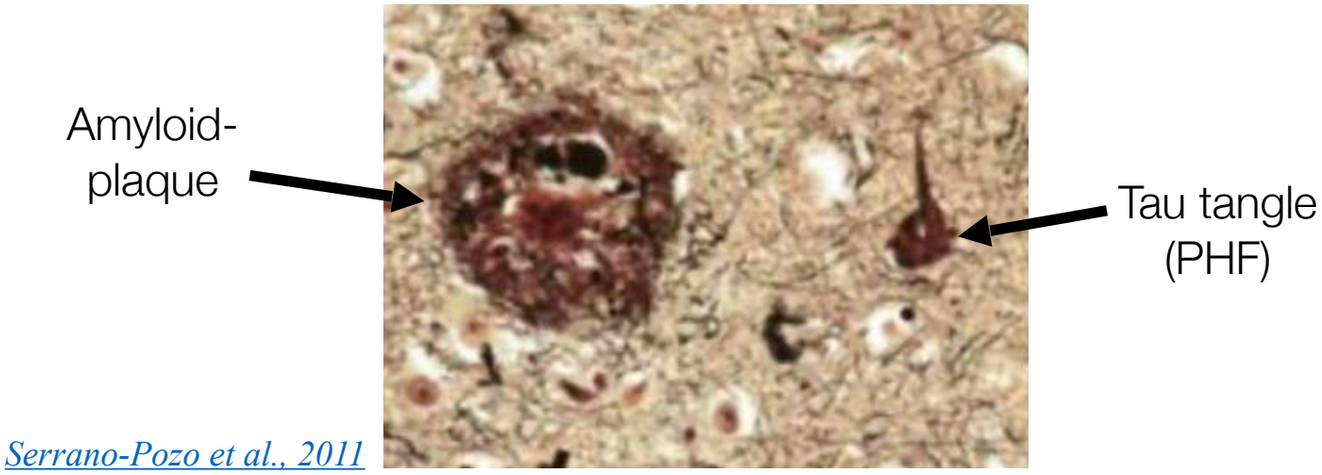
Amyloid Hypothesis of Alzheimer's Disease

- Amyloid-beta and tau accumulation are the neuropathological hallmarks of Alzheimer's disease
- Genetic evidence implicates amyloid-beta accumulation in familial Alzheimer's disease
- These observations led to the amyloid hypothesis of Alzheimer's disease pathophysiology

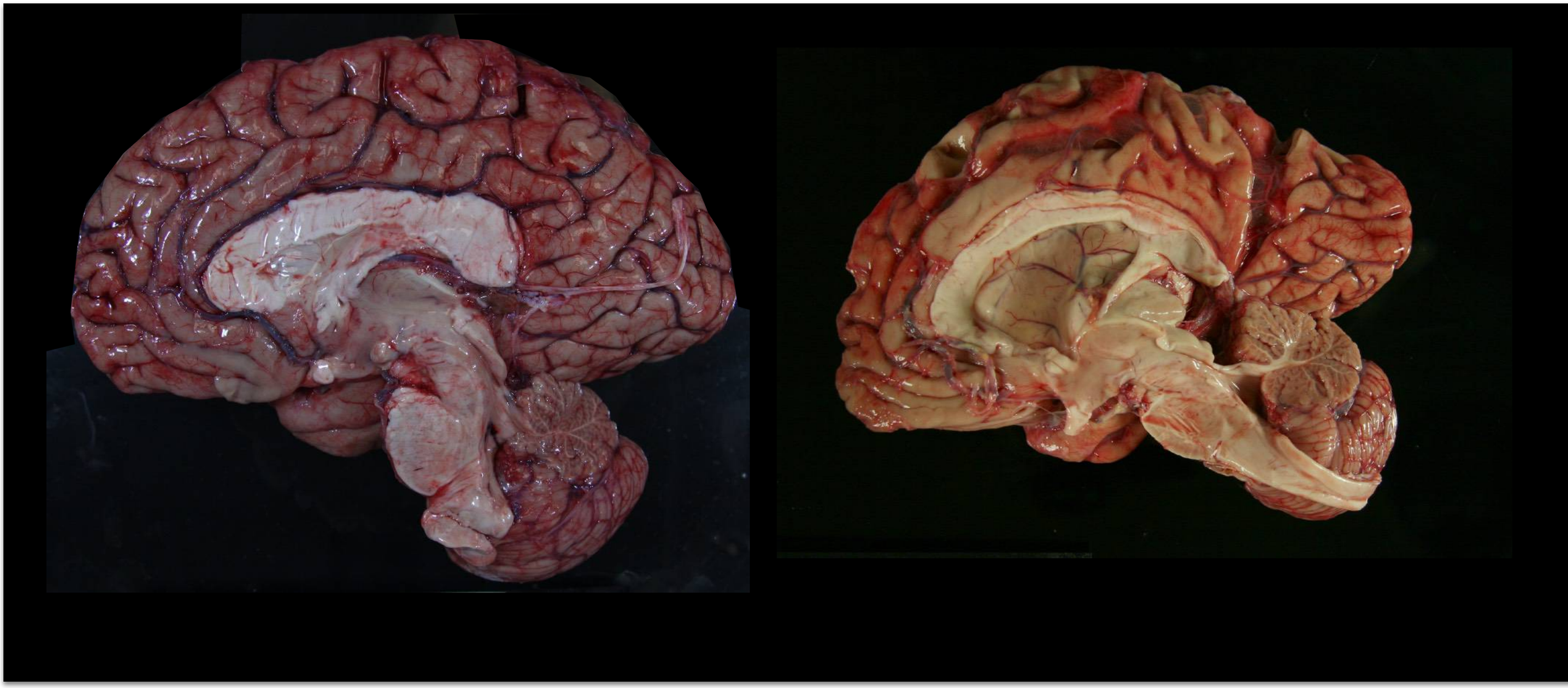


Serrano-Pozo et al., 2011

Parenchymal Loss in Alzheimer's Disease

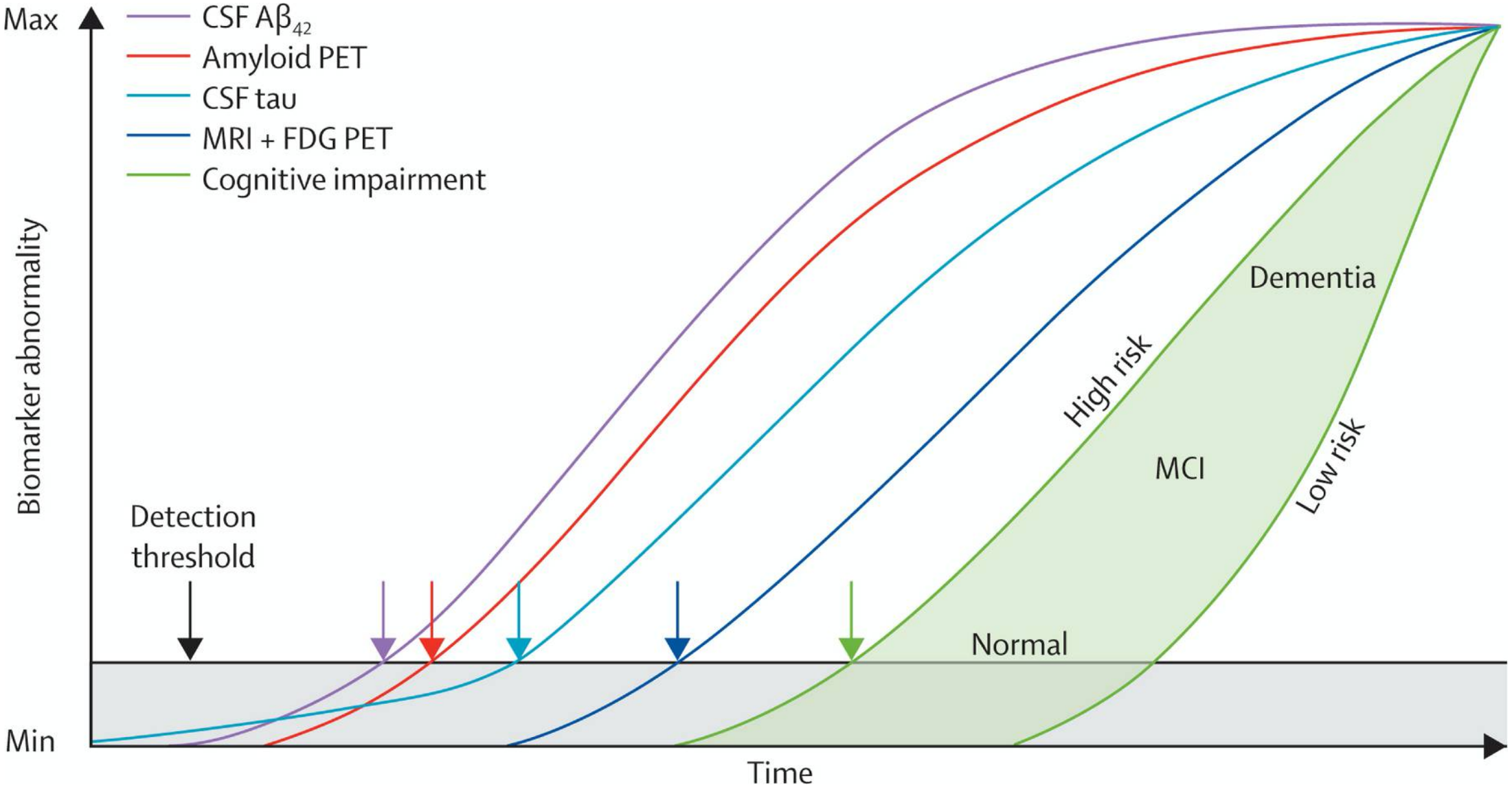
Cognitively Normal Senior

Alzheimer's Disease



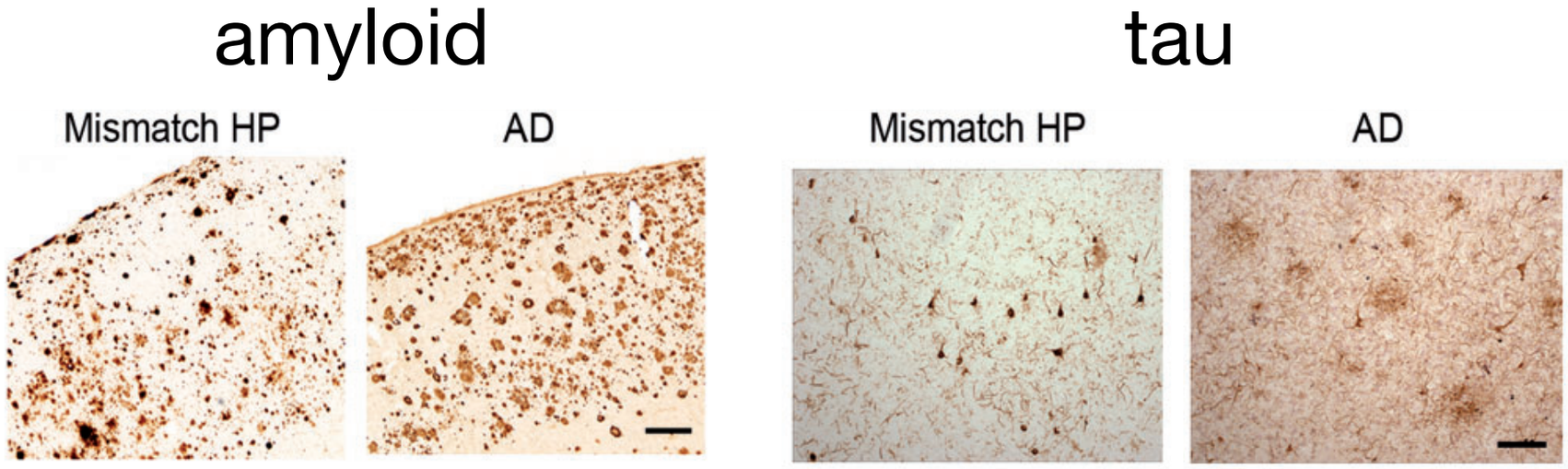
Mass General ADRC

Long preclinical prodrome before symptoms



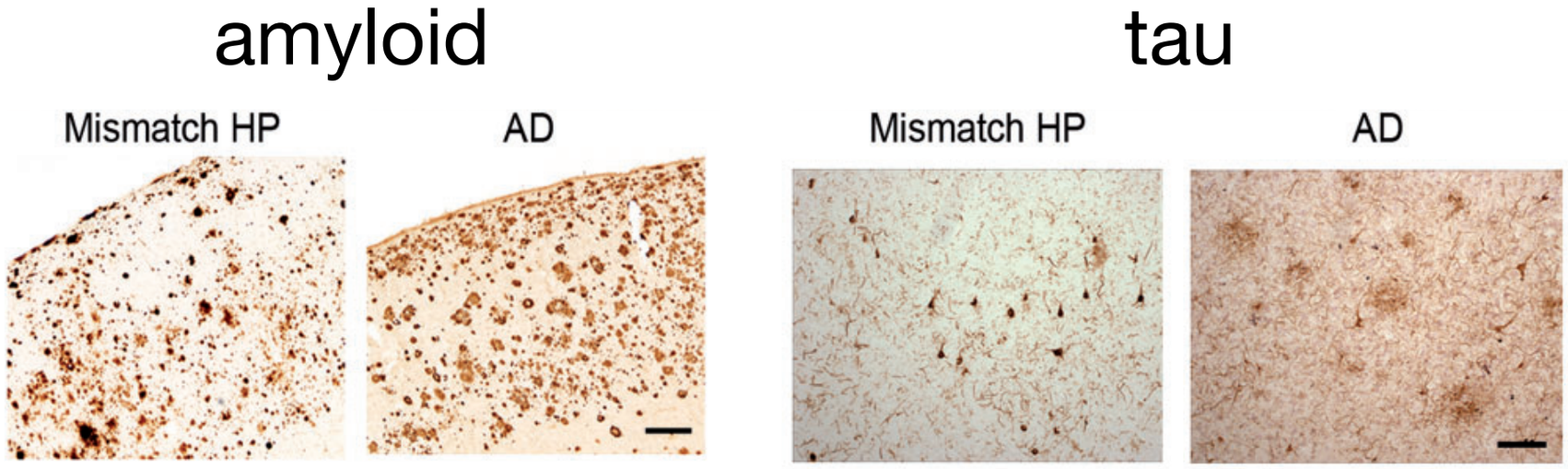
Jack et al, Lancet, 2013

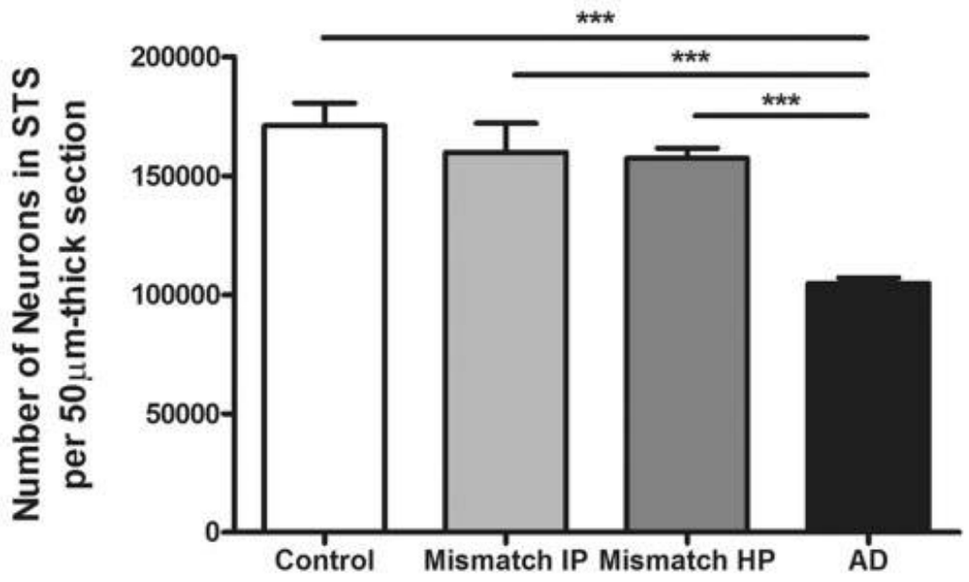
Parenchymal loss correlates with symptoms

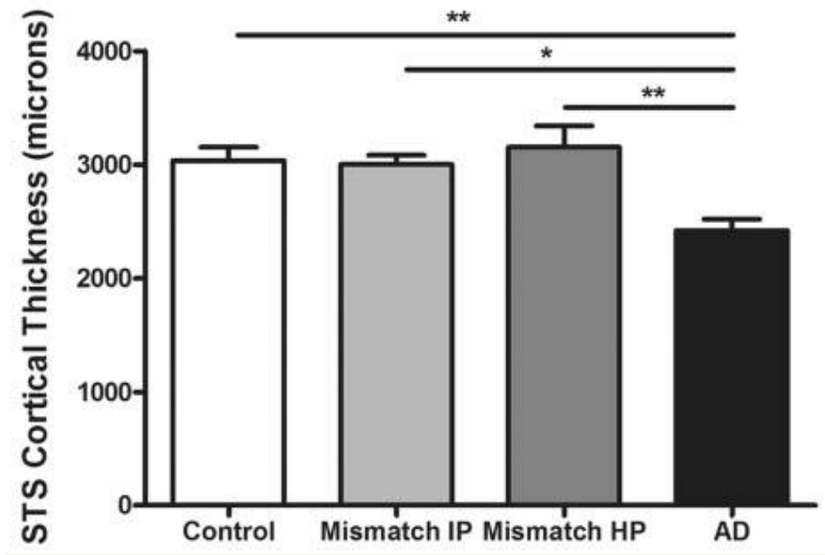


Perez-Nievas, et al., *Brain* (2013)

Parenchymal loss correlates with symptoms



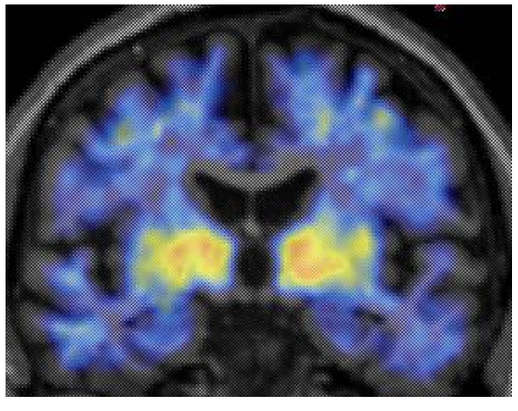


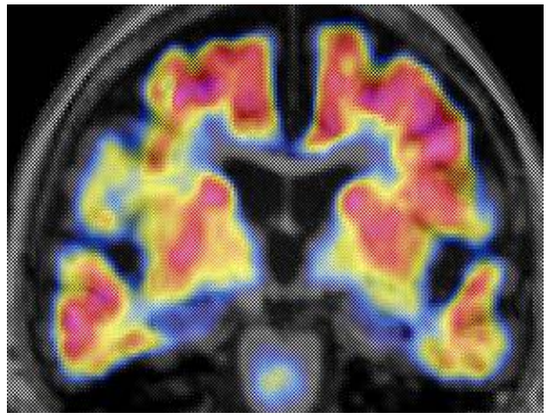


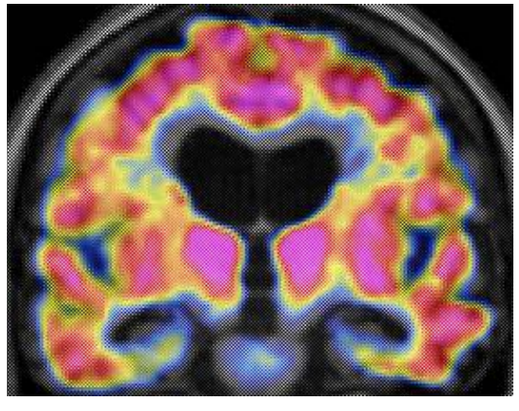
Perez-Nievas, et al., *Brain* (2013)

PET Amyloid and Tau Imaging in Living Seniors

Plaques (PiB)







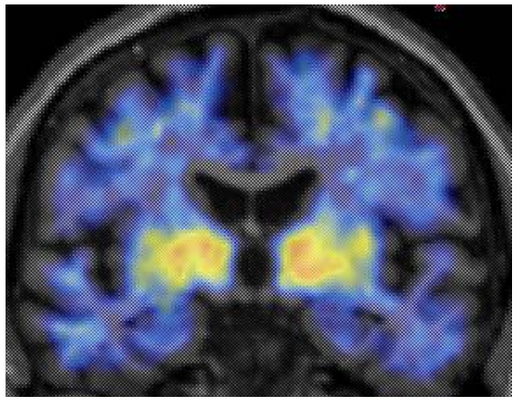
Clinically Normal

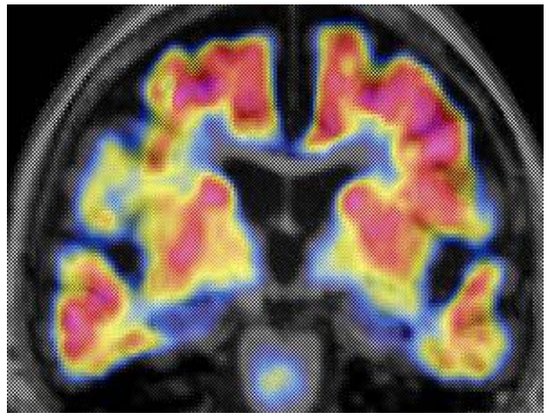
Clinically Normal: plaques +

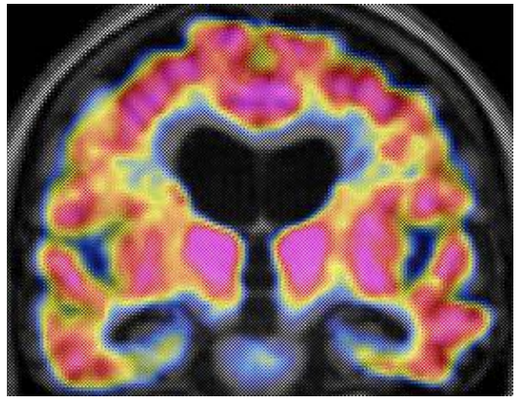
Alzheimer's Dementia

PET Amyloid and Tau Imaging in Living Seniors

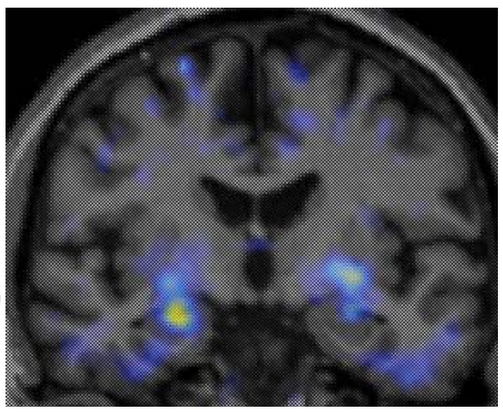
Plaques (PiB)

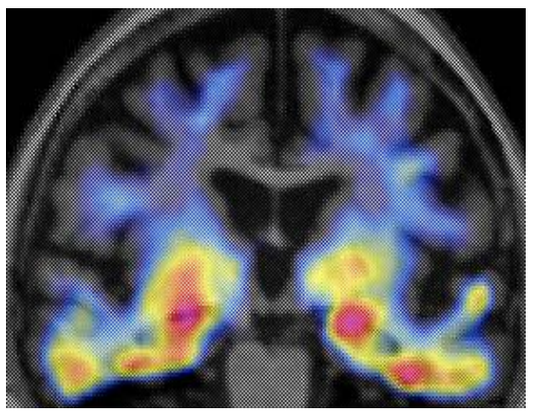


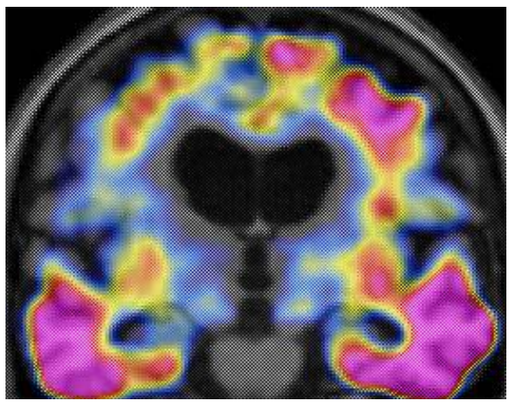




Tangles (fluortauapir)





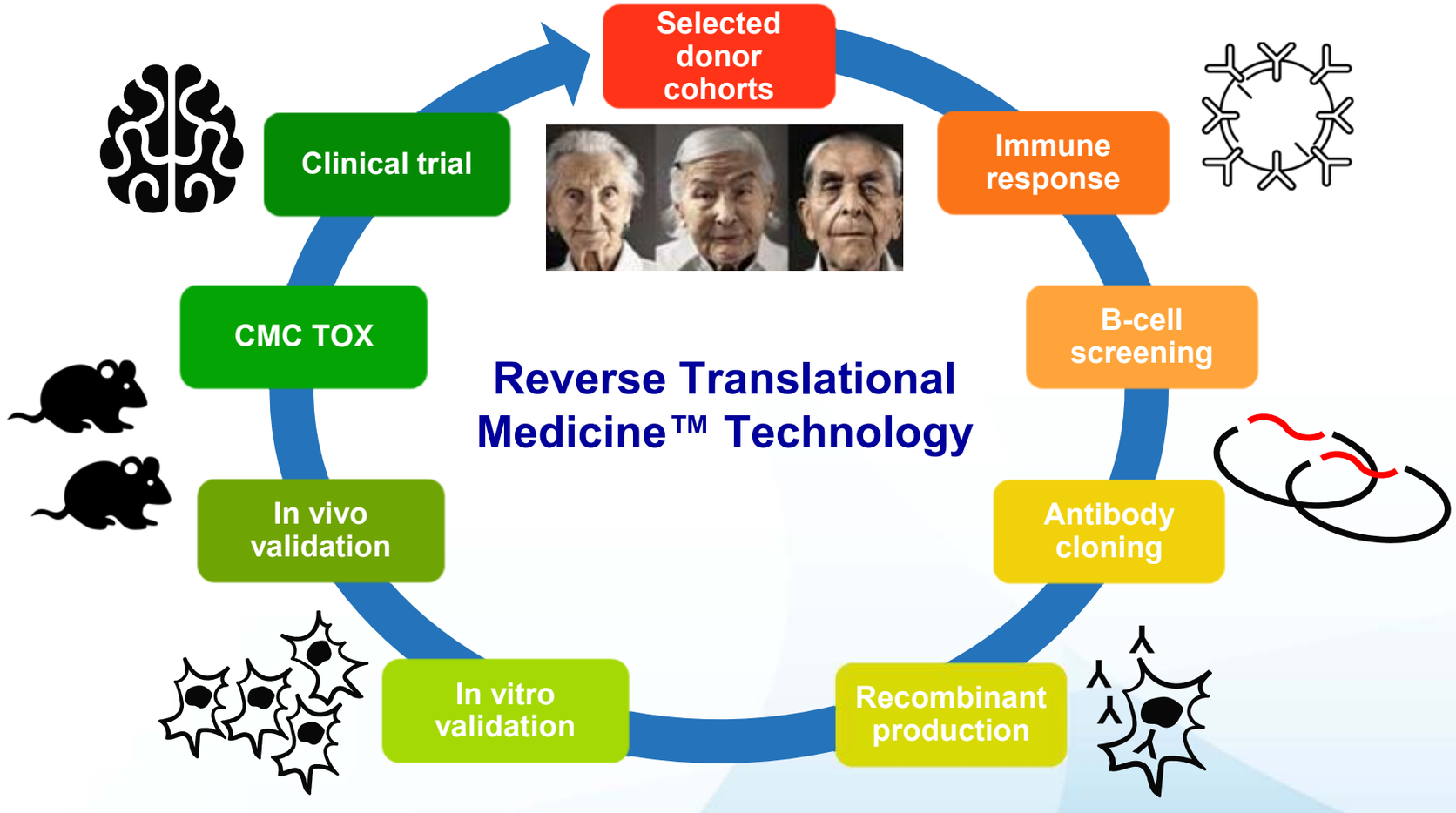


Clinically Normal

Clinically Normal: plaques +

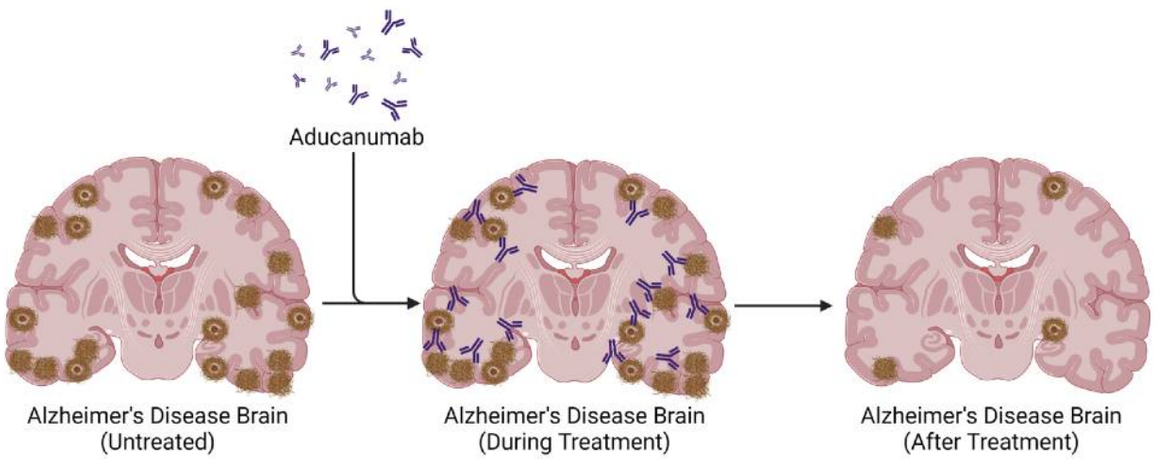
Alzheimer's Dementia

Aducanumab is a human IgG1 anti-Aβ monoclonal antibody developed in partnership with Neurimmune

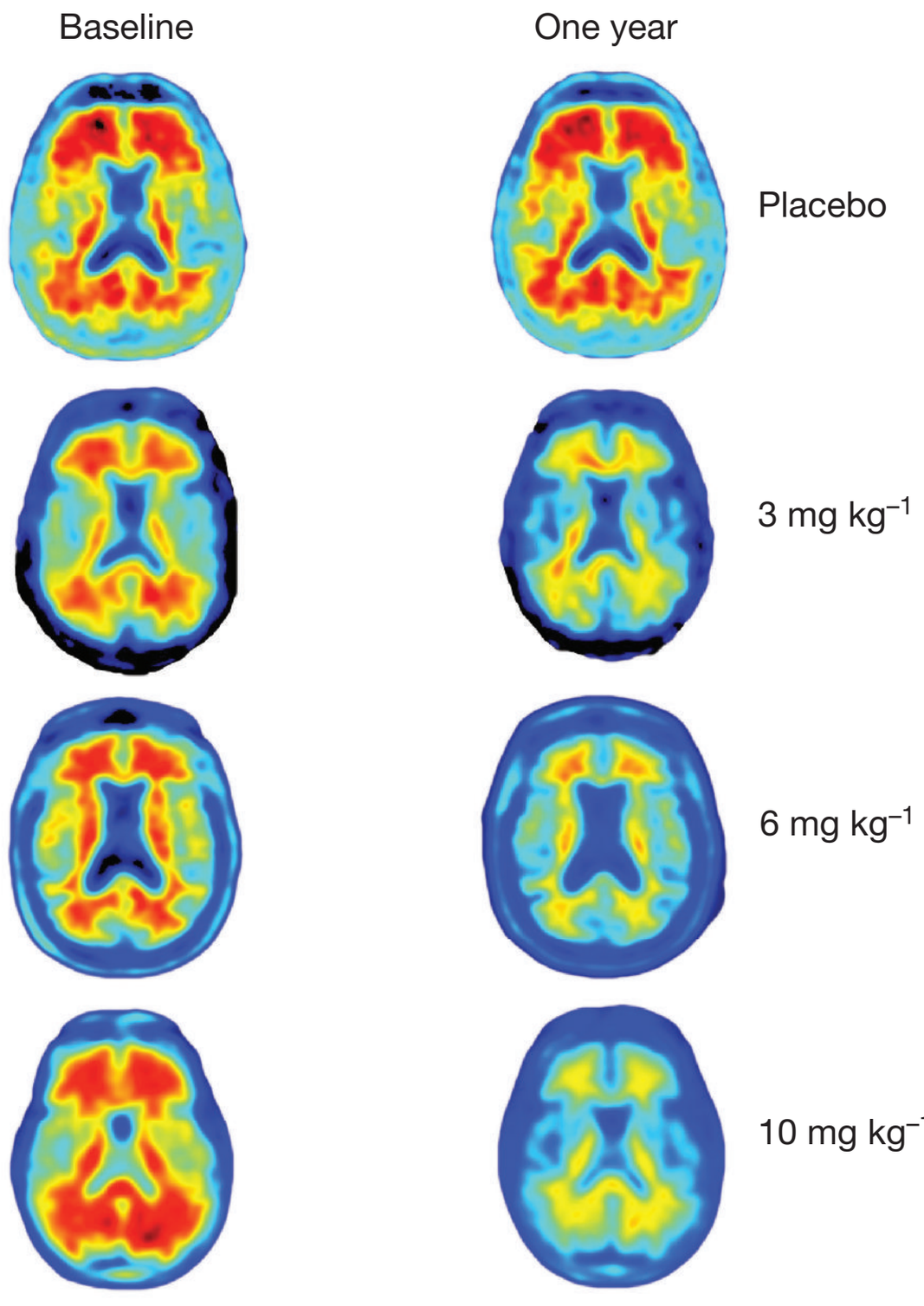


Budd-Heberlein, Biogen, CTAD, 2018

Aducanumab reduces plaques within 1 year



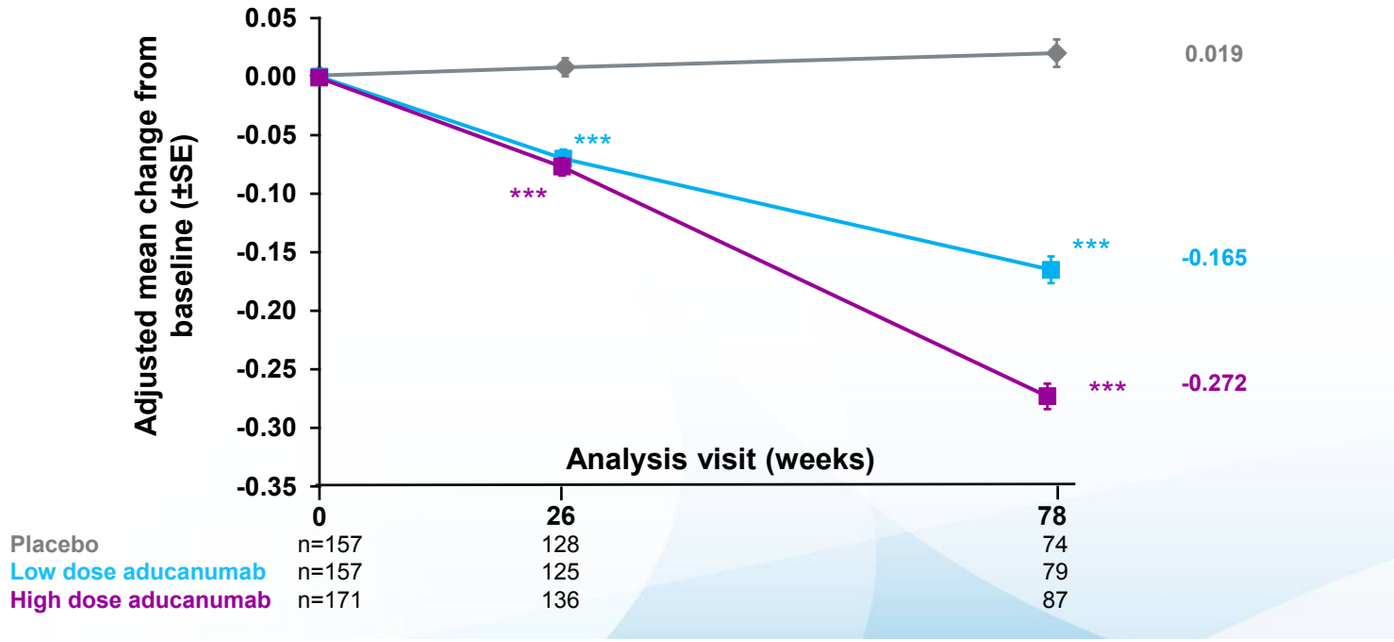
- Binds aggregated forms of amyloid-beta in brain parenchyma
- Immune-mediated clearance of amyloid-beta



Sevigny et al., 2016

Aducanumab reduces plaques within 1 year

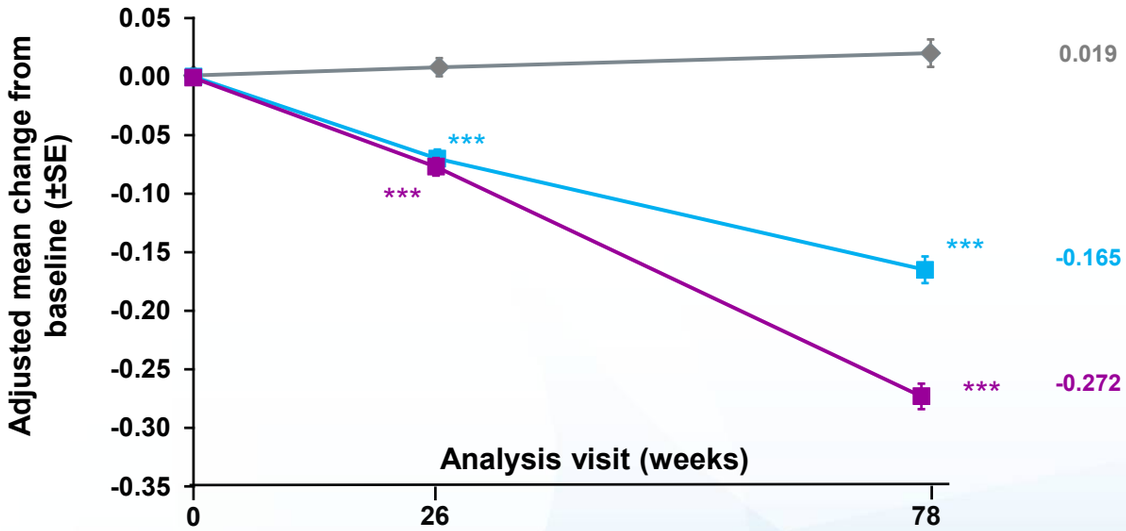
EMERGE: Longitudinal change from baseline in amyloid PET SUVR



Haeberlein et al. *CTAD* 2019

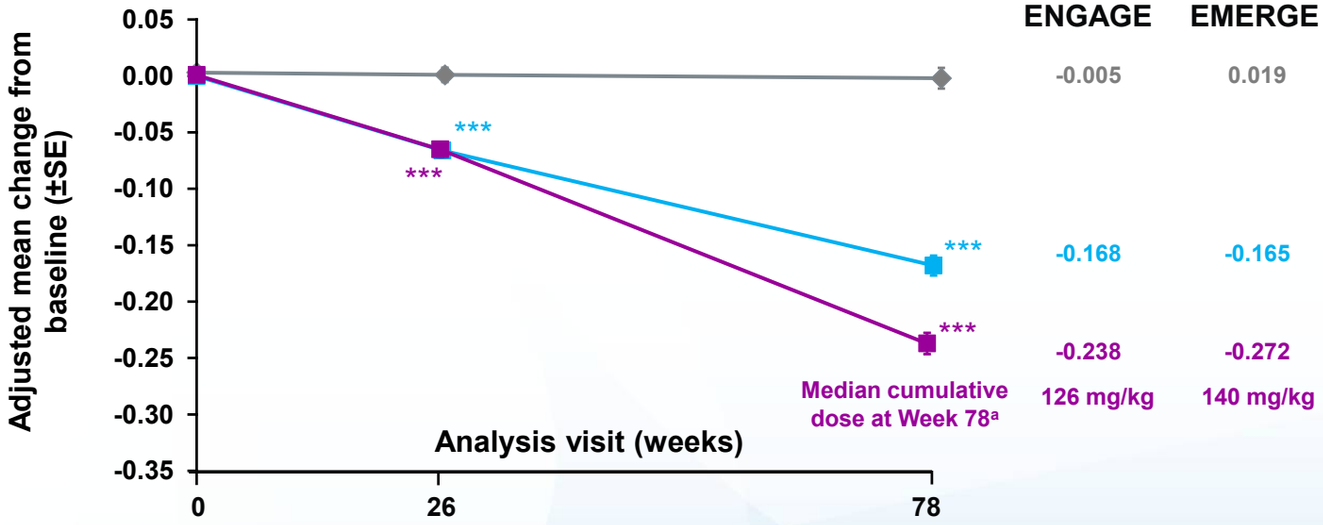
Aducanumab reduces plaques within 1 year

EMERGE: Longitudinal change from baseline in amyloid PET SUVR



Placebo	n=157	128	74
Low dose aducanumab	n=157	125	79
High dose aducanumab	n=171	136	87

ENGAGE: Longitudinal change from baseline in amyloid PET SUVR



Placebo	n=203	164	104
Low dose aducanumab	n=198	166	116
High dose aducanumab	n=181	149	97

Haeberlein et al. *CTAD* 2019

CDR-SB (sum of boxes) definition

Table 1 - Classification of the categories evaluated by the Clinical Dementia Rating.

Impairment level	None (0)	Questionable (0.5)	Mild (1)	Moderate (2)	Severe (3)
Memory	No memory loss or slight inconsistent forgetfulness	Consistent forgetfulness, partial recollection of events.	Moderate memory loss; more marked for recent events; defect interferes with daily activities.	Severe memory loss; only highly learned material retained.	Severe memory loss; only fragments remain.
Orientation	Fully oriented.	Fully oriented except with slight difficulties with time relationships.	Moderate difficulty with time relationships, oriented in familiar areas.	Severe difficulty with time relationships, almost always disoriented to place.	Oriented to person only.
Judgement & Problem Solving	Solves everyday problems, such as financial affairs; judgement preserved.	Slight difficulty in solving problems, similarities and differences.	Moderate difficulty on handling problems, similarities and differences, social judgement maintained.	Severely impaired in handling problems, similarities and differences; social judgment impaired.	Unable to make judgements or solve problems.
Community Affairs	Independent function in job, shopping, social groups.	Slight impairment in these activities.	Is not independent in these activities, appears normal to casual inspection.	Is not independent outside home, appears well enough to be taken to events outside the home.	Is not independent outside the home, appears to be too ill to be taken to events outside the home.
Home and Hobbies	Daily life at home, hobbies and intellectual interests well maintained.	Daily life at home, hobbies and intellectual interests slightly impaired.	Slight impairment of tasks at home, more difficult chores, hobbies and interests are abandoned.	Only simple chores are maintained, restricted interests, poorly maintained.	No significant function at home.
Personal Care	Fully capable of self-care.	Fully capable of self-care.	Needs assistance.	Requires assistance in dressing and hygiene.	Requires much help with personal care; frequent incontinence.

Fonte: Bertolucci et al[2]

0.5

0.5

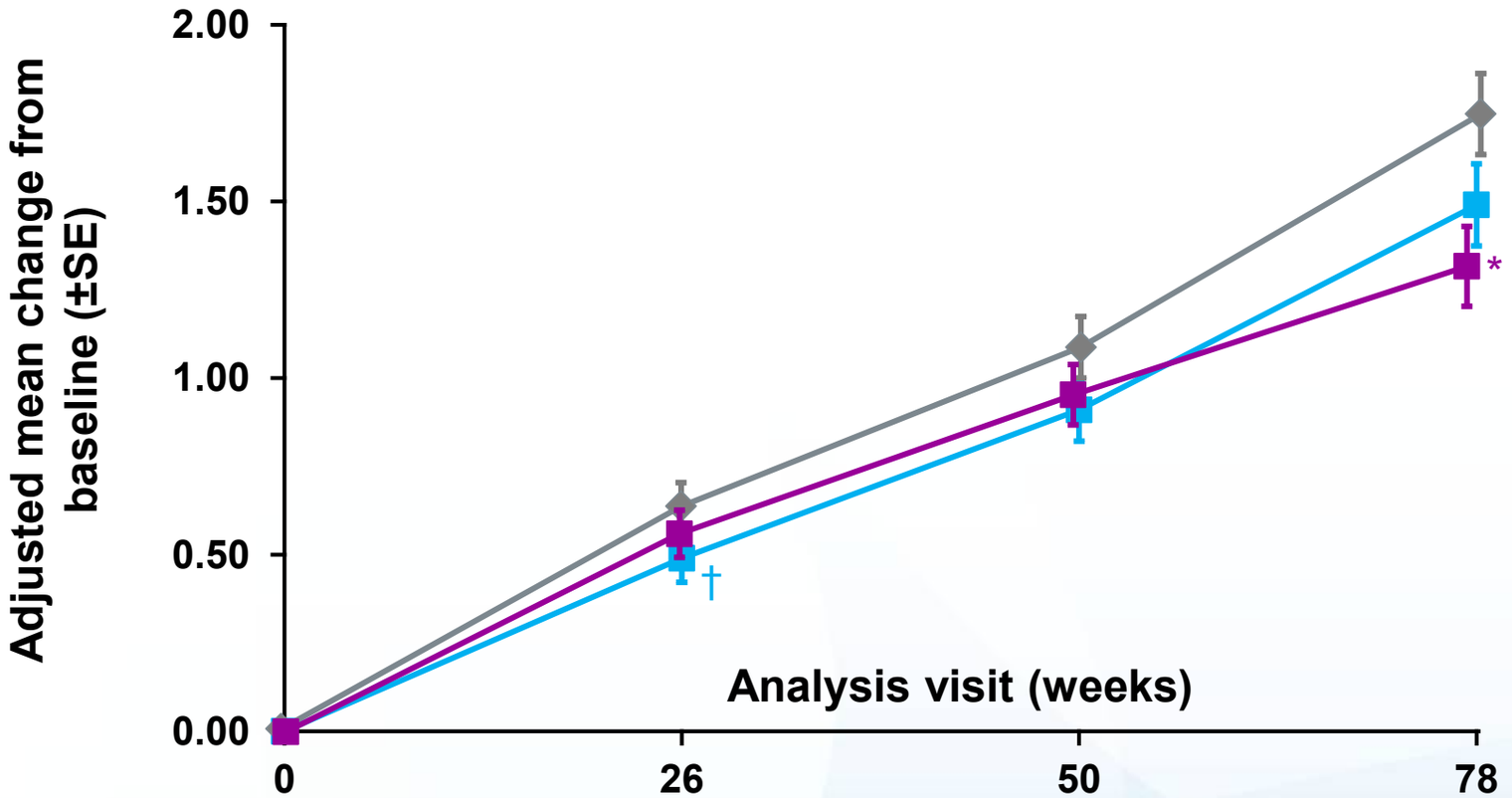
0.5

0.5

0.0

2.5

EMERGE: Longitudinal change from baseline in CDR-SB

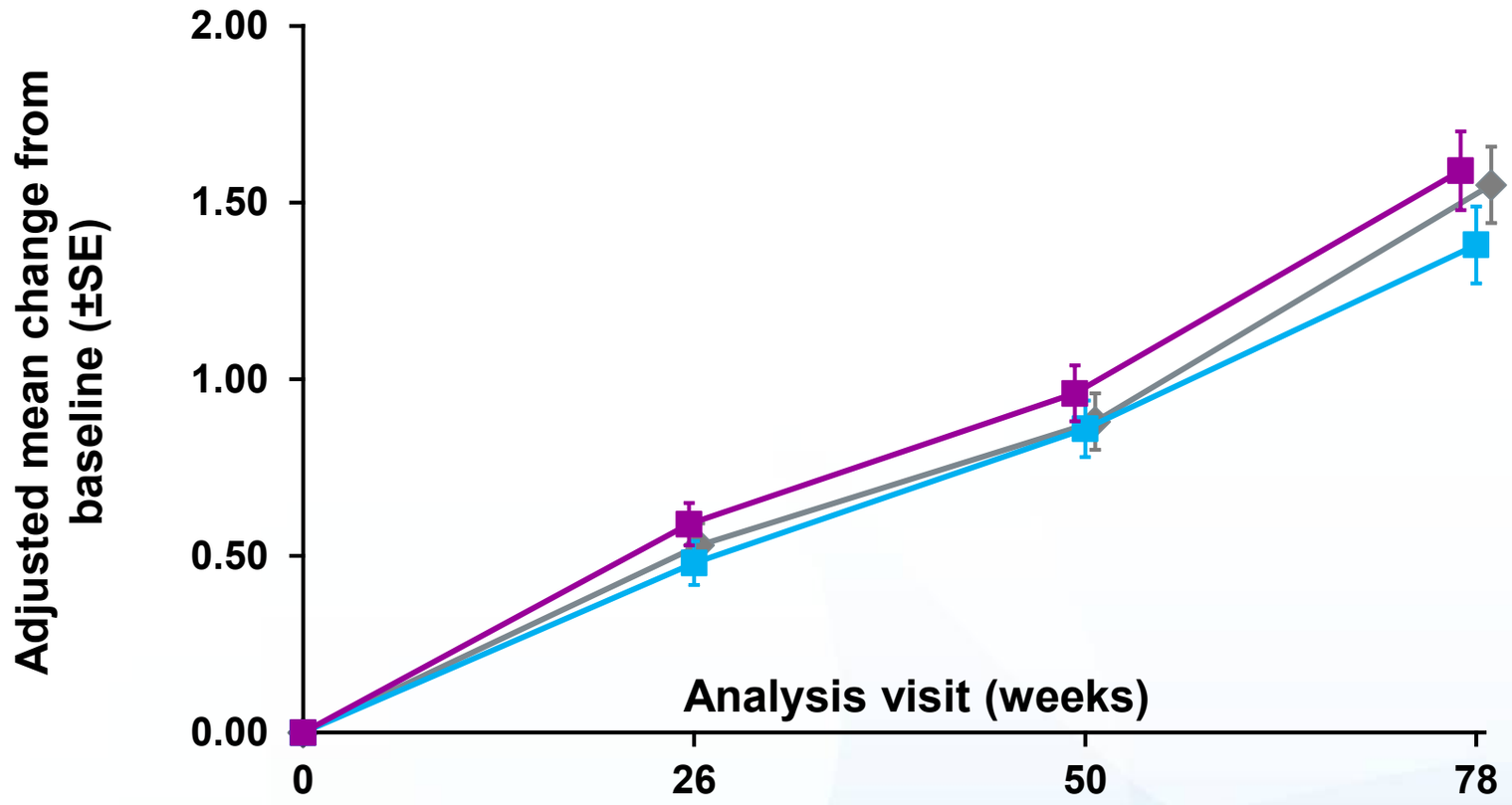


ITT population. *p <0.05, †p<0.1 and ≥0.05 compared with placebo (nominal). Values at each time point were based on an MMRM model, with change from baseline in CDR-SB as the dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline CDR-SB, baseline CDR-SB by visit interaction, baseline MMSE, Alzheimer's disease symptomatic medication use at baseline, region, and laboratory ApoE ε4 status. ApoE, apolipoprotein E; CDR-SB, Clinical Dementia Rating–Sum of Boxes; ITT, intent to treat; MMRM, mixed model for repeated measure; MMSE, Mini Mental State Examination; SE, standard error.

reduction in CDR decline of 0.5 at 78 months

Haeberlein et al. *CTAD* 2019

ENGAGE: Longitudinal change from baseline in CDR-SB



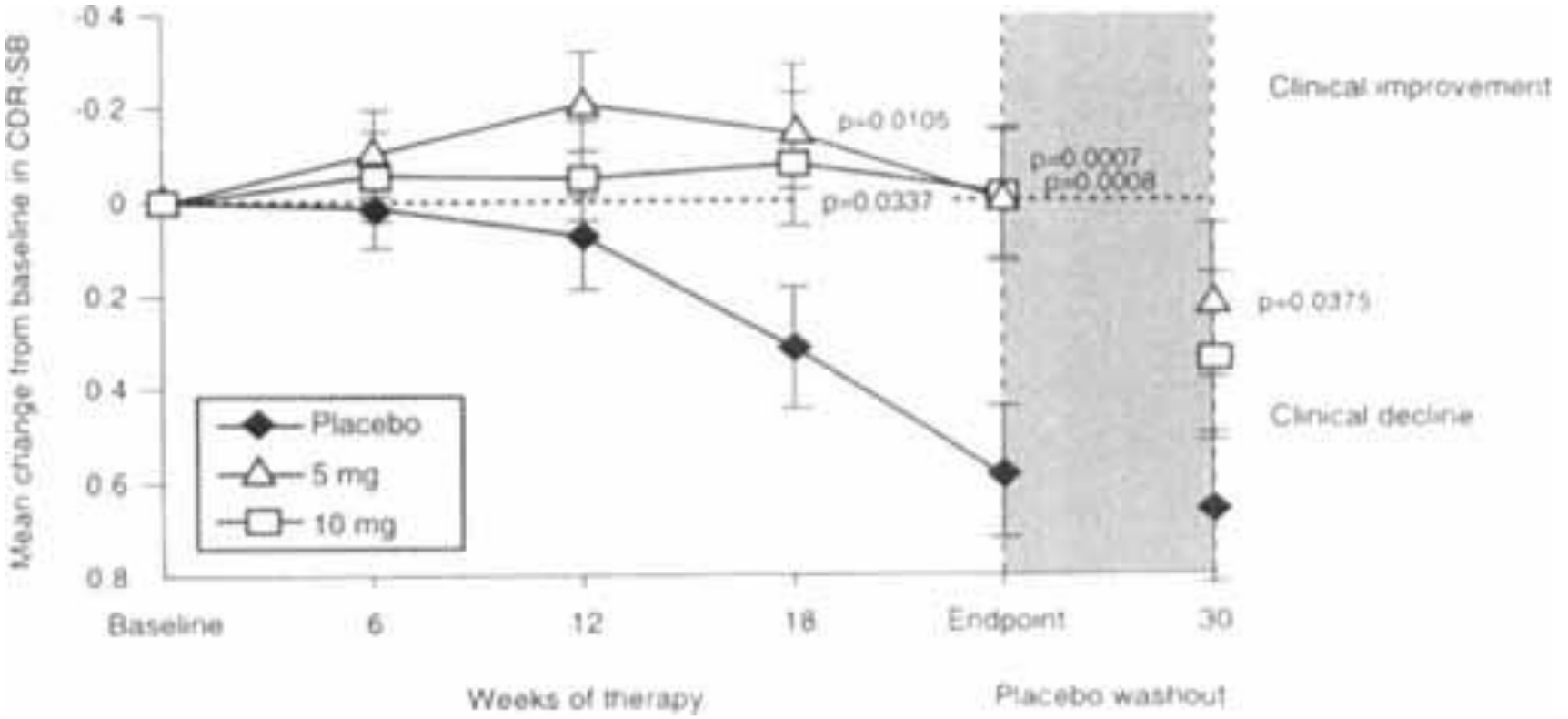
Placebo	n=545	522	455	333
Low dose aducanumab	n=547	529	454	331
High dose aducanumab	n=554	532	448	293

ITT population. Values at each time point were based on an MMRM model, with change from baseline in CDR-SB as the dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline CDR-SB, baseline CDR-SB by visit interaction, baseline MMSE, Alzheimer's disease symptomatic medication use at baseline, region, and laboratory ApoE ε4 status.
ApoE, apolipoprotein E; CDR-SB, Clinical Dementia Rating–Sum of Boxes; ITT, intent to treat; MMRM, mixed model for repeated measure; MMSE, Mini Mental State Examination; SE, standard error.

No reduction in CDR decline at 78 months

Haeberlein et al. *CTAD* 2019

How does this compare to Aricept?



reduction in CDR decline of 0.5 in 6 months

Rogers et al., Neurology, 1998

EMERGE and ENGAGE: Adverse events with incidence >10%

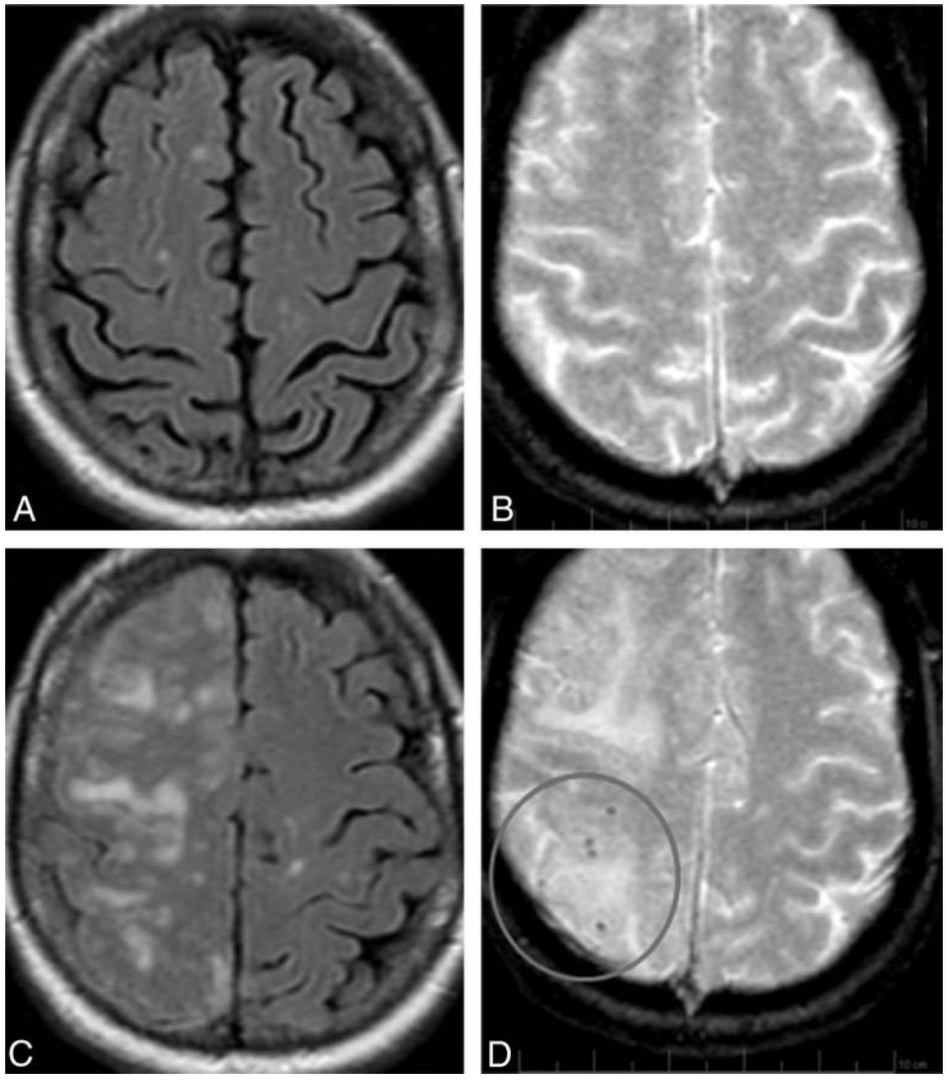
	EMERGE			ENGAGE		
	Placebo (n=547)	Low dose (n=544)	High dose (n=547)	Placebo (n=541)	Low dose (n=548)	High dose (n=558)
Patients with any event, n (%)	**476** (87.0)	**477** (87.7)	**505** (92.3)	**465** (86.0)	**491** (89.6)	**500** (89.6)
ARIA-E (%)	**12** (2.2)	**140** (25.7)	**186** (34.0)	**16** (3.0)	**139** (25.4)	**198** (35.5)
Headache (%)	**83** (15.2)	**106** (19.5)	**106** (19.4)	**81** (15.0)	**98** (17.9)	**114** (20.4)
ARIA-H, microhemorrhage (%)	**38** (6.9)	**88** (16.2)	**102** (18.6)	**31** (5.7)	**85** (15.5)	**98** (17.6)
Nasopharyngitis (%)	**90** (16.5)	**70** (12.9)	**87** (15.9)	**67** (12.4)	**64** (11.7)	**66** (11.8)
ARIA-H, superficial siderosis (%)	**14** (2.6)	**50** (9.2)	**73** (13.3)	**10** (1.8)	**48** (8.8)	**86** (15.4)
Fall (%)	**68** (12.4)	**64** (11.8)	**69** (12.6)	**55** (10.2)	**77** (14.1)	**83** (14.9)

This table includes patients who received at least one dose of investigational treatment.

Safety population. Patients randomized to placebo who accidentally received active dose are summarized under active groups (4 in ENGAGE and 1 in EMERGE).
All safety data presented are from the placebo-controlled period.
ARIA-E, amyloid related imaging abnormality-edema/effusion; ARIA-H, amyloid related imaging abnormality-micro-hemorrhages and hemosiderin deposits.

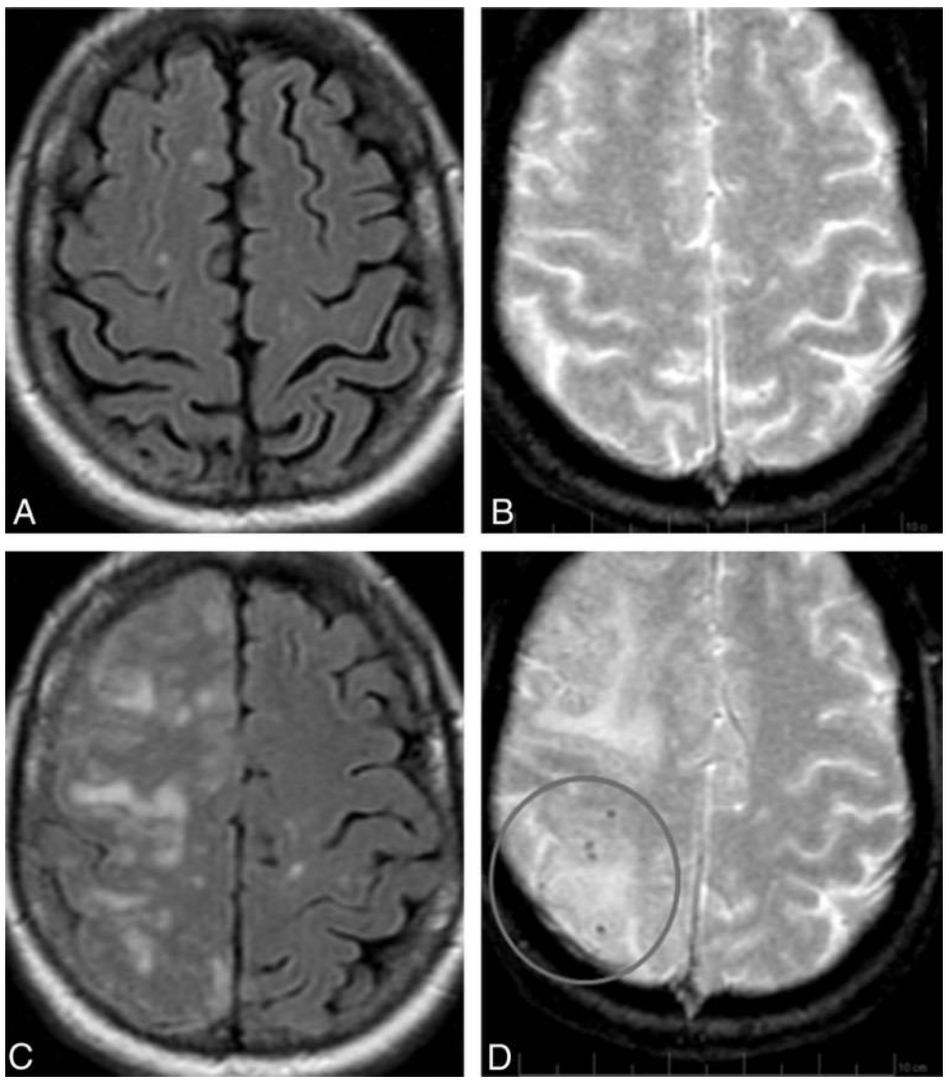
Haeberlein et al. *CTAD* 2019

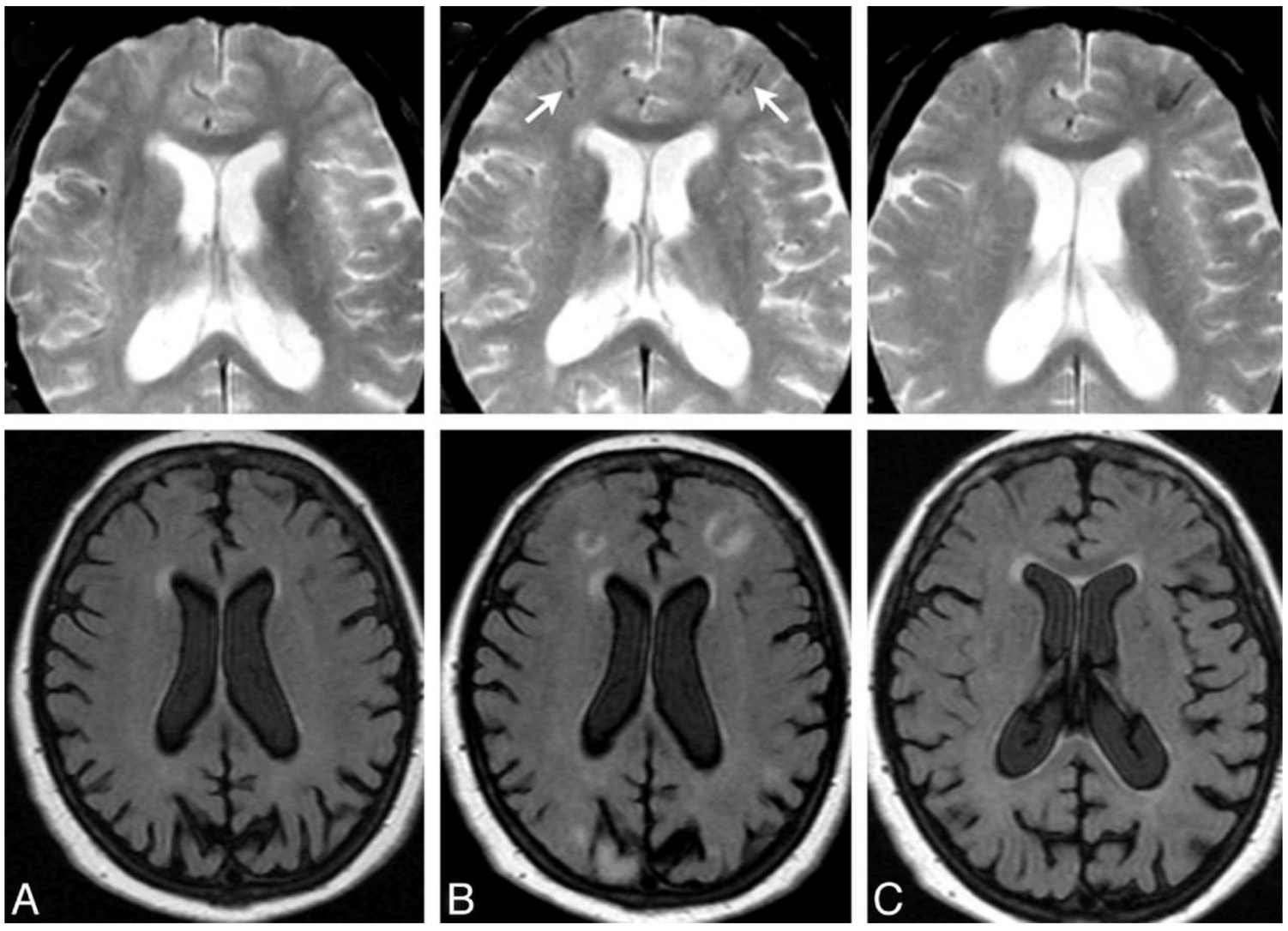
ARIA-E (edema) with incident ARIA-H (microhemorrhages) and (superficial siderosis)



J. Barakos et al. AJNR Am J Neuroradiol 2013;34:1958-1965

ARIA-E (edema) with incident ARIA-H (microhemorrhages) and (superficial siderosis)





J. Barakos et al. AJNR Am J Neuroradiol 2013;34:1958-1965

Aducanumab - Indications and Usage

"ADUHELM is an amyloid beta-directed antibody indicated for the treatment of Alzheimer's disease. This indication is approved under accelerated approval based on reduction in amyloid beta plaques observed in patients treated with ADUHELM. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s)."

Aducanumab - Dosage Schedule

2.1 Dosing Instructions

After an initial titration, the recommended dosage of ADUHELM is 10 mg/kg (see Table 1). ADUHELM is administered as an intravenous (IV) infusion over approximately one hour every four weeks and at least 21 days apart.

Table 1: Dosing Schedule

IV Infusion (every 4 weeks)	ADUHELM Dosage (administered over approximately one hour)
Infusion 1 and 2	1 mg/kg
Infusion 3 and 4	3 mg/kg
Infusion 5 and 6	6 mg/kg
Infusion 7 and beyond	10 mg/kg

2.2 Monitoring for Amyloid Related Imaging Abnormalities

Obtain recent (within one year) brain magnetic resonance imaging (MRI) prior to initiating treatment. Obtain MRIs prior to the 7th infusion (first dose of 10 mg/kg) and 12th infusion (sixth dose of 10 mg/kg). If 10 or more new incident microhemorrhages or > 2 focal areas of superficial siderosis (radiographic severe ARIA-H) is observed, treatment may be continued with caution only after a clinical evaluation and a follow-up MRI demonstrates radiographic stabilization (i.e., no increase in size or number of ARIA-H) *[see Warnings and Precautions (5.1)]*.

Aducanumab - Management of ARIA

5 WARNINGS AND PRECAUTIONS

5.1 Amyloid Related Imaging Abnormalities

ADUHELM can cause amyloid related imaging abnormalities-edema (ARIA-E), which can be observed on MRI as brain edema or sulcal effusions, and amyloid related imaging abnormalities-hemosiderin deposition (ARIA-H), which includes microhemorrhage and superficial siderosis.

Obtain recent (within one year) brain magnetic resonance imaging (MRI) prior to initiating treatment *[see Dosage and Administration (2.2)]*. The safety of ADUHELM in patients with any pre-treatment localized superficial siderosis, 10 or more brain microhemorrhages, and/or with a brain hemorrhage greater than 1 cm within one year of treatment initiation has not been established.

In clinical studies of ADUHELM, the severity of ARIA was classified by radiographic criteria, as shown in Table 2.

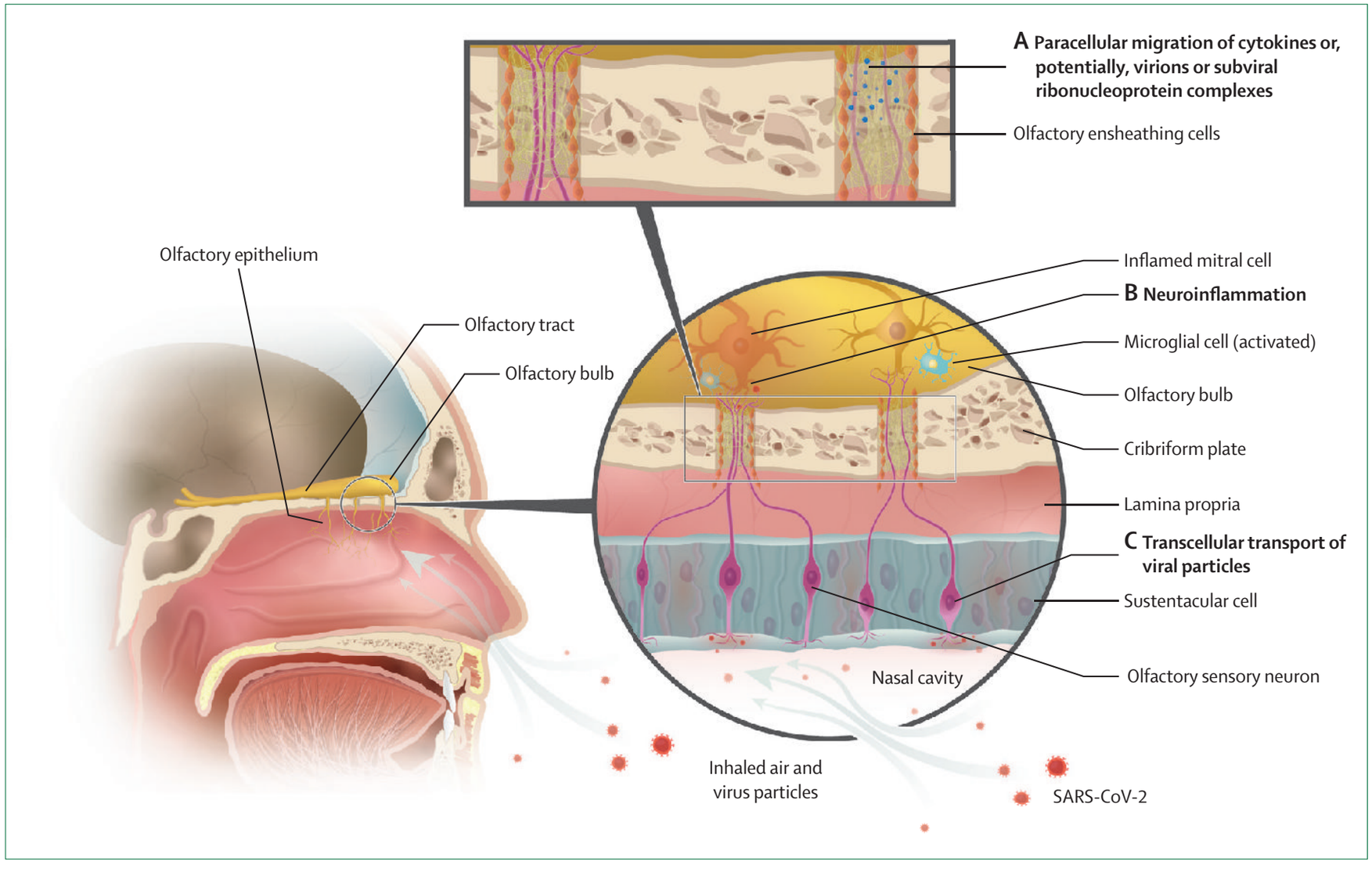
Table 2: ARIA MRI Classification Criteria

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

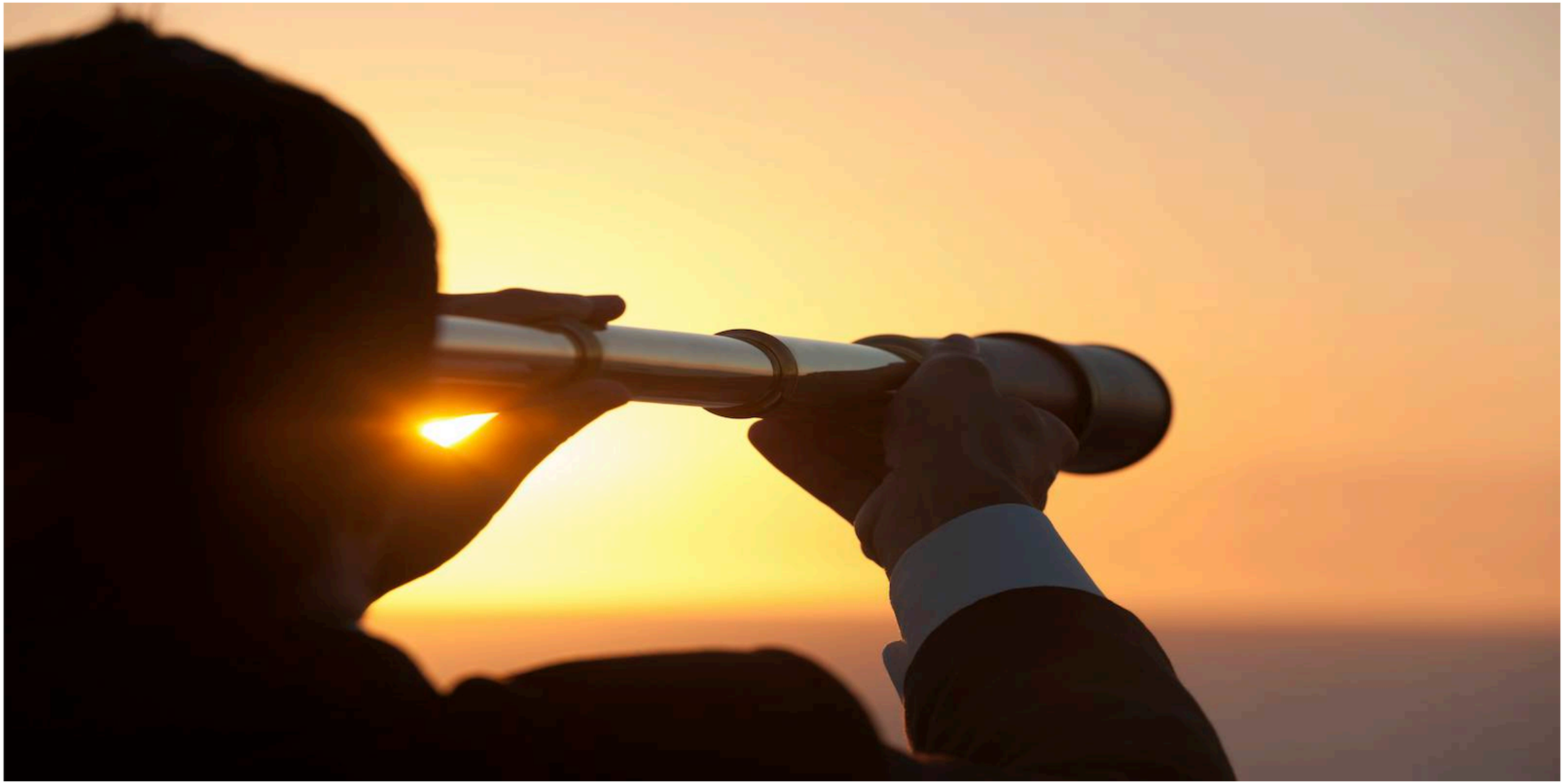
Top Ten Clinical Issues Related to Aduhelm

1. Confirm the patient has amyloid
    1. lumbar puncture, e.g., ADmark 177 (Athena Labs)
    2. Amyloid PET not covered by Medicare
2. Recommend ApoE genotyping for risk of ARIA
3. Brain MRI before first infusion
4. Brain MRIs before 7th infusion and before 12th infusion
5. Do not expect a clinical response for over a year
6. Adverse effects in ~ 90% of patients
7. Vigilance for symptoms while on Aduhelm - may need another MRI to rule out ARIA
8. Clinical judgements on stopping and restarting Aduhelm in the setting of ARIA
9. Continue other Alzheimer's medication
10. Cost and insurance coverage - ENVISION trial

COVID and Dementia - Neuroinflammatory Accelerator?



Xydakis MS, Albers MW, et al. Post-viral effects of COVID-19 in the olfactory system and their implications. *The Lancet Neurology*. **2021**



Thank you and happy to take questions!