

# **Alzheimer's, and the problem with the Amyloid-Beta hypothesis**

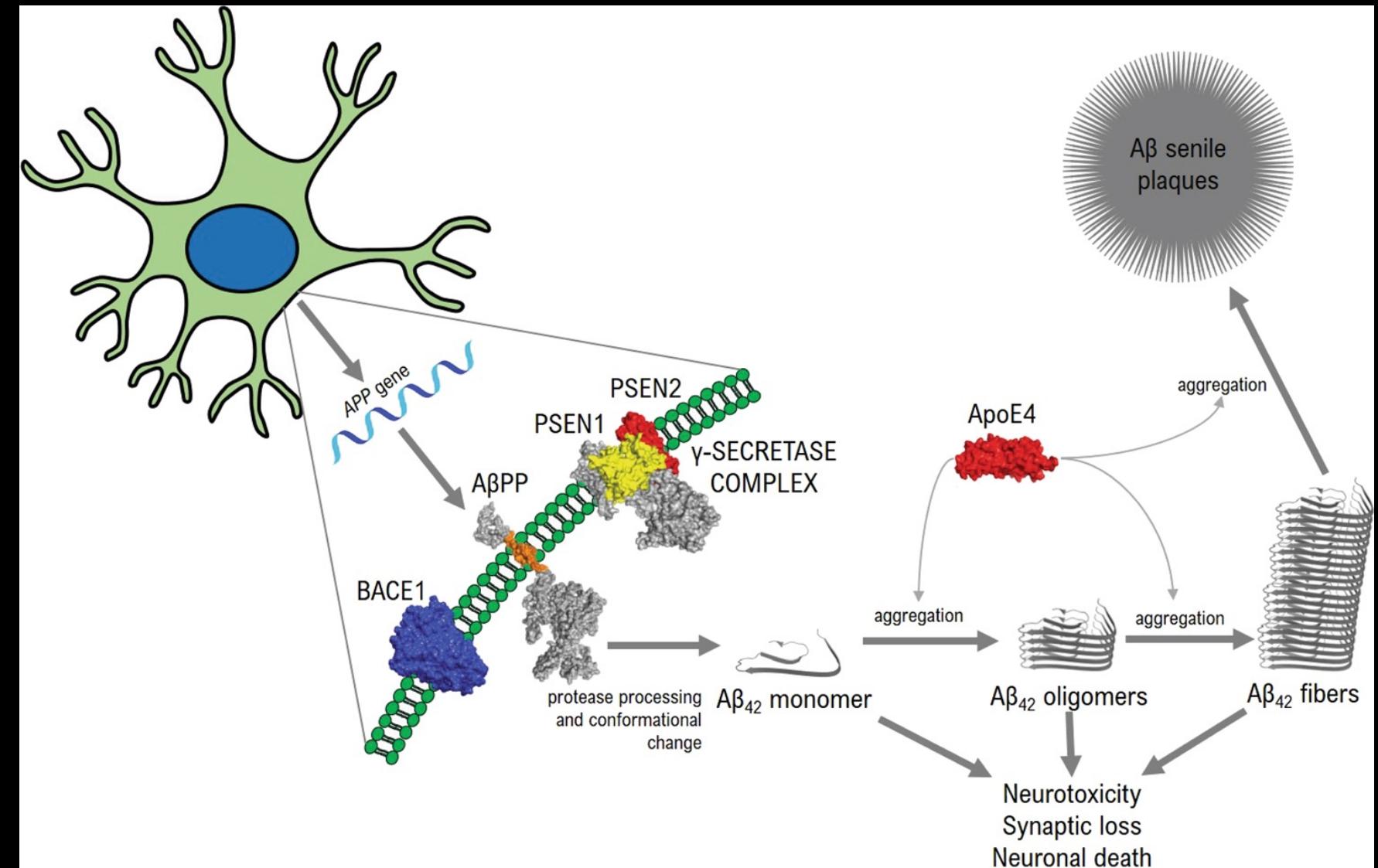
**Alfredo Lucas, PhD**

# The Amyloid-beta hypothesis

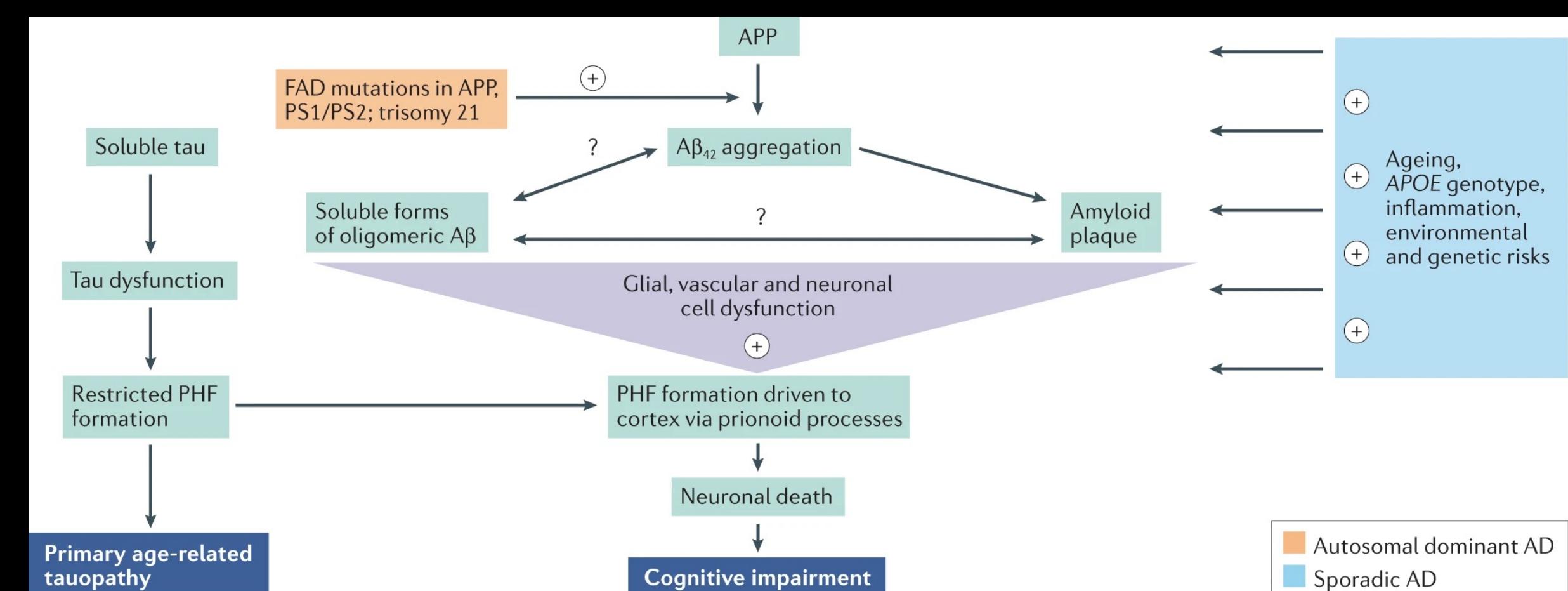
Theory that suggests the accumulation of amyloid-beta (A $\beta$ ) peptides in the brain is a central cause of Alzheimer's disease (AD). The hypothesis was first proposed in 1991 and has been a dominant research topic for over 25 years. It's supported by neuropathological and genetic evidence.

The hypothesis suggests that when A $\beta$  clumps together to form deposits in the brain, it can trigger neurodegenerative processes that lead to memory loss and cognitive decline. These processes can include:

- Disrupting cell-to-cell communication
- Activating immune cells that trigger inflammation
- Destroying brain cells
- Binding to specific receptor sites on neurons, which may have direct toxic effects



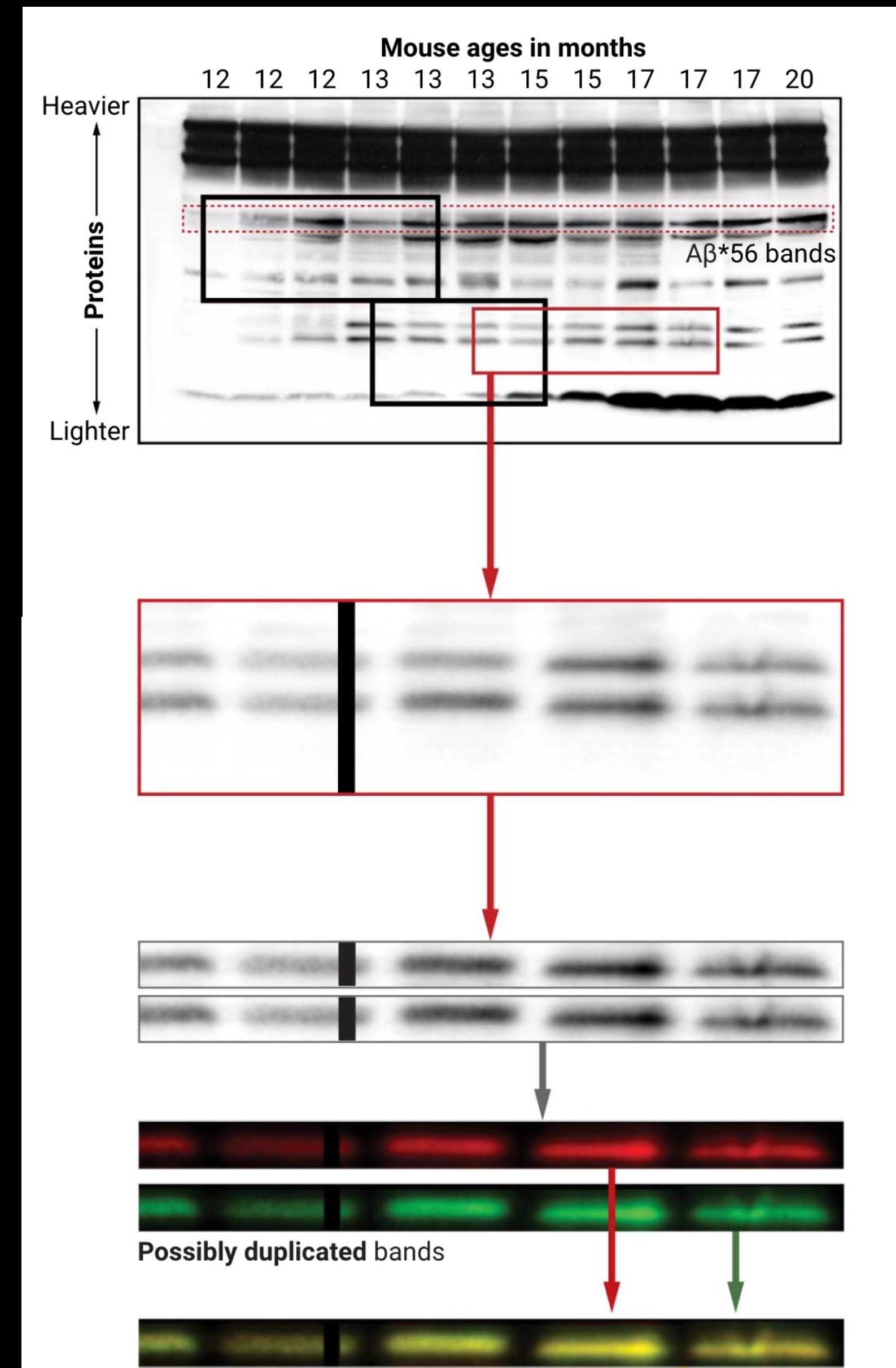
Castellani et. al. 2019



Karran et. al. 2022

# “A $\beta$ ” Star is Born

- It had been thought that the failure of many trials to date that target A $\beta$  amyloid, but that do not lead to a clinically meaningful change in cognitive score, was because the wrong type of A $\beta$  amyloid was being targeted
- In 2006 a paper was published that showed the discovery of a new A $\beta$  protein (A $\beta$ 56) which seemed to have a direct causal effect in the development of Alzheimer's
  - The protein purified from transgenic mice was injected in younger mice, it led to the younger mice to develop Alzheimer's-like symptoms
  - Certain findings in this paper were found to be falsified, which later put into significant question the entirety of the paper
    - Scientists have not been able to reproduce any of the findings



Charles Piller, 2022

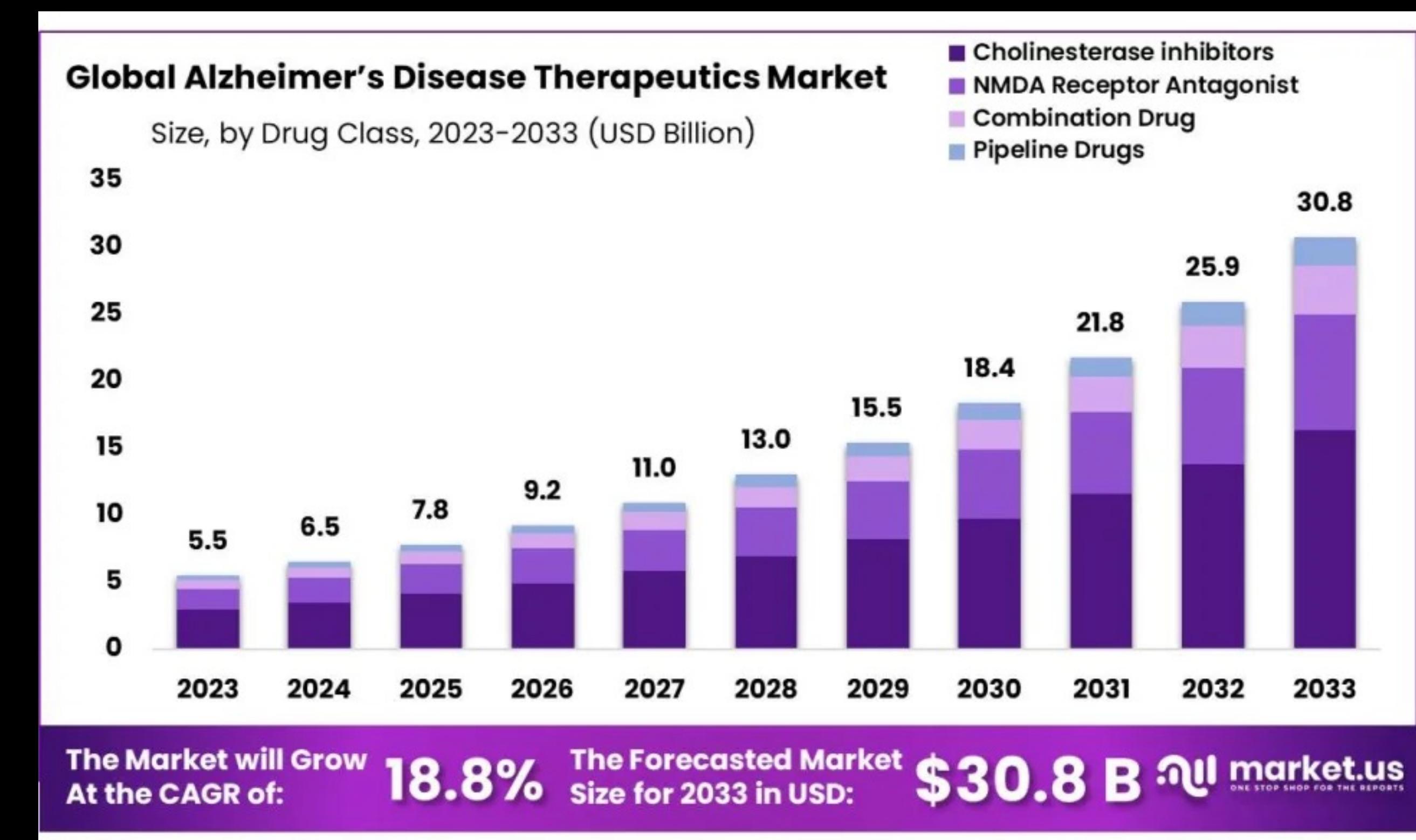
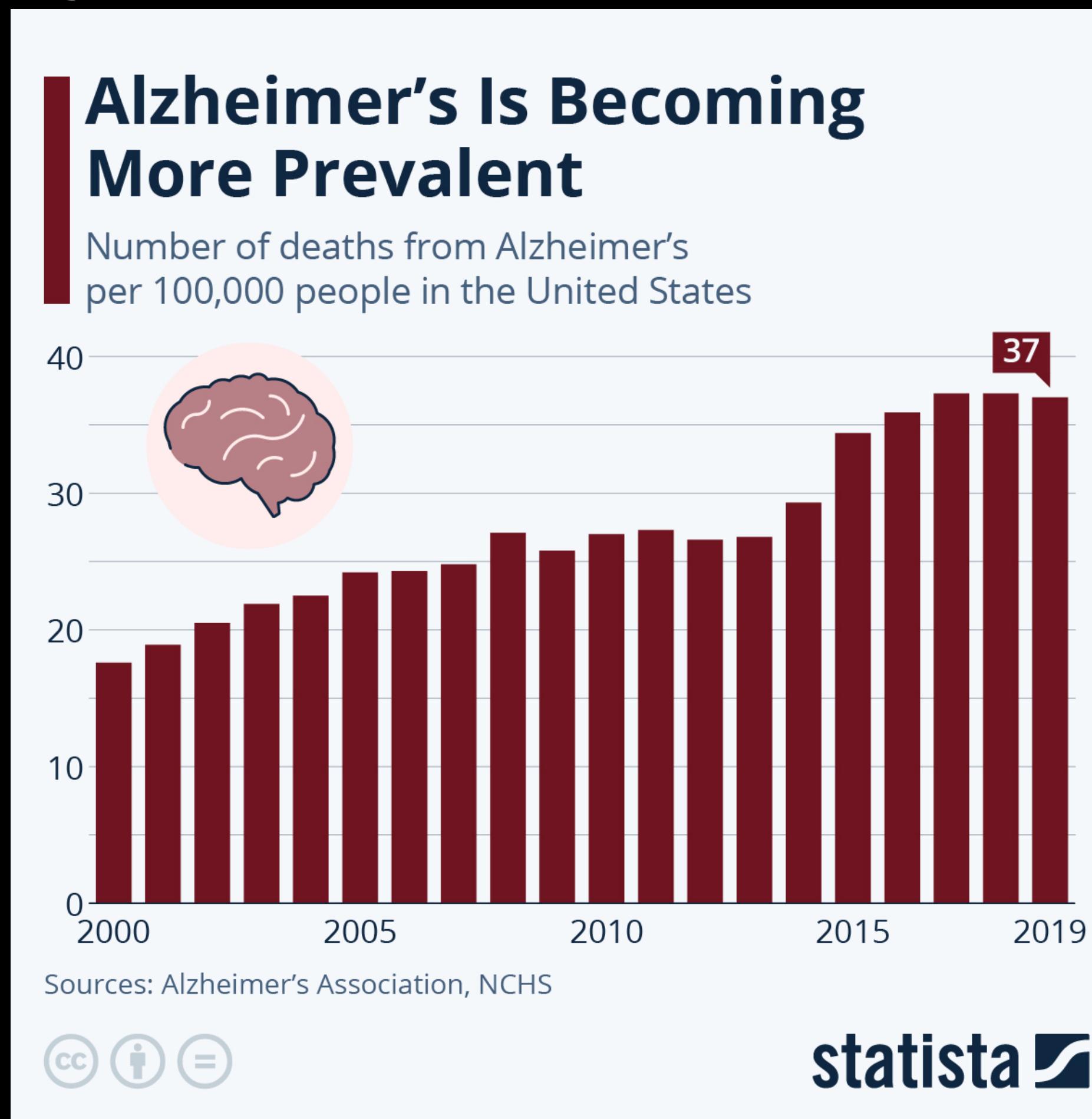
# Clinical trials targeting A $\beta$

Most of them have failed, and even those that haven't, have...

- List of trials that have targeted A $\beta$ : <https://www.nature.com/articles/s41573-022-00391-w/tables/1>
- For the aducanumab (Aduhelm) trial that led to the accelerated approval even after failure in early trials
  - When asked to consider whether the combined evidence in this application supported the effectiveness of aducanumab for AD, **the FDA's Peripheral and Central Nervous System Drugs Advisory Committee voted 0 for and 10 against, with 1 member uncertain**
  - The FDA still provided accelerated approval for the drug (-\_-) in 2021

# Why the hype?

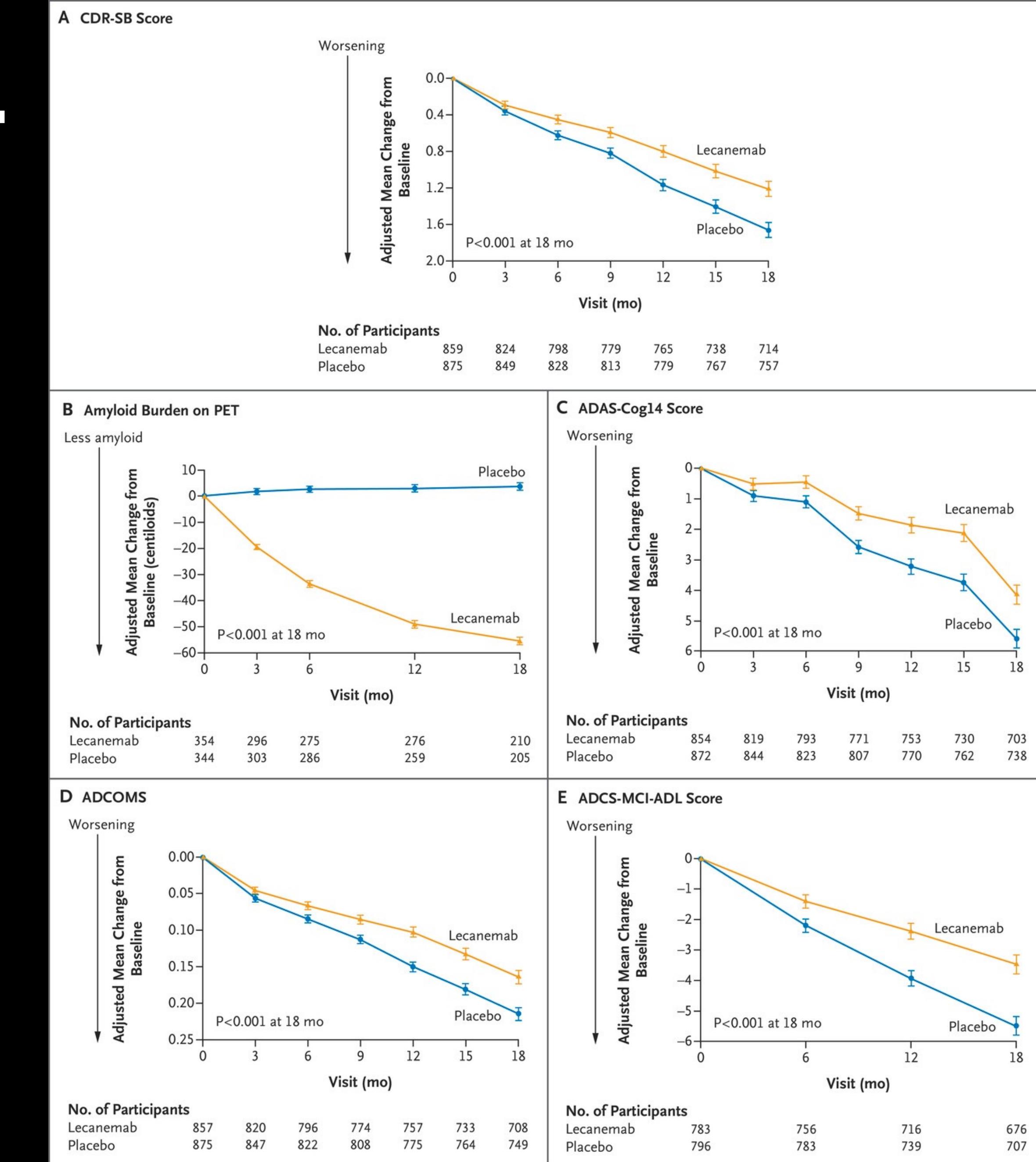
Incidence and prevalence of AD is increasing as people live longer, there is also a lot of \$\$\$ in play



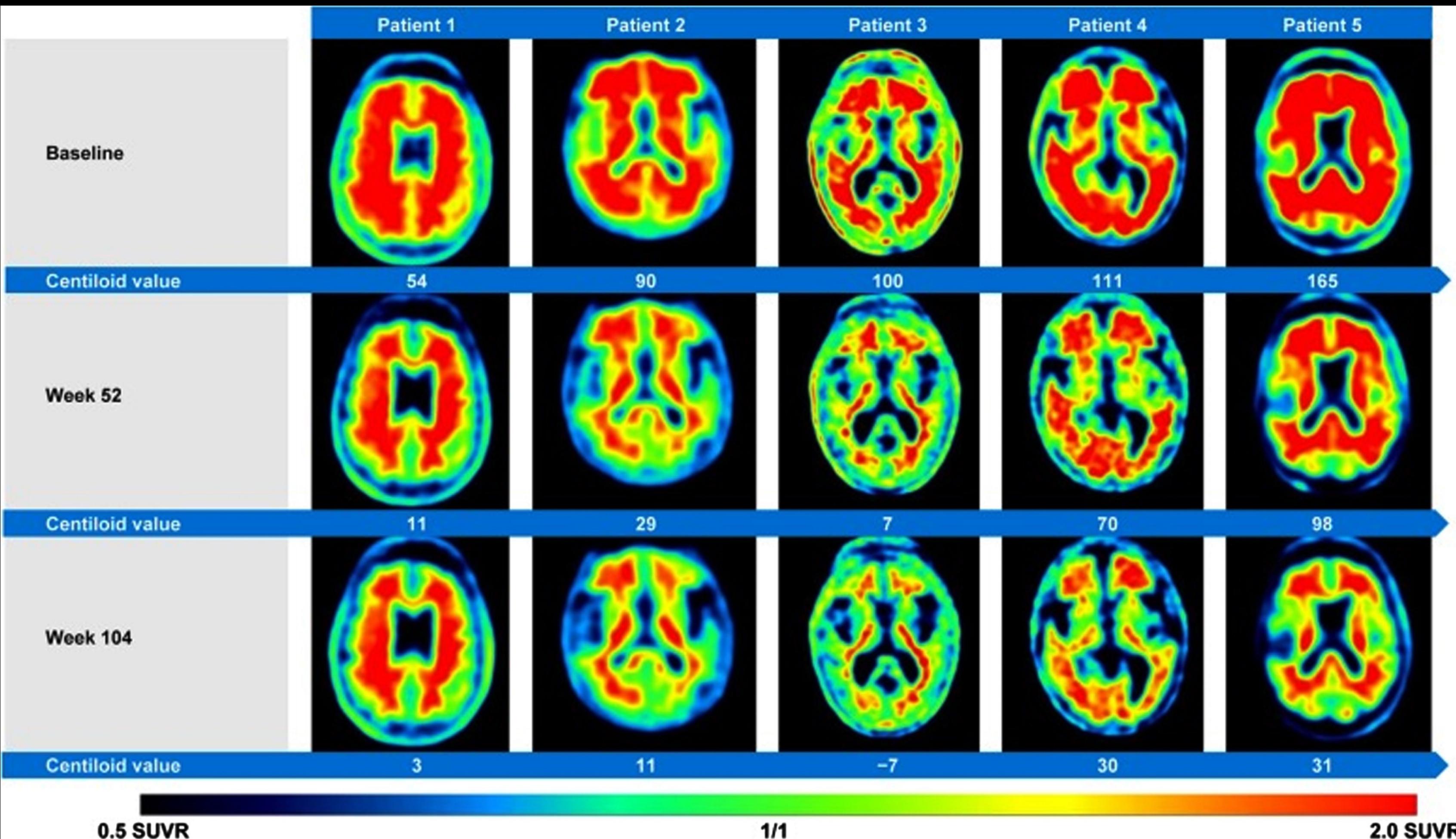
Market.us/Yahoo Finance, 2024

# And here comes lecanemab...

- **What people say:** Lecanemab decreased the progression of Alzheimer's at 18 months compared to placebo
- **What actually happened:** Lecanemab decreased the decline in cognitive impairment by 0.40 points in the CDR-SB  
(<https://www.mdcalc.com/calc/10160/clinical-dementia-rating-cdr-scale>), and significantly decreased amyloid burden



# Decrease in Amyloid PET Levels with Lecanemab



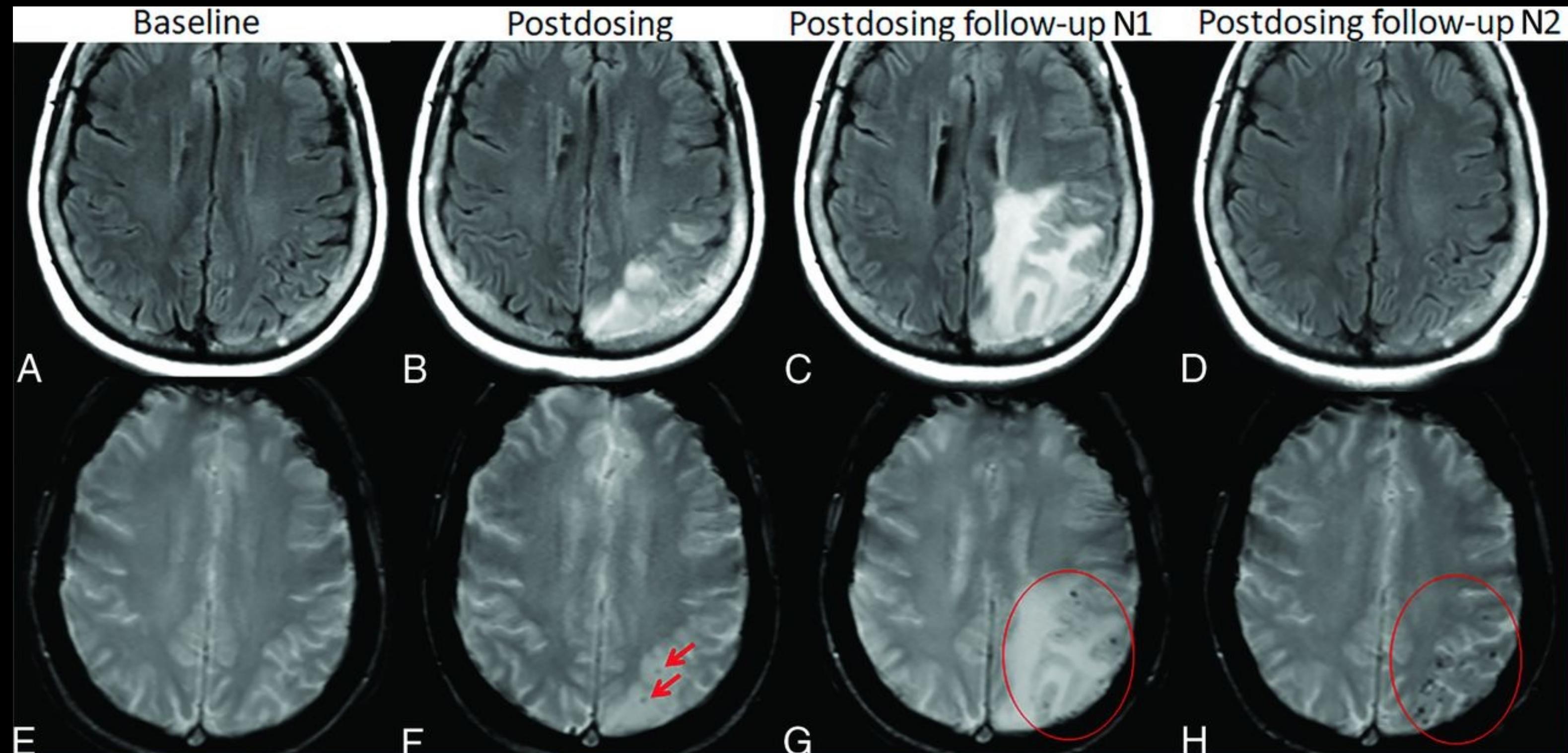
Klein et. al. 2019

# Lecanemab does not come without risks

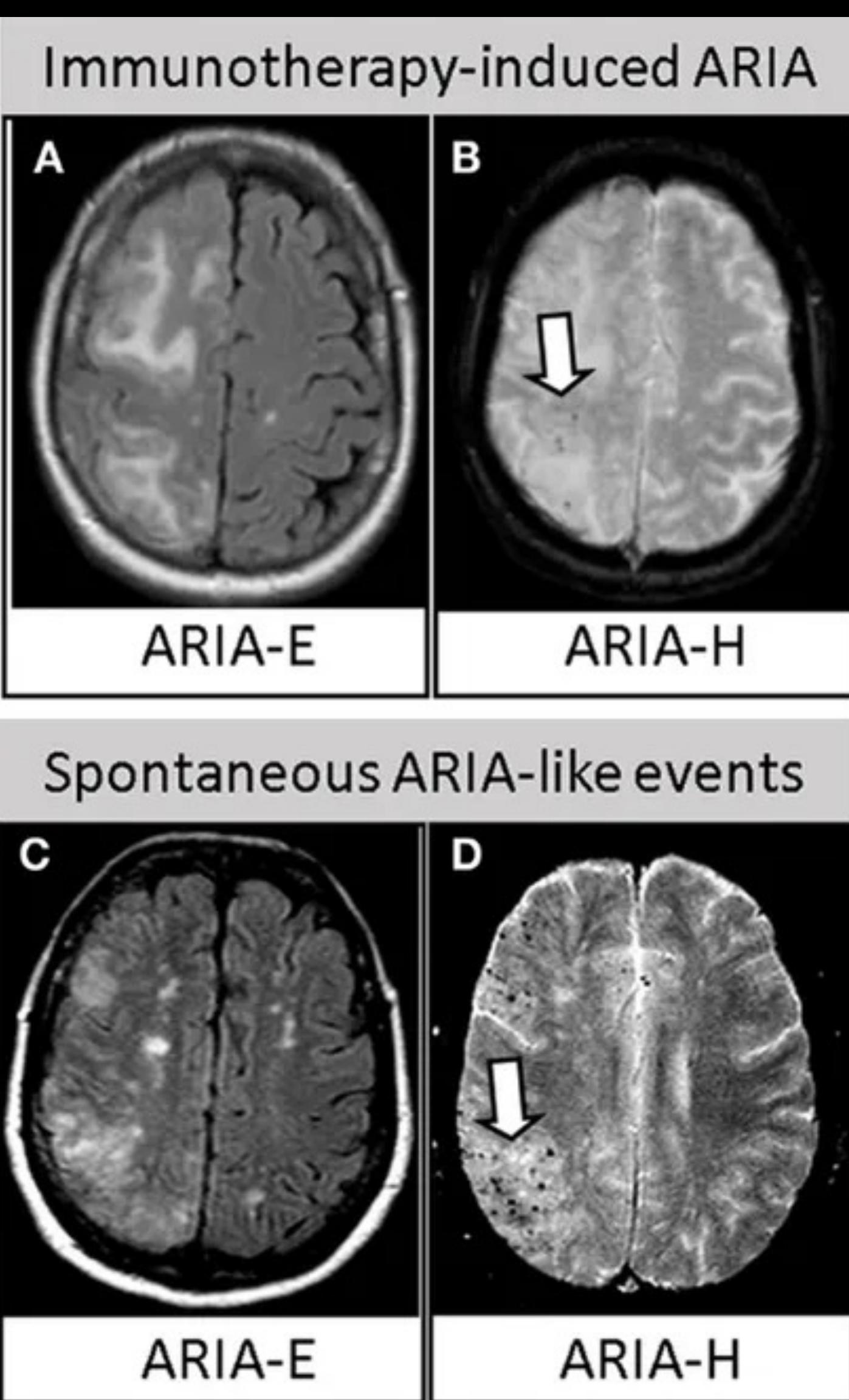
- ~26% of participants had an infusion related reaction (compared to ~7% in placebo)
- Amyloid-Related Imaging Abnormalities (ARIA) with cerebral microhemorrhages, cerebral macrohemorrhages, or superficial siderosis (ARIA-H; 17.3% with lecanemab and 9.0% with placebo)
- ARIA-E (12.6% with lecanemab and 1.7% with placebo)



# ARIA-E and ARIA-H



Cogswell et. al. 2022



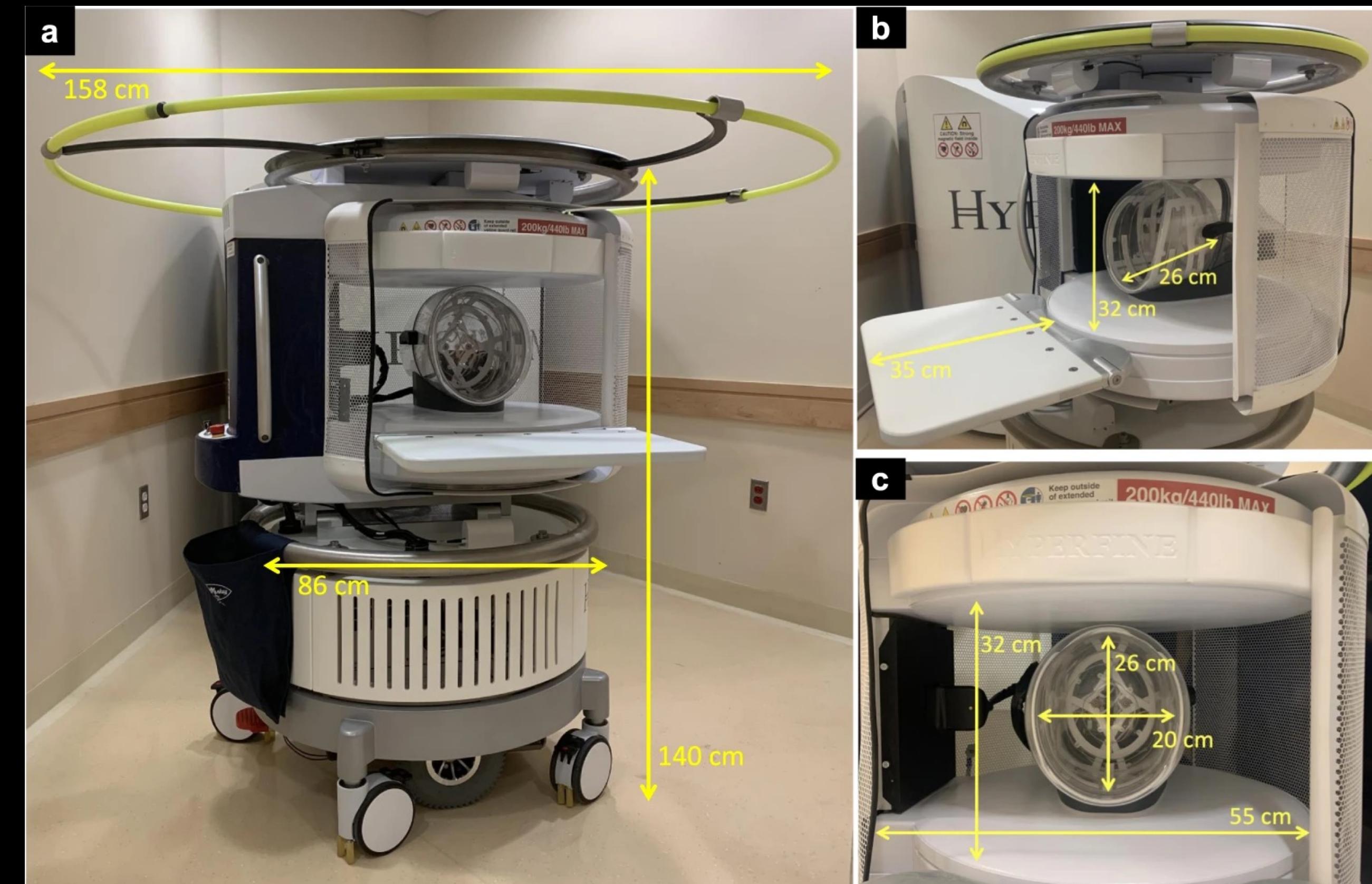
DiFrancesco et. al. 2015

# The value of POC MRI for ARIA monitoring

## Portable low-field MR Imaging

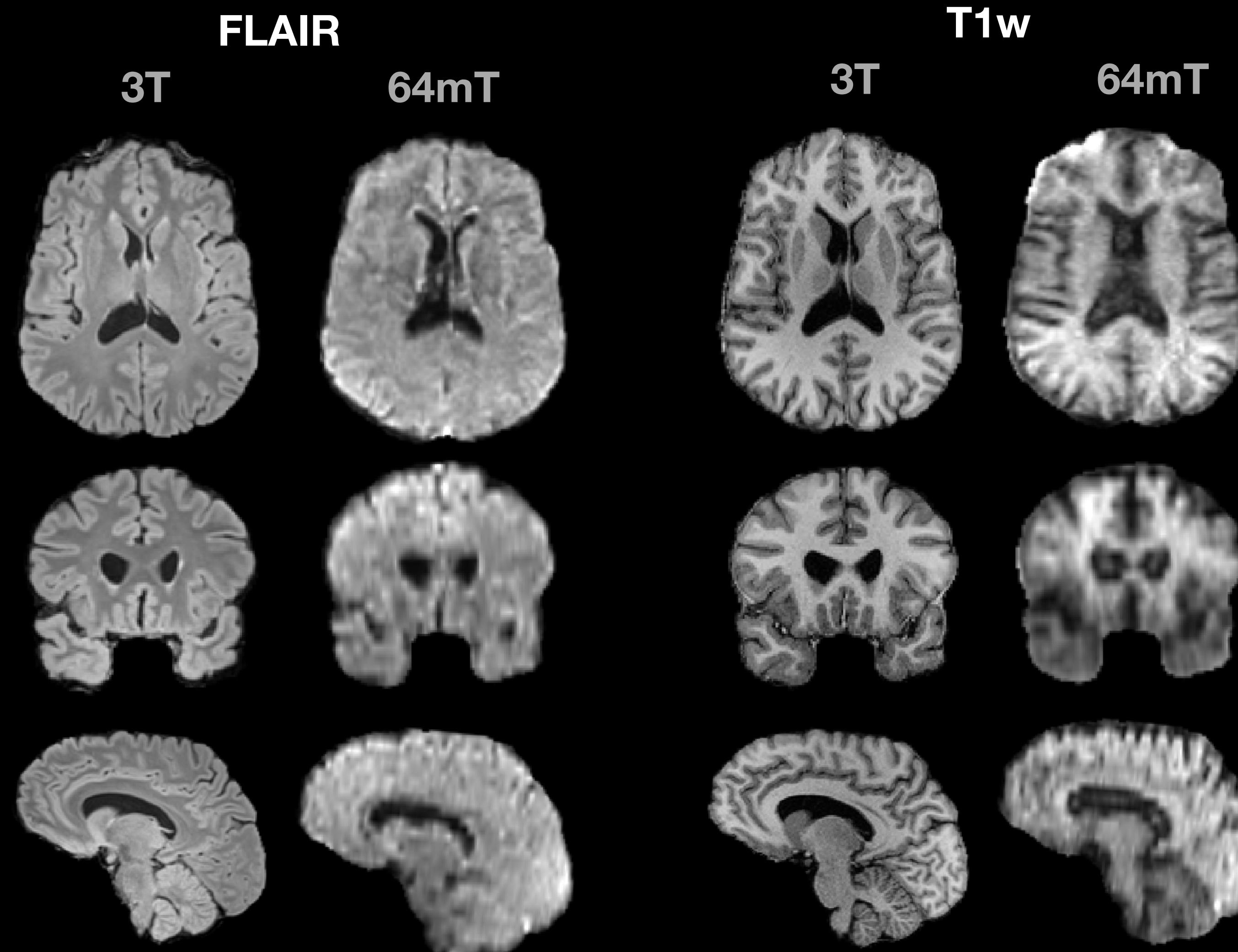
- Low-field MRI is portable and can be kept on the different floors of the hospital, but also in clinic
- Can be rolled into patient's beds, instead of having to move the patient
- Has poor sensitivity, but high specificity:
  - If you see something on it, you have something
  - If you do not see something, you still have to do advance imaging to rule out

Hyperfine SWOOP 64mT



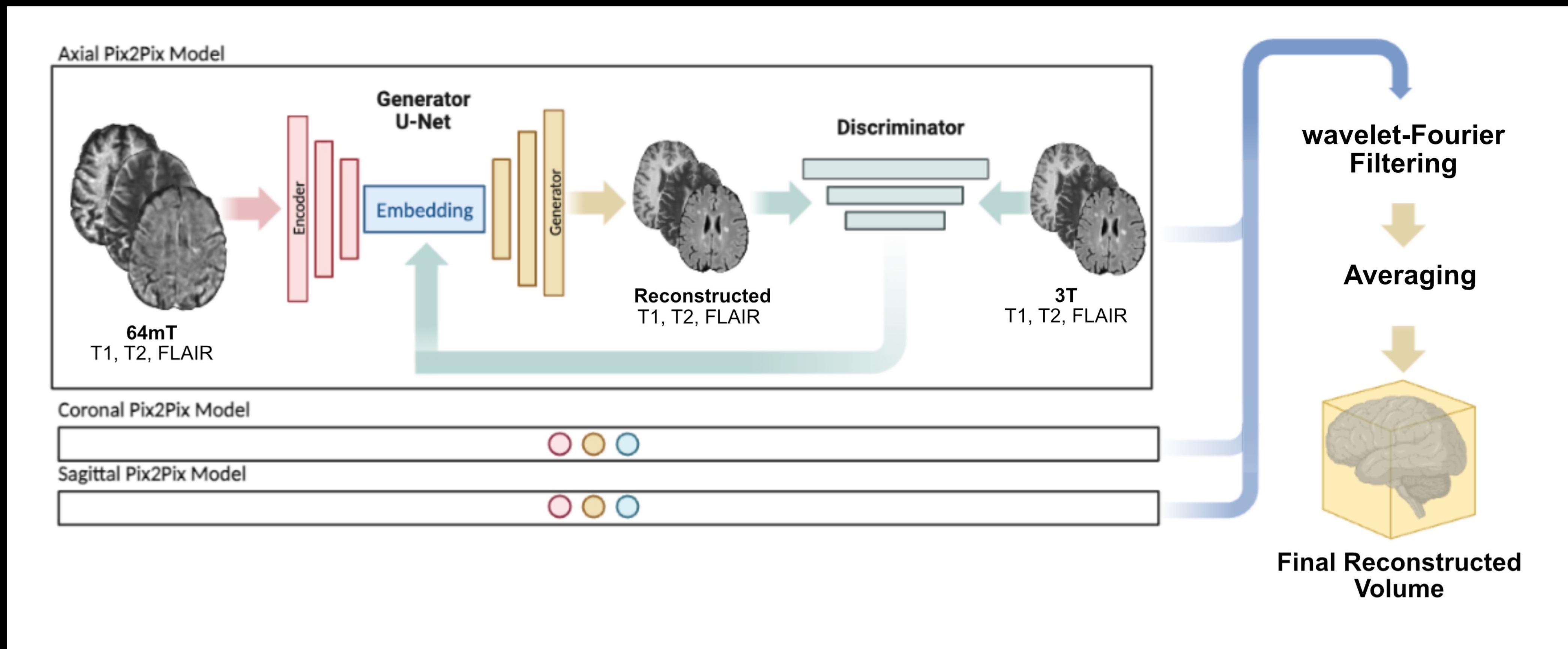
# Low-field imaging

**High accessibility at the cost of low image quality**

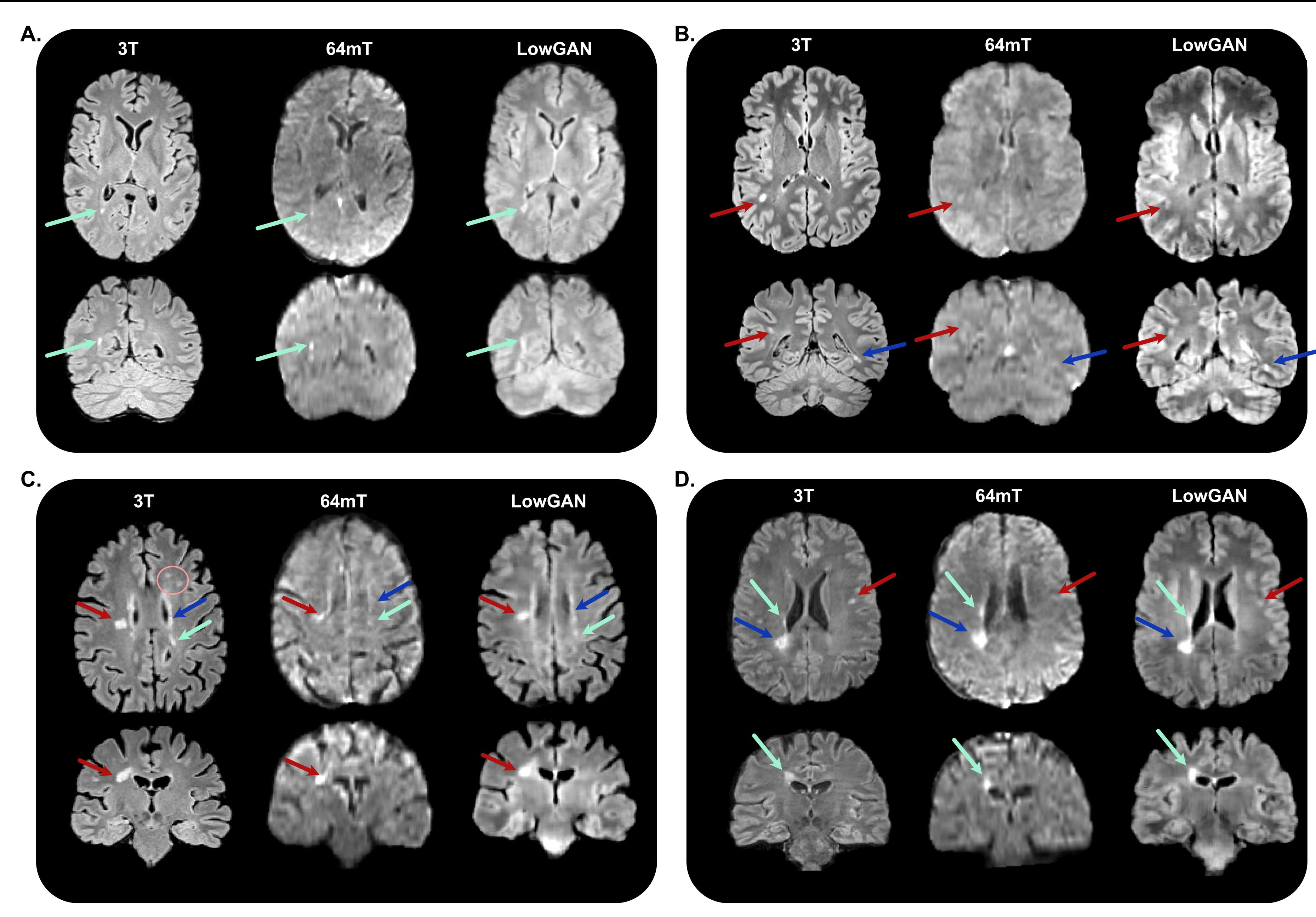


# AI can help improve the quality of Low-Field Imaging

## LowGAN - A generative adversarial network for super-resolution



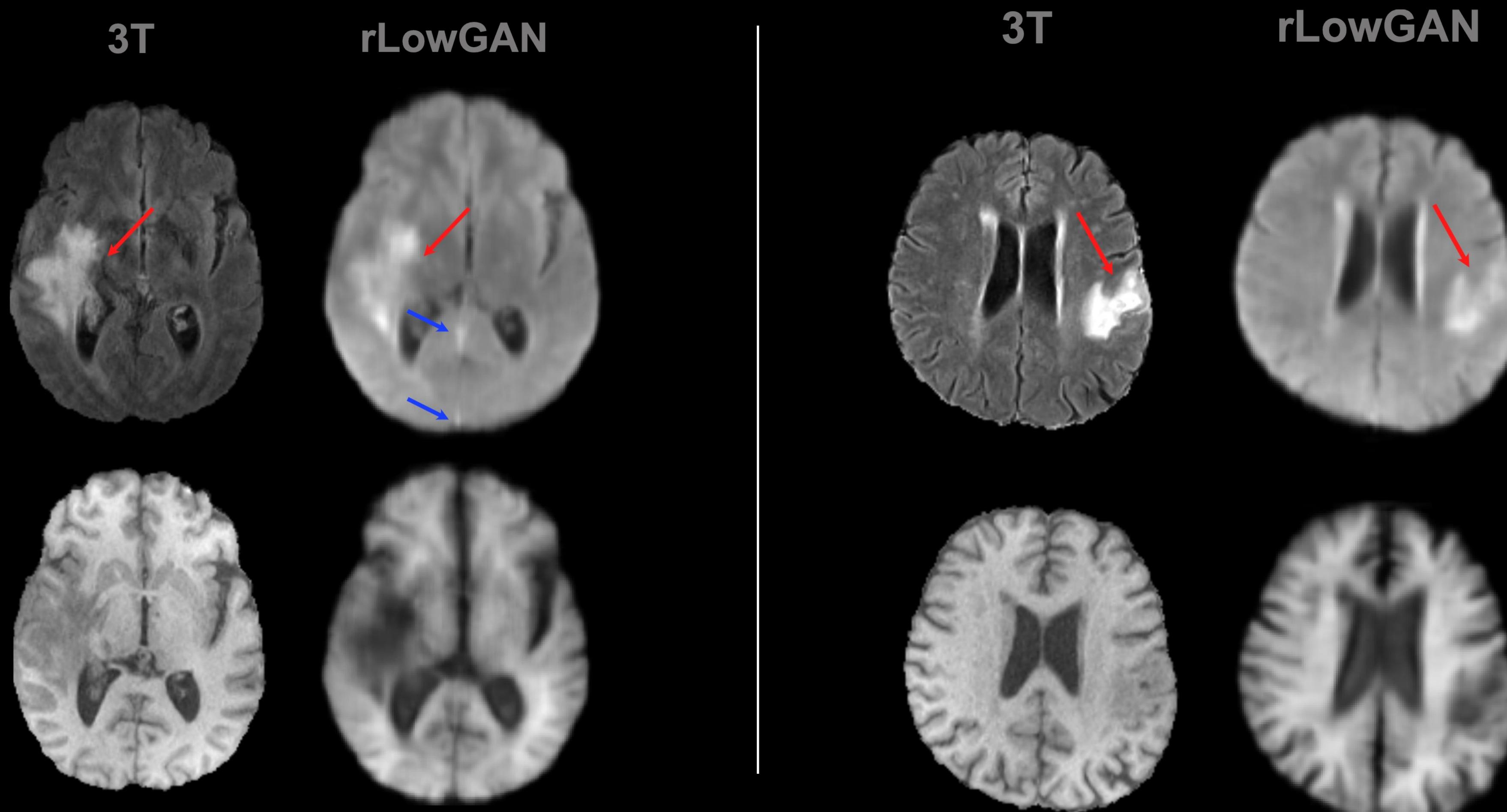
Lucas et. al. 2023



# Can we see ARIA with low-field imaging?

We do not know, we haven't scanned anyone with it yet...

- Simulating low-field imaging using AI



# Teaching points

- While amyloid is a feature of Alzheimer's disease, it is unclear if amyloid burden is directly related to cognitive outcomes
- Anti-amyloid therapy are excellent at removing amyloid burden, but they have little to no effect on functional and cognitive outcomes
- ARIA and infusion reactions are real risks of anti-amyloid therapy, and MRI is the only way of monitoring them
- Low-field MRI provides a low-cost accessible solution for monitoring ARIA