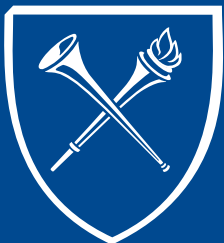


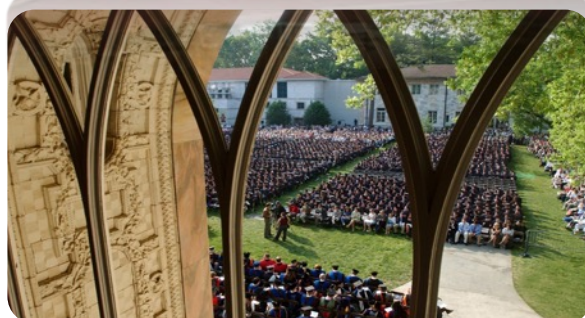
EMORY



# Update on Diagnosis and Management of Alzheimer's Disease

25 April 2022

James Lah, MD, PhD and Chad Hales, MD, PhD



EMORY  
UNIVERSITY

Goizueta Alzheimer's  
Disease Research Center

[www.alzheimers.emory.edu](http://www.alzheimers.emory.edu)

EMORY

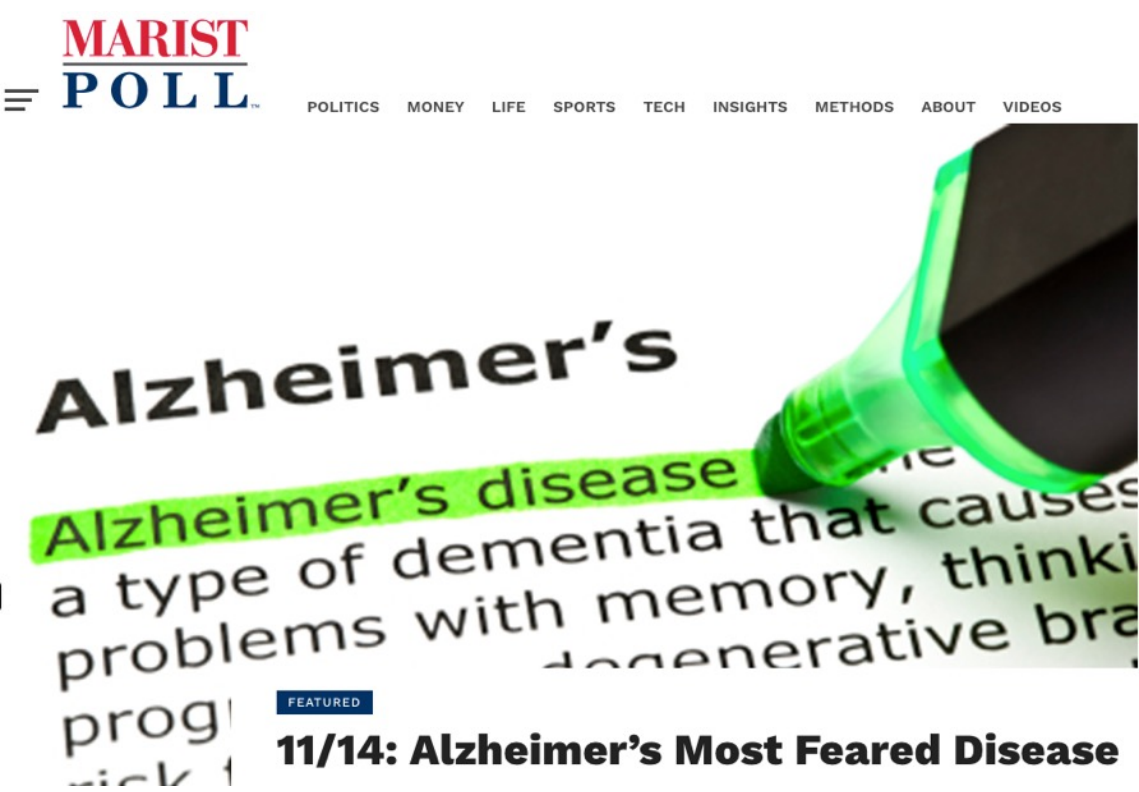
Healthy Brain Study

# Disclosure

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- Consultant for Roche Diagnostics
  - Advising on development of Roche blood-based biomarker platform
- Investigator/sub-investigator for clinical trials (Biogen, Alector, Janssen)

# Is there anything I can do to reduce my risk of Alzheimer's?



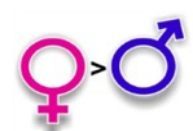
1. Aging!



2. Genes



3. Gender



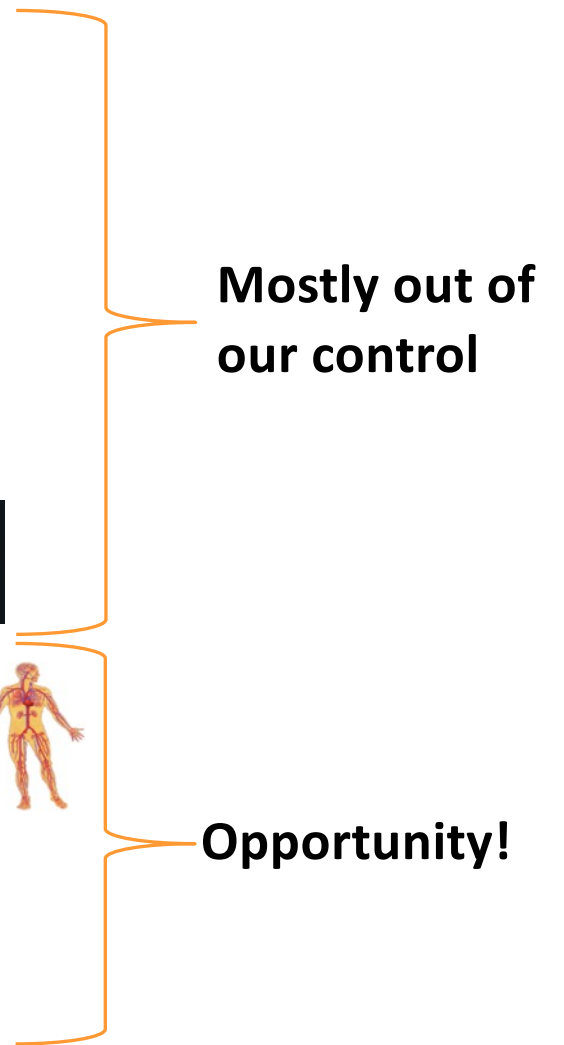
4. Head injury



5. Vascular disease

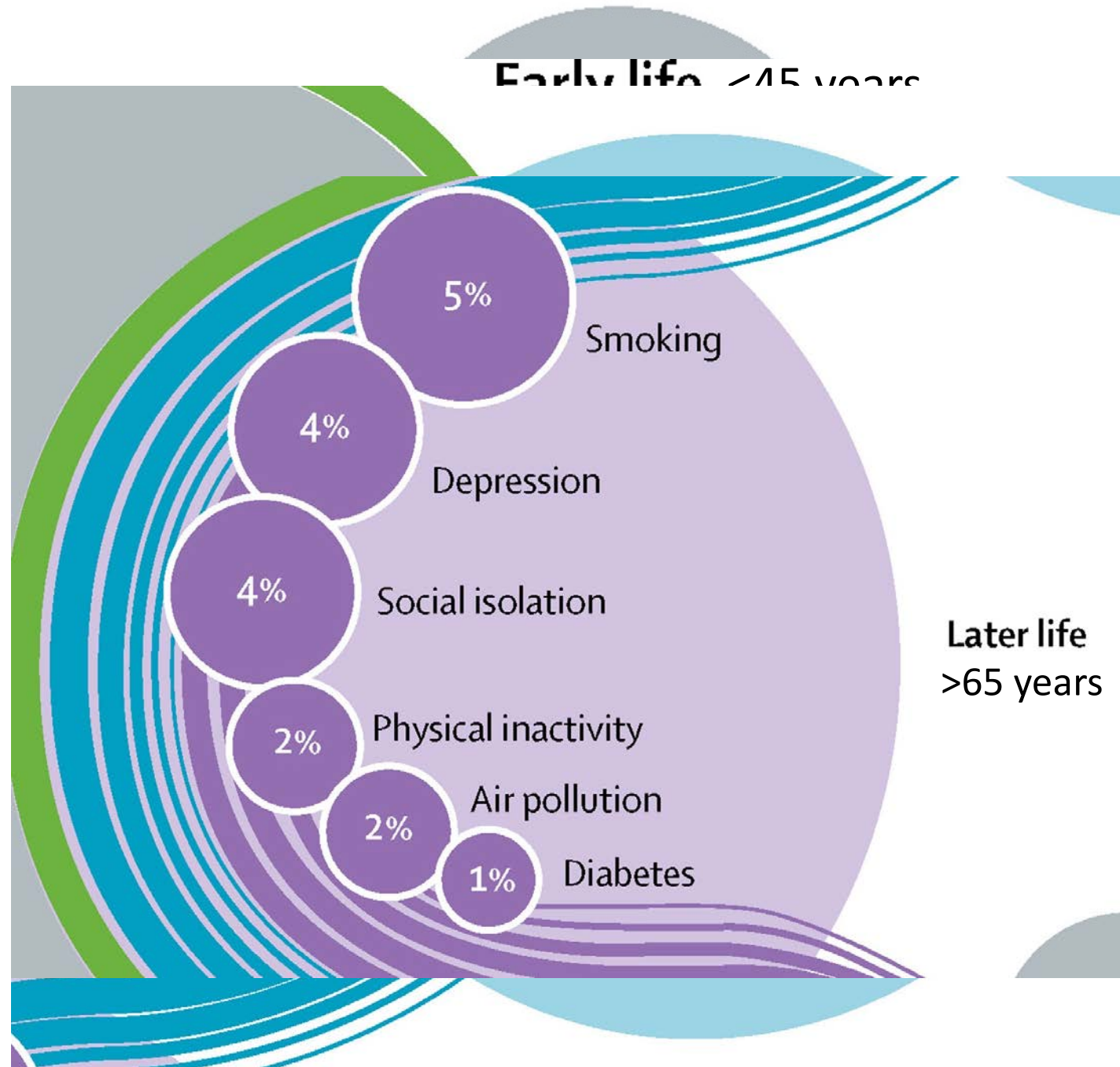
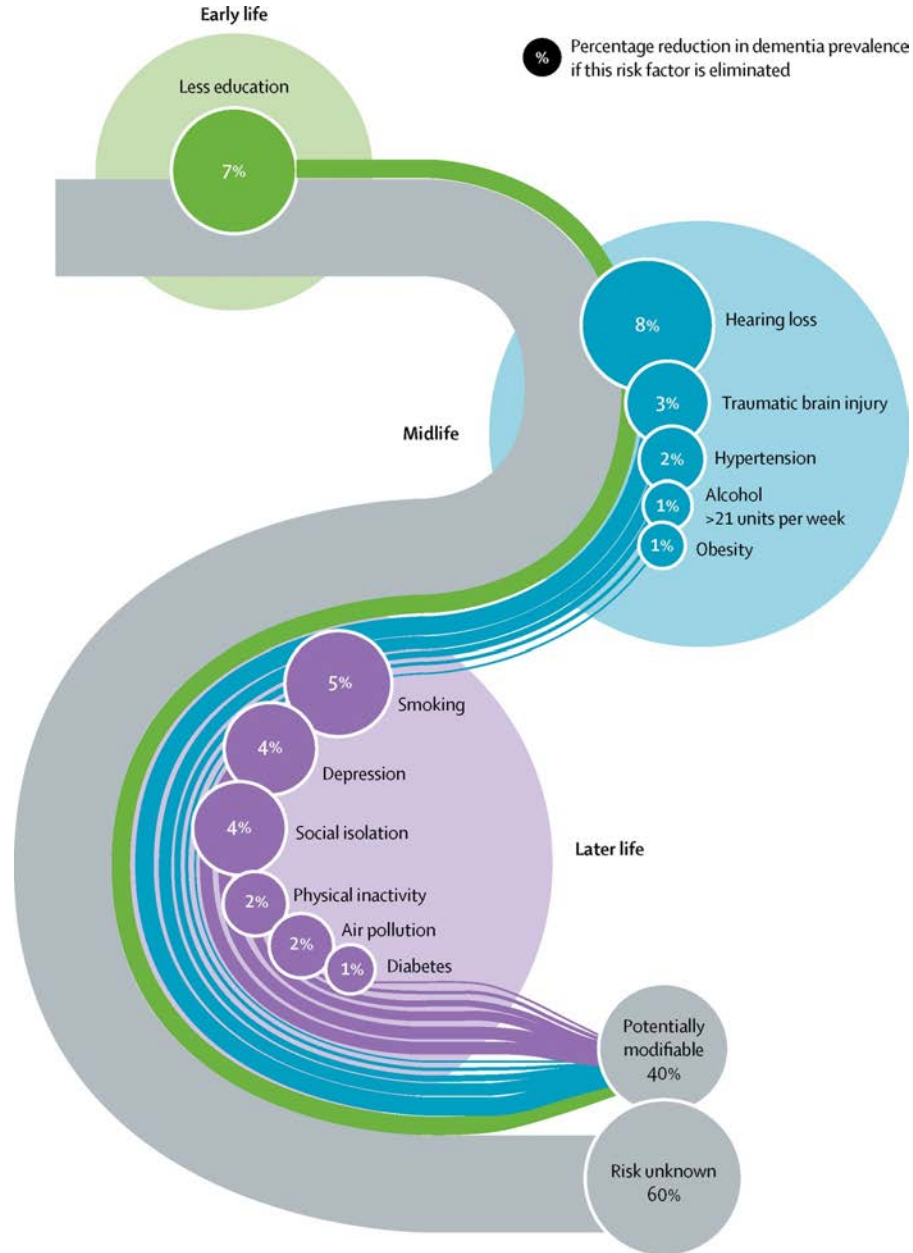


6. Lifestyle





# The Lancet Commission 2020



# What is Mild Cognitive Impairment? Dementia? Alzheimer's?

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*You have MCI*



*You have Dementia*



*You have Alzheimer's*

# What's the difference between Alzheimer's and Dementia?

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**"I have a stomach ache..."**

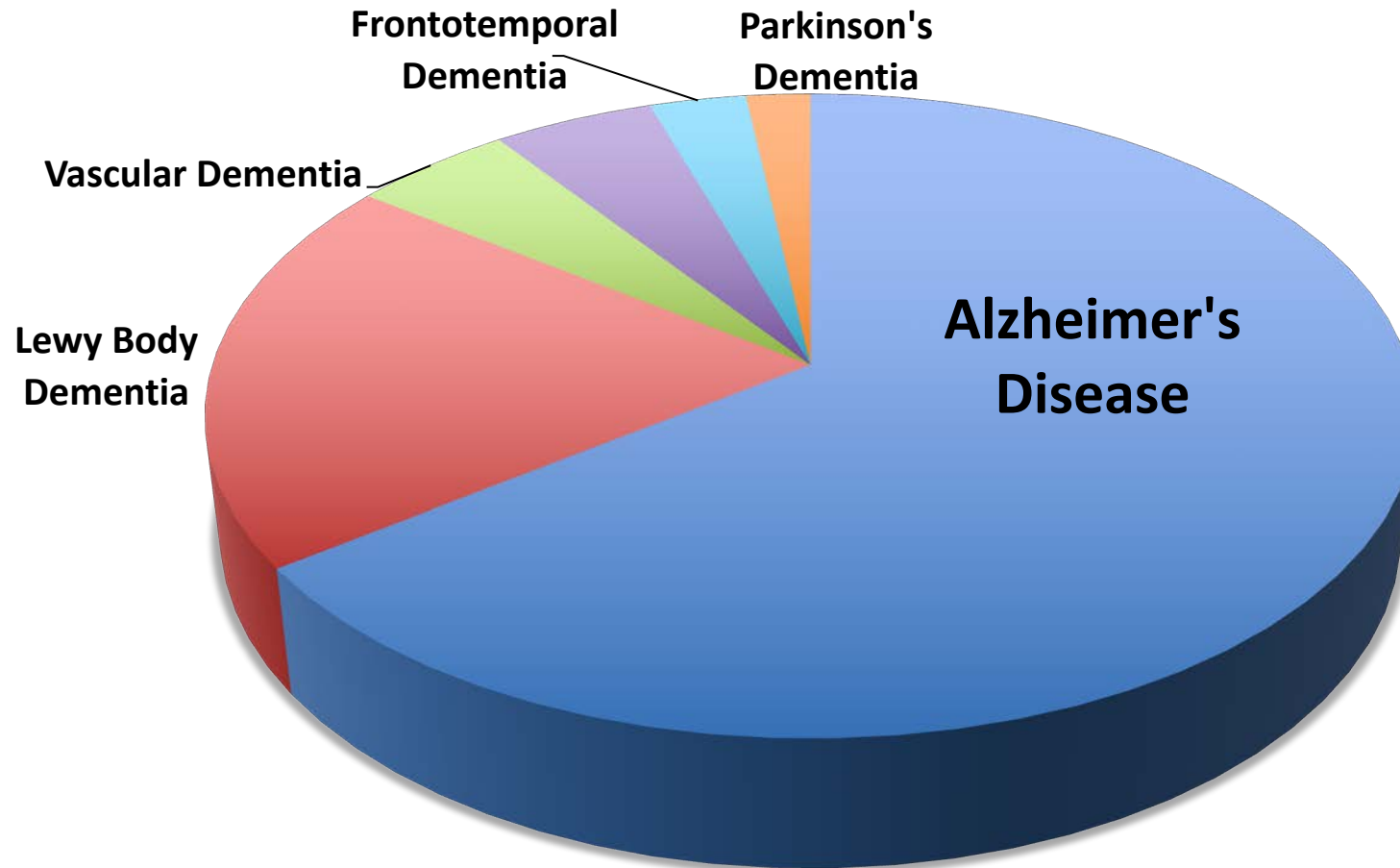


**"...because I ate too much"**



# Common Dementing Illnesses

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# Amyloid Cascade Hypothesis of Alzheimer's Disease

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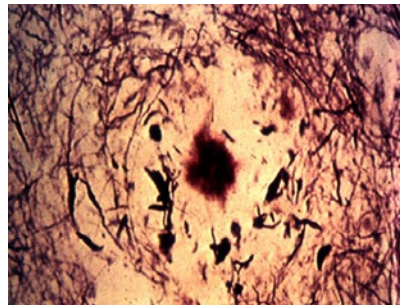
## Hypothesis:

The accumulation of extracellular amyloid initiates a cascade of events leading to neurotoxicity and clinical symptoms in AD.

## Corollary:

Prevention of amyloid accumulation will slow or prevent the development of symptoms.

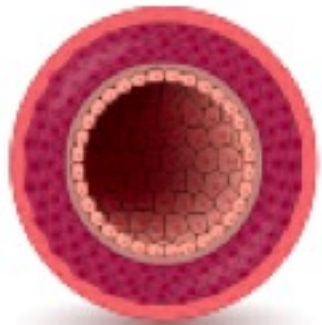
*Beta-amyloid  
accumulation* →



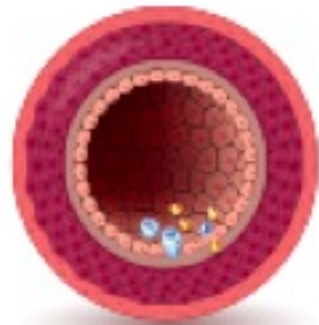


# Understanding Alzheimer's as a Chronic Disease

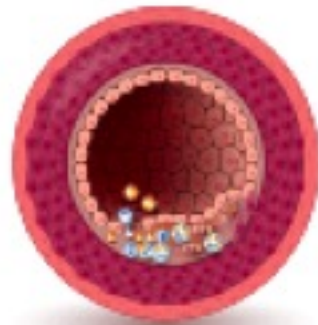
## Progression of Coronary Heart Disease



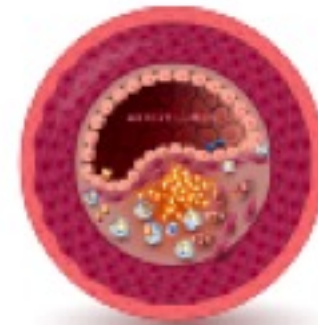
normal



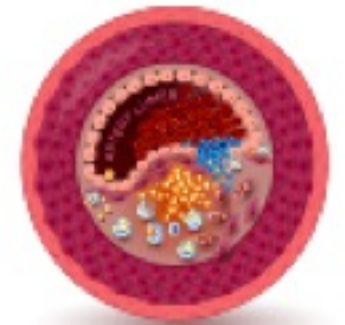
fat deposition



plaque buildup  
with macrophage  
infiltration

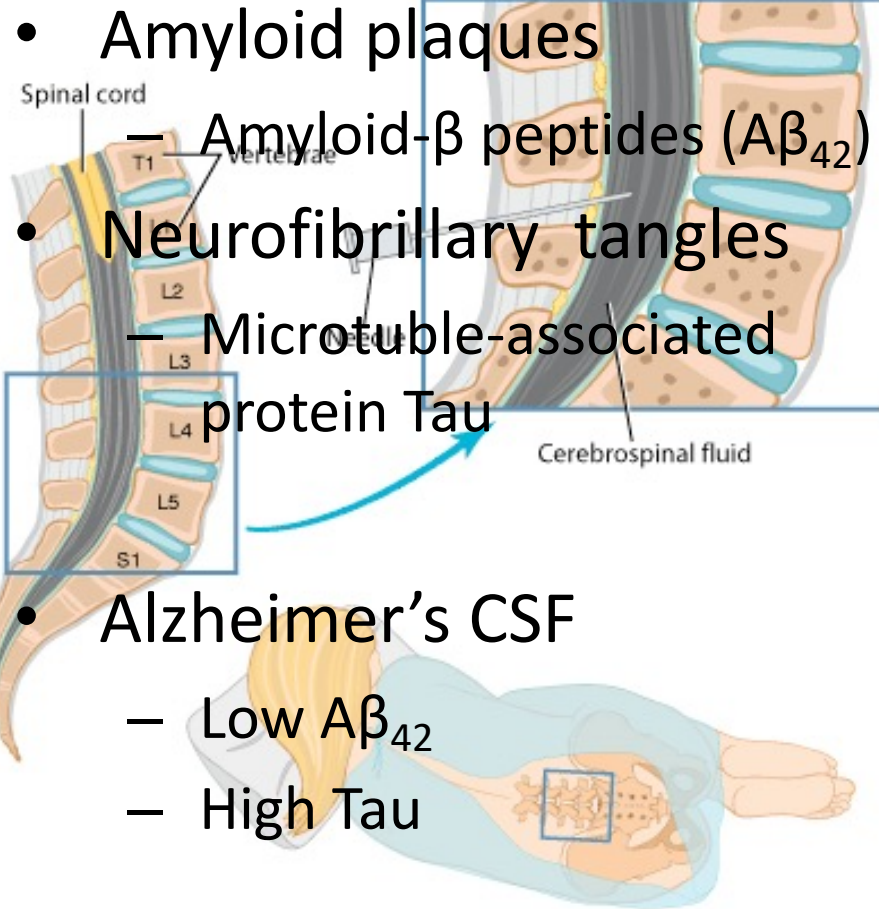


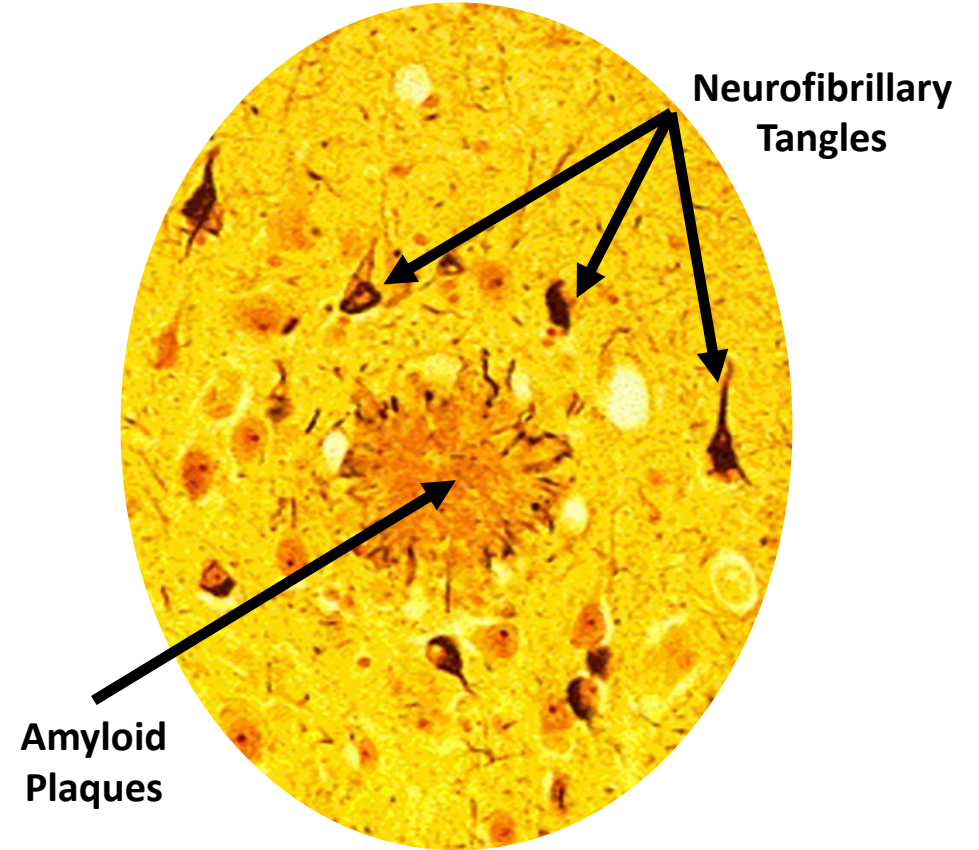
damage to  
plaque attracting  
clotting machinery



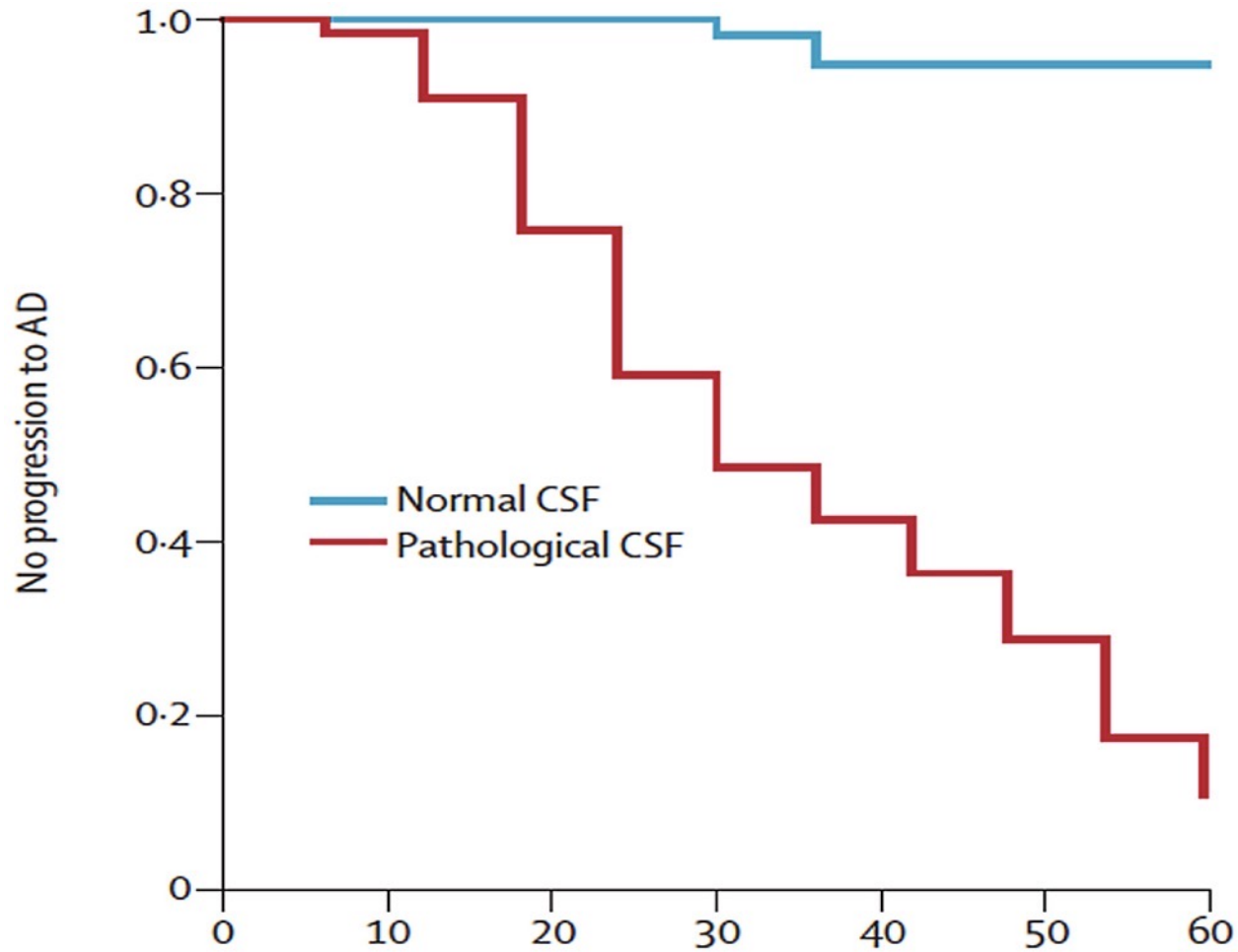
complete or  
near-complete  
arterial blockage

# Current Diagnostics: CSF AD Biomarkers

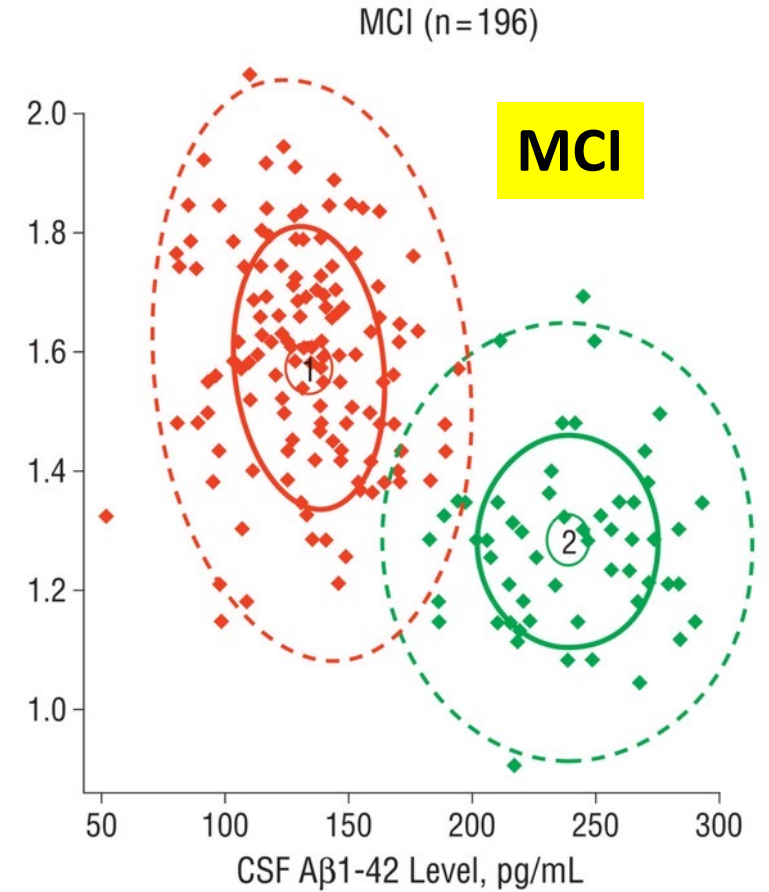
- Amyloid plaques
    - Amyloid- $\beta$  peptides ( $A\beta_{42}$ )
  - Neurofibrillary tangles
    - Microtubule-associated protein Tau
  - Alzheimer's CSF
    - Low  $A\beta_{42}$
    - High Tau
- 

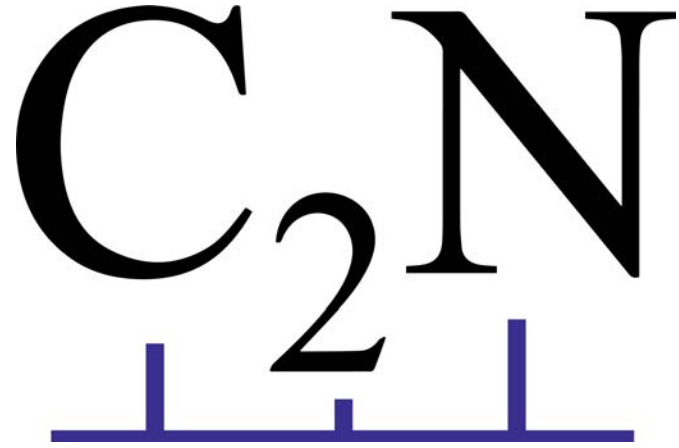


# CSF AD Biomarkers Predict Outcome in MCI



Hansson et al., Lancet Neurol (2006) Time (months)





## What is Alzheimer's Disease





# Blood Based Biomarkers for Alzheimer's Disease

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## Assays developed or in development

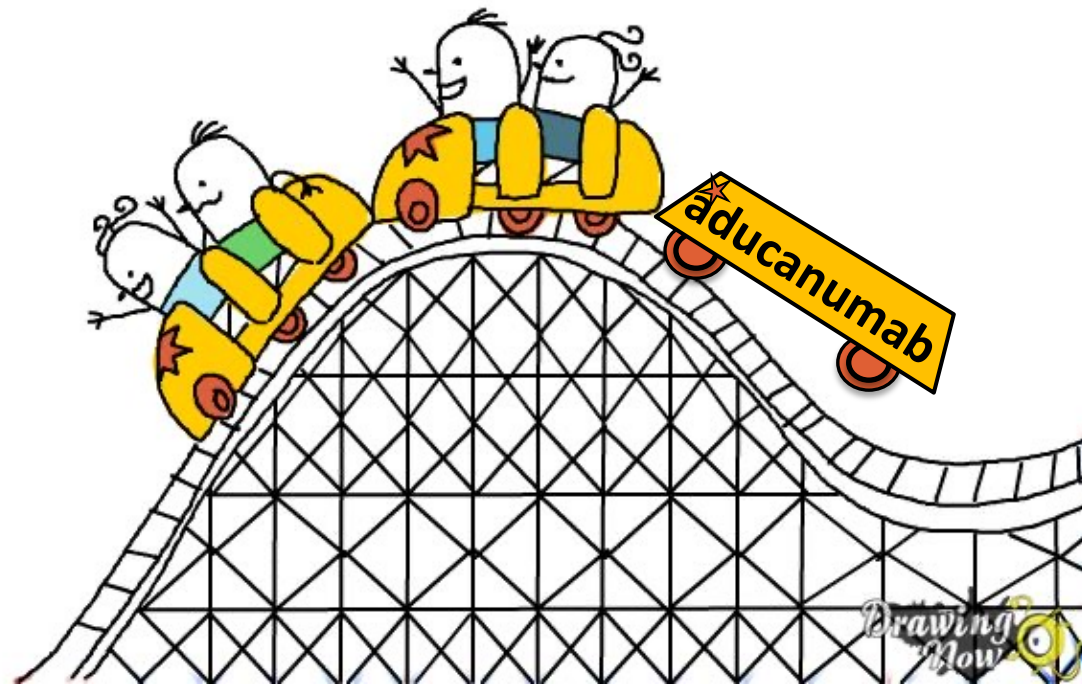
- C2N: Ratio of  $A\beta_{42}/A\beta_{40}$ 
  - First to market
  - Laboratory developed test
  - Not FDA approved
  - Not covered by insurance (\$1250)
- Lilly/Quanterix: P-Tau217
- Fujirebio: P-Tau181
- Roche: Panel including P-Tau

## Next steps and implications

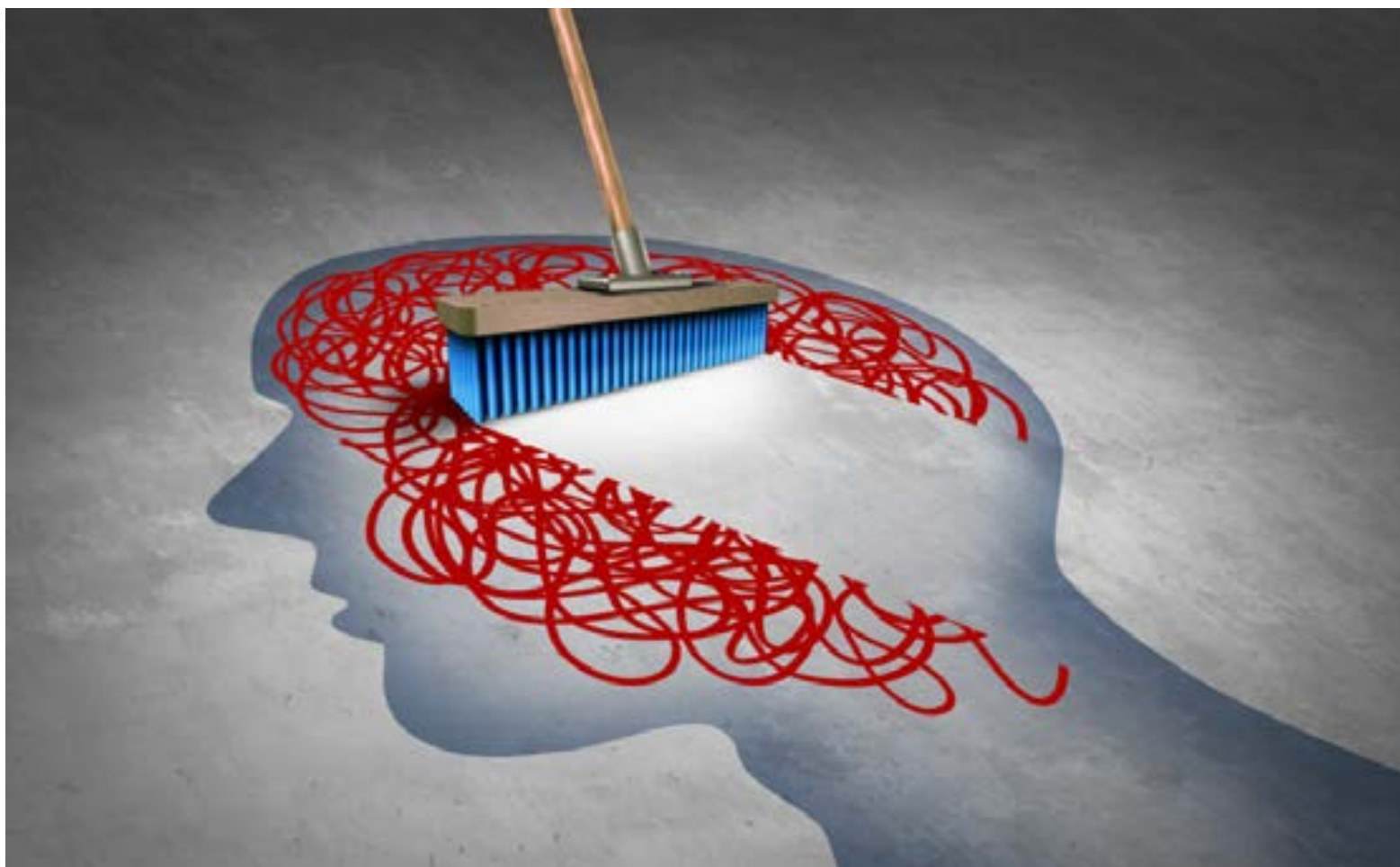
- Test accuracy
  - Sensitivity and specificity of tests
  - Positive and Negative Predictive Values of tests
- How will tests be used?
  - Screening in Primary Care?
  - Will tests be adequate for diagnosis?
  - Use for risk assessment in healthy individuals?



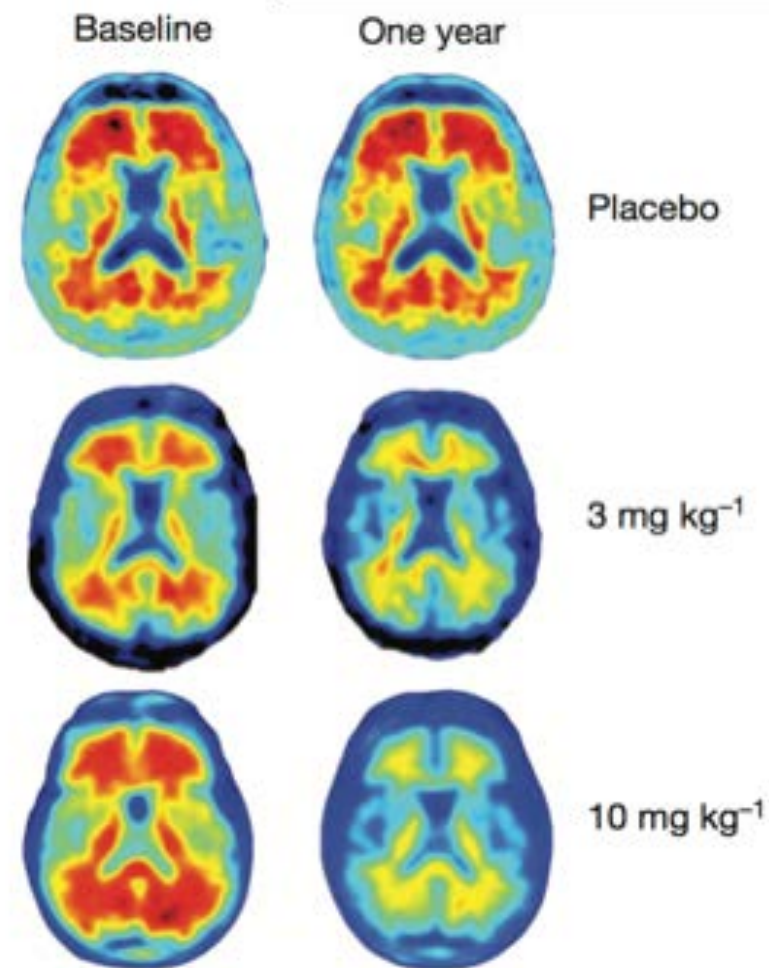
Why all the excitement... confusion... (pick your own emotion) about Alzheimer's disease-modifying therapies?



# What if we remove the Alzheimer's proteins?



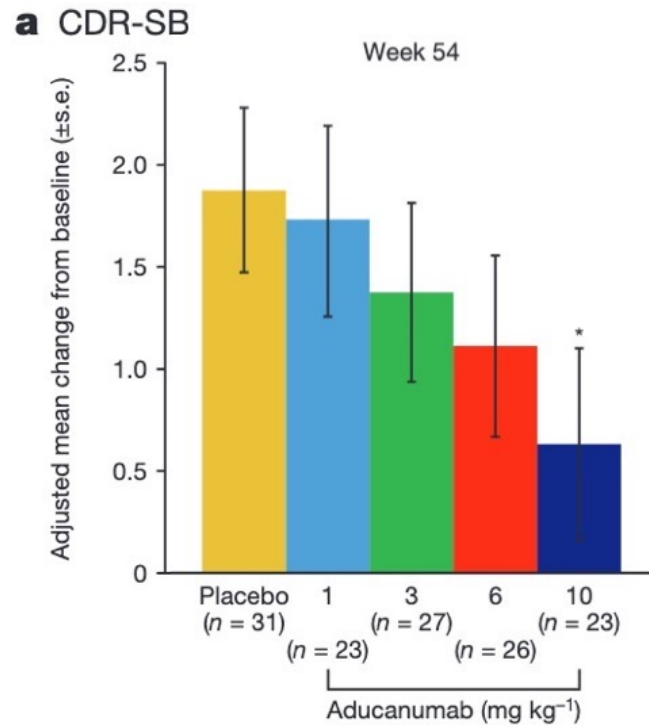
Brain tap



Sevigny et al., Nature (2016)



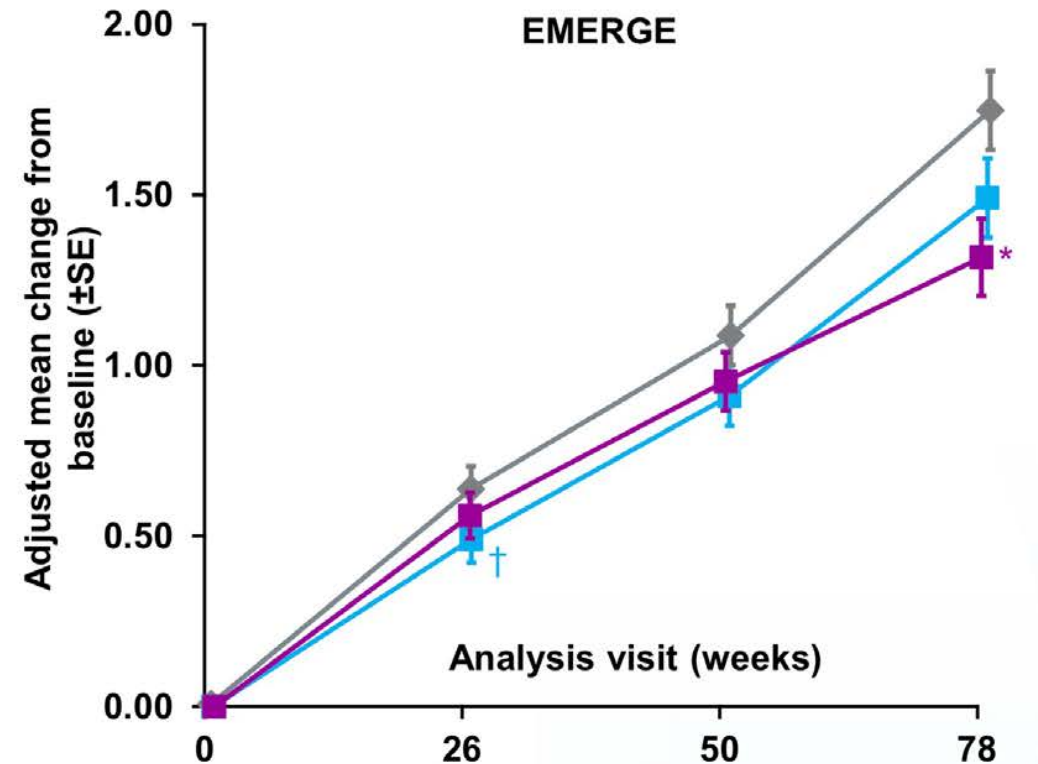
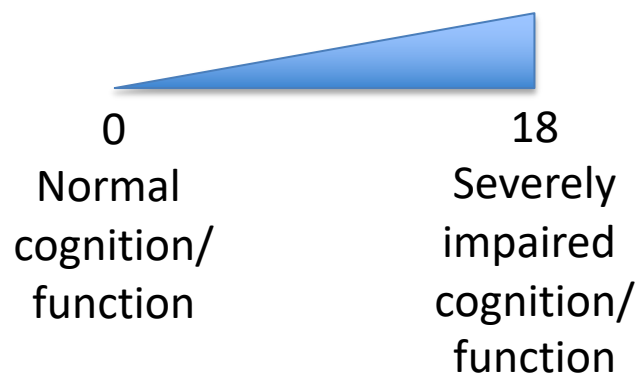
# Does a 'clean sweep' of these proteins lead to a significant difference in memory symptoms?



Sevigny et al., Nature (2016)

## CDR-SB

- Memory
- Orientation
- Judgement/problem solving
- Community affairs
- Home and hobbies
- Personal care



# Is this significant difference on the CDR clinically significant and significantly meaningful to patients and families significantly?



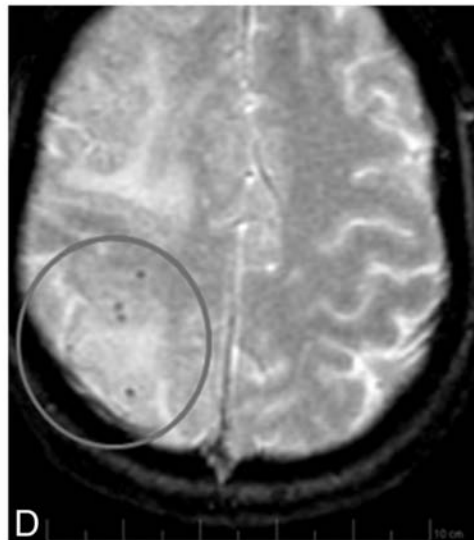
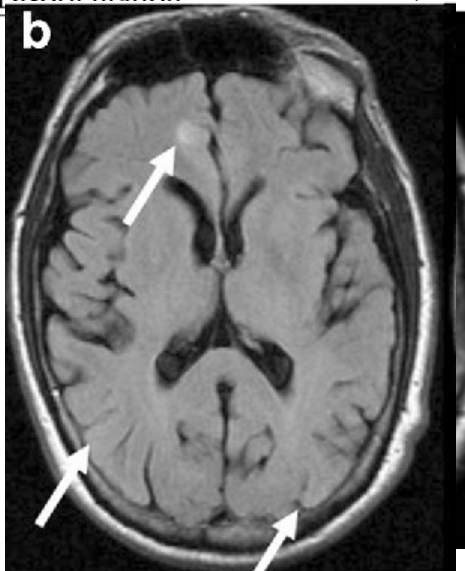
© Asspience



# Is aducanumab worth the cost and risk?

**Table 3: Adverse Reactions Reported in at Least 2% of Patients Treated with ADUHELM 10 mg/kg and at Least 2% Higher Than Placebo in Studies 1 and 2**




Adverse Reaction	ADUHELM 10 mg/kg N=1105 %	Placebo N=1087 %
ARIA-E	35	3
Headache <sup>a</sup>	21	16
ARIA-H microhemorrhage	19	7
ARIA-H superficial siderosis	15	2
Fall	15	12
Diarrhea <sup>b</sup>	9	7
Confusion/Delirium/Altered Mental Status/Disorientation <sup>c</sup>	8	4



- Side effect profile requires very close monitoring
- Cost \$56K/yr (cut to \$28K/yr)
  - Record 14.5% hike in Medicare Part B premium in 2022
- Disparities in trial and access
  - 6 total AA participants
- Ancillary costs
  - Diagnostics, safety MRIs, infusion center, clinic visits
- Impact of time, costs, side effects on quality of life

# Summary of the aducanumab approval saga.....

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- FDA advisory panel November 2020 
- FDA accelerated approval June 2021 
- VA and multiple hospital systems 
- Medicare determination 2022
  - Two public comment sessions
  - Over 10,000!

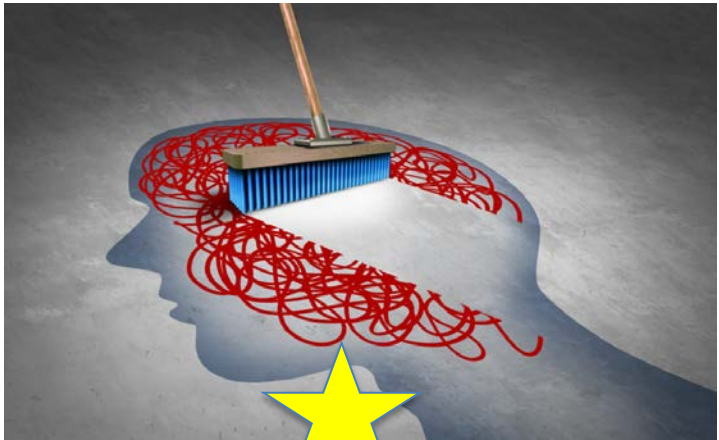


  
"I BITE MY  
THUMB  
AT THEE,  
FDA"  
  
LAZY J



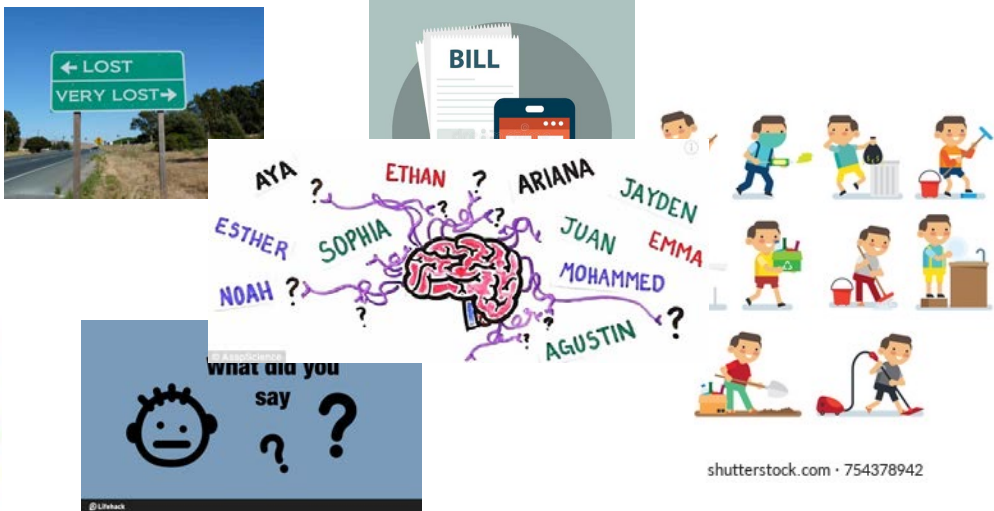
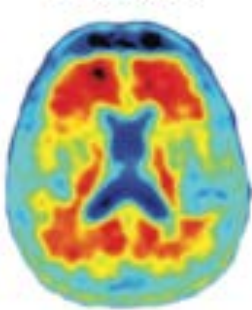
# Two options in which Medicare will cover aducanumab or any other amyloid disease modifying therapy...

- If the medication clears amyloid, then CMS will pay for the medication in context of randomized clinical trials that further test benefit.



We are here (aducanumab)

- If the medication clears amyloid and has clinical benefit, then it will pay for the medication in the context of comparative studies.

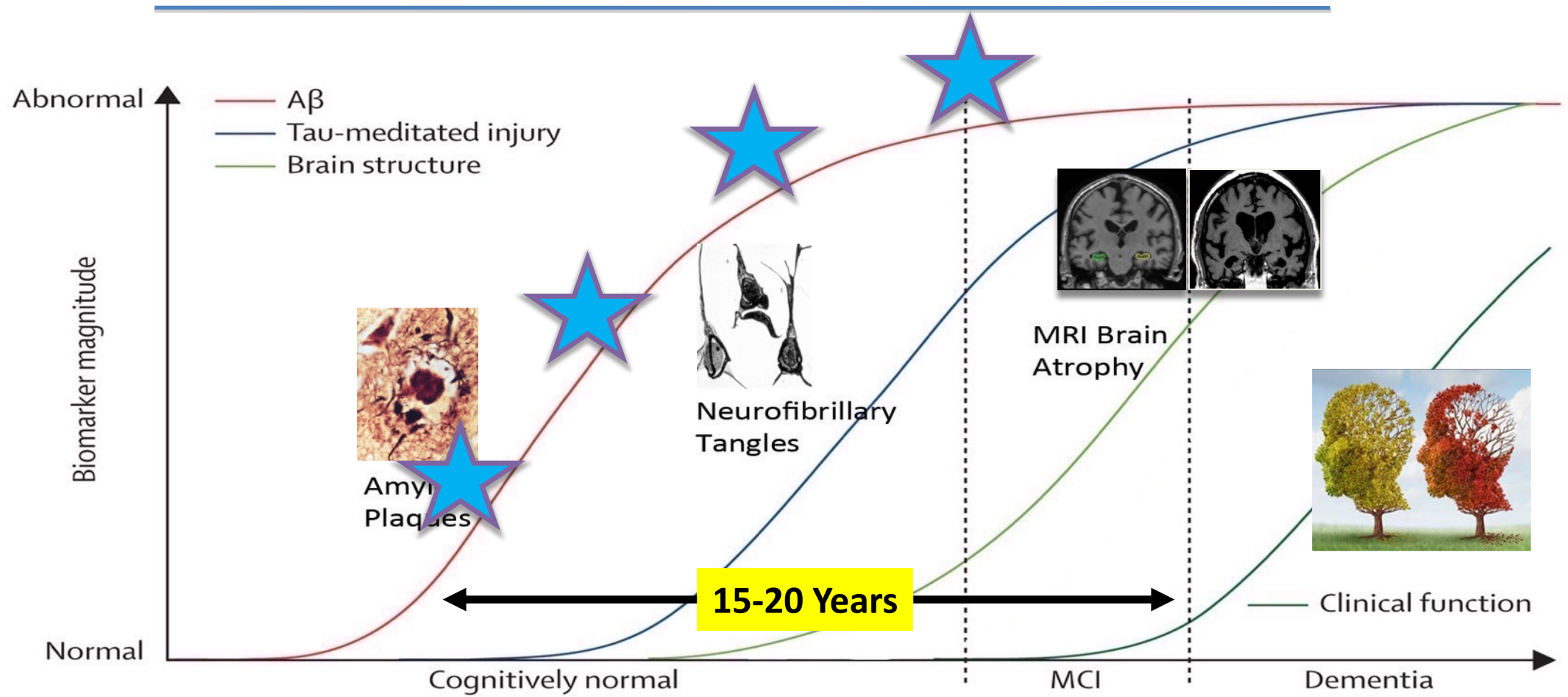


# What do we do now?

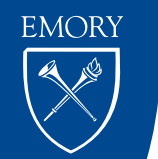
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- There is still hope!
- The 'growing pains' with aducanumab has taken us closer to the goal.
- FDA opens door to Accelerated Approval for other amyloid-clearing drugs
  - lecanemab
  - donanemab
  - gantenerumab
- Other approaches:
  - tau
  - inflammation
  - new targets

# Future State of AD: Not Treatment, Prevention



Modified from Jack et al., Lancet Neurol (2009)



# Questions?

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- The middle.