THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

# Alzheimer's Disease Update

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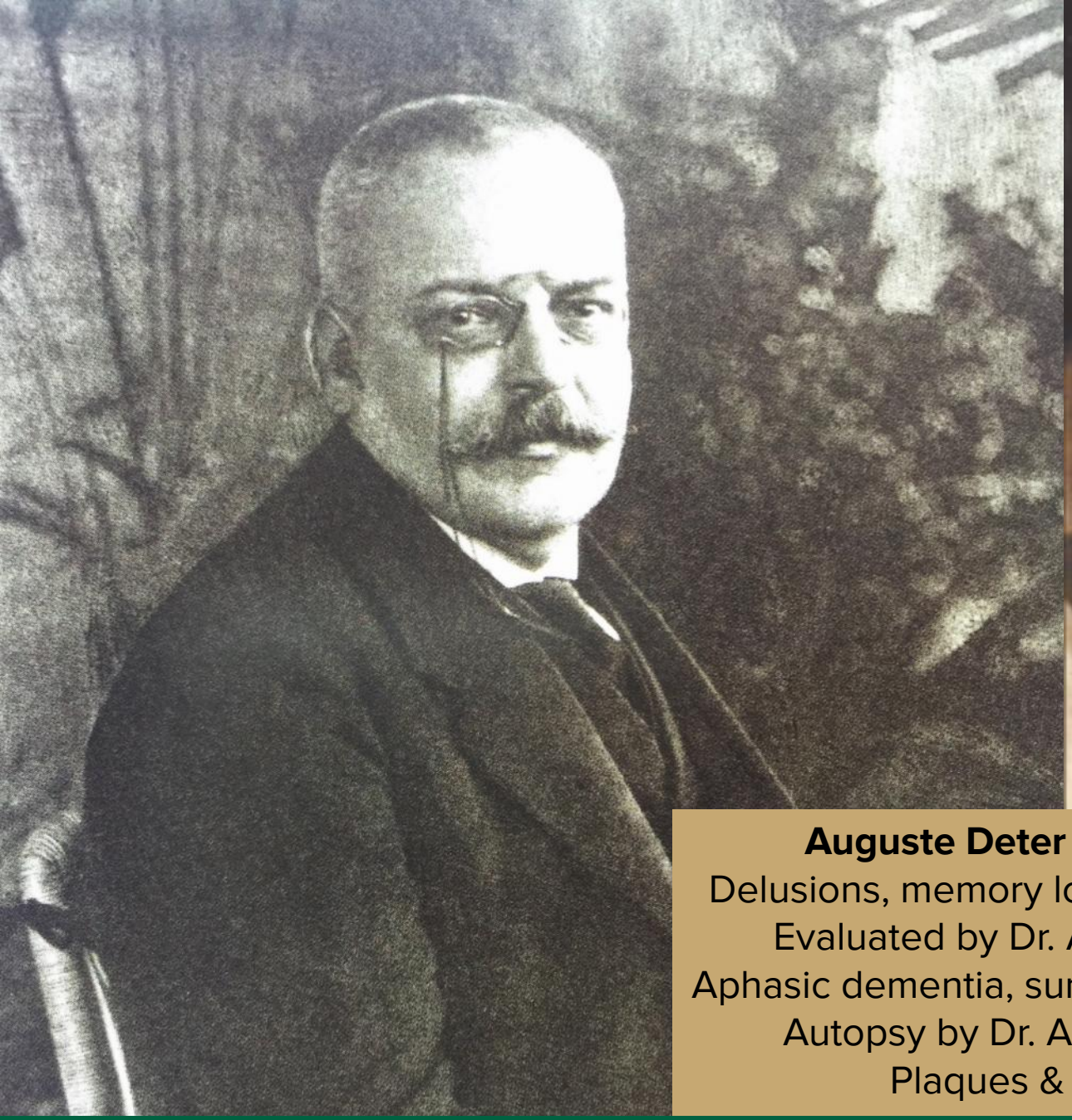
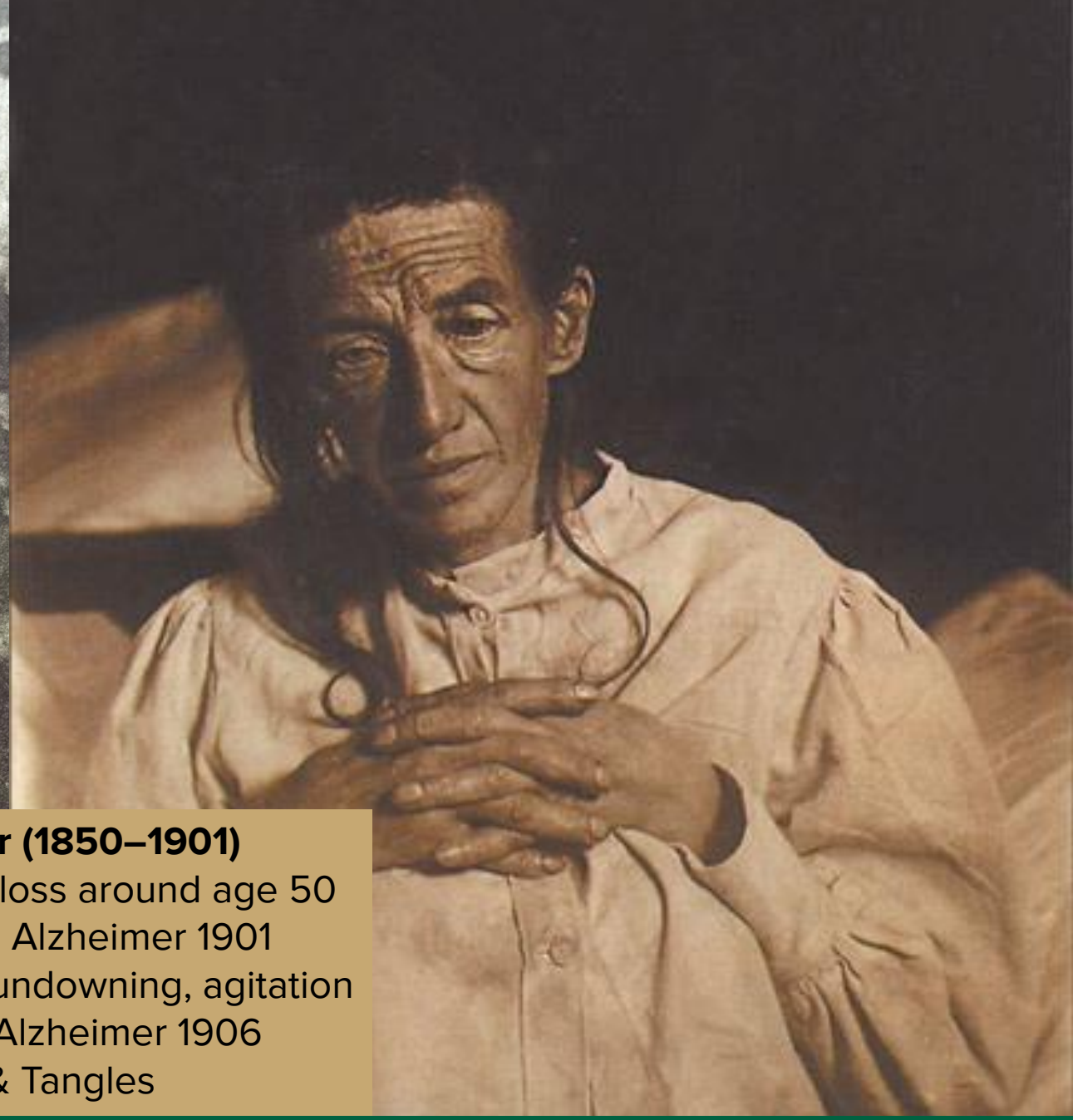
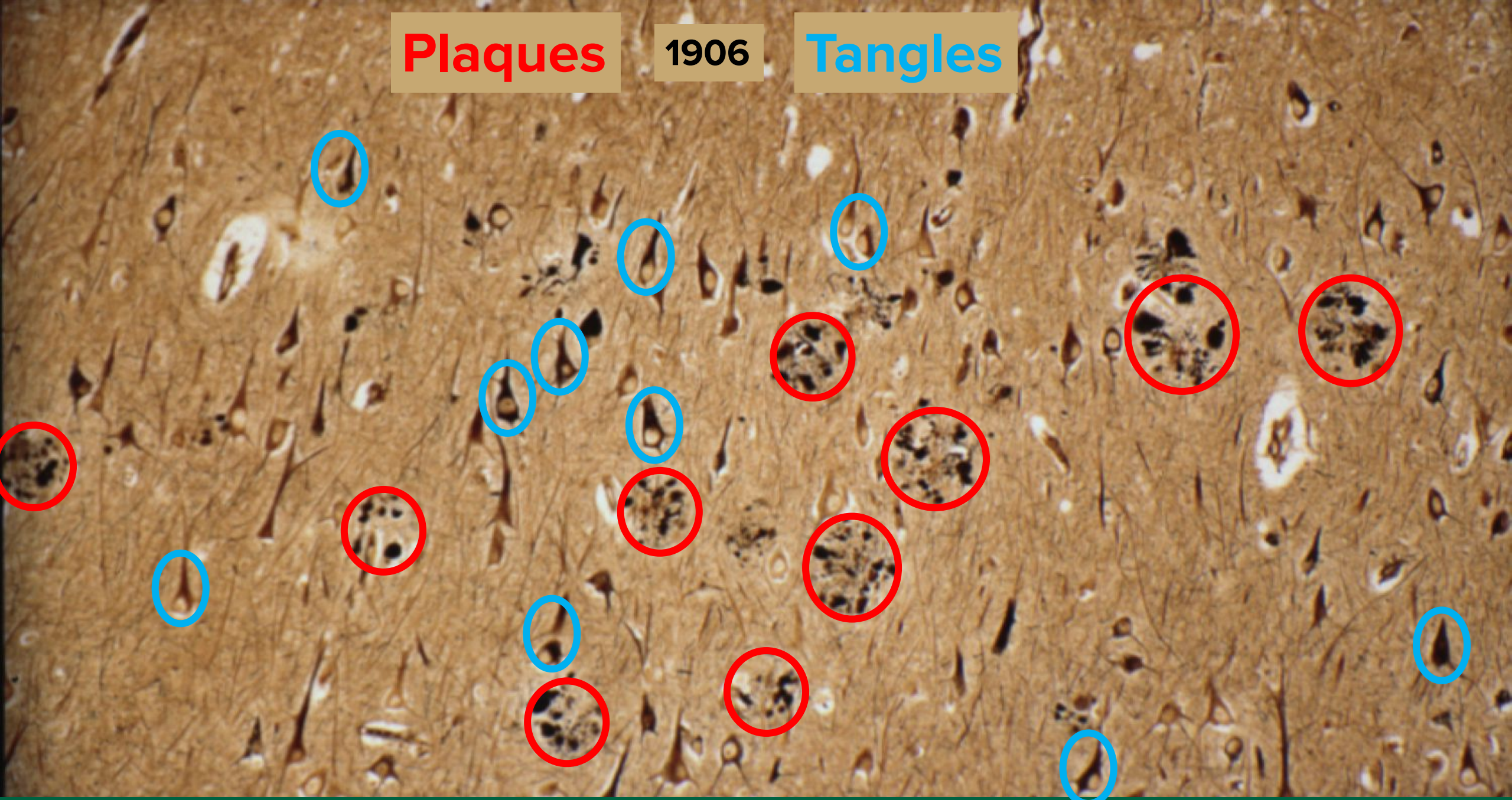
# Outline

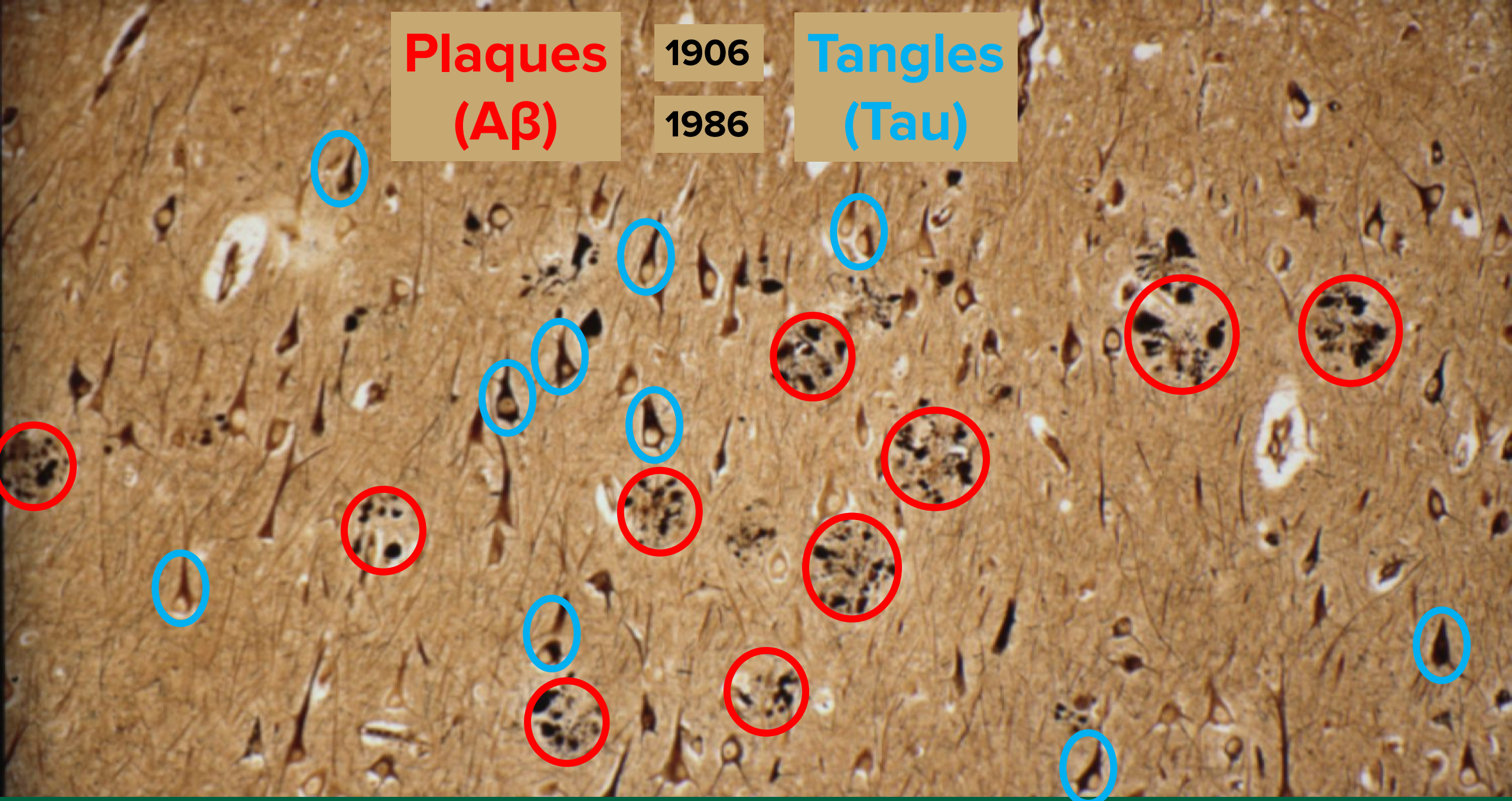
1. What causes Alzheimer's disease?
2. How do we accurately diagnose Alzheimer's disease? (now and in the near future)
3. How do we optimally treat Alzheimer's disease? (now and in the near(?) future)





**Auguste Deter (1850–1901)**
Delusions, memory loss around age 50
Evaluated by Dr. Alzheimer 1901
Aphasic dementia, sundowning, agitation
Autopsy by Dr. Alzheimer 1906
Plaques & Tangles





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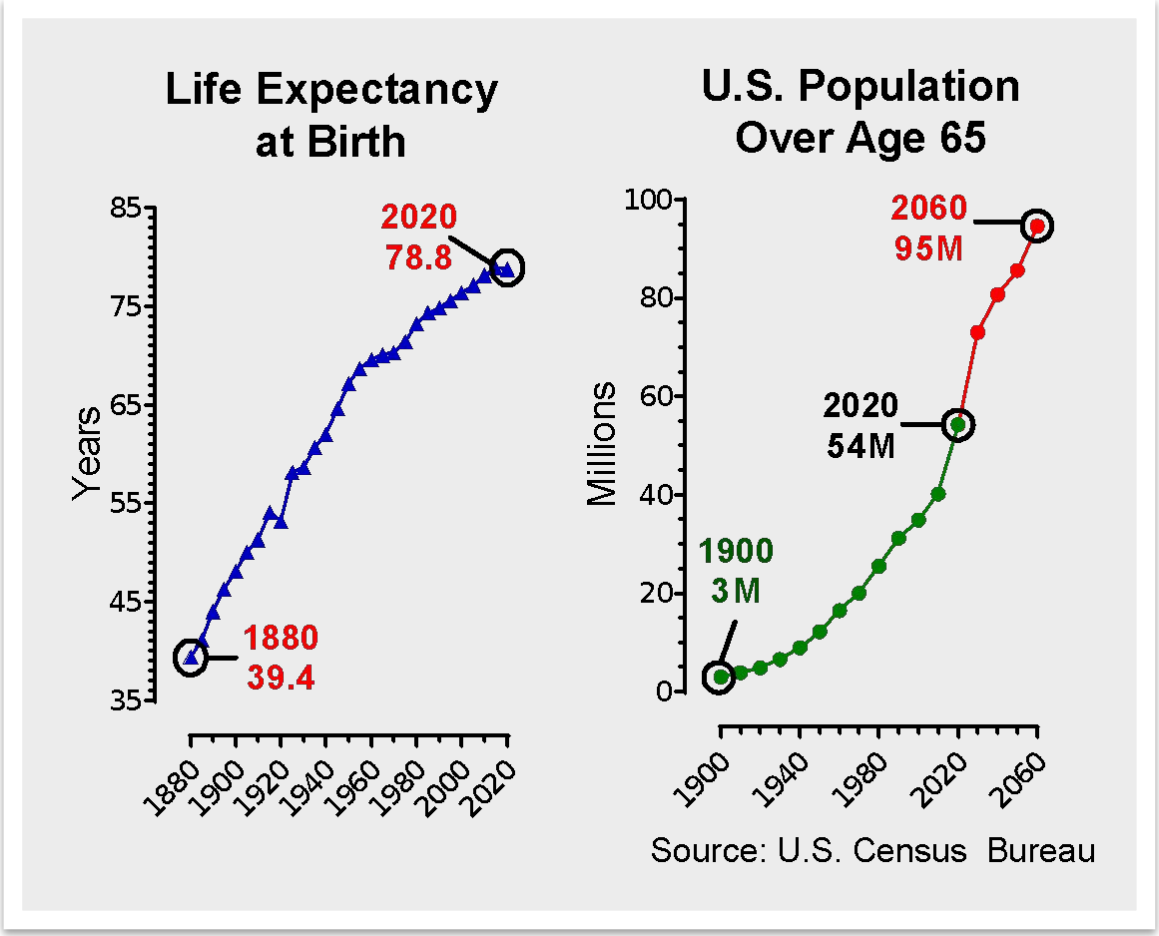
# What causes Alzheimer's disease?

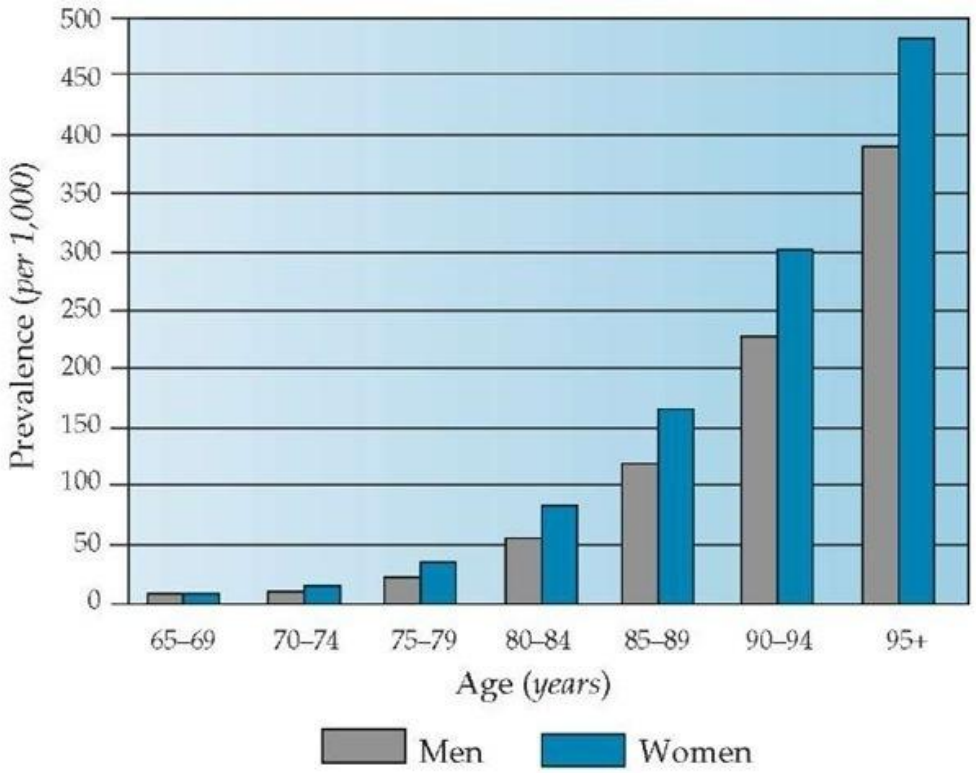
Aging

Genetics

Aβ (amyloid hypothesis)

# Aging of the U.S. Population

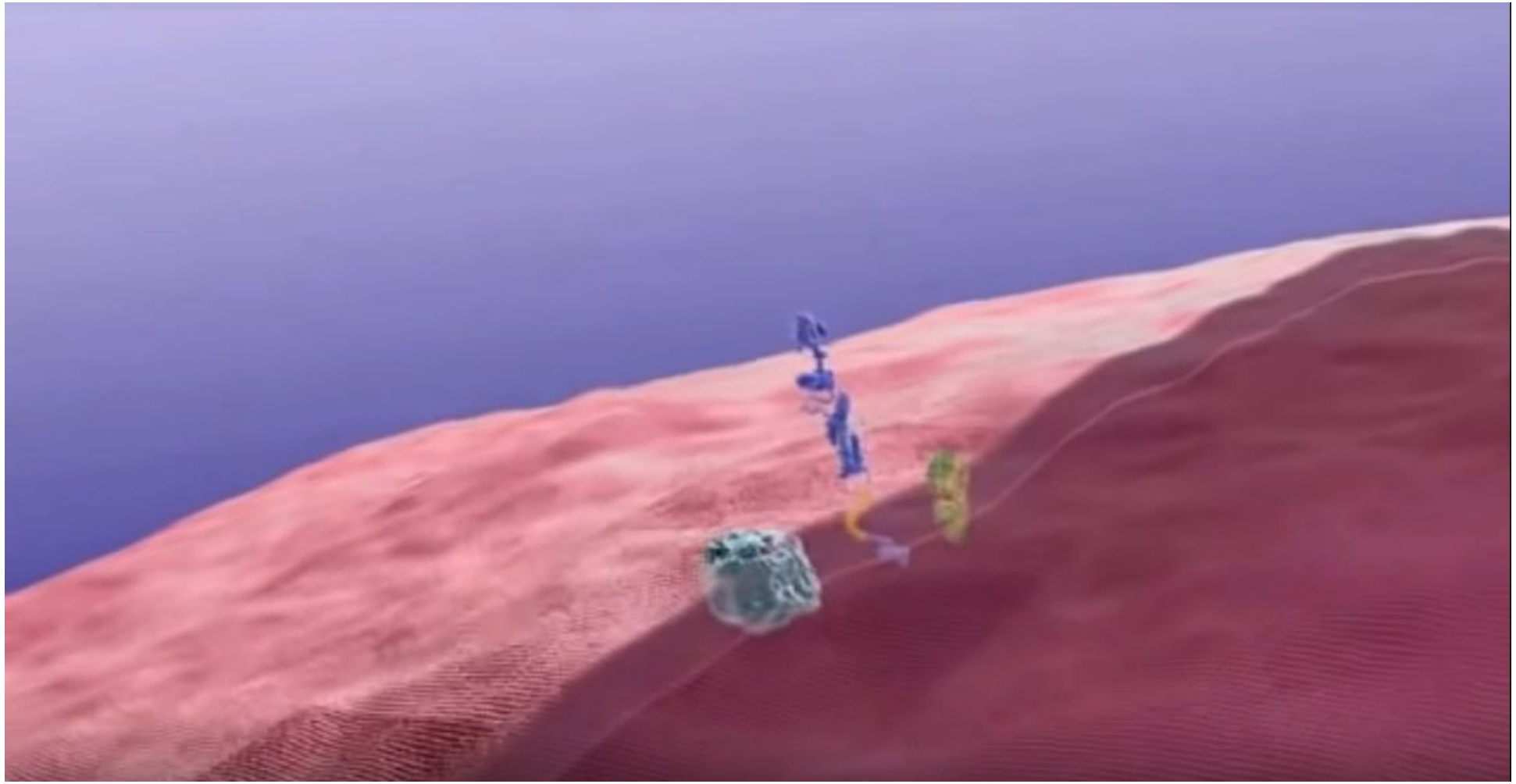


# Genes Causing Autosomal Dominant AD

| Gene | Protein | Function |
|---|---|---|
| *APP* | Amyloid Precursor Protein | Contains Aβ peptide |
| *PSEN1* | Presenilin 1 | Cleaves Aβ from APP |
| *PSEN2* | Presenilin 2 | Cleaves Aβ from APP |

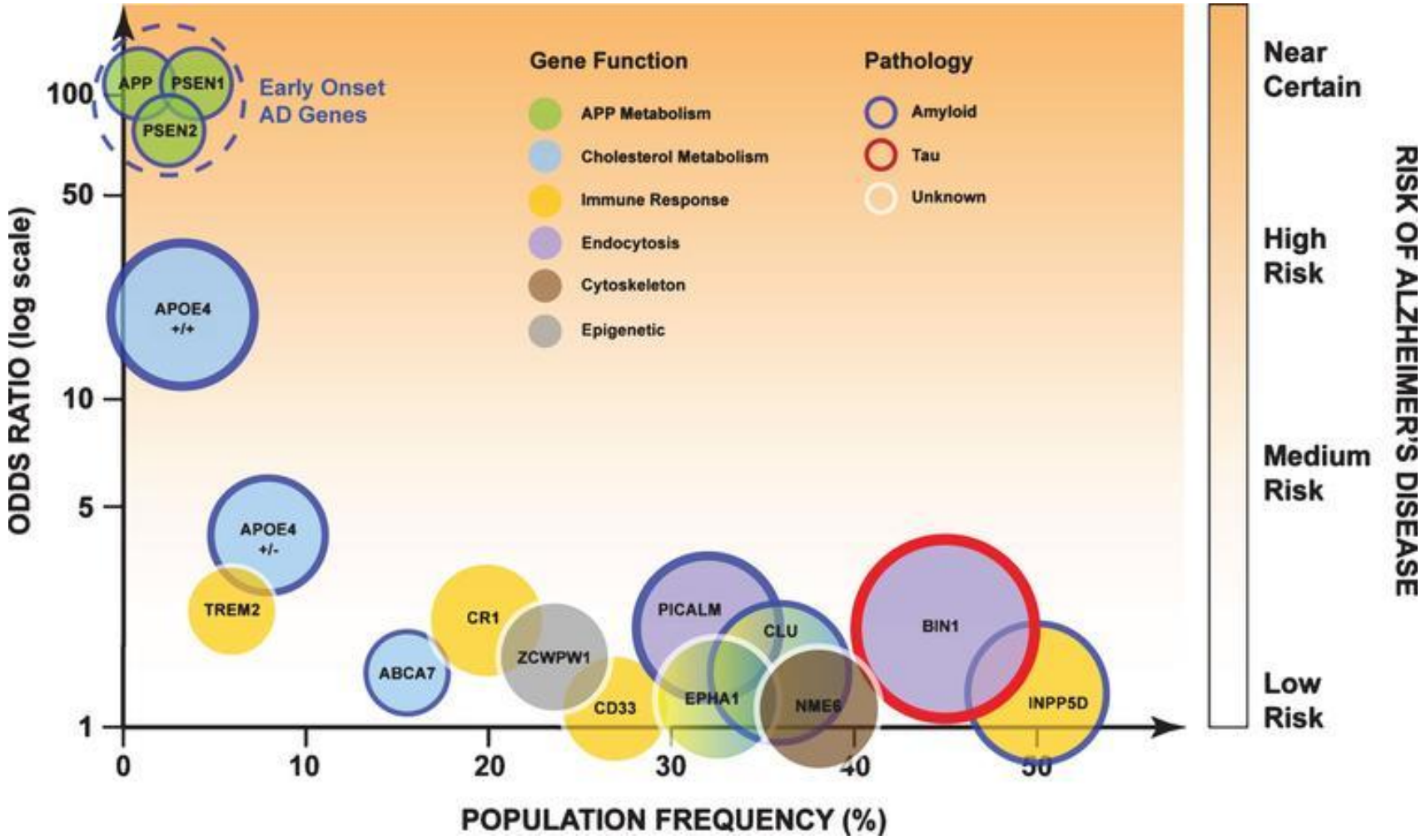
Net effect of APP/PSEN mutations is increase in toxic $A\beta_{42}$ production



Alzheimer's Disease Education and Referral Center, a service of the National Institute on Aging

https://www.youtube.com/watch?v=NjgBnx1jVIU

# Genetic Risk Factors for Alzeimer's Disease



# Late-onset vs. Early-onset AD

- Late Onset (LOAD)
  - Onset age 65 or older
  - 6.5% of elderly population (6500/100,000)
- Early Onset (EOAD)
  - Onset age 60 or before
  - 40/100,000
  - Can be autosomal dominant (5/100,000)
    - Usually onset in 40s
  - Most cases due to genetic risk factors, often in combination

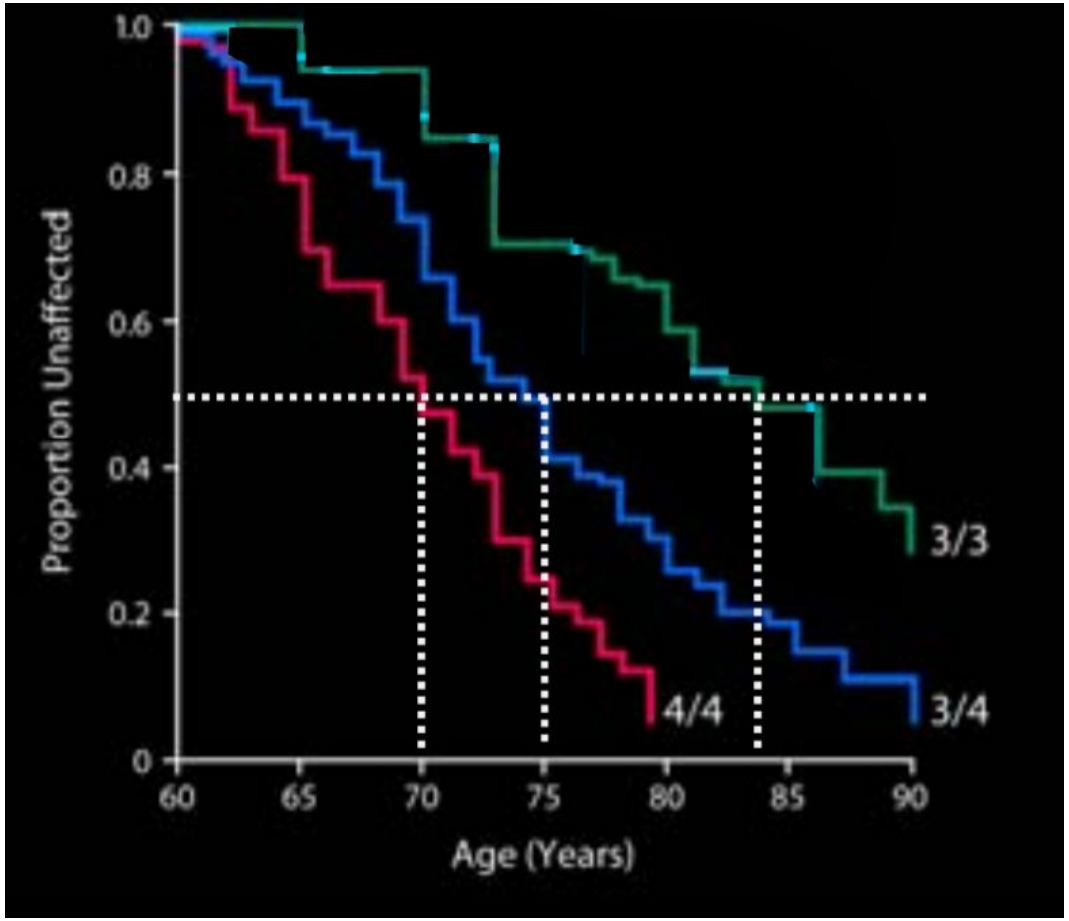
# ApoE is the Strongest Genetic Risk Factor for AD

Median Age at Onset

3/3: 84 years old

3/4: 75 years old

3/3: 70 years old



# Structural Differences Between E3 and E4

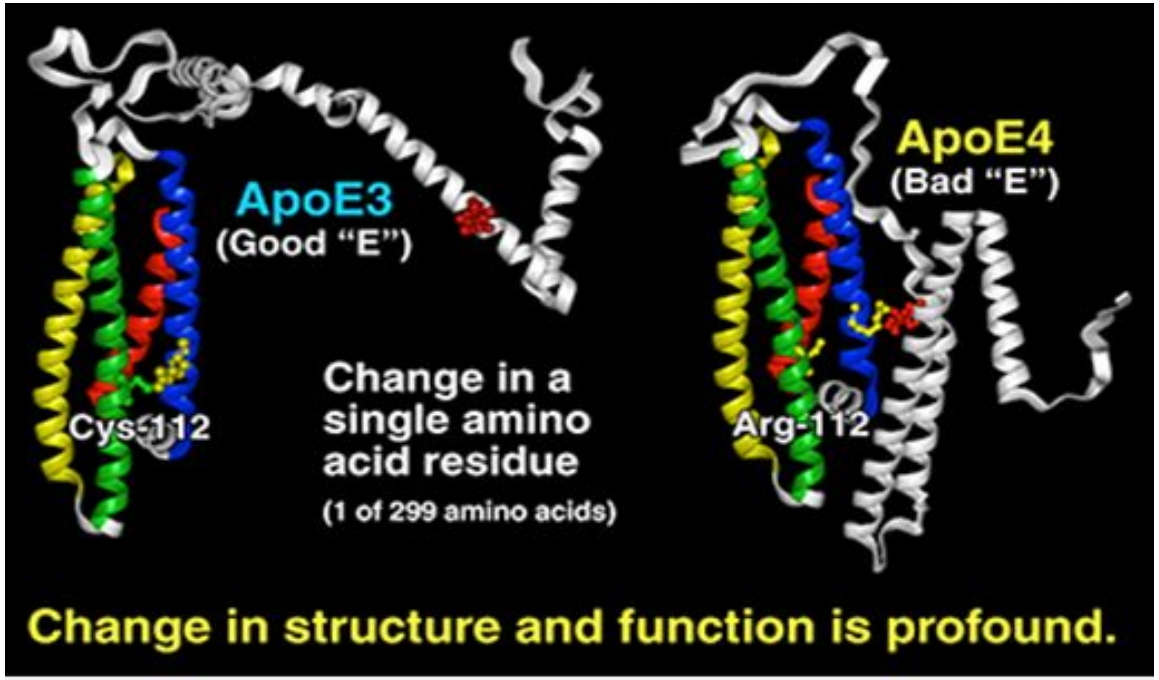
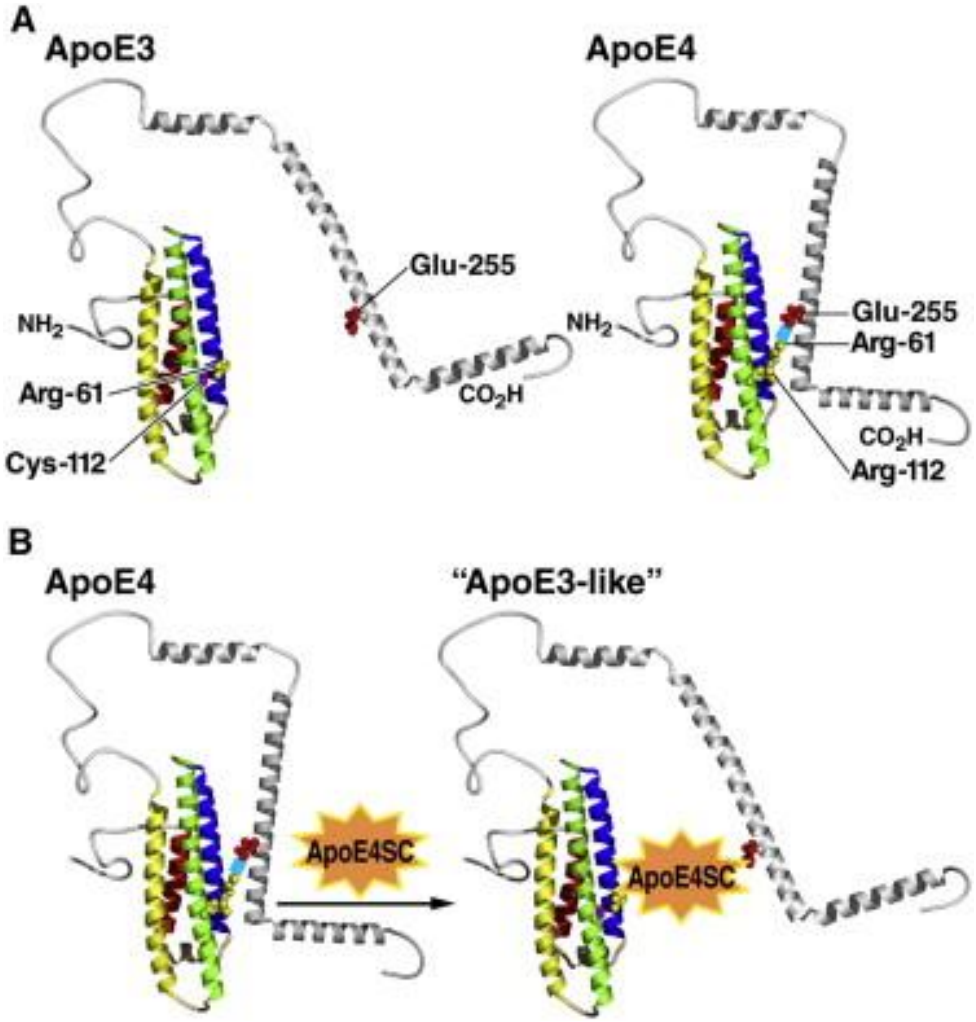



Image from Robert Mahley, MD, PhD of the Gladstone Institutes. http://gladstoneinstitutes.org/node/11371



# Genetic Testing for ApoE

NIA does not recommend routine ApoE testing

- Psychological distress
- Insurance or employment discrimination
- Inadvertent effects on family members
- Only a risk factor, but genetics connotes determinism
- Long time between testing and disease
- Not modifiable

# The Amyloid Hypothesis: that Aβ is a primary driver of AD

- Genetic evidence
  - Autosomal dominant mutations: all increase Aβ
  - Protective variants in APP that decrease Aβ production reduce AD
- Experimental evidence
  - Aβ has toxic effects on cultured neurons and in animal models
- Clinical trial evidence
  - Signals that reducing Aβ has beneficial effects in AD trials

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# How do we diagnose Alzheimer's disease?

MCI vs. Dementia

Clinical syndromes vs. Pathologic diagnoses

Biomarkers

# Step 1: Syndromal Staging

MCI vs. Dementia

# Diagnostic Criteria for MCI and Dementia (2011)

## MCI

- Concern of cognitive change (i.e., historical or observed evidence of decline over time)
- Objective evidence of impairment in one or more cognitive domains
- Preservation of independence in functional abilities
- Not demented

## Dementia

Cognitive or behavioral symptoms that:

- Interfere with work or ADLs
- Cause a decline from prior level of functioning
- Are not explained by delirium or psychiatric illness
- Are detected by both subjective (history) and objective (exam) methods
- Involve at least two domains
  - Memory, Executive, Visuospatial, Language, Neuropsychiatric

# Step 2: Clinical classification
# Step 3: Pathological prediction

- Clinical classification
  - Clinical syndromes based on symptom profile
  - Symptoms are driven by *location* of pathology
  - For example
    - Amnestic Alzheimer's disease: medial temporal lobe
    - Primary progressive aphasia: left language cortex
- Pathological prediction
  - Pathological diagnoses based on *type* of pathology (e.g., tau, TDP-43, Aβ, αSyn)
  - Ultimately, made postmortem by pathologist
  - Can be predicted based on clinical classification and biomarkers

# Diagnostic Criteria for Dementia due to AD (2011)

- Dementia, with these characteristics:
  - Insidious (slow) onset
  - Clear-cut history of worsening
  - Initial and most prominent deficits are:
    - Amnestic: memory
    - Nonamnestic: Language, visuospatial, or executive
- No substantial concomitant vascular disease, or feature of other neurodegenerative disorders that could explain the symptoms

# Clinical Syndromes with AD (Plaque/Tangle) Pathology

| Classic Amnestic AD | Logopenic Primary Progressive Aphasia | Posterior Cortical Atrophy |
| --- | --- | --- |
| Medial temporal predominance of pathology | Left frontal/temporal predominance of pathology | Posterior cortical predominance of pathology |
| Episodic memory deficits (recent worse than remore) | Word-finding problems, slower speech | Blurred vision, difficulty reading, misperceiving visual stimuli |
| ApoE4 association | | |

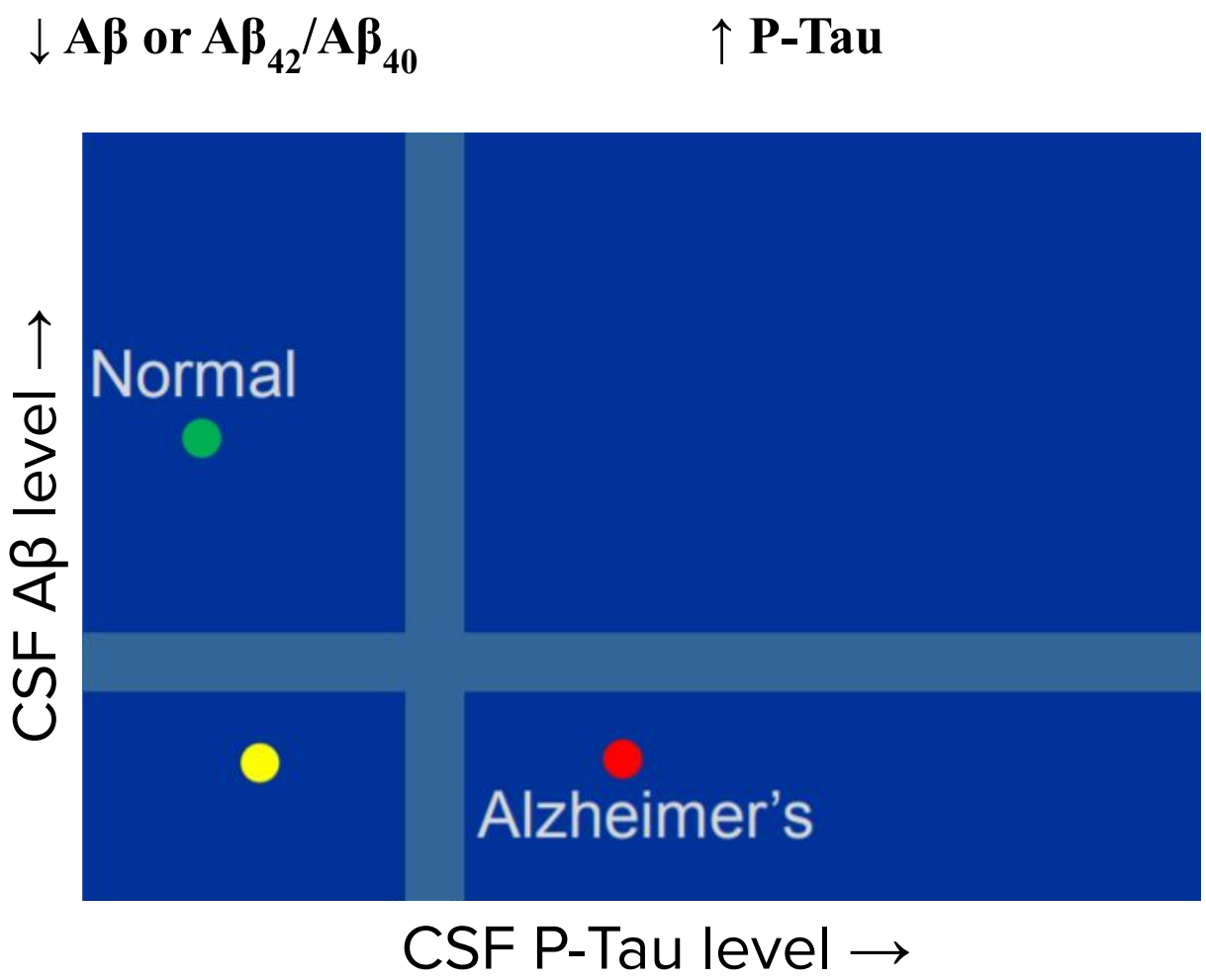
# Clinical Syndromes with non-AD Pathology

| Behavioral Variant FTD (bvFTD) | Semantic Variant PPA (svPPA) | Nonfluent Variant PPA (nvPPA) | Dementia with Lewy Bodies (DLB) |
|---|---|---|---|
| Personality change<br>Social withdrawal<br>Disinhibition<br>Repetitive behavior<br>Apathy | Fluent speech<br>Loss of word meanings<br>Surface dyslexia | Nonfluent, effortful speech<br>Loss of grammatic structure | Parkinsonism<br>REM Sleep Behavior disorder<br>Visual hallucination<br>Fluctuations |
| Frontal/temporal (often R>L) | Left temporal pole | Left frontal | |
| Tau or TDP-43 pathology | TDP-43 pathology | Tau pathology | α-Synuclein pathology |

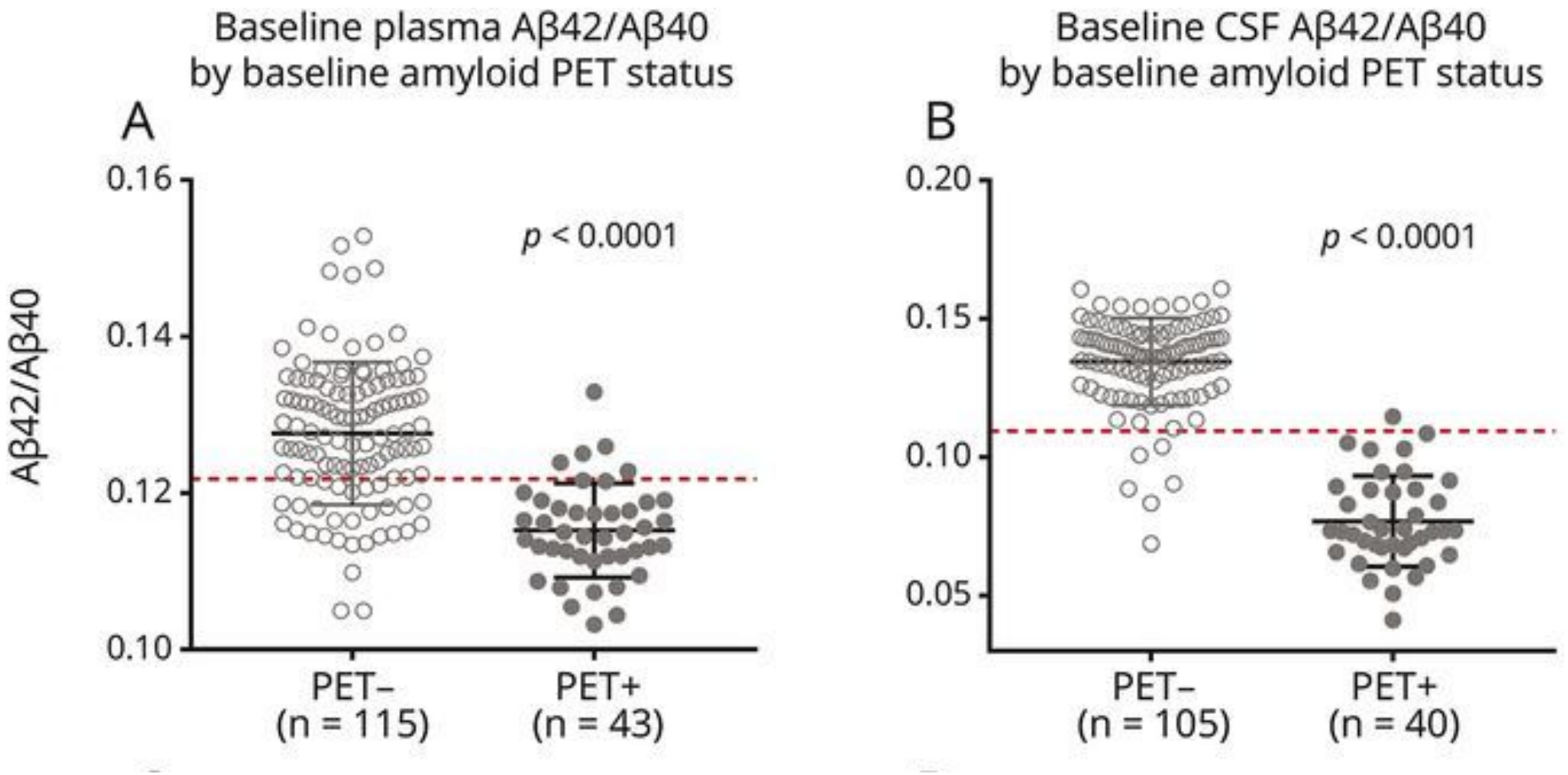
# AT(N) Framework: Biologically based AD criteria (2018)

| | A | T | (N) |
|---|---|---|---|
| Measuring | Aggregated Aβ | Aggregated Tau | Neurodegeneration |
| CSF (state) biomarker | ↓ Aβ or $A\beta_{42}/A\beta_{40}$ | ↑ P-Tau | ↑ T-Tau |
| Imaging (load) biomarker | Amyloid PET ligand binding | Cortical Tau PET ligand binding | FDG PET, MRI atrophy |

# CSF Aβ (A) and Tau (T) in Combination

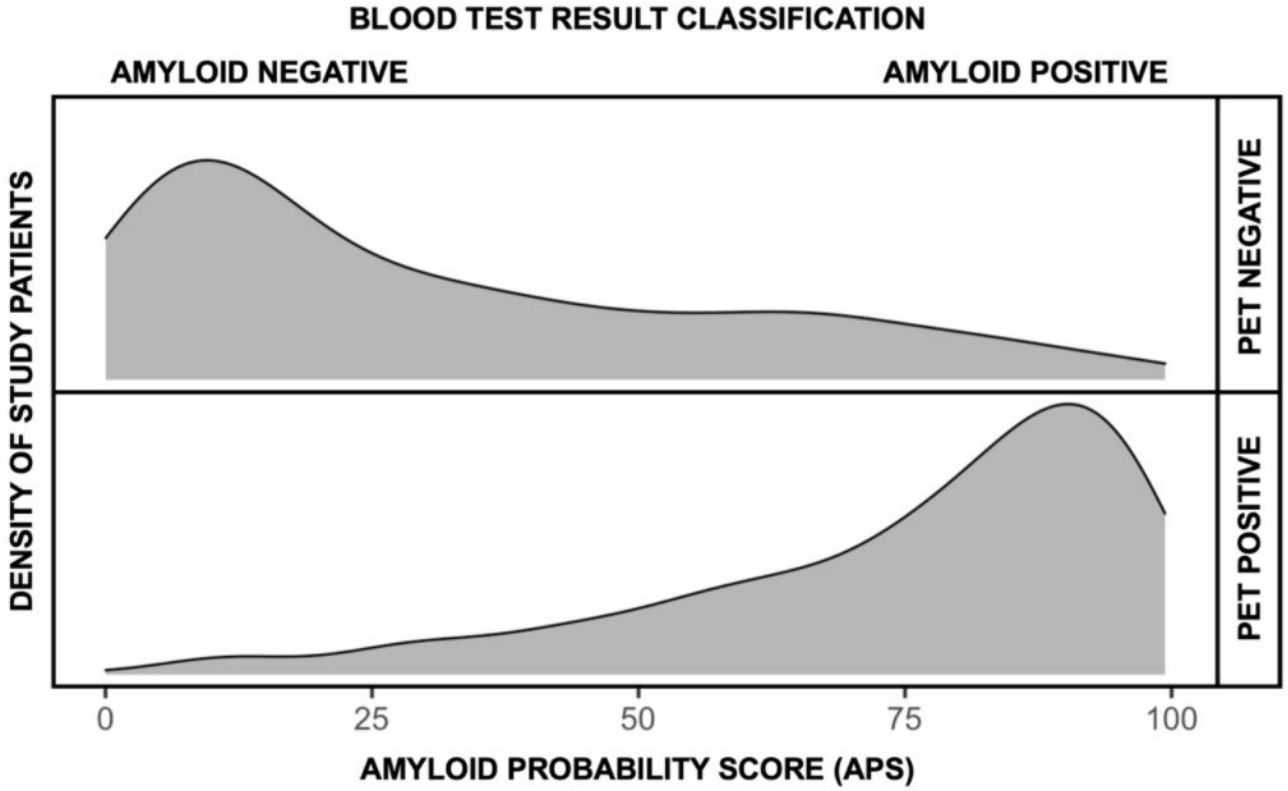


# New blood-based biomarkers for AD are coming



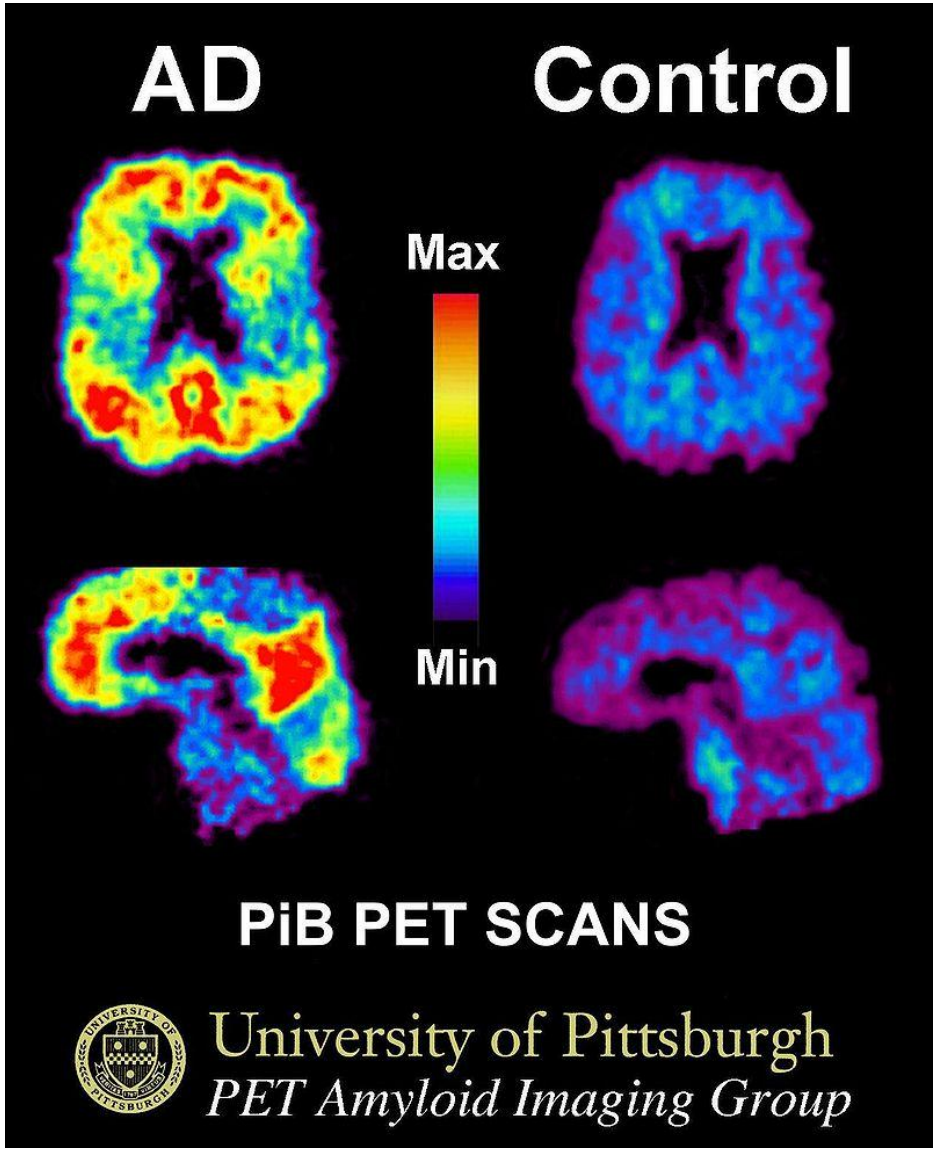
# PrecivityAD (A) now available

- Amyloid Probability Score (APS) based on
  - Plasma Aβ ratio
  - APOE genotype
  - Age

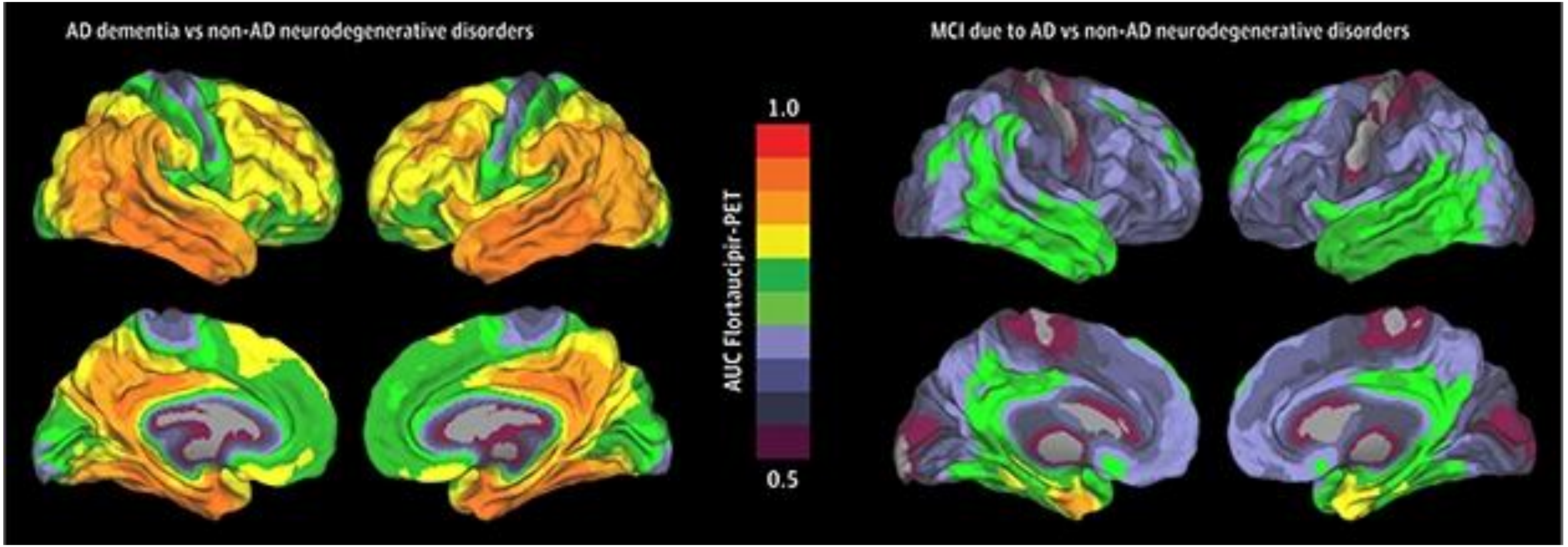


# Amyloid PET (A)

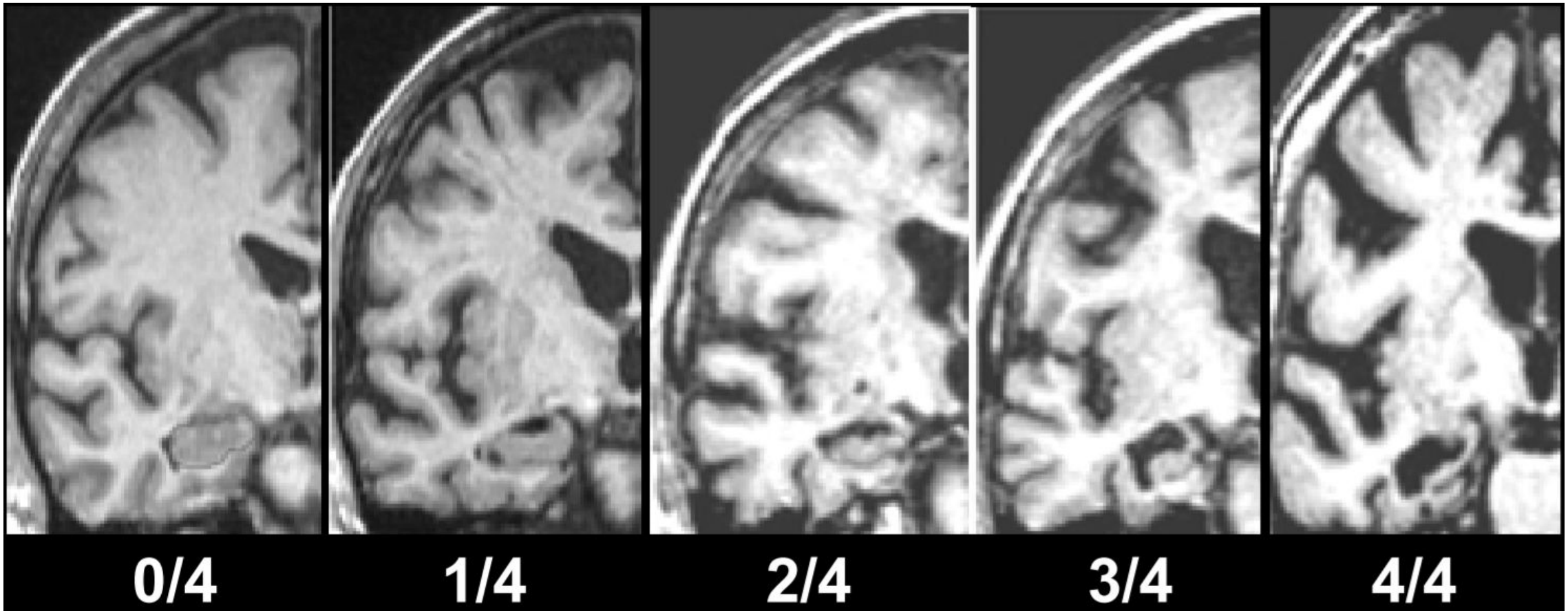
- Clinically available since 2012 (multiple F18 tracers)
- Not reimbursed by insurance so rarely ordered



# Tau PET (T): Research only for now

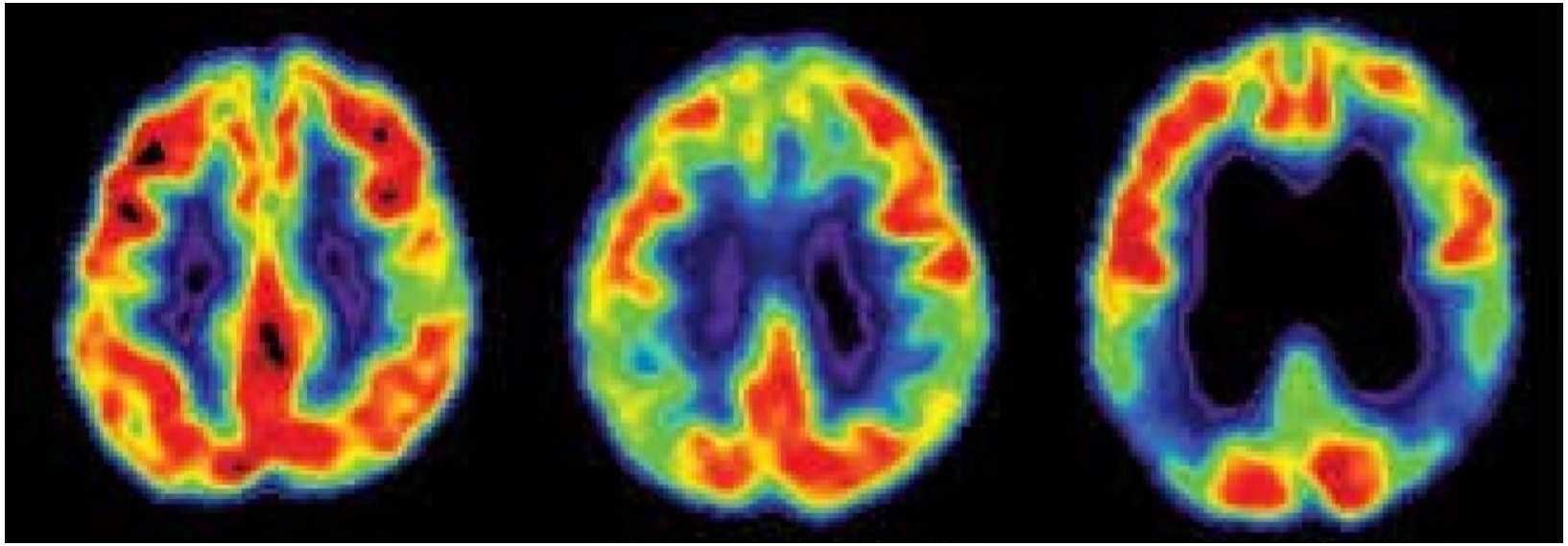


# Structural MRI: hippocampal atrophy (N)



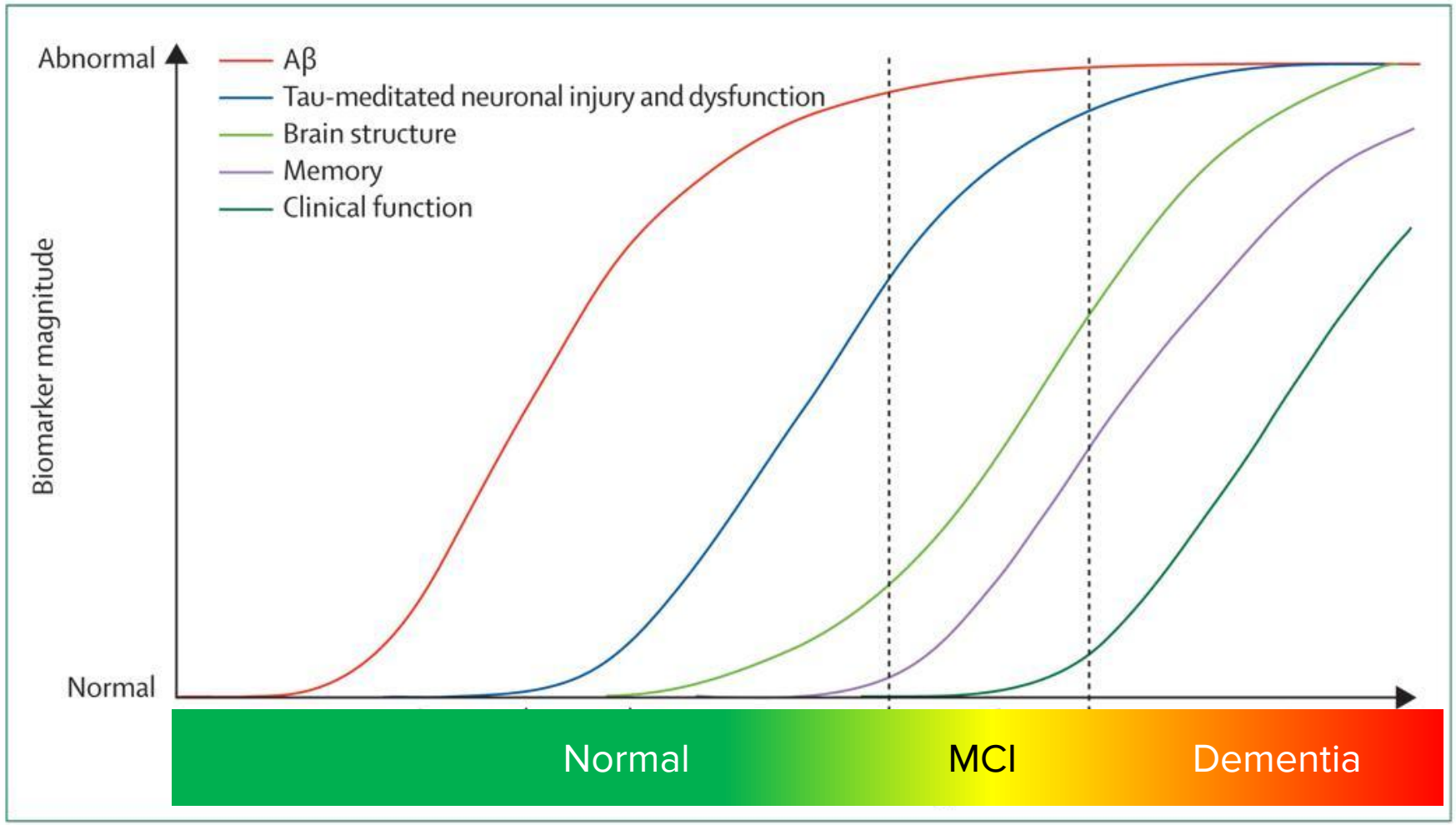
# FDG PET: cortical hypometabolism (N)

- $^{18}$F-Flurodeoxyglucose
- Marker for metabolically active brain regions
- Posterior cortical hypoactivity typical in AD



Normal MCI AD

# Timing of Amyloid and Tau in AD



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# How do we treat Alzheimer's disease?

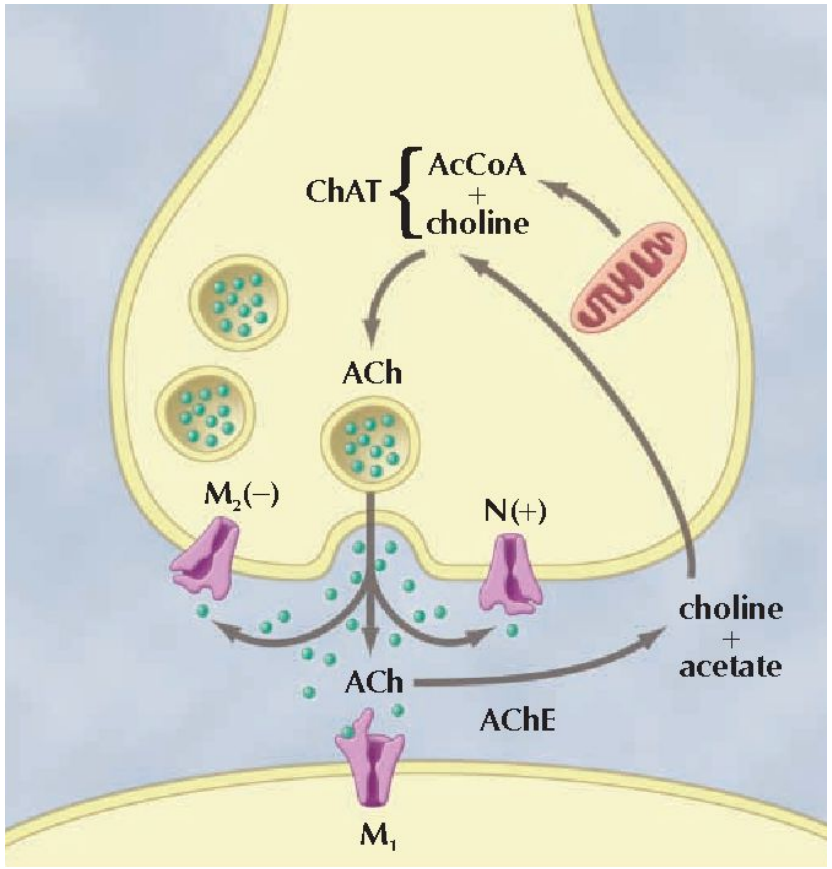
Cholinesterase inhibitors and memantine

Lifestyle changes

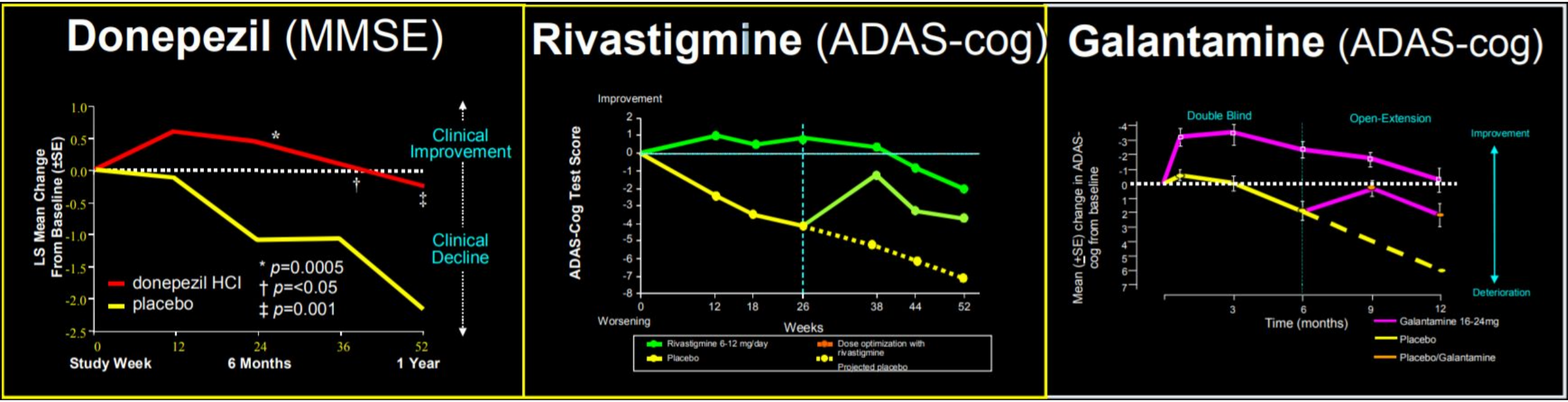
Disease-modifying therapies?

# FDA-Approved AD Therapeutics

- Acetylcholinesterase Inhibitors
  - Donepezil (1996)
  - Rivastigmine (1997)
  - Galantamine (2000)
- NMDAR Antagonist
  - Memantine (2003)
- Namzaric (2014)
  - Donepezil + Memantine



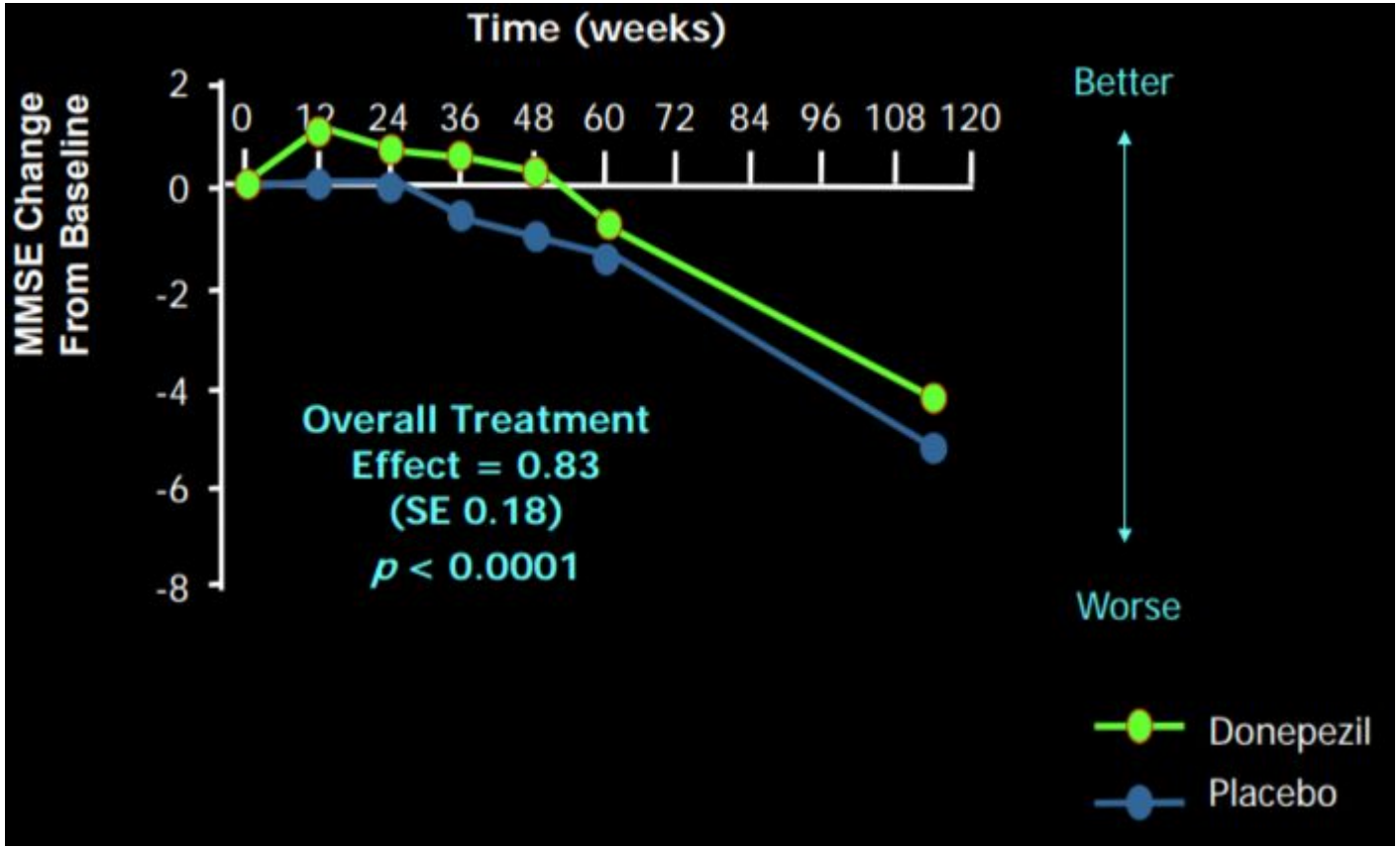
# AChE Inhibitors: Short-term Benefit in AD




At the end of 1 year, all three show no statistically significant decline from baseline on cognitive tests in mild-moderate AD px.

Winblad, 2001
Bloom, 1998
Raskind, 2000

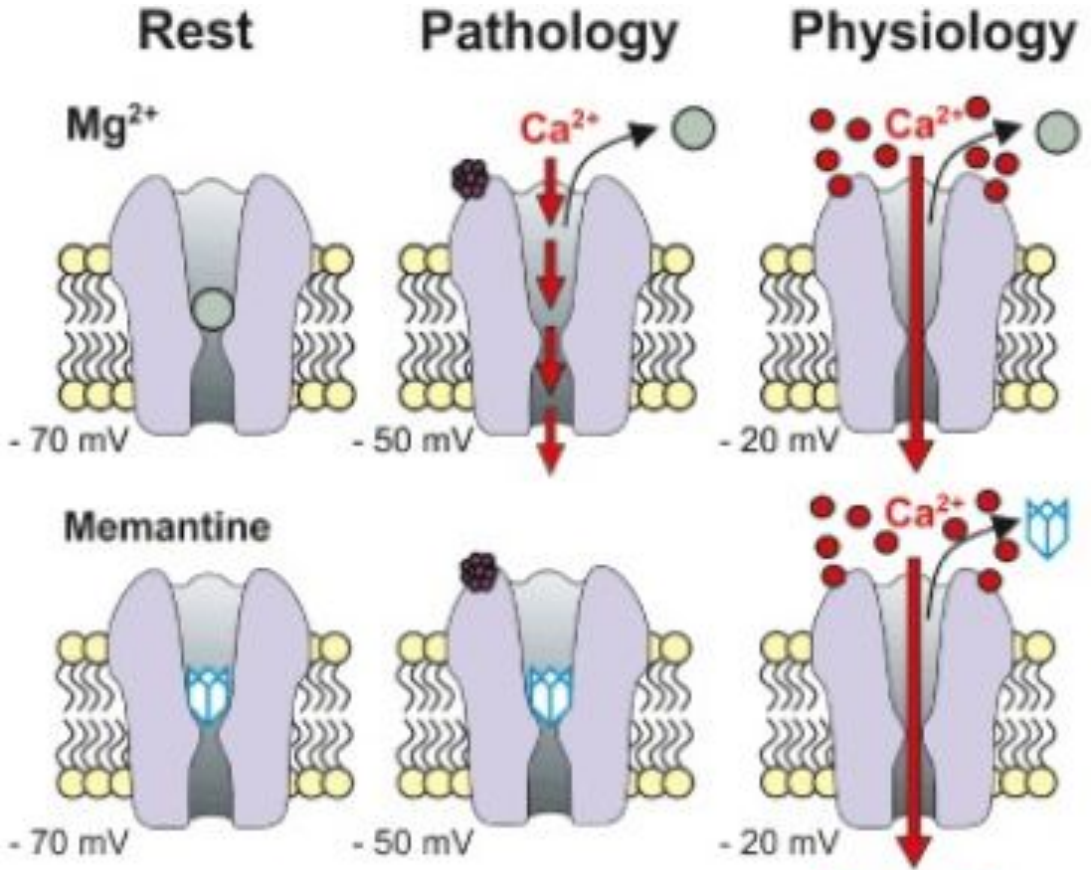
# AChE Inhibitors: Long-term Decline Resumes



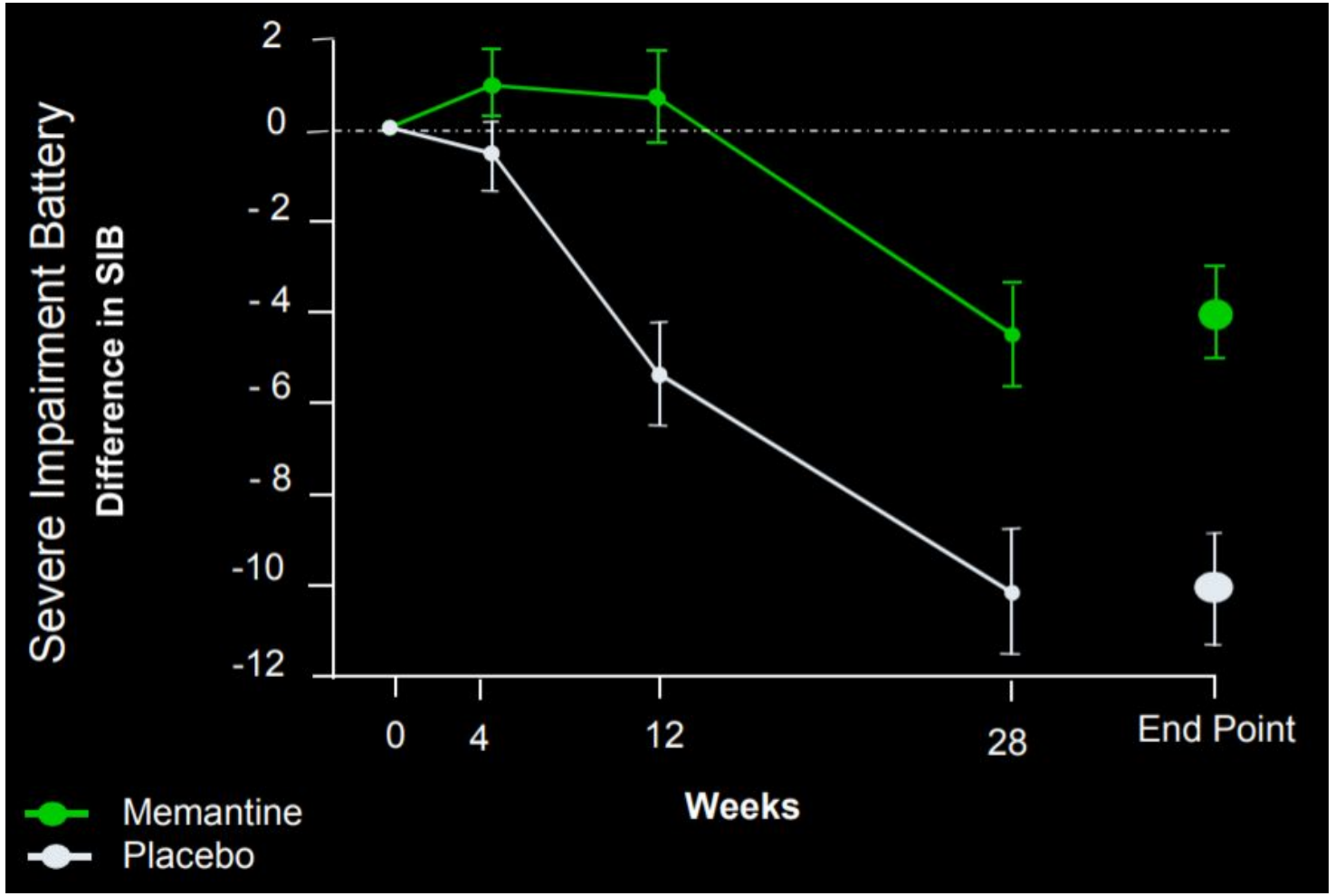

Courtney, 2004

# NMDAR Antagonist for AD (memantine)

Goal: Reduce excitotoxic calcium influx through NMDARs



# Memantine: Short-term Benefit in AD (<13 MMSE)




Reisberg, 2003

# Other Treatment Strategies for AD

## Pharmacological

SSRIs, esp. citalopram

Atypical antipsychotics

## Lifestyle

Exercise

Mental activity

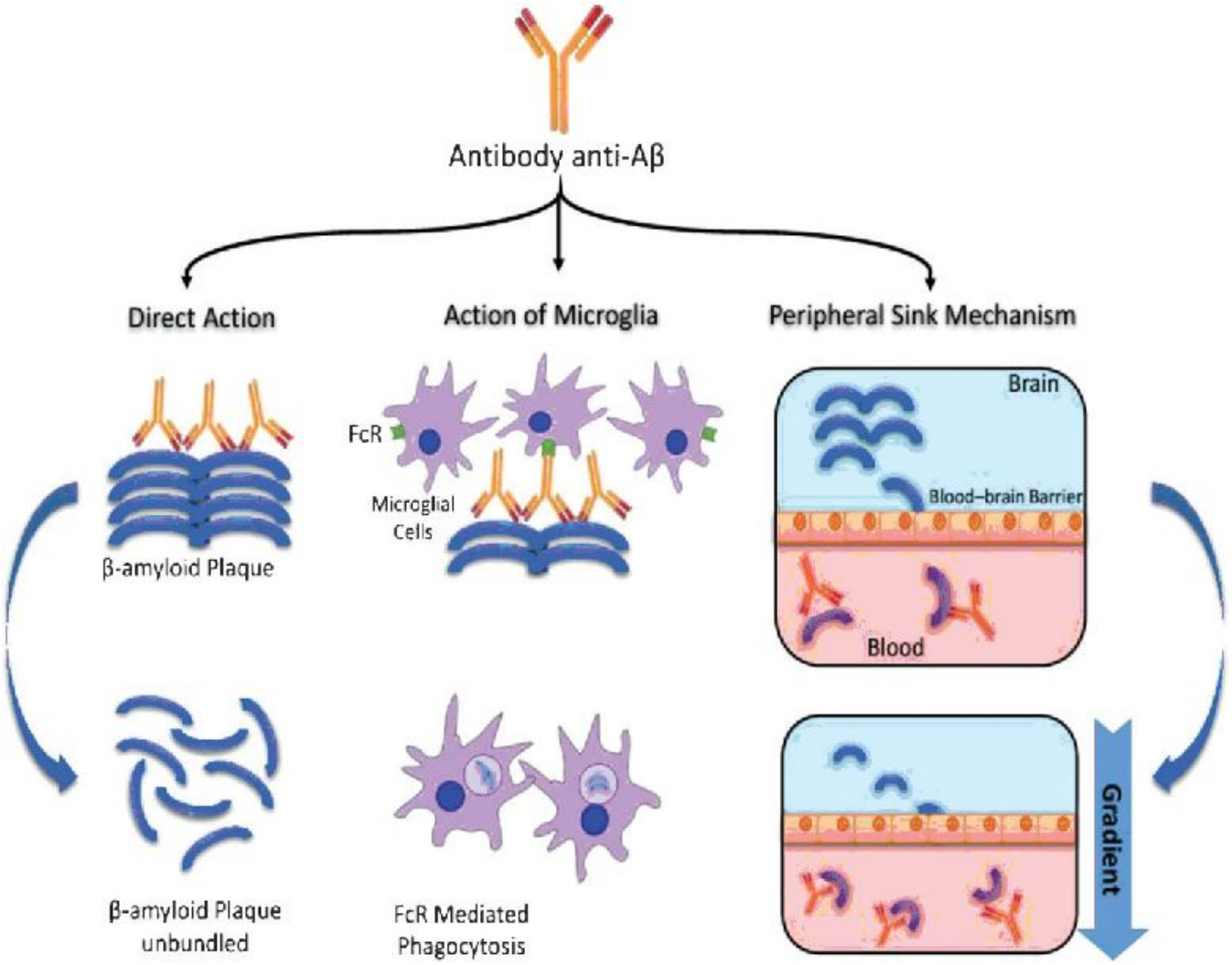
Diet

Sleep

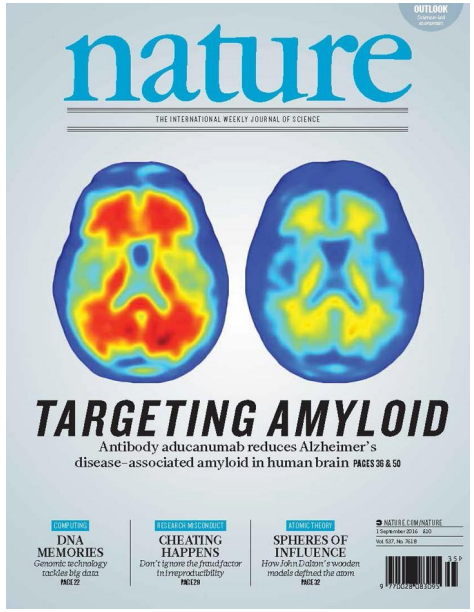
CV Risk factor reduction

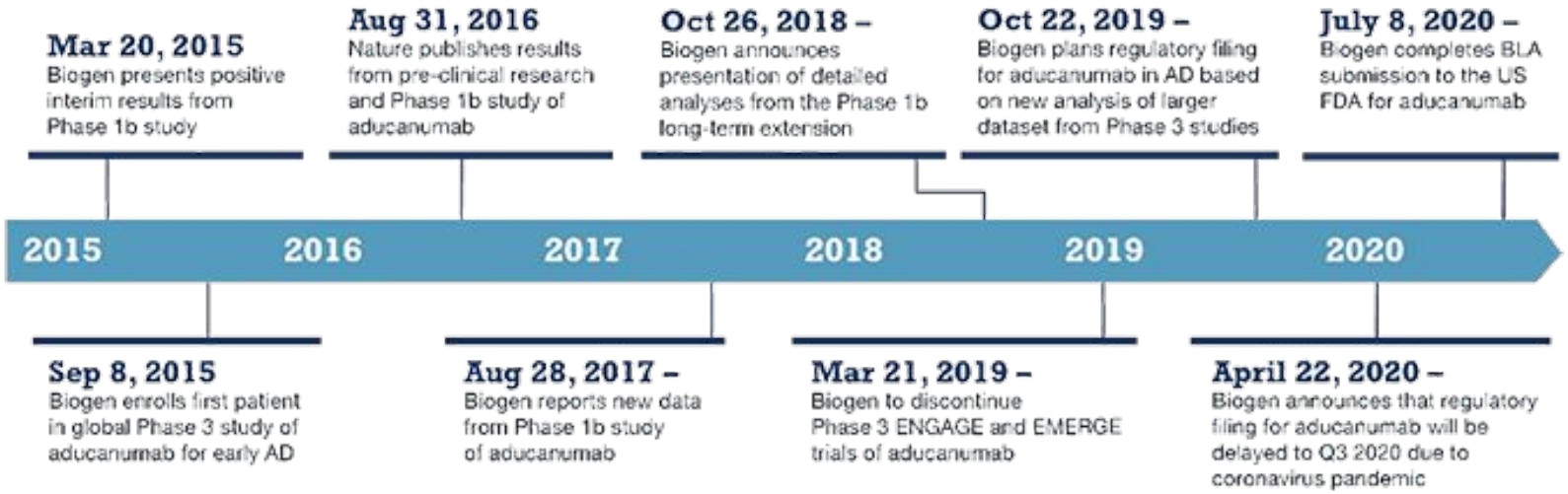
- Hypertension
- Cholesterol

# Amyloid Immunotherapy



# Aducanumab: the next AD drug?



# Brain Aging and Memory in the South


- NIA-funded network of AD research centers
- Theme: Deep South disparities
- Focus: Black or African American recruitment

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# Take Homes

1. Early onset AD is often genetic, but not usually autosomal dominant
   - Genetic risk factors, especially *APOE*
2. AD pathology starts decades before symptoms, and can be detected by clinically available biomarkers
   - Amyloid PET, CSF Aβ/Tau, blood-based biomarkers
3. Cholinesterase inhibitors and lifestyle modifications are first-line treatment recommendations
   - SSRI's often helpful; Memantine in more advanced dementia
4. The era of disease-modifying treatments for AD is near
   - Amyloid immunotherapy likely will be first