebo	810	798	778	752	713	678	672
Donanemab	301	297	294	292	290	275	275

Sims JR, AAIC July 2023; Sims et al NEJM 2023;

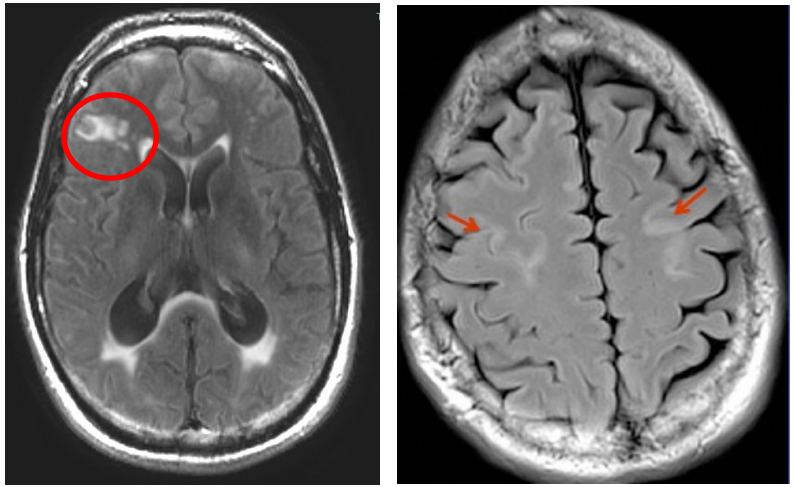
Plaque-lowering mAb Safety, Side Effects & Required Monitoring

- **Amyloid-Related Imaging Abnormalities (ARIA):** is a radiographic and common side effect of treatment with amyloid-lowering monoclonal antibodies. Two types of ARIA occur:
  - **ARIA-E with edema/effusion** (representing inflammation and fluid exudation)
  - **ARIA-H with hemorrhagic changes** (more commonly brain microhemorrhages, occasionally superficial siderosis and, rarely, macrohemorrhage)
- ARIA is typically mild or moderate radiographically, asymptomatic, or mildly symptomatic clinically, and, with appropriate monitoring and management, is self-limited (reversible). However, uncommonly serious ARIA can occur, leading to hospitalization and, rarely, to disability or death.
- **Infusion-related Reactions:** occurred in 26.4% of participants on lecanemab in CLARITY AD. Typically reactions were mild to moderate in severity; occurred during first 2 treatments and were seen during the infusion or up to several hours afterwards.

Van Dyck, C. H., Swanson, C. J., Aisen, P., Bateman, R. J., et al. (2023). Lecanemab in early alzheimer's disease. *New England Journal of Medicine*, *388*(1), 9–21. https://doi.org/10.1056/nejmoa2212948
Cummings J, Apostolova L, Rabinovici GD, Atri A, Aisen P, Greenberg S, Hendrix S, Selkoe D, Weiner M, Petersen RC, Salloway S. Lecanemab: Appropriate Use Recommendations. J Prev Alzheimers Dis. 2023;10(3):362-377. doi: 10.14283/jpad.2023.30. PMID: 37357276; PMCID: PMC10313141.

Amyloid Related Imaging Abnormalities (ARIA)

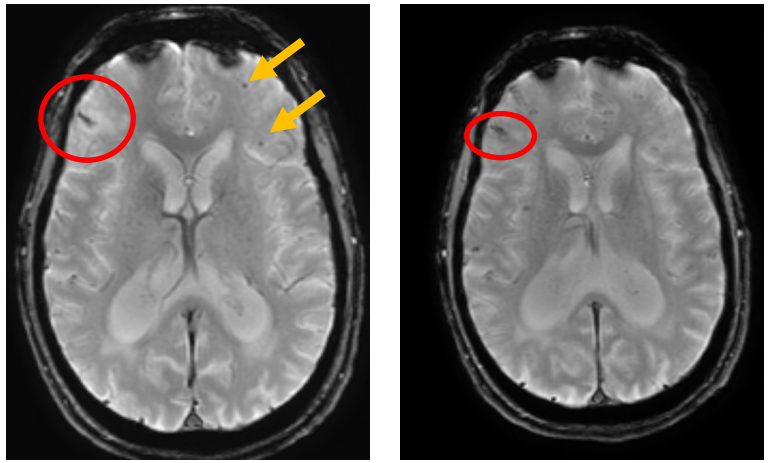
ARIA-E



Parenchymal (edema)

Superficial (effusion)

ARIA-H



Parenchymal (microhemorrhage)

Superficial (siderosis)

Images courtesy of Alireza Atri, MD, PhD.

Macrohemorrhage (not shown)

Radiographic and Clinical Presentations –

- During clinical trials, ARIA is frequently:
  - Asymptomatic - 78% for lecanemab
  - Detected incidentally and early in the course of treatment on surveillance MRI - 71% in first 3 months for lecanemab
  - Mild or moderate radiographic severity -- 91% for lecanemab
- **ARIA-E** is more strongly associated with symptoms than **ARIA-H** CMHs/SS
- ARIA-E rate associated with e4 status (and baseline CAA/CMHs)
  - ~1:20 no-e4; ~1:6 e4+heterozygote; ~1:3 e4++homozygote for lecanemab
- Clinical symptoms tend to resolve in tandem with **ARIA-E**
  - Approximately 80% (81% for lecanemab) of symptoms and **ARIA-E** resolved in tandem within 4 months
- With rigorous detection protocols and dose-management strategies, ARIA is usually detected early in the course of treatment, are mild/moderate radiographically, asymptomatic, transient, and self-limiting

Mintun MA, et al. *N Engl J Med*. 2021;384(18):1691-1704; van Dyck CH, et al. *N Engl J Med*. 2023;388(1):9-21

Clinical Presentation – Symptoms

Common symptoms of ARIA:

- Headache
- Confusion/disorientation
- Dizziness/vertigo
- Nausea
- Visual disturbances
- Fatigue
- Gait difficulty

Severe symptoms associated with ARIA are uncommon

Severe or serious symptoms can include:

- Exacerbations of common symptoms (most often headache)
- Seizures
- Status epilepticus
- Malignant hypertension
- Encephalopathy/delirium
- Stupor
- Focal neurological deficits

Mintun MA, et al. *N Engl J Med*. 2021;384(18):1691-1704; van Dyck CH, et al. *N Engl J Med*. 2023;388(1):9-21

Adverse Events from CLARITY-AD (Lecanemab Phase 3 Clinical Trial)

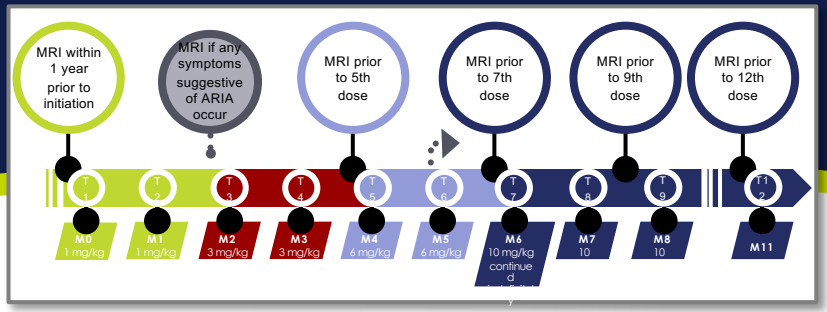
Event	Lecanemab (N = 898)	Placebo (N = 897)
Overall – no. (%)		
ARIA		
ARIA-E – no. (%)	113 (12.6)	15 (1.7)
Symptomatic ARIA-E – no. (%)	25 (2.8)	0
ApoE ε4 noncarrier – no./total no. (%)	4/278 (1.4)	0/286
ApoE ε4 carrier – no./total no. (%)	21/620 (3.4)	0/611
ApoE ε4 heterozygote	8/479 (1.7)	0/478
ApoE ε4 homozygote	13/141 (9.2)	0/133
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 – no. (%)	155 (17.3)	81 (9.0)
Microhemorrhage	126 (14.0)	68 (7.6)
Superficial siderosis	50 (5.6)	21 (2.3)
Macrohemorrhage	5 (0.6)	1 (0.1)
Symptomatic ARIA-H	6 (0.7)	2 (0.2)
Isolated ARIA-H: no concurrent ARIA-E	80 (8.9)	70 (7.8)

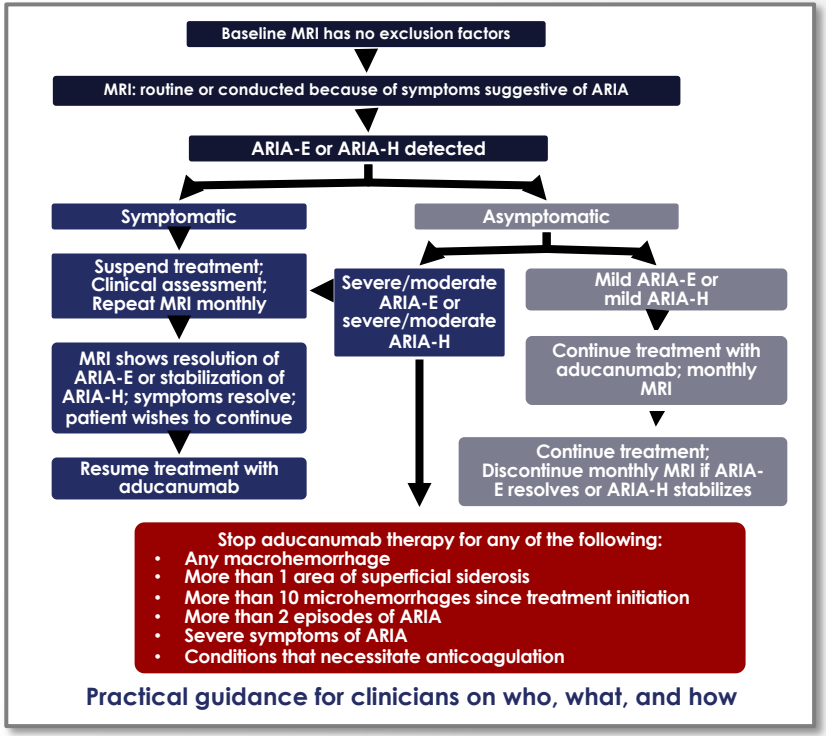
van Dyck CH, et al. *N Engl J Med*. 2023;388(1):9-21.

Appropriate Use Recommendations for Amyloid Plaque Lowering MAbs

A Completely New Paradigm for AD Treatments: Appropriate Use Recommendations (Aducanumab to Lecanemab)

- Provide detailed practical guidance for clinicians for appropriate use (more than provided in FDA label (PI)), including:
  - Patient selection, safety considerations, and monitoring
  - Dose suspensions/terminations for ARIA
  - Counseling *(e.g., no contraindications listed on the FDA label),* and team planning & resources
- **Recommendations are "on label" but in many cases are more specific, restrictive, and conservative regarding patient selection and safety monitoring**
  - For example, confirmation of A+; exclusion criteria; ApoE-ε4 status to inform benefit-risk, 4 MRIs for safety → led to several FDA label (PI) updates for aducanumab
- Expect recommendations will continue to evolve as more data from trials and clinical practice become available → Lecanemab Appropriate Use Recommendations (AUR) published in March 2023





Practical guidance for clinicians on who, what, and how

Cummings J, et al. *J Prev Alzheimers Dis*. 2021;8(4):398-410; Cummings J, et al. *J Prev Alzheimers Dis*. 2022;9(2):221-230. ; Cummings J et al. J Prev Alzheimers Dis. 2023 published on line 27 March 2023

Selecting Patients to Treat With Anti-Aβ Monoclonal Antibodies[1-6]

FDA Prescribing Info and Appropriate Use Recommendations (AUR): specific to approved monoclonal antibody
AUR for lecanemab based on phase 2 data/accelerated approval, not phase 3 data/full FDA approval
AUR for lecanemab more restrictive than the FDA prescribing information

Appropriate Use Recommendations: Eligibility Criteria for Treatment With Lecanemab

Inclusions	Exclusions
1. Clinical diagnosis of MCI or mild dementia due to AD 2. Confirmed amyloid positivity (PET or CSF) 3. MMSE = 22-30 or other cognitive screening instrument with a score compatible with early AD (eg, MOCA ≥18)	1. MRI with >4 microhemorrhages, >1 area of superficial siderosis or significant cerebrovascular disease, severe white matter changes on MRI, macrohemorrhage, >2 lacunar infarcts, a single infarct >1 cm 2. MRI contraindication 3. Anticoagulation 4. Unstable medical/psychiatric conditions

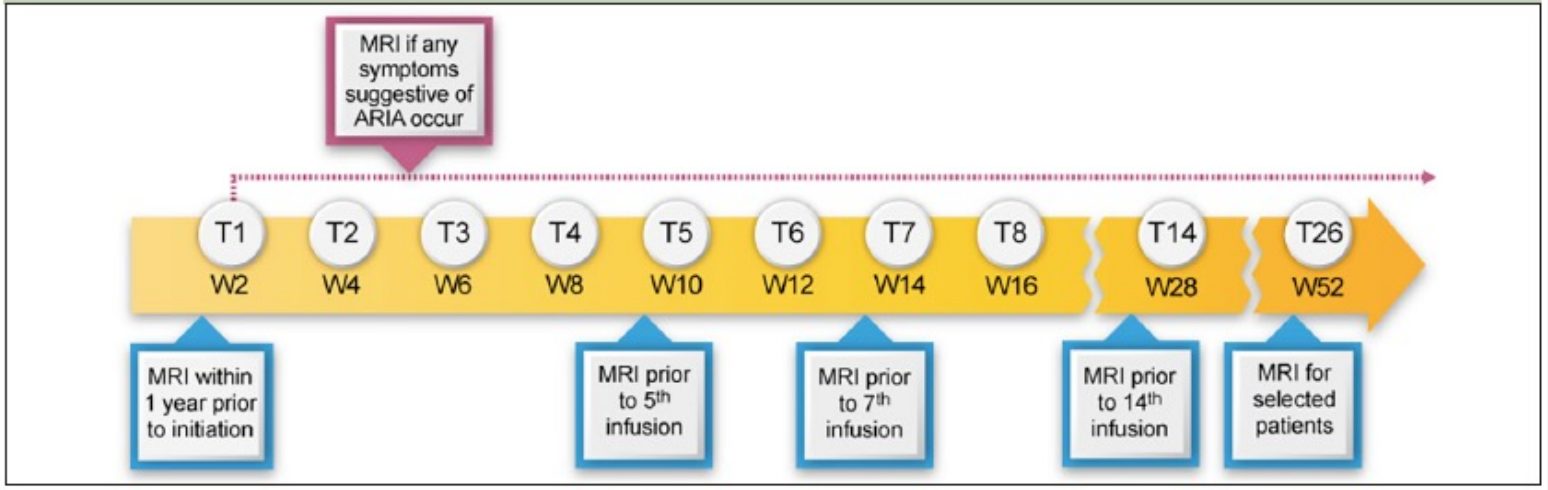
1. Cummings J et al. *J Prev Alzheimers Dis*. 2023;10:362-377. 2. Cummings J et al. *J Prev Alzheimers Dis*. 2022;2:221-230. 3. Cummings J et al. *J Prev Alzheimers Dis*. 2021;4:398-410. 4. van Dyck CH et al. *N Engl J Med*. 2023;388:9-21. 5. Aduhelm (aducanumab) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761178s007lbl.pdf. 6. Leqembi (lecanemab) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761269s001lbl.pdf.

Lecanemab AUR – MRI Monitoring

- **Lecanemab**: at baseline and then
  - 6 subsequent post-baseline MRIs in Phase 3 (weeks 9, 13, 27, 53, 79, 91)
  - FDA PI 3 MRIs: before 5th, 7th and 14th infusions (before week 10, 14 and 28)
  - Lecanemab AUR 4 MRIs before 5th, 7th,14th and 26th infusions (before week 10, 14, 28 and 52*)

*especially selected patients – e.g. had ARIA-E, e4+/++

Figure 1. MRI monitoring for lecanemab



Cummings et al. JPDA 2023 (Lecanemab AUR)

Figure 2. Monitoring and management of ARIA

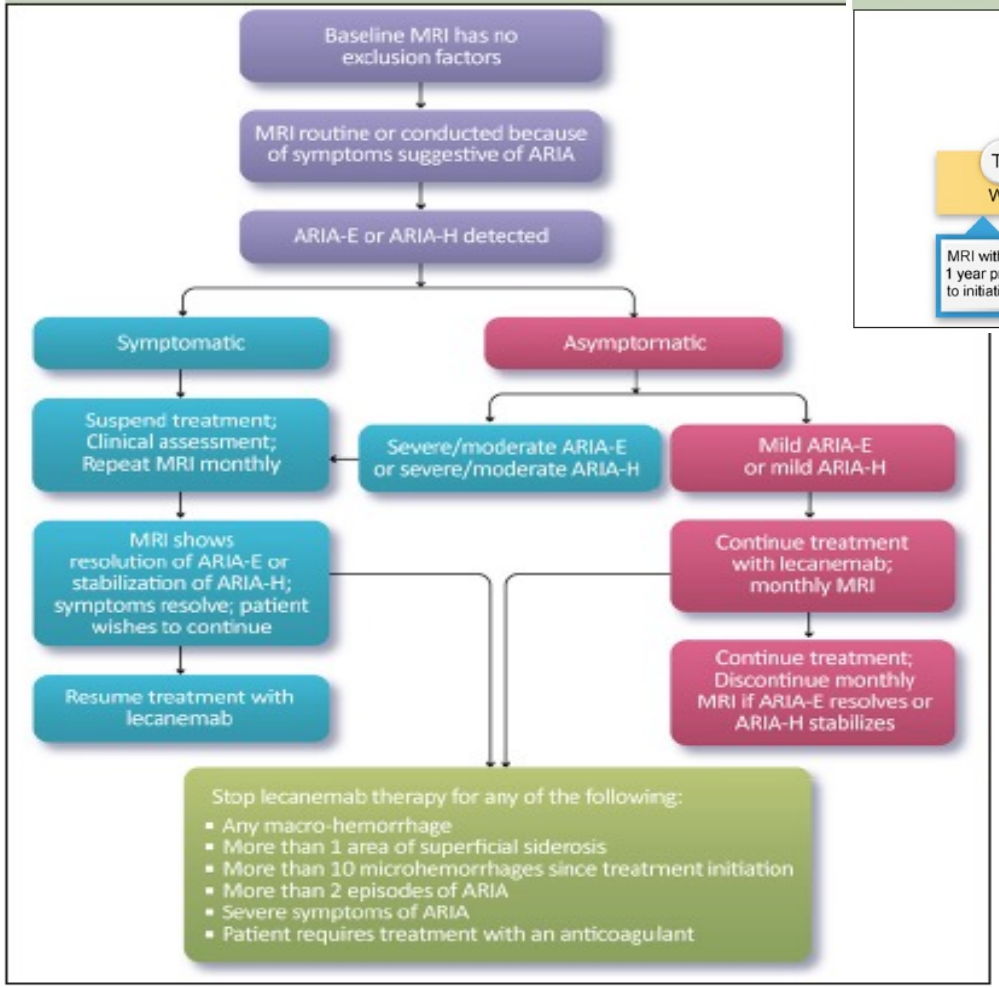


Figure 1. MRI monitoring for lecanemab

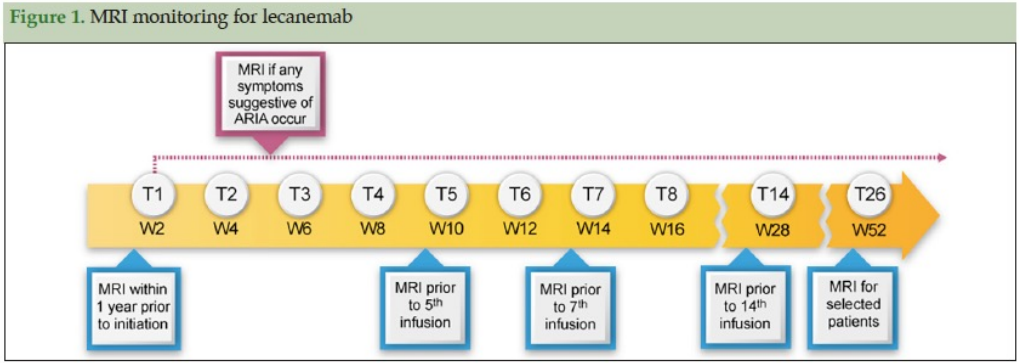


Table 9. Medical Center resources needed to manage serious or severe ARIA

• Emergency department with resources to assess suspected or known ARIA
• MRI scanners readily available for unscheduled scanning of symptomatic patients
• Knowledgeable MRI readers proficient in detection and interpretation of ARIA
• Clinicians with experience in the management of cerebral edema or ARIA
• Hospital ward for monitoring and management
• Intensive care unit availability
• Electroencephalography available to inpatients
• Neurologist with experience in management of seizures and status epilepticus

Cummings J et al. J Prev Alzheimers Dis. 2023 published on line 27 March 2023

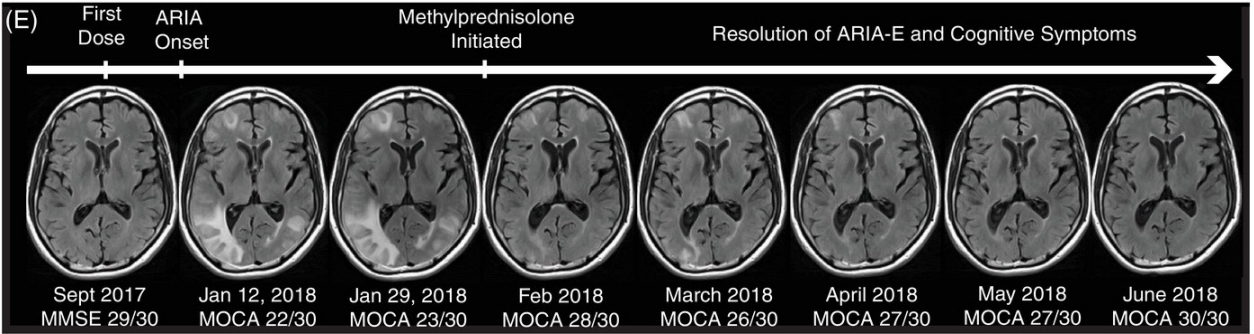
Severe and Serious ARIA

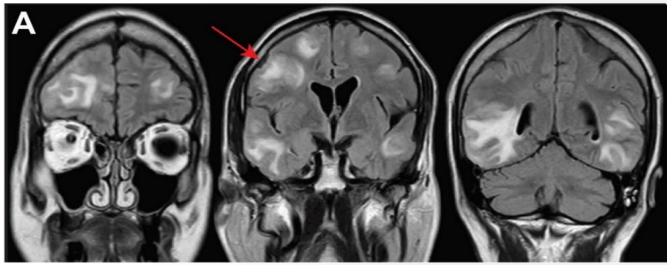
VandeVrede L, Gibbs DM, et al Symptomatic amyloid-related imaging abnormalities in an APOE ε4/ε4 patient treated with aducanumab. Alzheimers Dement (Amst). 2020

- 66 year old male neurologist [Gibbs DM. Early awareness of Alzheimer disease: a neurologist's personal perspective. JAMA Neurol. 2019;76(3):249.]
- ApoE ε4 homozygous (ε4/ ε4)
- Received aducanumab in ENGAGE trial
- Age 55: Olfactory impairment
- Age 61: Mild memory symptoms
- Age 62: Retired from medical practice Entered ENGAGE on placebo arm, then open-label extension
- Sudden explosive onset of headache, fluctuating confusion and alexia without agraphia (self-diagnosed) -> hospital with BP 206/116 and admitted to ICU – brain MRI severe ARIA-E
- Treated with IV nicardipine

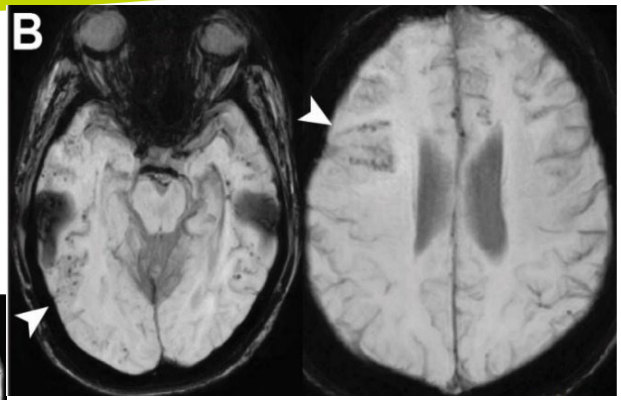
Abnormalities improved, discharged on oral anti-hypertensives

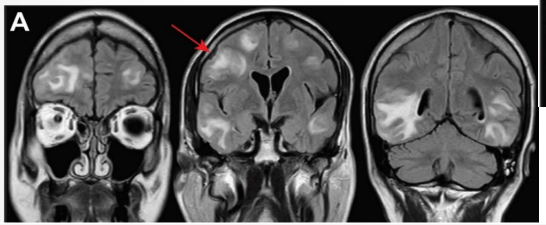
- 1 month later, worsened alexia without agraphia and worsened ARIA-E
- EEG showed left temporal sharp waves; brain MRI ARIA-E improved c/w previous MRIs
- Treated with levetiracetam and methylprednisolone
- Headache and alexia resolved → returned to baseline within 4 months

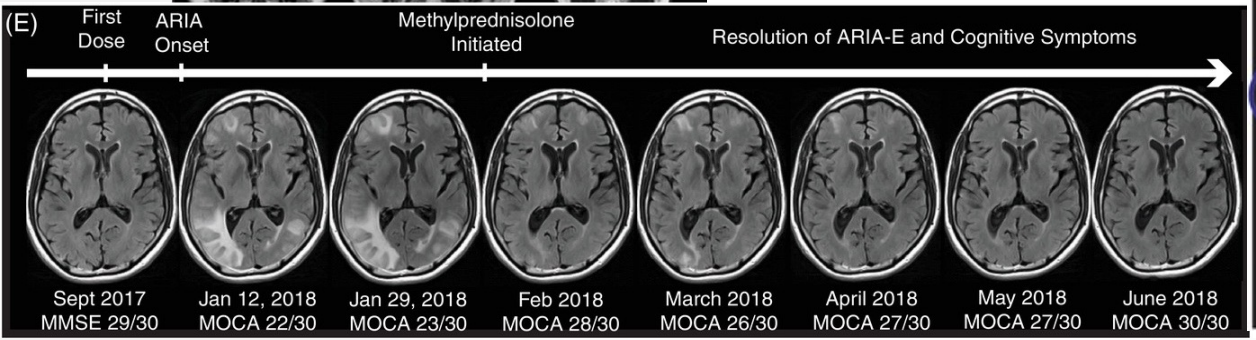


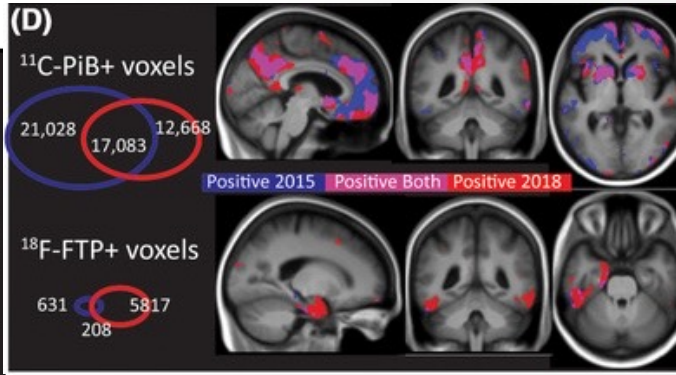


VandeVrede L, Gibbs DM, et al Symptomatic amyloid-related imaging abnormalities in an APOE ε4/ε4 patient treated with aducanumab. Alzheimers Dement (Amst). 2020



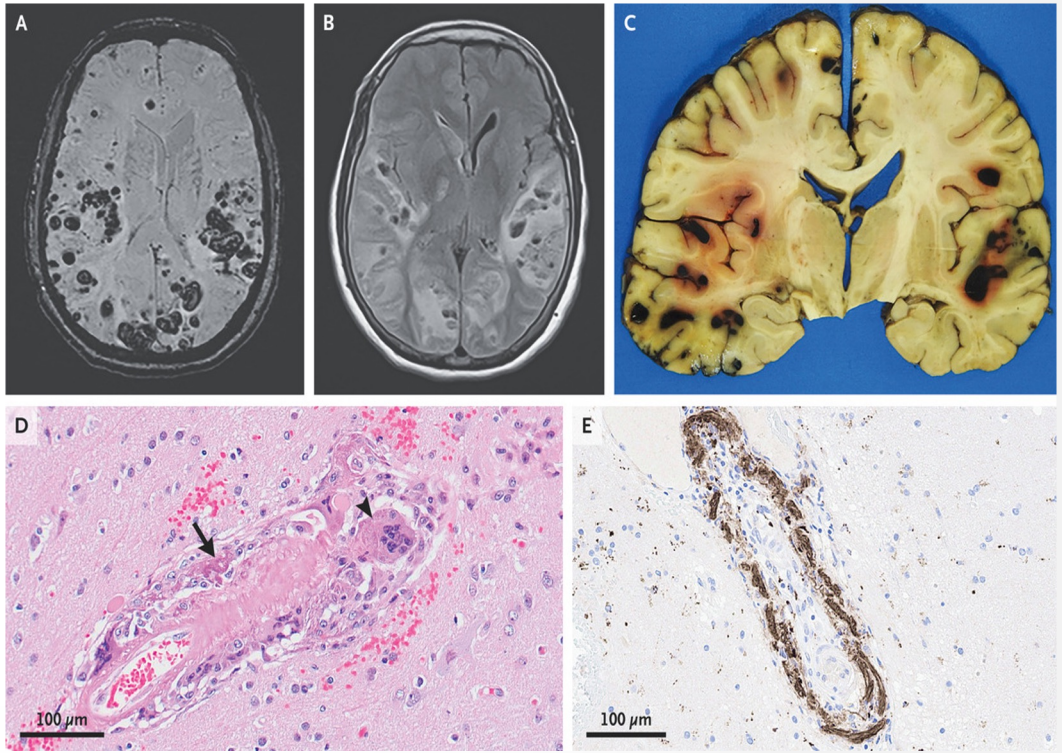






Lecanemab and thrombolysis-related ICH

- 65 yr old woman, APOE ε4/ε4
- 3 doses open-label lecanemab, last 4d prior
- acute onset aphasia, CT with L temperoparietal hypodensity
- IV tPA infusion, CT with multifocal ICH
- agitation, nonconvulsive seizures, comfort measures



Reish *NEJM* 2023;

Key Stages in the Diagnostic Process[1]

Patient presentation

Step 1: Detect
(***Do not dismiss mild memory complaints***)

Patient and family history, quick memory or cognitive test

Step 2: Assess/Differentiate

Blood test, neurologic and physical exams

In depth cognitive and functional assessments

Structural imaging

Step 3: Diagnose

Access to AD biomarkers, communicate diagnosis, select treatment option

Diagnosis

Step 4: Treat

AD treatment, monitoring treatment response (MRI/ vital signs, quick memory or cognitive test), AE reporting

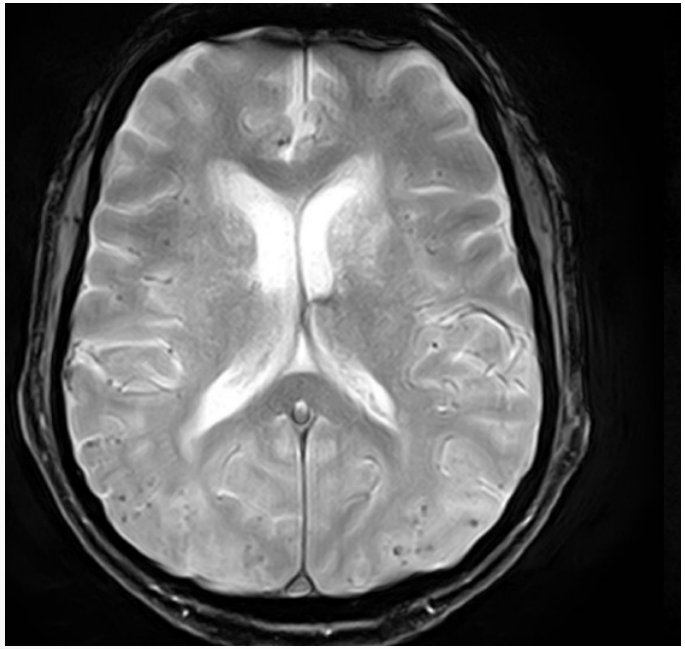
Patient management

Nonspecialists (eg, PCPs) | **Optimal referral window** | **Specialists (eg, memory clinics)**

1. Porsteinsson AP et al. *J Prev Alz Dis*. 2021;3:371-386.

Sensitive Detection of MCHs is Highly Dependent on:

Technique (GRE vs SWI), MRI Field Strength (1.5T vs 3T), and Reader Proficiency



T2* GRE

Images courtesy of Frederik Barkhof – and Alzheimer's Association (CE program)

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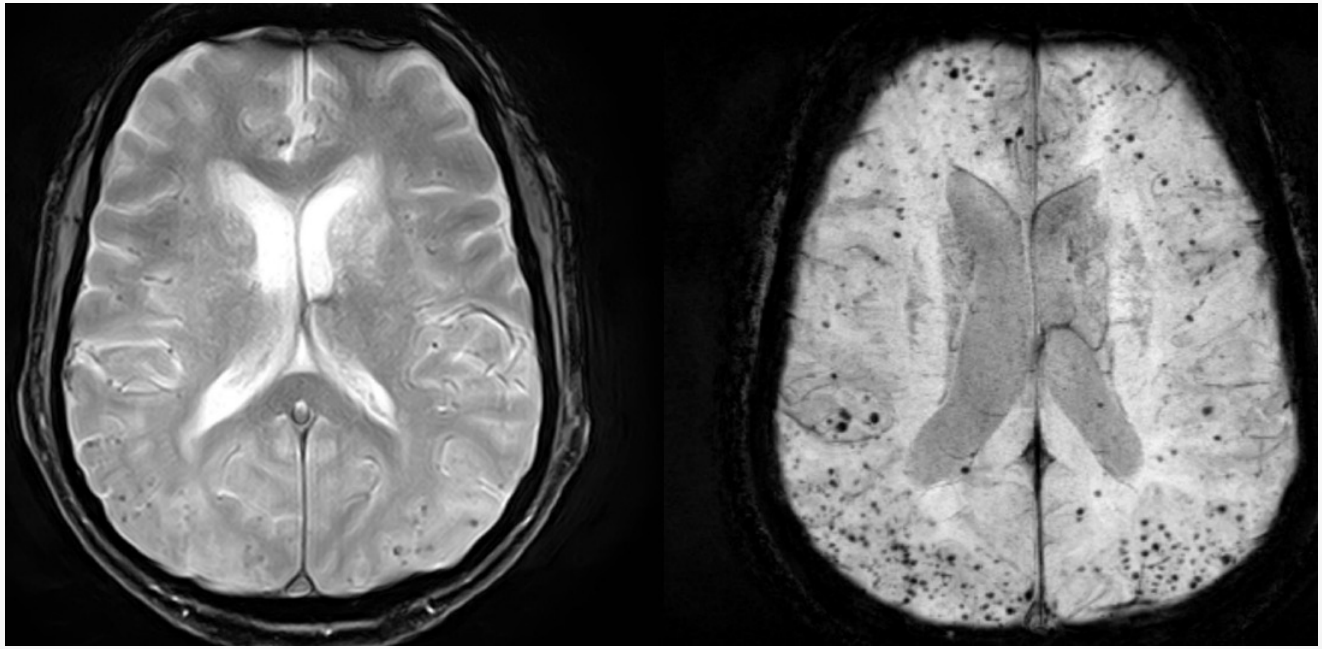

T2* GRE

SWI

Images courtesy of Frederik Barkhof – and Alzheimer's Association (CE program)

ARIA E&M Plan: Importance of Having A Priori Developed Strategic Plan and Team for ARIA Triage Evaluation and Management in Patients With Suspected Severe ARIA

Patient care can be optimized by development of a triage strategy for evaluation and management of patients with symptoms and signs of severe ARIA. The plan will vary to accommodate clinical judgment, as well as institutional resources and circumstances but will typically include these elements

Referral of patient to emergency department for thorough assessment of suspected/known ARIA

Brain MRI without contrast enhancement if not already obtained (FLAIR, T2*-GRE or SWI, and DWI sequences)

MRI review by a reader proficient in detection of ARIA (preferably with access to past MRIs for comparison) and rapid communication between MRI reader and clinicians responsible for patient's aducanumab treatment and AD care

Discontinuation of anti-amyloid therapy

Consultation by a neurologist, preferably a vascular neurologist with experience in management of ARIA-like syndromes

Admittance to hospital ward for close neurologic monitoring and tiered level of monitoring and management

Admit or transfer to a stroke care unit or neurological intensive care unit if warranted

Protocols for, when warranted:

- Early initiation of treatment with intravenous methylprednisolone 1 g/day for 5 days
- Conducting electroencephalography to detect epileptiform activity
- Treatment with anticonvulsants for seizure management or prophylaxis if electroencephalography suggests they are indicated
- Consideration of additional immunosuppressive treatment if not responding to methylprednisolone after 5 days of treatment
- Plan transition to oral steroid treatment and taper as outpatient

Support and communicate with patient and family members/care partners throughout the event with informed patient-centered decision-making

DWI, diffusion-weighted imaging; SWI, susceptibility weighted imaging.

Cummings J, et al. *J Prev Alzheimers Dis*. 2021;8(4):398-410; Cummings J, et al. *J Prev Alzheimers Dis*. 2022;9(2):221-230.

Summary

- We are at the beginning of a new, hopeful and foundational era – informed by established and emerging biomarkers and new therapies
- AD treatments can “save clinical progression time” – this matters and is meaningful
- No magic bullets or cures but there is a rational basis for hope that we can achieve substantial and iterative advances in the coming 5-10 years, but will need to:
  - ➢ Be thoughtful, methodical, rigorous and “patient”
  - ➢ Proceed with “okay,” for now, “modest” stepping stones; and build on them!
  - ➢ Build our care infrastructure as we translate innovative therapies to clinical practice
  - ➢ Use patient-centered precision and personalized medicine approaches
    - Precision medicine in oncology has accelerated research and substantially improved clinical care and outcomes (e.g. breast CA) we will do the same for AD in the coming decades
    - Will utilize biomarkers to learn who may benefit more, how to gauge treatment responses and increase benefits and to lower burdens/risks

Summary

- We need to develop and use combination treatments (that impact different disease-related neurodegenerative mechanisms) → amyloid is only partly a driver of cognitive impairment once symptoms begin
- Greater autonomy and access (justice) to biomarkers and treatments → will lead to improvements in more timely and accurate diagnosis and better care in general
  - Intervention prior to dementia, before widespread irreversible loss of brain cells/synapses
  - We do not just wait until symptoms appear in cancer, stroke, and heart disease/heart failure (we treat high blood pressure and high cholesterol), HIV, diabetes, osteoporosis...why wait for brain “organ failure” before we diagnose and begin treatments
- Even more rational basis and for hope for prevention (it is the best cure)!

Please remember to complete and submit your Post-Test and Evaluation for CE credit.

PeerView.com/Alzheimers-Survey-GAZ

Thank you and have a good day.

PeerView Live

Abbreviations

AAIC: Alzheimer's Association International Conference
AAN: American Academy of Neurology
ADAS-Cog14: Alzheimer's Disease Assessment Scale–Cognitive Subscale
ADCS MCI-ADL: Alzheimer's Disease Cooperative Study/Activities of Daily Living scale adapted for MCI patients
apoE: apolipoprotein E
ARIA: amyloid-related imaging abnormalities
AUR: appropriate use recommendation
CDR-SB: Clinical Dementia Rating Scale Sum of Boxes
CLIA: Clinical Laboratory Improvement Amendments
CMS: Centers for Medicare and Medicaid Services
CSF: cerebrospinal fluid
CTAD: Clinical Trials on Alzheimer's Disease Conference
EDTA: ethylenediaminetetraacetic acid
GFAP: glial fibrillary acidic protein
IQR: interquartile range
LC: liquid chromatography
LP: lumbar puncture
MMSE: Mini Mental State Examination
MS: mass spectrometry
PDUFA: Prescription Drug User Fee Act
PET: positron emission tomography
PHQ-9: Patient Health Questionnaire-9
TSH: thyroid-stimulating hormone
WMS-IV LMSII: Wechsler Memory Scale IV-Logical Memory (subscale) II