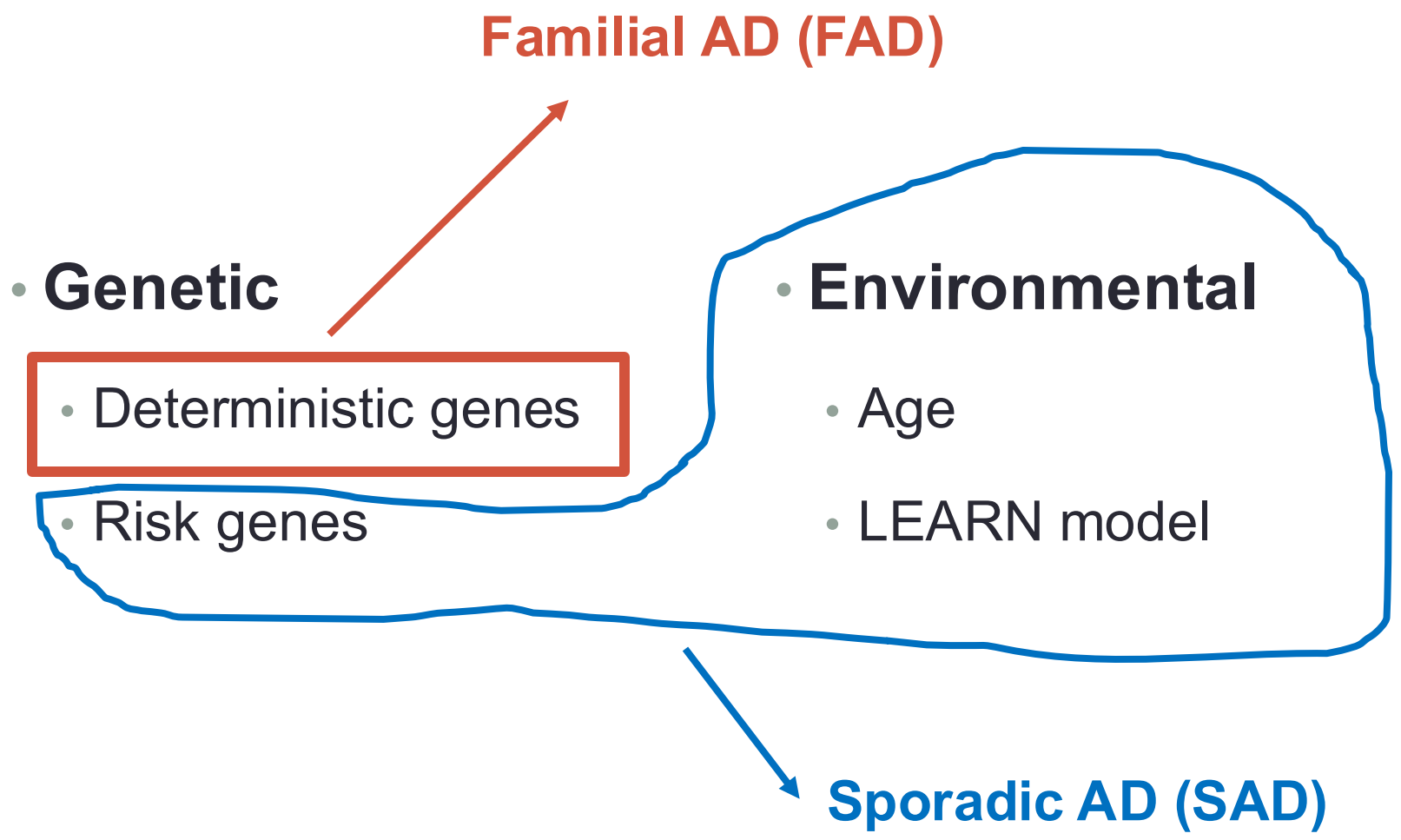
# WEEK 9

# ALZHEIMER'S DISEASE PART II

# Alzheimer's Disease – Overview

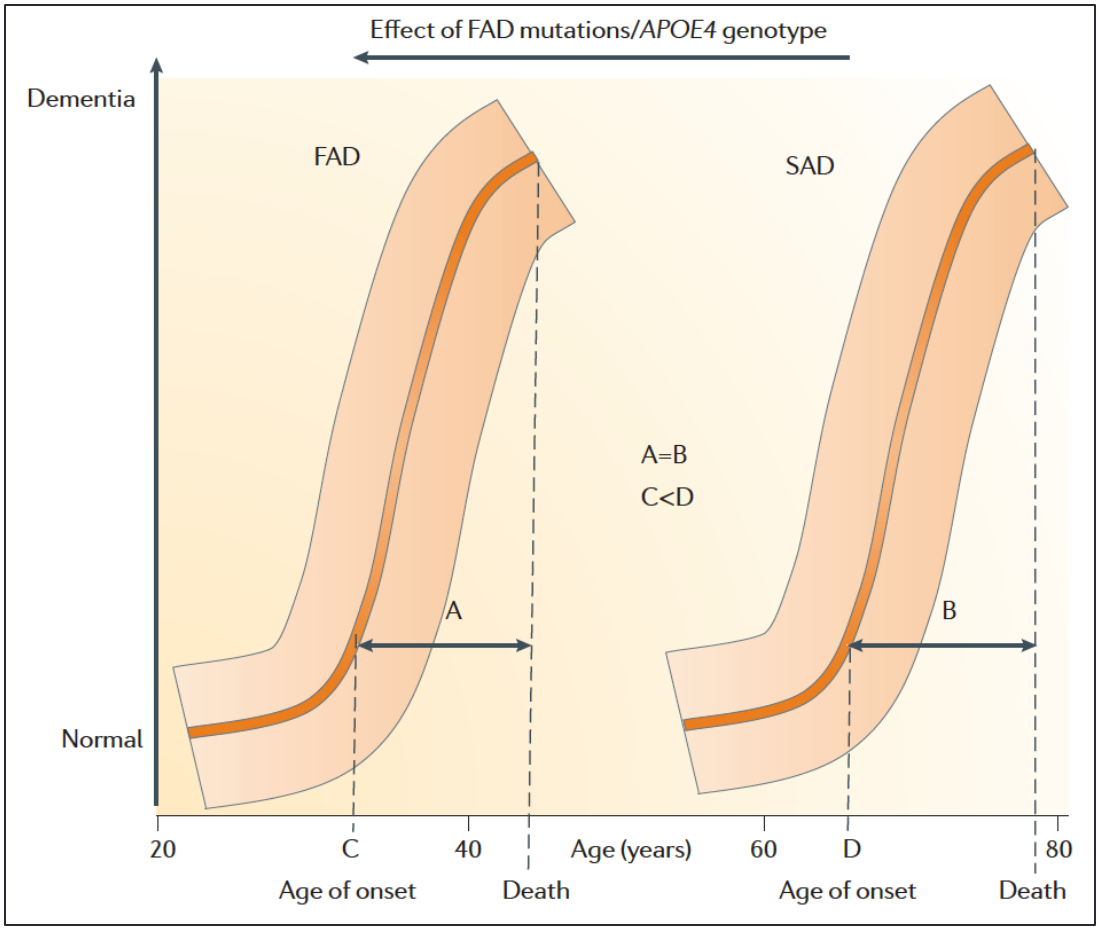
1) Check your knowledge about AD
2) Prevalence and history
3) Symptomatology
4) Pathophysiological hallmarks
   - Tau tangles
   - Amyloid plaques
5) **Risk factors**
   - Genes
   - Environment
6) Treatment approaches
7) Diagnostics and biomarkers

# Risk factors for AD



# Familial vs sporadic AD:

Familial AD (FAD)




Sporadic AD (LOAD)

LOAD=Late-onset Alzheimer's disease

# Familial AD is driven by genetic factors

**"Deterministic" genes**

= Directly cause a disease, everyone inheriting them will develop the disorder.

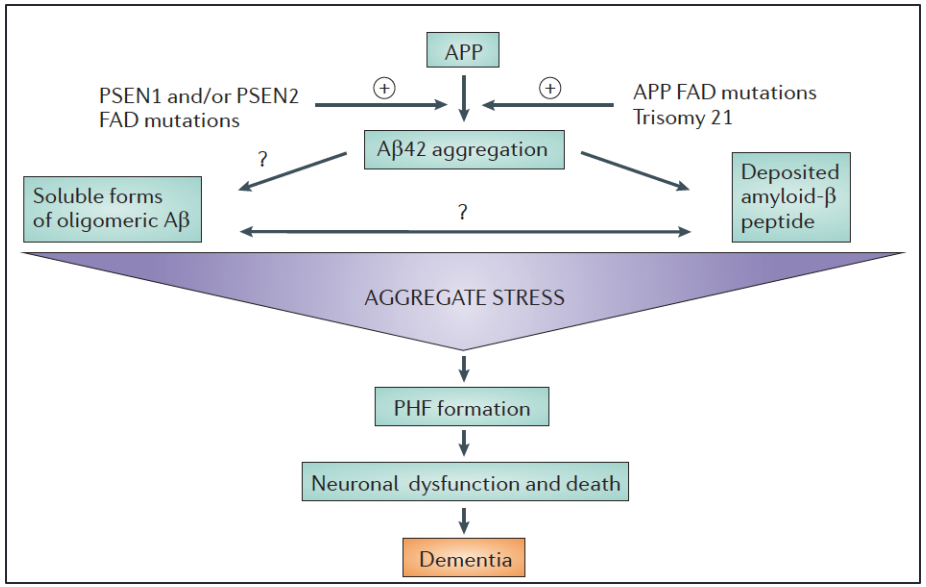
- Rare genes that directly cause Alzheimer's in only a few hundred extended families worldwide.
- These genes cause an early-onset of the disease
- This type is known as **"Familial Alzheimer's disease" (FAD)**
- **BUT**: True familial AD accounts for **less than 5%** of the cases.
  - The majority of cases do not have a genetic underpinning with high penetrance
  - This type of the disease is known as **"Sporadic Alzheimer's disease"**

# Familial AD is driven by genetic factors

- **There are two types of "deterministic", early-onset genes**:
  - APP mutations
  - Mutations in PSEN1 and/or PSEN2:
    - Code for γ-secretase complex

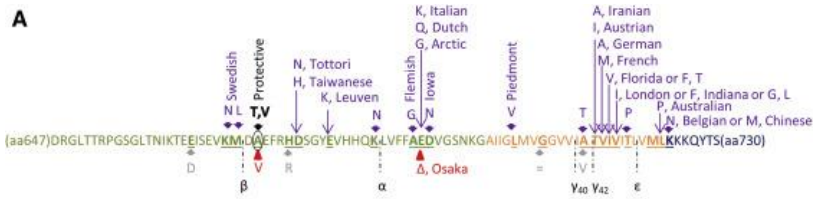
## AD-Mutations

| Chromosome 21 | Chromosome 14 | Chromosome 1 |
|---|---|---|
| Abnormal **amyloid precursor protein (APP).** | Abnormal **presenilin 1** | Abnormal **presenilin 2** |

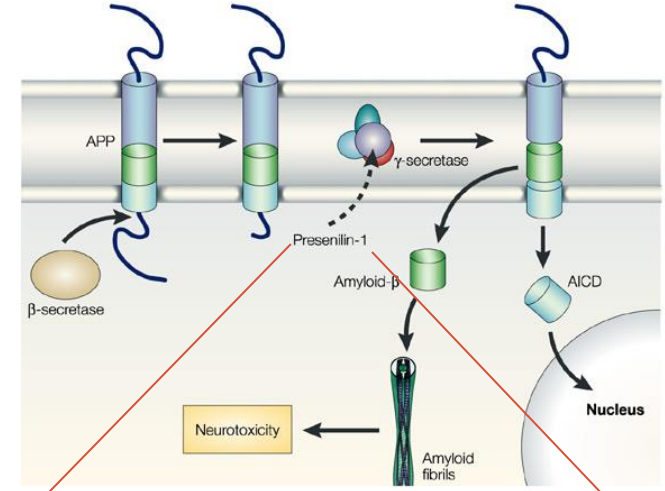


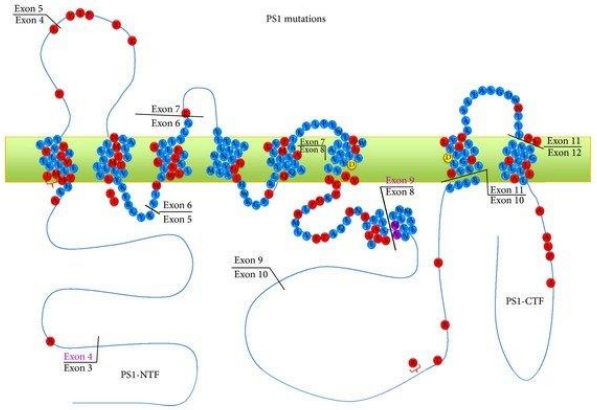
# Genetic risk factors for AD

- APP mutations:




- PSEN mutations



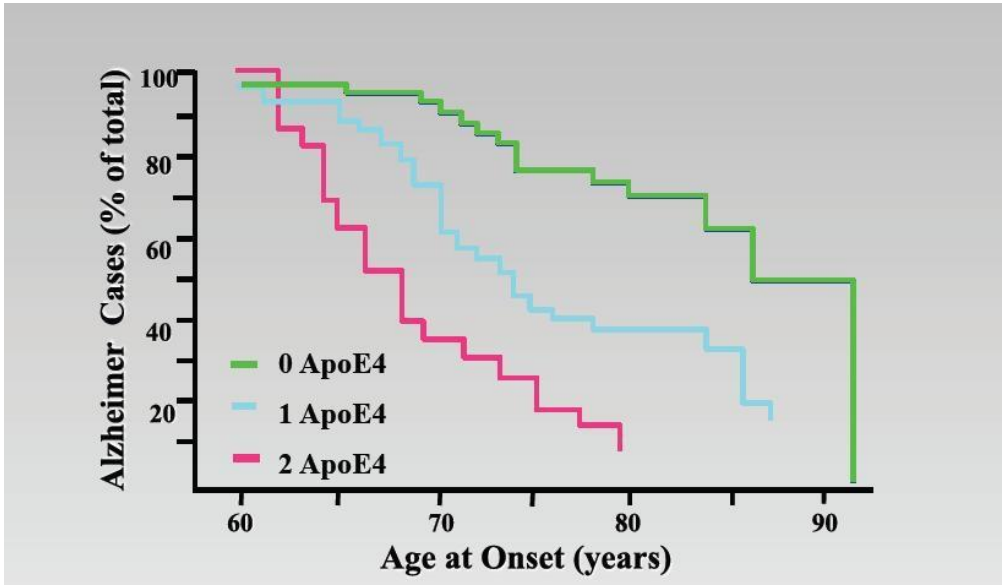
# Sporadic AD can be predisposed by risk genes

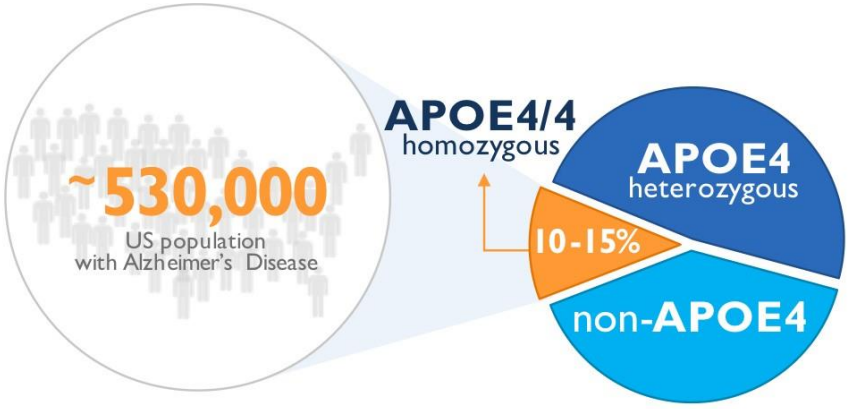
## Risk Genes

- Risk genes increase the likelihood of developing a disease but do not guarantee it will happen.
- **APOE-e4**
  - best known example for SAD
  - Those who inherit one copy of APOE-e4 have an increased risk of developing Alzheimer's.
  - Those who inherit two copies have an even higher risk.
  - In addition to raising risk, APOE-e4 may tend to make symptoms appear at a younger age than usual.

# APOE4 is the strongest genetic risk factor for patients with late-onset (sporadic) Alzheimer's disease

## Survival Curve



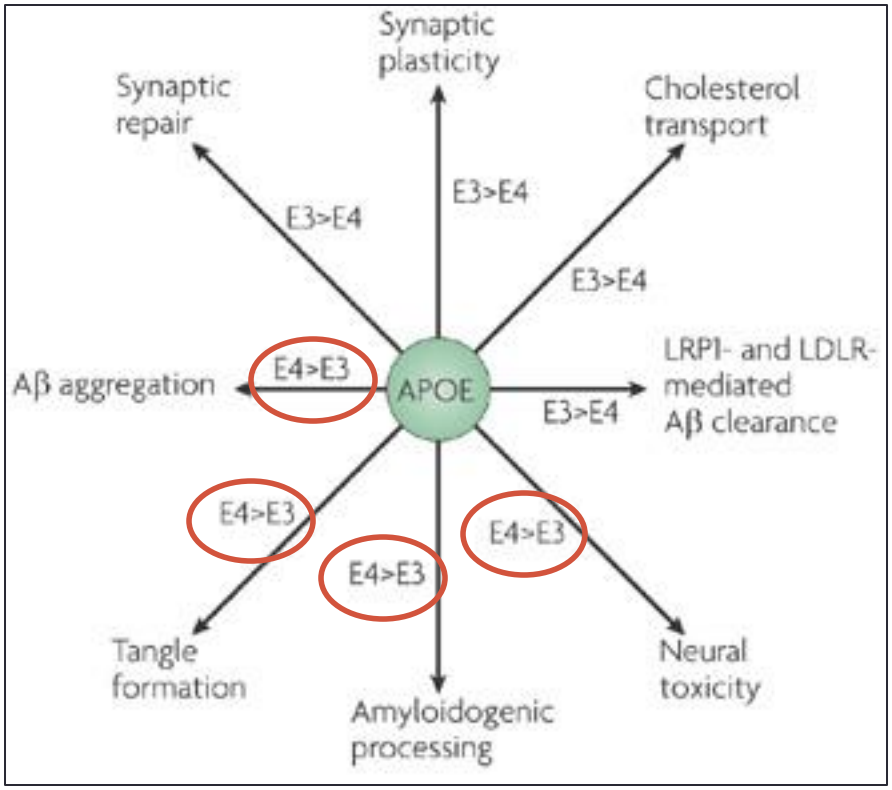

There are three major isoforms (ApoE2, ApoE3, and ApoE4) in humans.

- ApoE2 is produced predominantly by astrocytes and to some extent microglia
- ApoE3 is also expressed in neurons in response to excitotoxic injury
- ApoE4 plays important role in the transport of HDL-like particles cholesterol and phospholipid between cells.

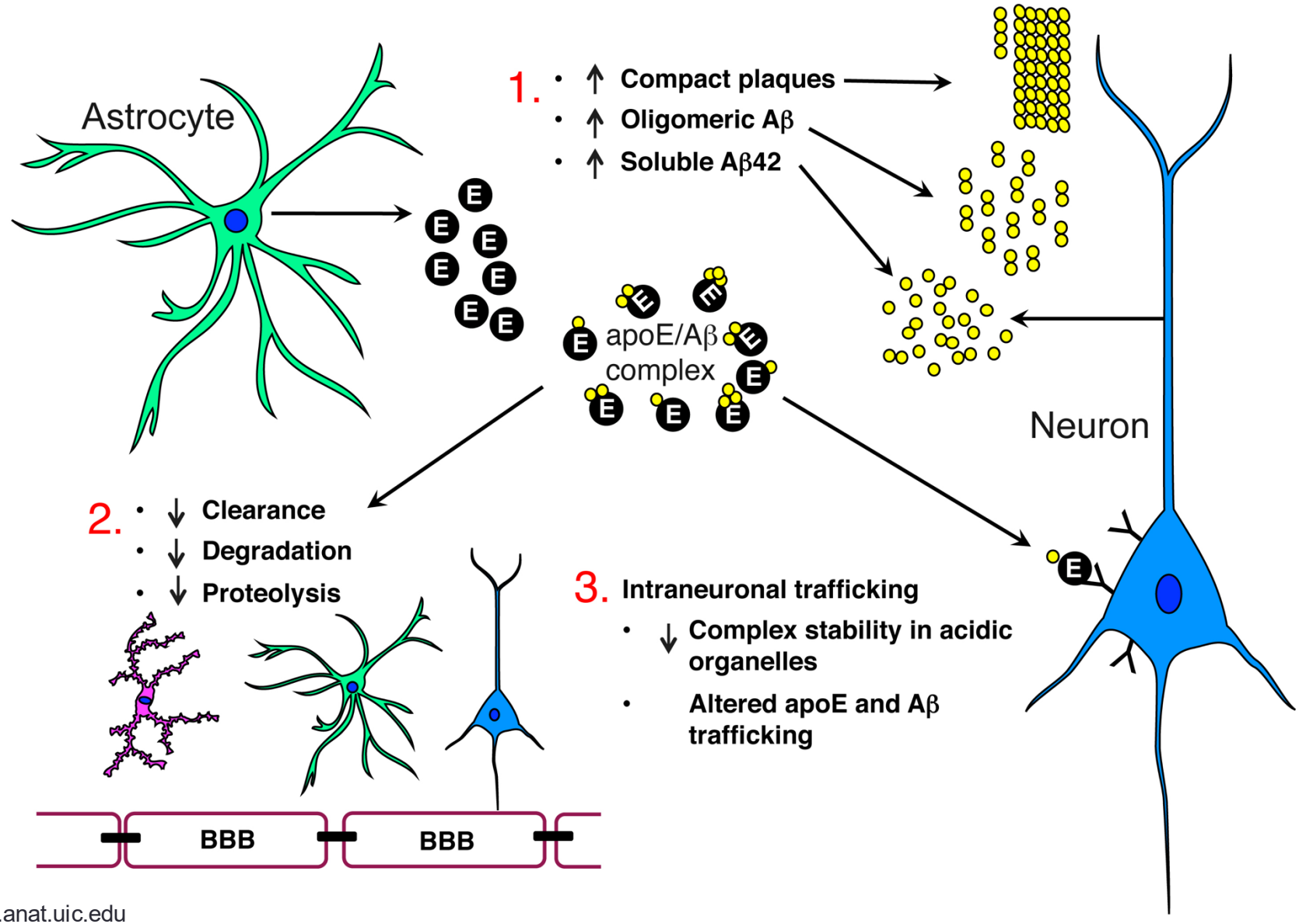
# Genetic risk factors for AD: APOE4

- Mechanism of Action:

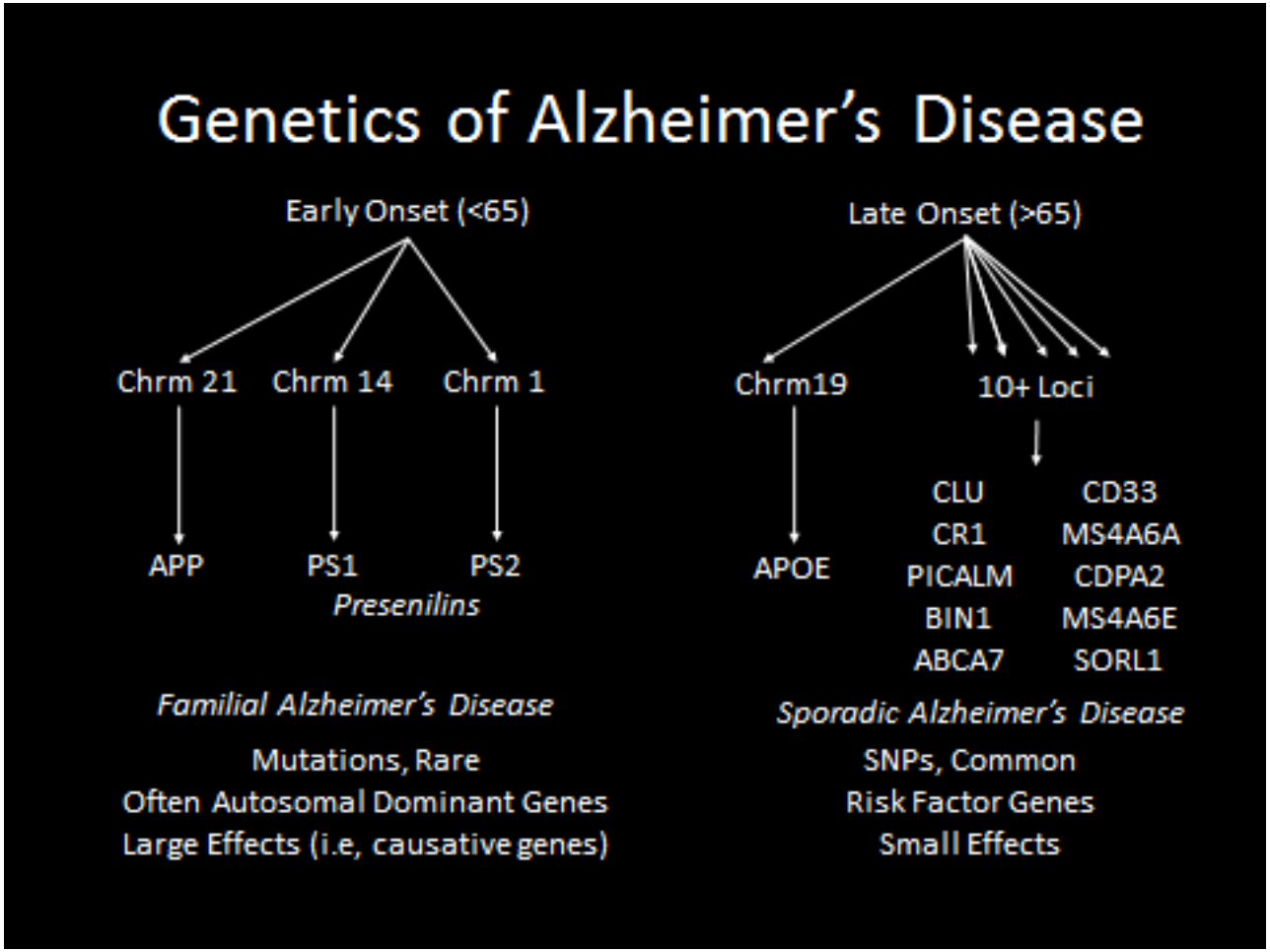
ApoE4



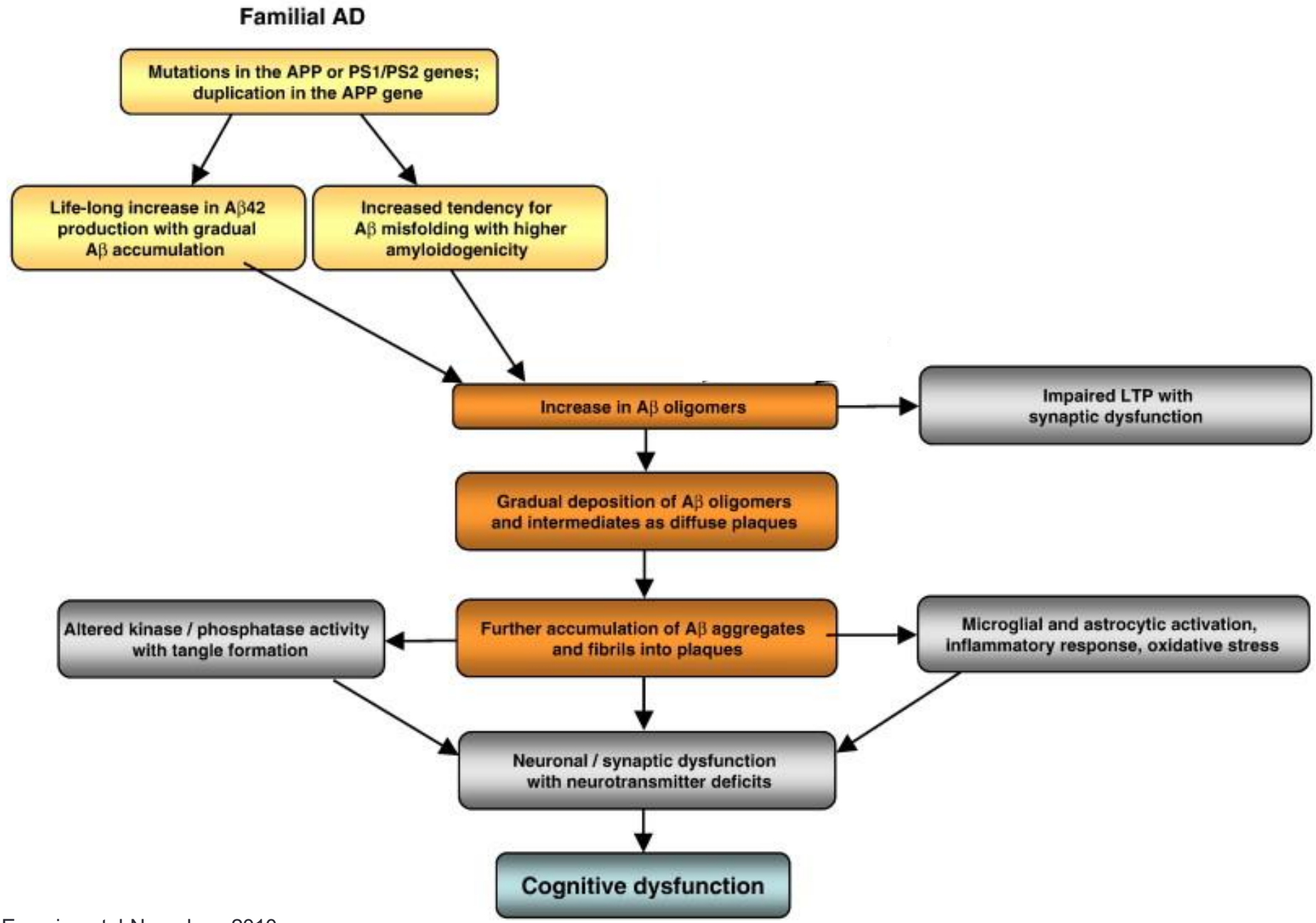
# Proposed mechanism: APOE4/Aβ complex



# Summary genetic risk factors:

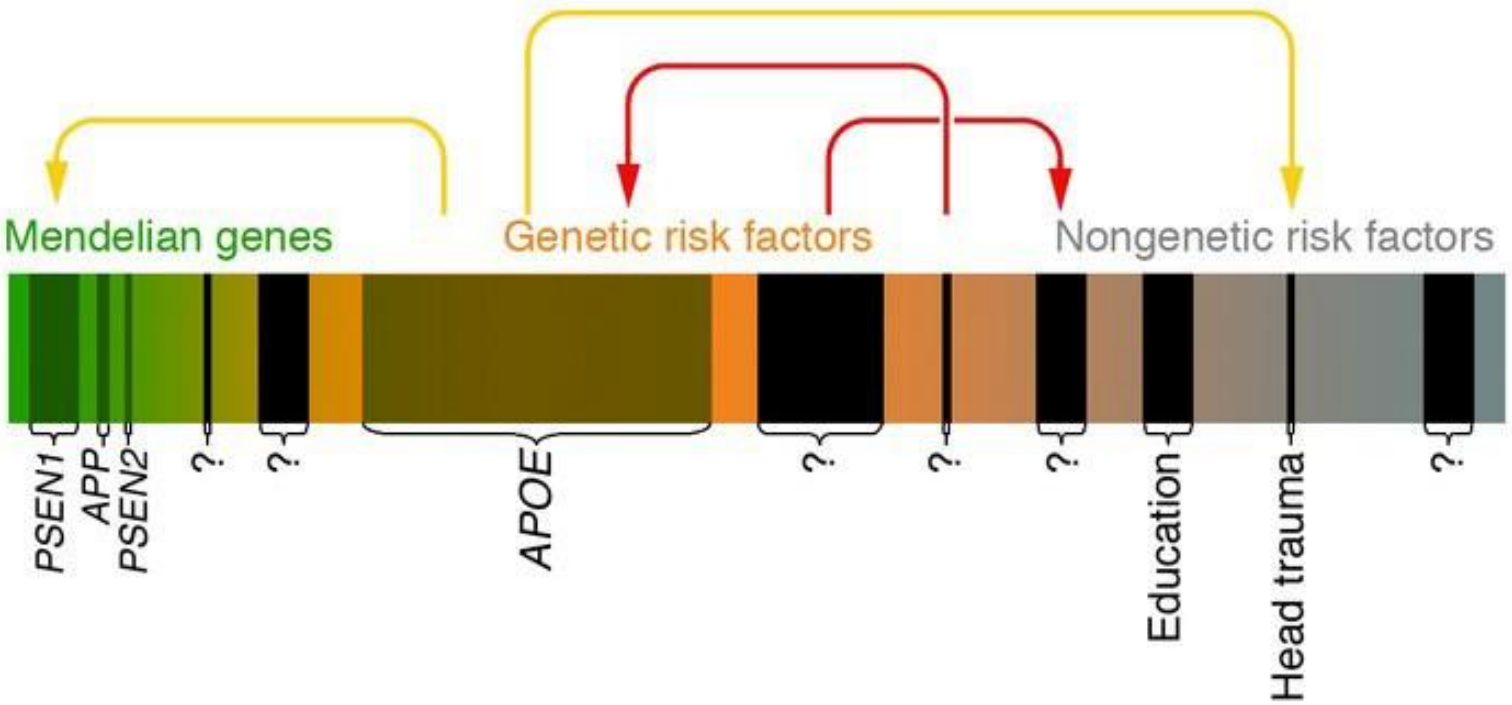


# Alzheimer's Disease: FAD vs SAD



# The (genetic) etiology of AD

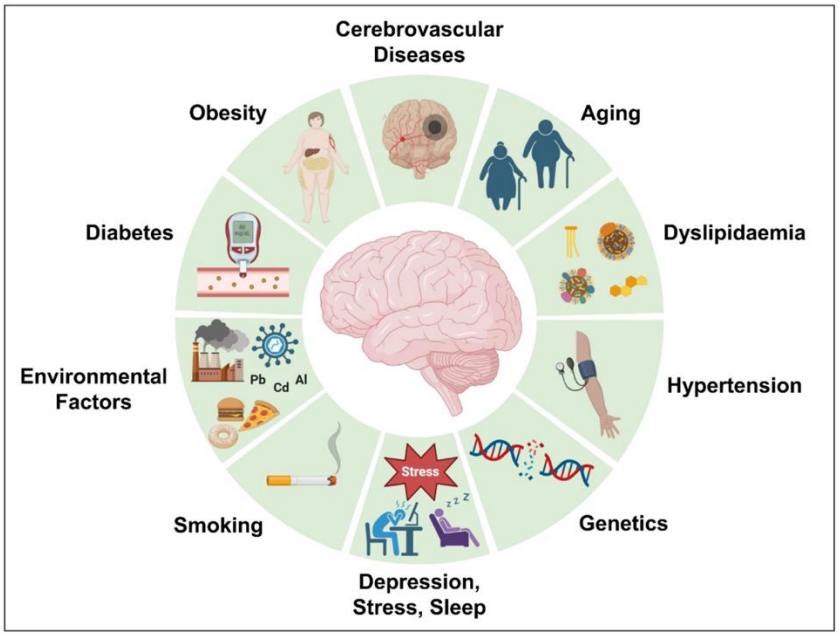
The **risk spectrum** predisposing to AD as one continuum




- The width of these boxes approximately represents the relative contribution to the overall risk
- Colored arrows indicate possible gene-gene and gene-environment interaction patterns

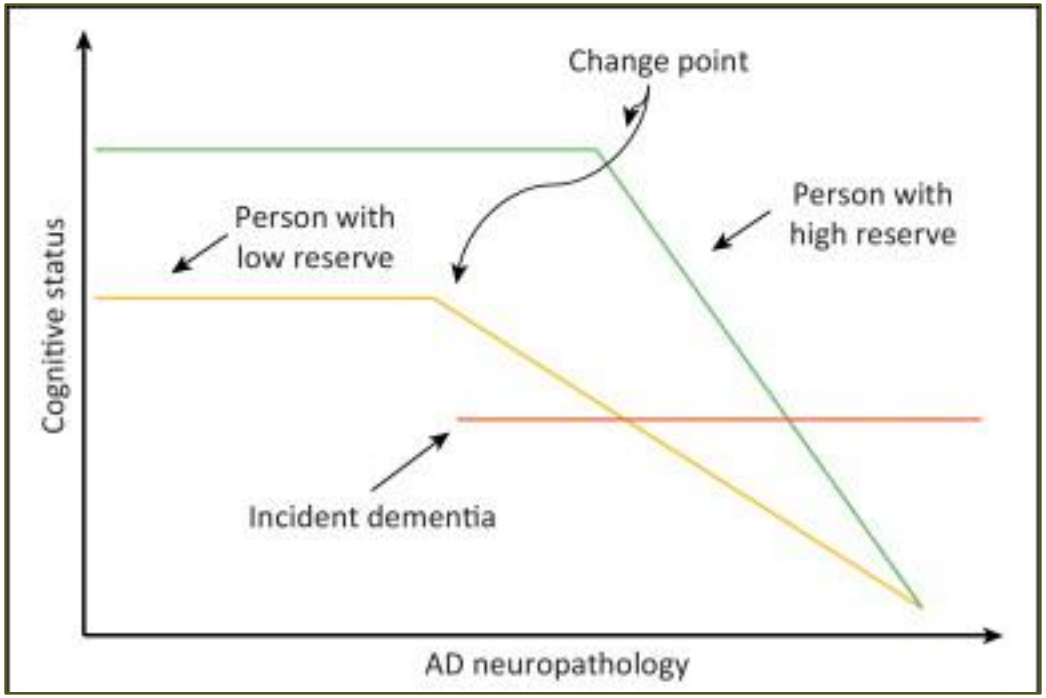
# Environmental risk factors for AD

- Age
- Carrying a risk gene (APOE4 and others)
- Others:
  - Diabetes mellitus
  - Midlife hypertension
  - Midlife obesity
  - Midlife inactivity
  - Depression
  - Smoking
  - Low educational attainment



# Low educational attainment and AD:

- Cognitive Reserve Hypothesis



# Low educational attainment and AD:

- Cognitive Reserve Hypothesis

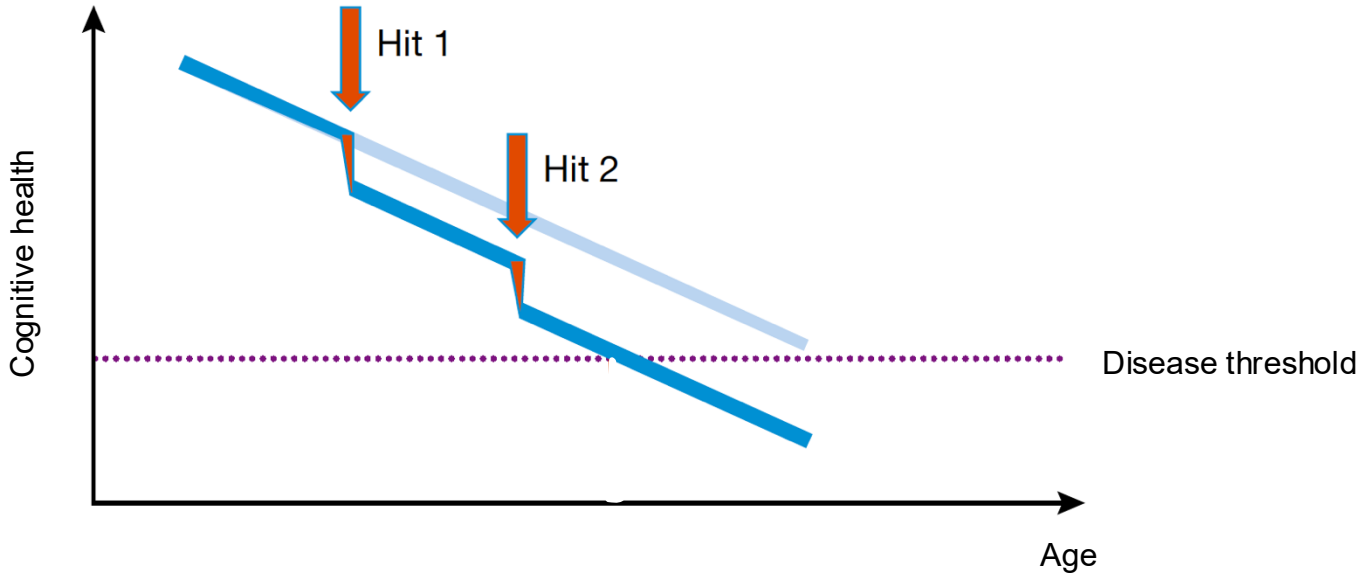
**TABLE 3. Relative risks of clinically diagnosed Alzheimer's disease or dementia associated with combinations of education and occupation-based socioeconomic status (lifetime longest-held job), The Kungsholmen Project, Stockholm, Sweden, 1987–1993**

| | All subjects (no.) | Alzheimer's disease | | | | | All types of dementia | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | No. of cases | RR*,† | 95% CI* | RR‡ | 95% CI | No. of cases | RR† | 95% CI | RR‡ | 95% CI |
| High education/high SES* | 353 | 14 | 1 | | 1 | | 22 | 1 | | 1 | |
| High education/low SES | 36 | 1 | 0.6 | 0.1, 4.7 | 0.7 | 0.1, 5.5 | 3 | 1.2 | 0.4, 4.1 | 1.3 | 0.4, 4.4 |
| Low education/high SES | 220 | 25 | 3.1 | 1.6, 6.0 | 3.2 | 1.6, 6.1 | 30 | 2.4 | 1.4, 4.2 | 2.3 | 1.3, 4.1 |
| Low education/low SES | 301 | 36 | 3.2 | 1.7, 5.9 | 3.1 | 1.6, 5.7 | 46 | 2.6 | 1.6, 4.4 | 2.4 | 1.5, 4.0 |

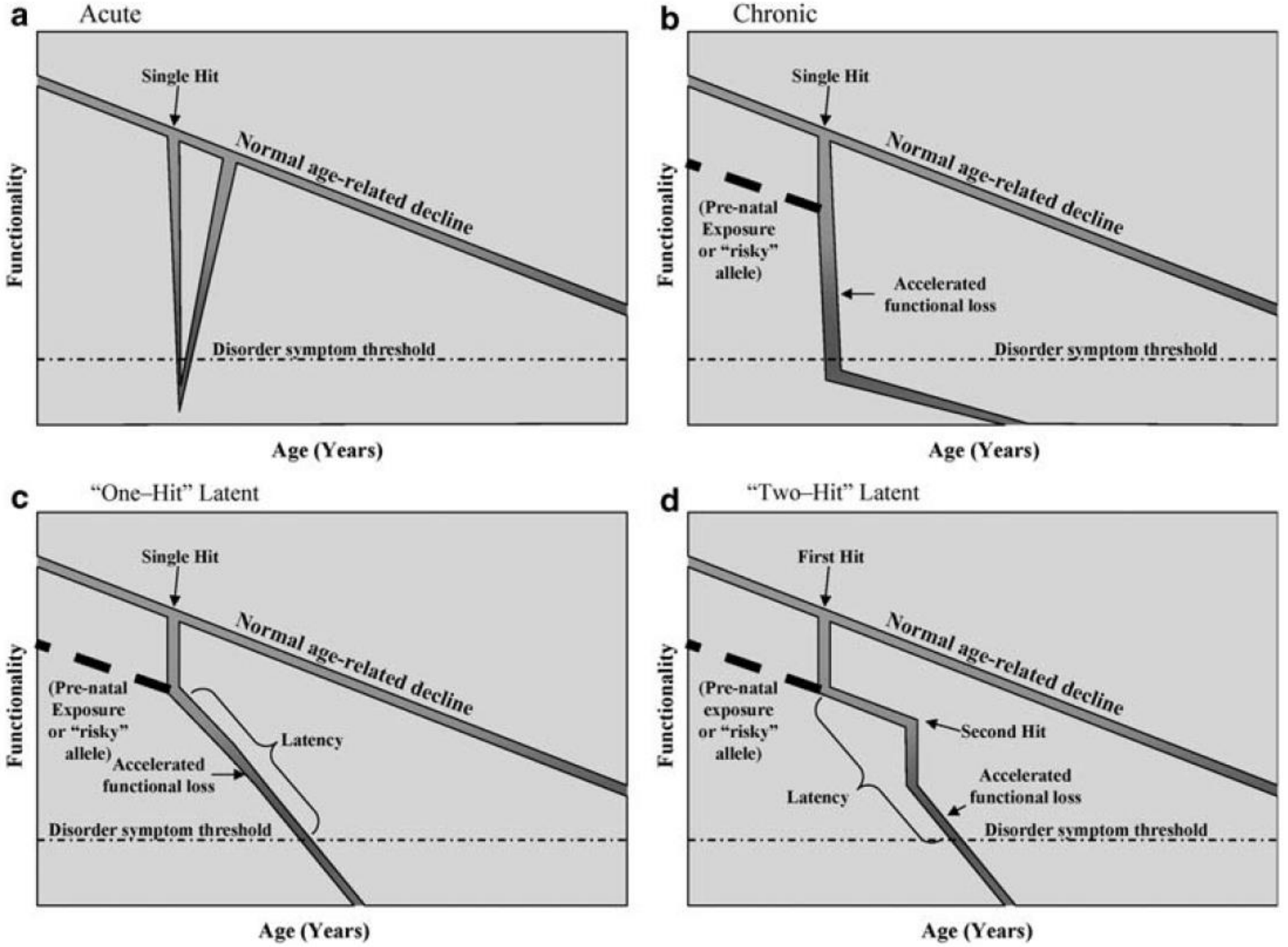
* RR, relative risk; CI, confidence interval; SES, socioeconomic status.
† Relative risks were estimated after adjustment for age and gender.
‡ Relative risks were estimated after adjustment for age, gender, vascular diseases index, and alcohol data.

# The LEARn model:

- =Latent Early-Life Associated Regulation
- Not a single hit can explain the disease
- "Multiple hit hypothesis" for idiopathic neurodegenerative disorders:



# Alzheimer's Disease



# Alzheimer's Disease is a monogenetic disorder.

A. True
B. False

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# What are differences between familial and sporadic AD?

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# Alzheimer's Disease – Overview

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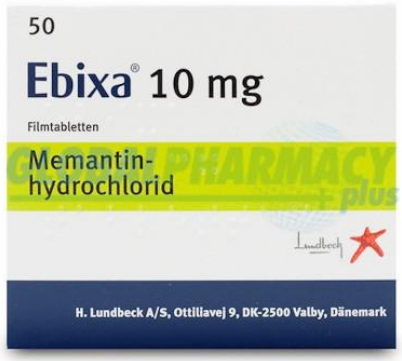
6) **Treatment approaches**
7) Diagnostics and biomarkers

# Treatment approaches for AD:

- Goals:
- reduce (cognitive) symptoms
- reduce (or slow down) pathologies

# 1) Reduce cognitive symptoms

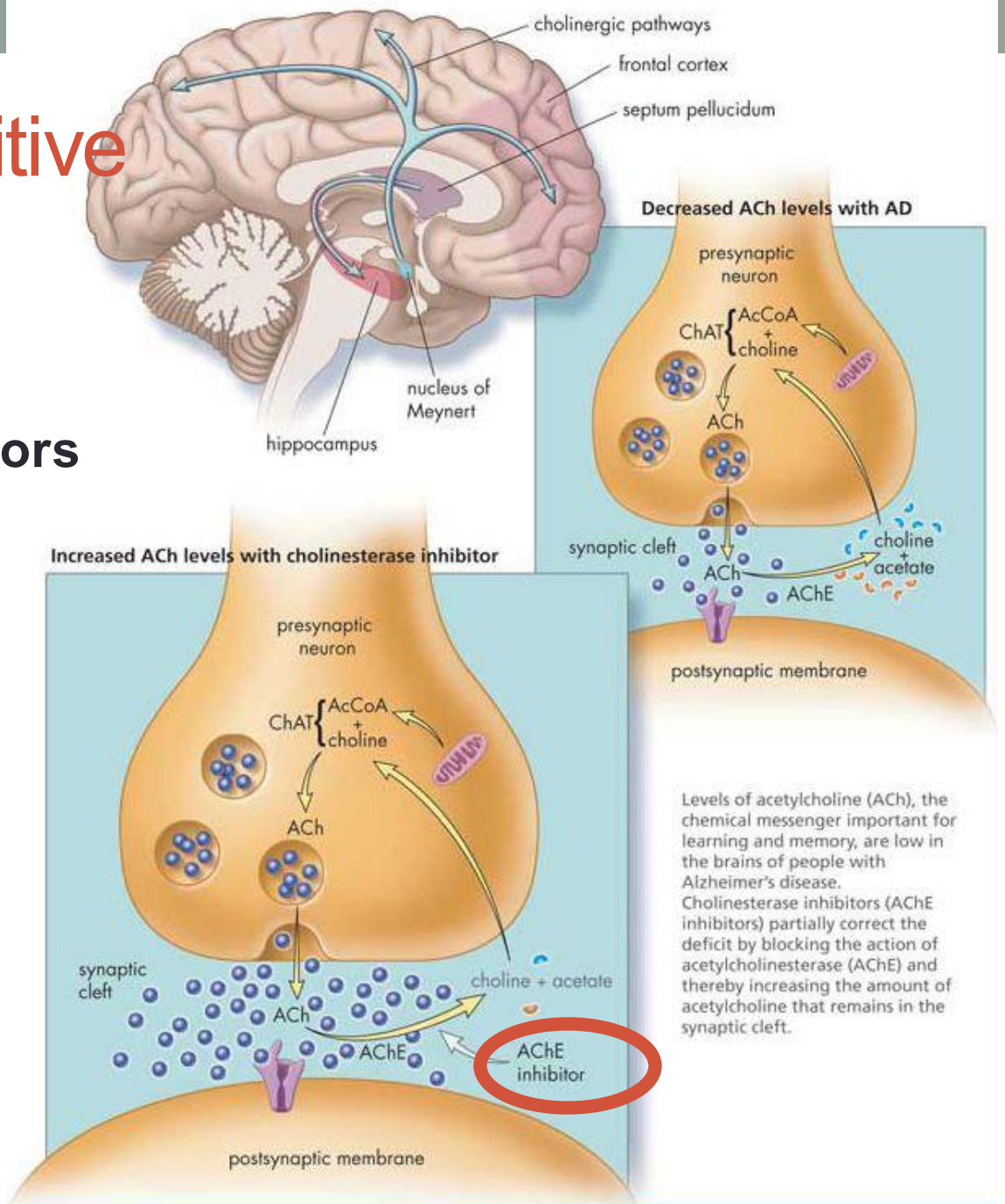
- 2 types of FDA approved drugs against **cognitive symptoms**
  - **Cholinesterase inhibitors**
    - Donepezil (Aricept)
    - Rivastigmine (Exelon)
    - Galantamine (Razadyne)
    - Tacrine (Cognex)


  - **NMDA receptor antagonist:**
    - Maintenance of glutamatergic synaptic transmission, thereby increasing learning and memory capacities
      - Memantine (Ebixa)

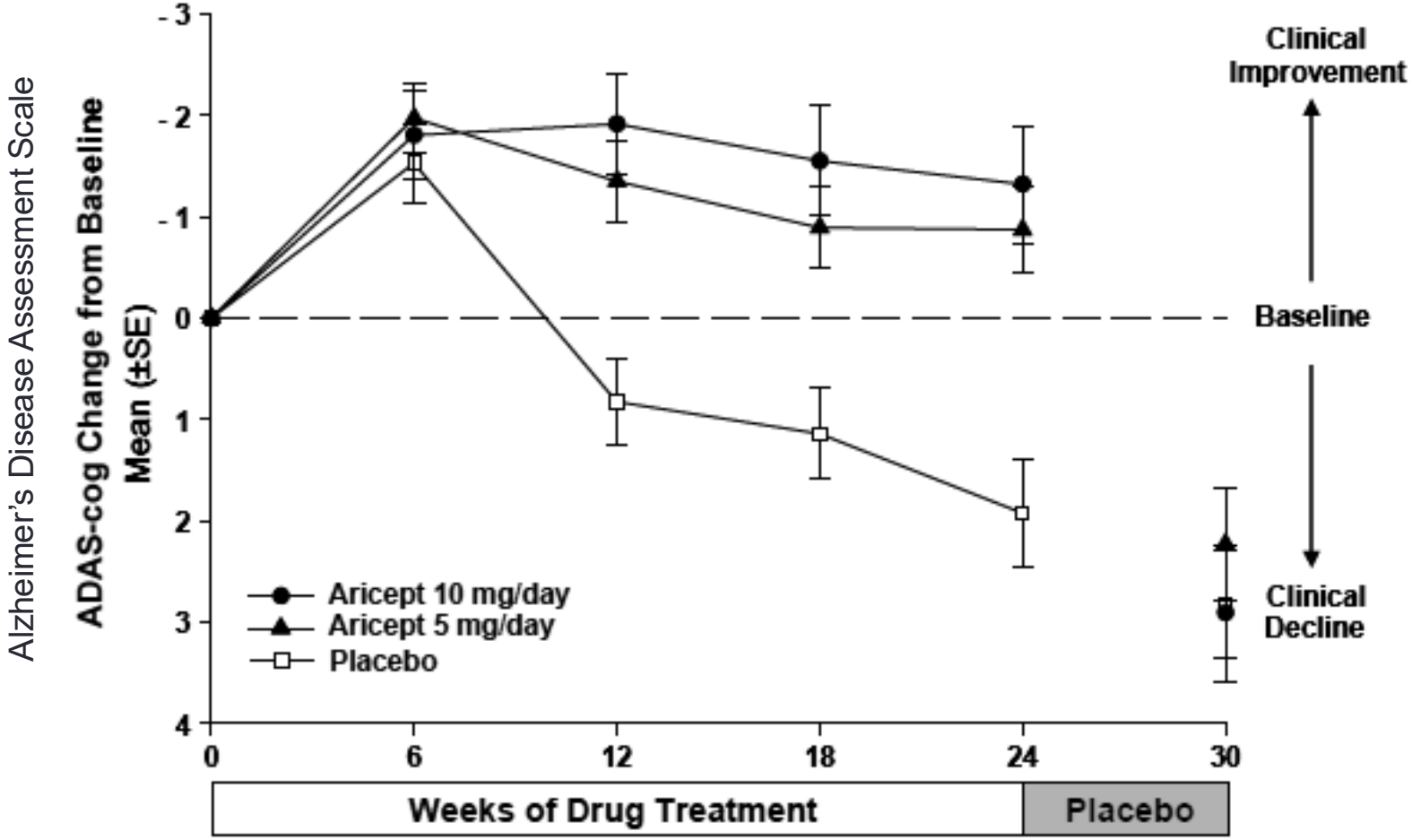
# 1) Reduce cognitive symptoms

- **Cholinesterase inhibitors**
  - Prevent the breakdown of acetylcholine, a chemical messenger important for learning and memory.



# 1) Reduce cognitive symptoms

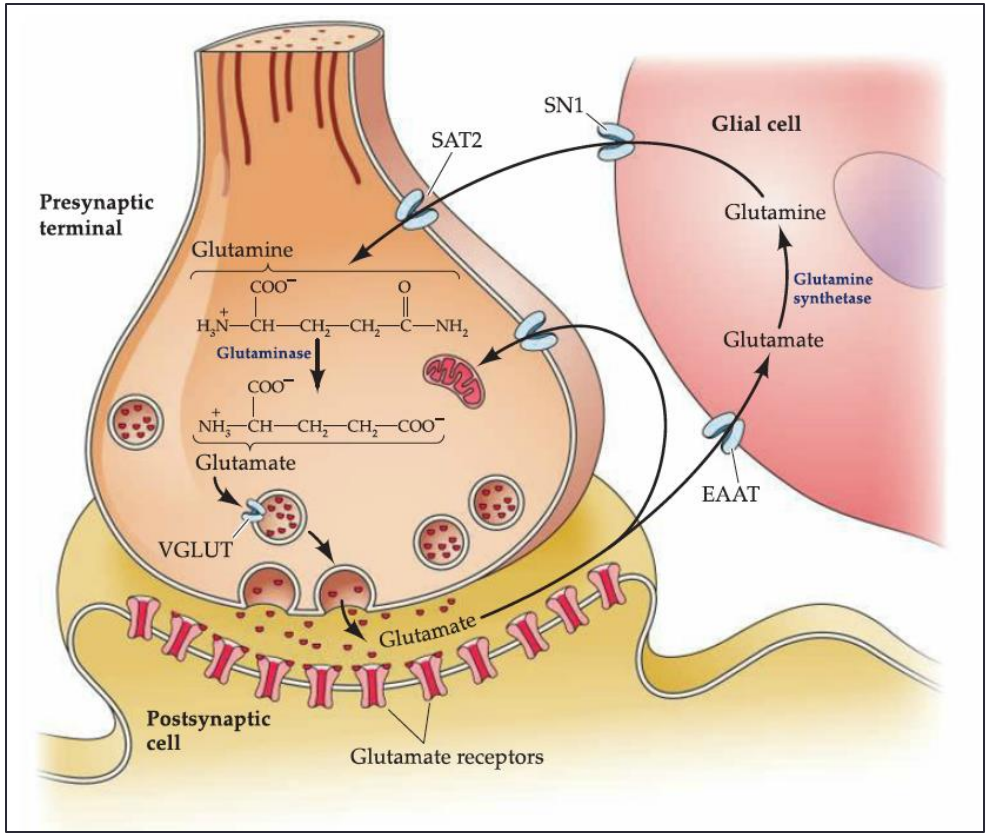
- Cholinesterase inhibitors, e.g., Aricept:



# 1) Reduce cognitive symptoms

- **NMDA receptor antagonist**
  - Mode of action:
    1) Maintenance of glutamatergic synaptic transmission, thereby increasing learning and memory capacities

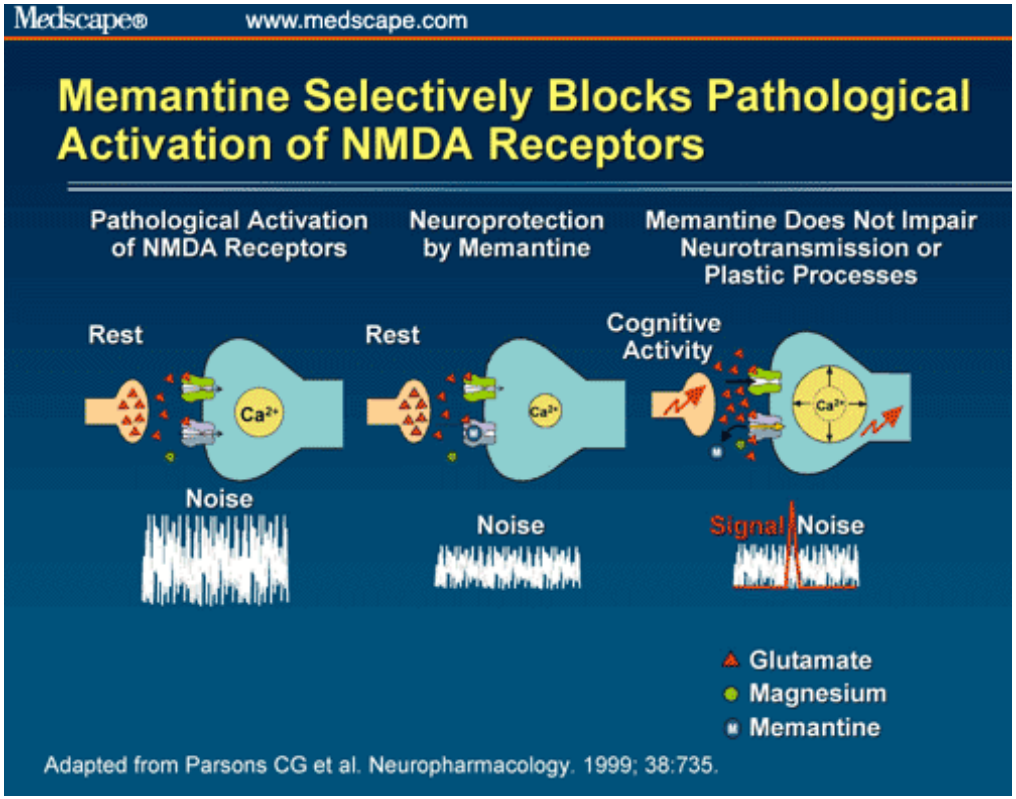
(glutamate is the major excitatory neurotransmitter in the brain)




EAAT= Excitatory amino acid transporter VGLUT= Vesicular glutamate transporter

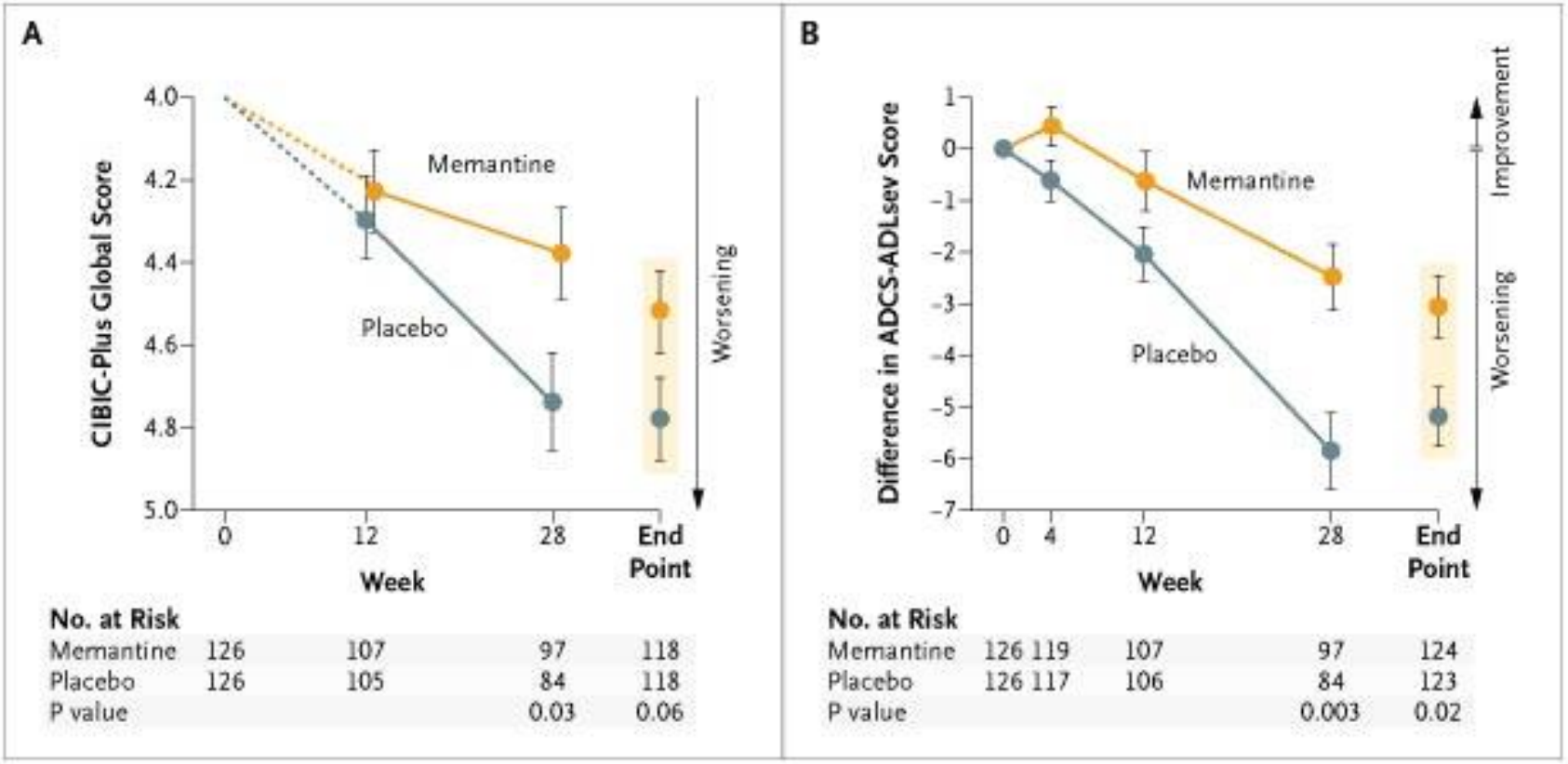
# 1) Reduce cognitive symptoms

- **NMDA receptor antagonist**
  - Mode of action:
    2) Reduction of excessive excitatory glutamatergic neurotransmission



# 1) Reduce cognitive symptoms

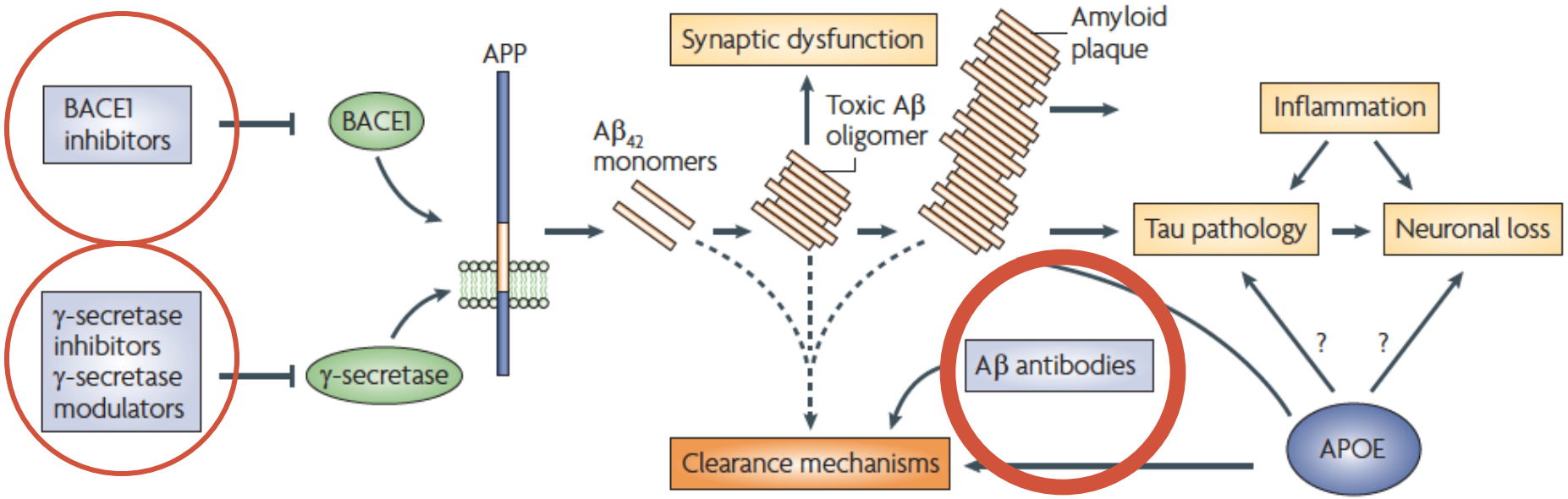
- NMDA receptor antagonist, e.g., memantine:




CIBC=Clinician's interview based impression of change

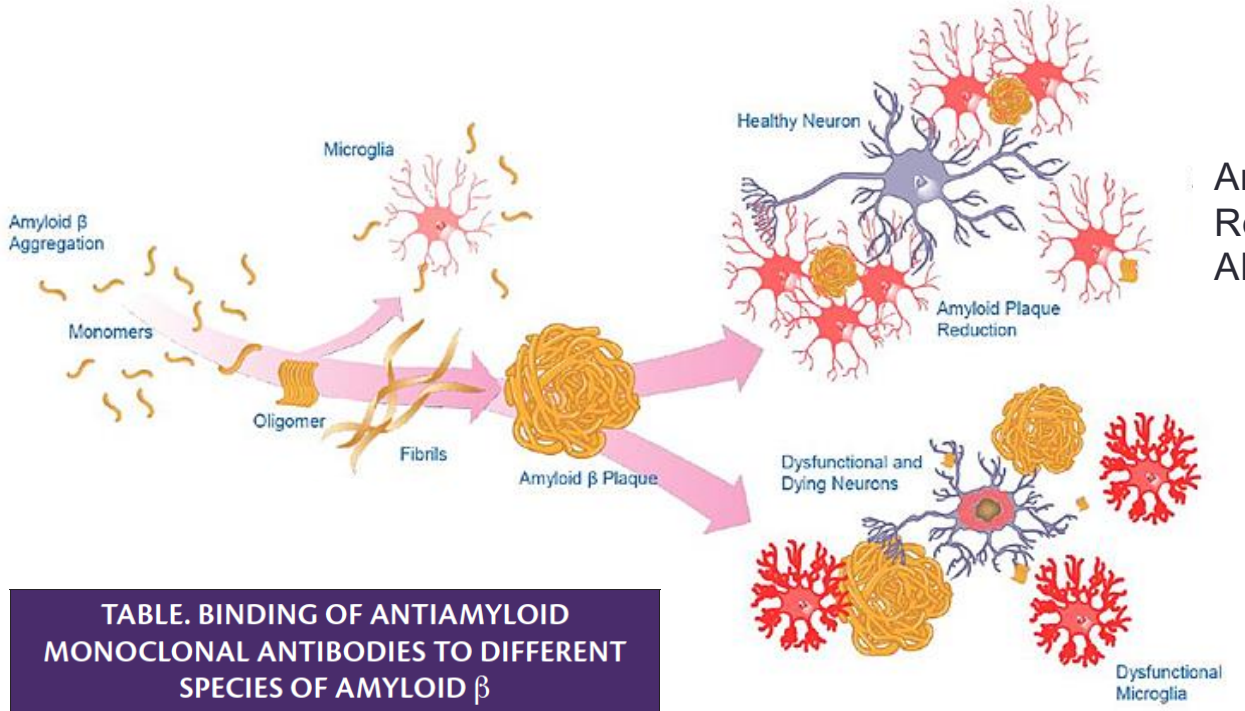
ADCS=Activities of Daily Living

# 2) Reduce pathologies – Focus on amyloid



# 2) Reduce pathologies – Focus on amyloid

- Principle of antibody-mediated amyloid clearance




Antibody treatment: Reduced progression of AD

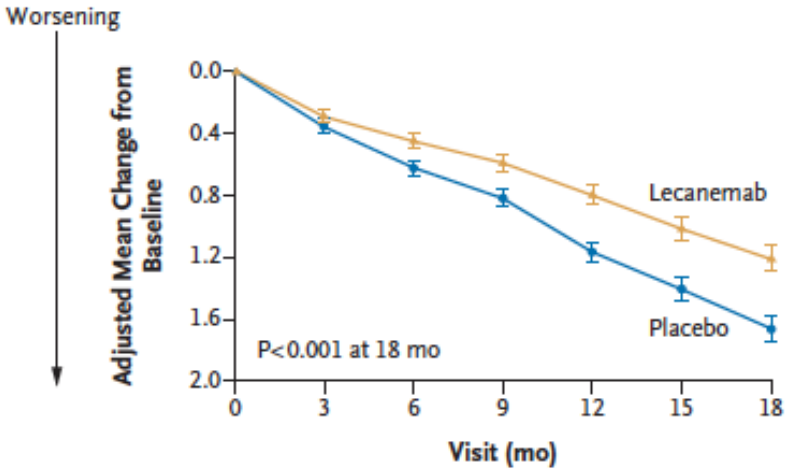
No treatment

**TABLE. BINDING OF ANTIAMYLOID MONOCLONAL ANTIBODIES TO DIFFERENT SPECIES OF AMYLOID β**

| Antibody | Targets | Off-target binding |
|---|---|---|
| Aducanumab | Plaque | Fibrils, none to oligomer |
| Donanemab | Plaque | None |
| Gantenerumab | Plaque | Fibrils>protofibrils, monomers |
| Lecanemab | Protofibril | Protofibrils, oligomers>fibrils, monomers |

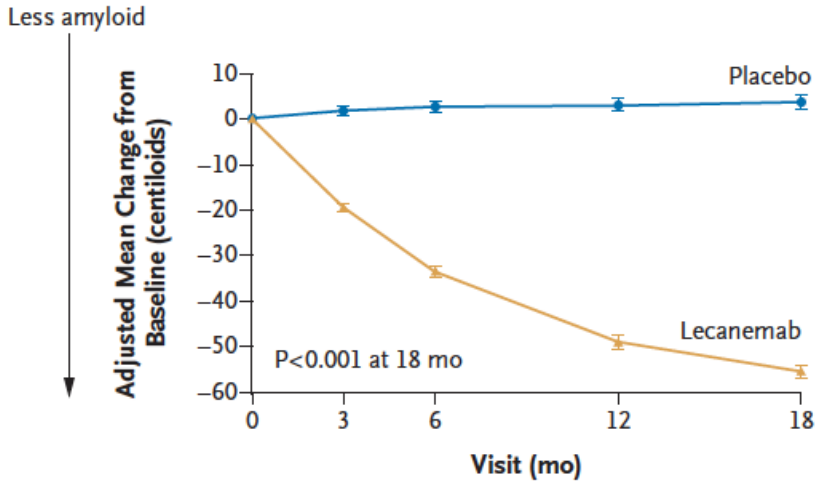
# 2) Reduce pathologies – Focus on amyloid

- **Lecanemab**:
  - Developed by pharmaceutical company Eisai
  - Approved in 2023 (USA)
  - Targets protofibril-to-plaque transition
  - **Effects on Cognition:**




| No. of Participants | | | | | | | |
|---|---|---|---|---|---|---|---|
| Lecanemab | 859 | 824 | 798 | 779 | 765 | 738 | 714 |
| Placebo | 875 | 849 | 828 | 813 | 779 | 767 | 757 |

**Amyloid burden:**

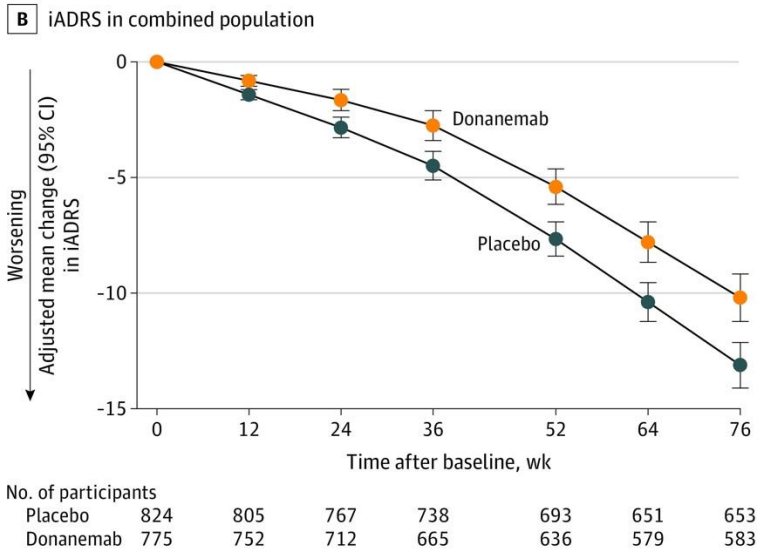


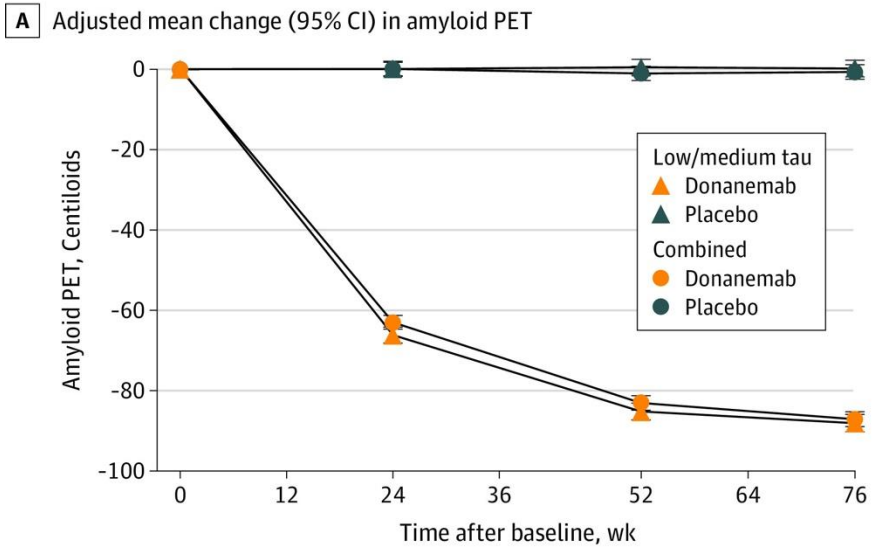

| No. of Participants | | | | | |
|---|---|---|---|---|---|
| Lecanemab | 354 | 296 | 275 | 276 | 210 |
| Placebo | 344 | 303 | 286 | 259 | 205 |

# 2) Reduce pathologies – Focus on amyloid

- **Donanemab**:
  - Developed by pharmaceutical company Eli Lilly
  - Approved in 2024 (USA)
  - Targets plaque deposition
  - **Effects on Cognition:**

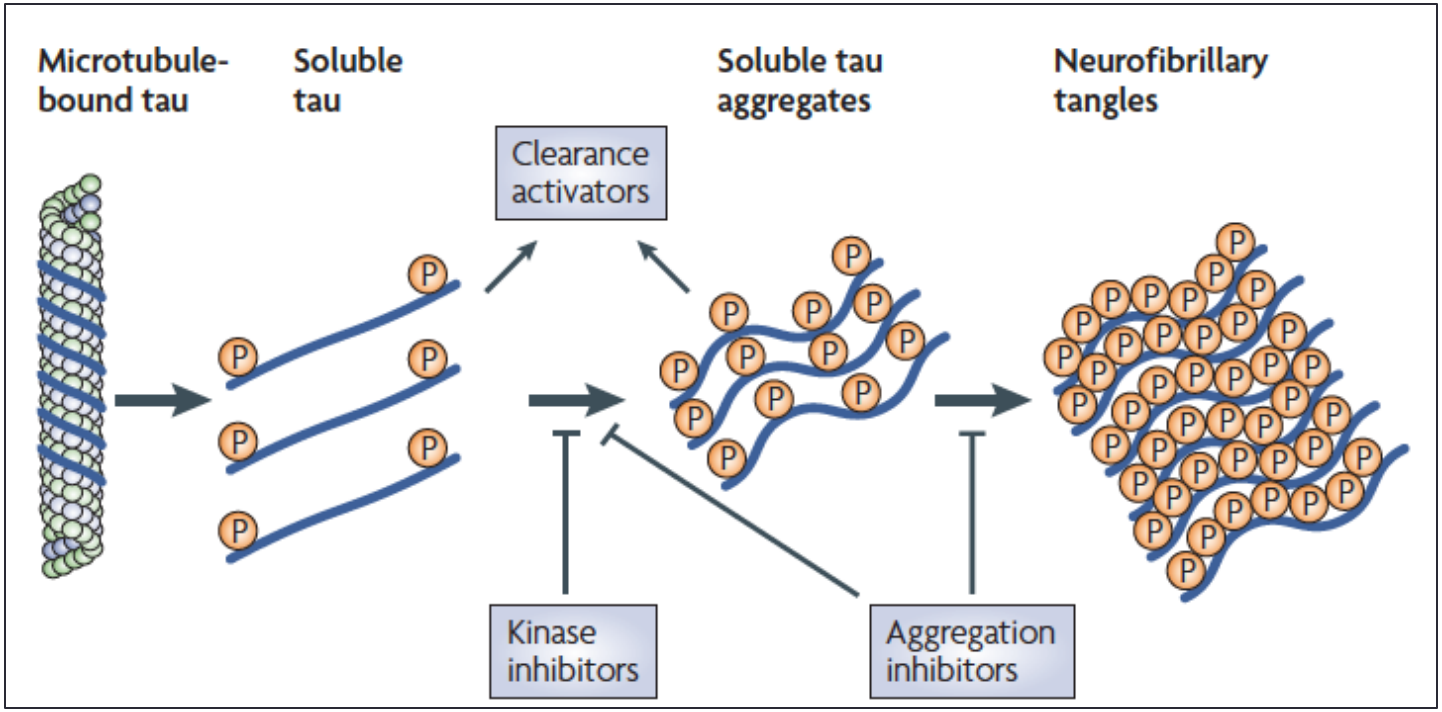
**Amyloid burden:**



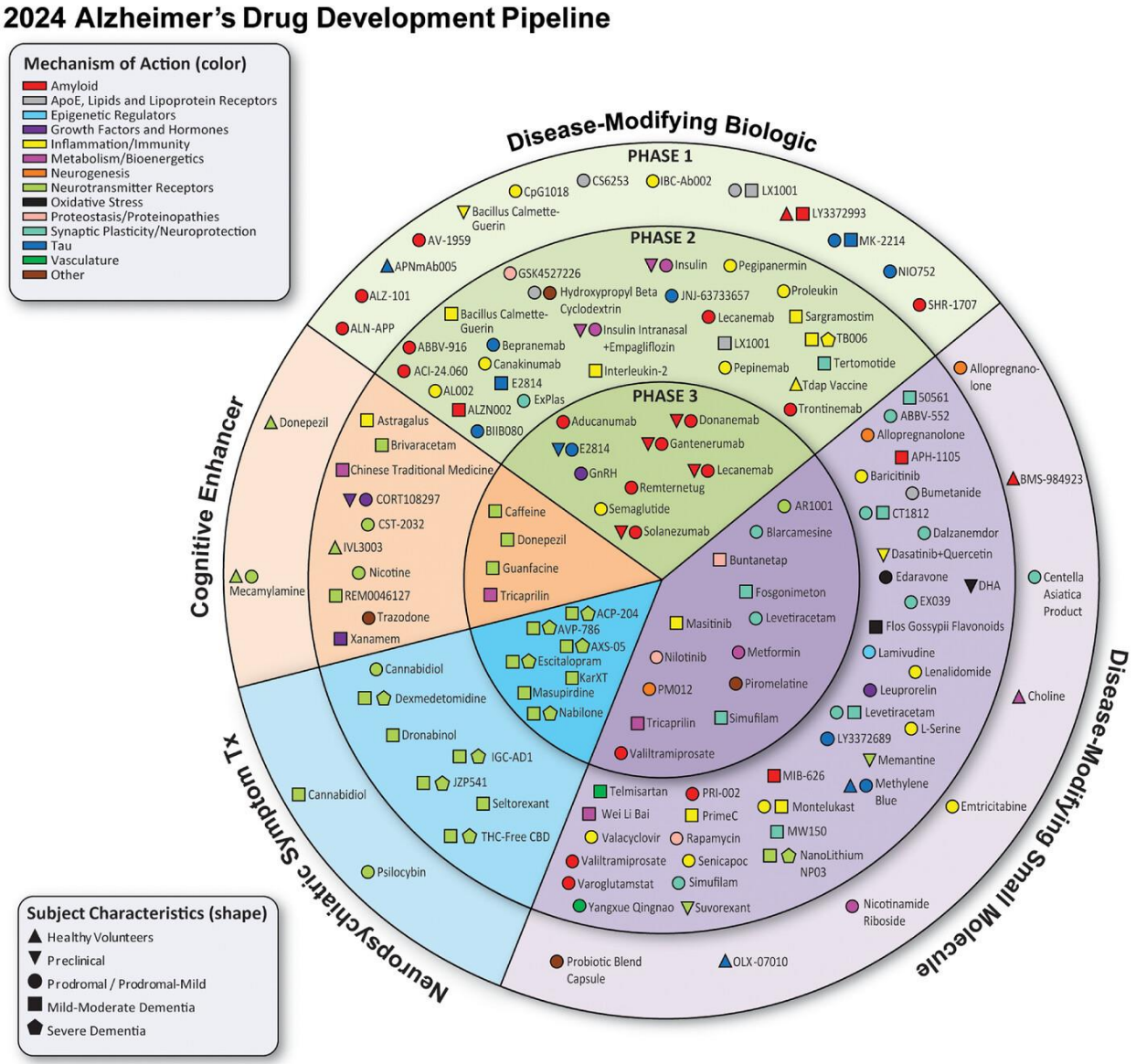
# 2) Reduce pathologies: Focus on Tau

- Hyperphosphorylation of tau protein leads to aggregation

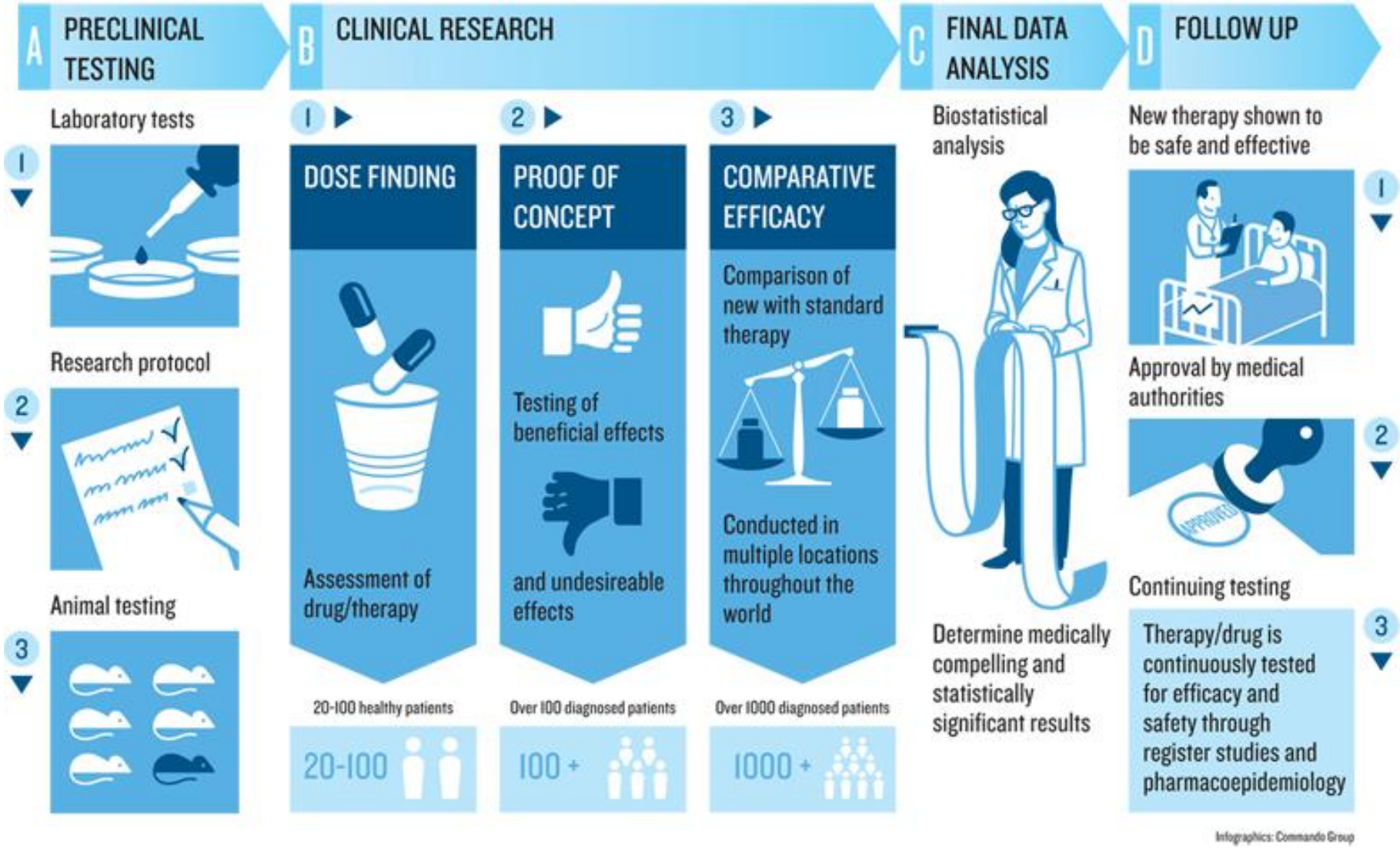



- still in clinical trials

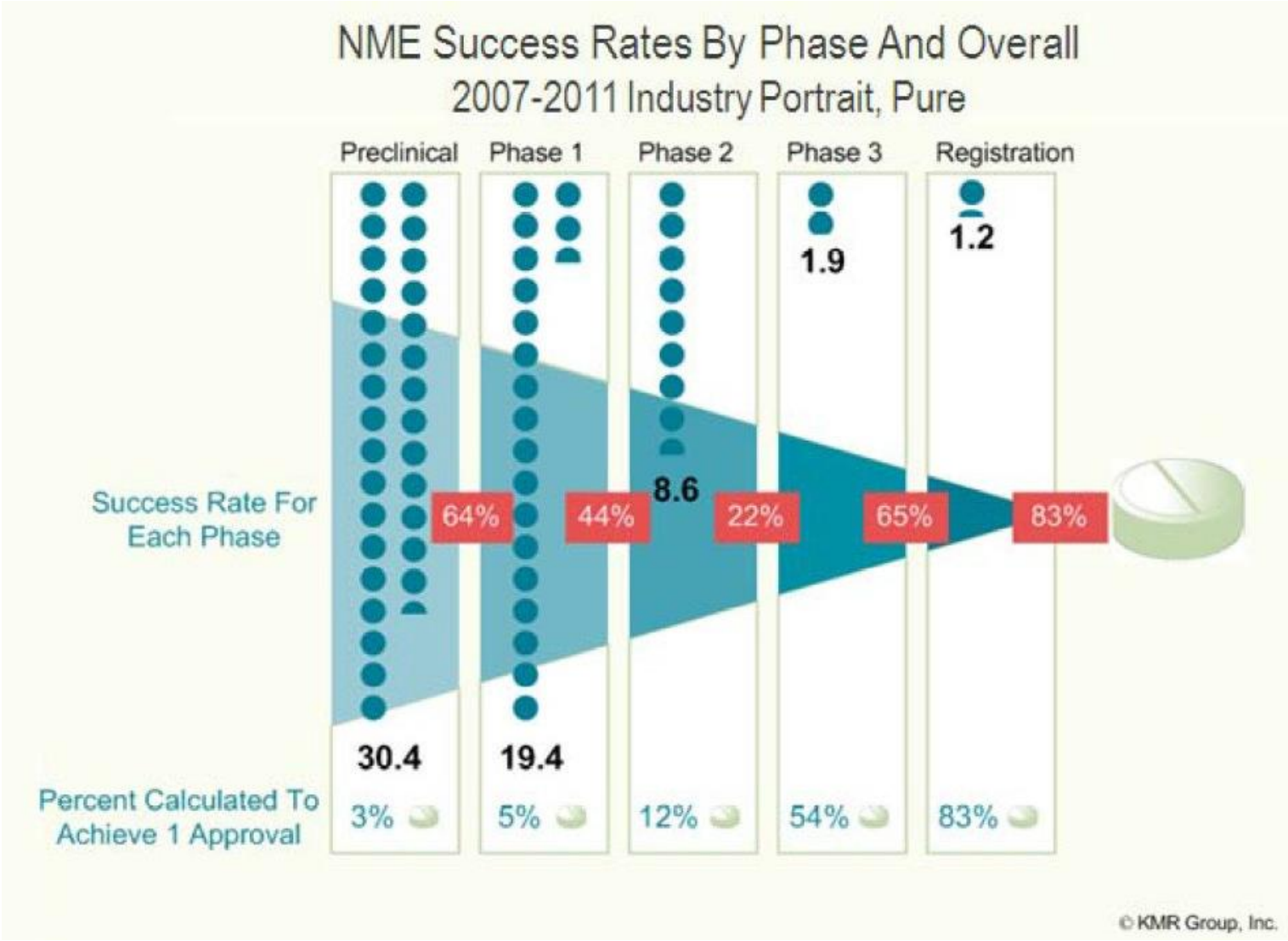
# Overview clinical trials:



# Phases of Clinical trials:



# Success rate of clinical trials:



# Alzheimer's Disease – Overview

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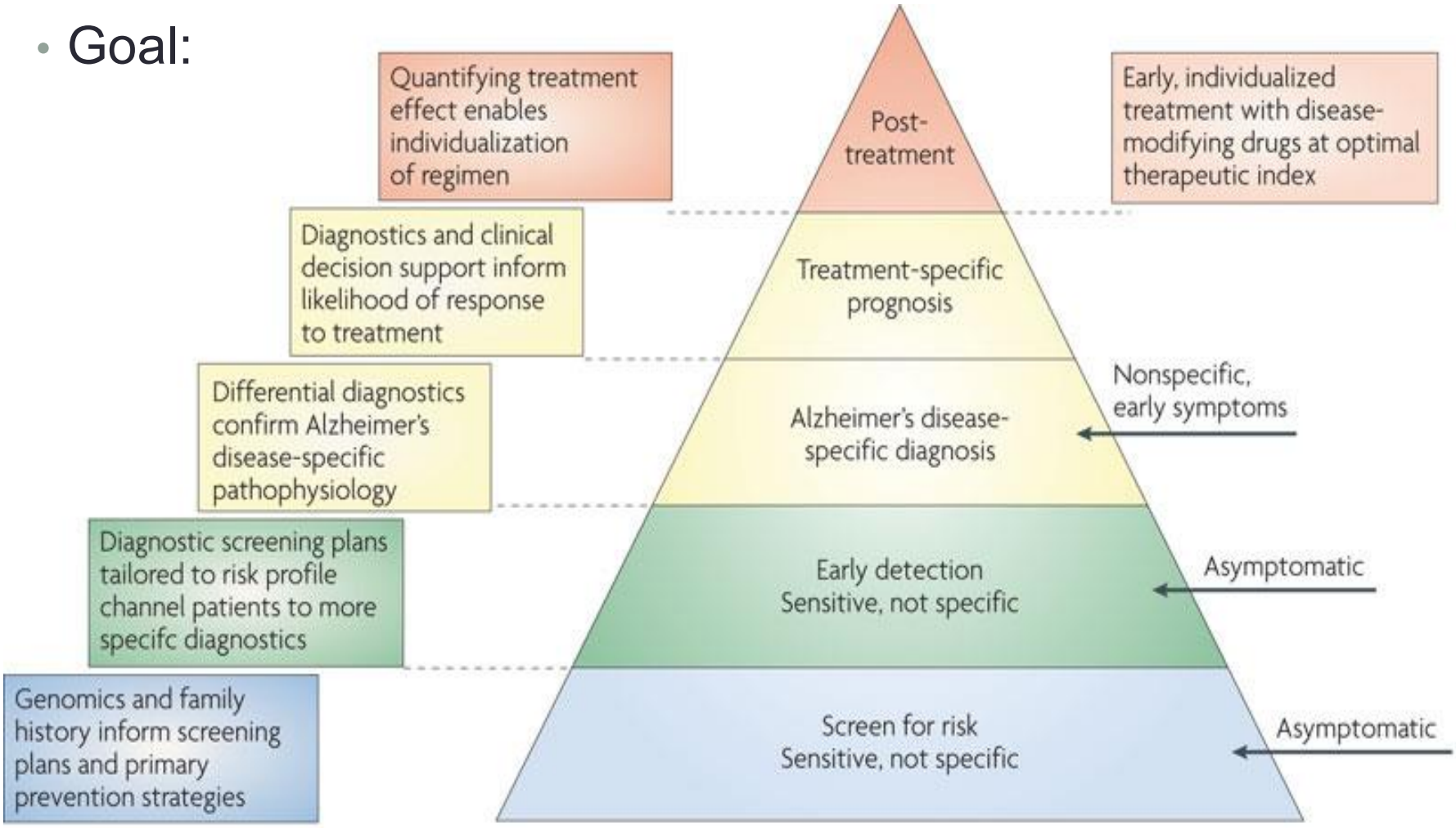
2) Prevalence and history
3) Symptomatology
4) Pathophysiological hallmarks
   - Tau tangles
   - Amyloid plaques
5) Risk factors
   - Genes
   - Environment
6) Treatment approaches
7) **Diagnostics and biomarkers**

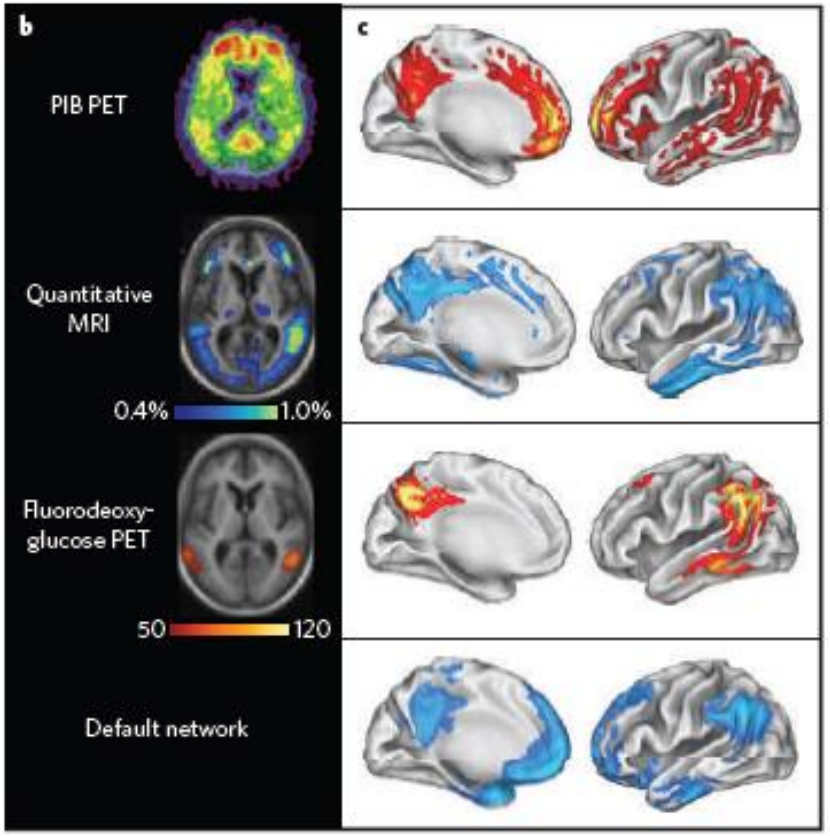
# AD Diagnostics

- Goal:



# AD Diagnostics

- Diagnostic tools:
  - Cognitive assessments
    - MMSE and other tests
  - Brain-based biomarkers
    - PIB PET
    - Quantitative MRI
    - Fluorodeoxyglucose PET
  - Blood based biomarkers



# AD Diagnostics

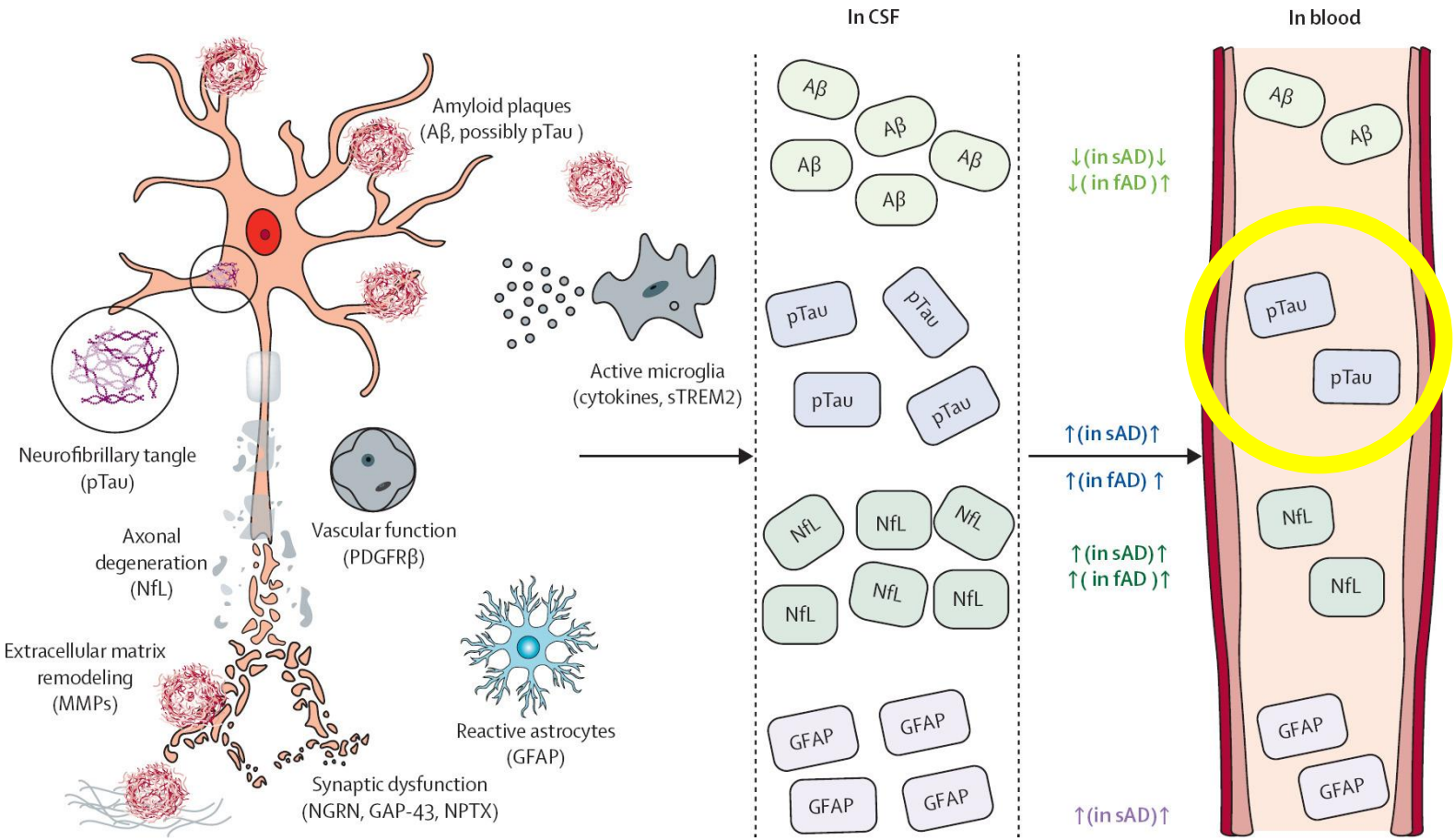
- PIB PET
  - PIB=Pittsburgh Compound B
    - $^{11}$C-PIB is a fluorescent derivative of thioflavin T
  - Type of measurement: Amyloid plaques
    - PIB preferentially targets and binds to fibrillar Aβ forms found in dense core plaques with high affinity and specificity
  - no binding to tau
  - Problem: Amyloid plaques don't necessarily predict AD

# AD Diagnostics

- Quantitative MRI
  - Type of measurement: Neurodegeneration
    - Sensitive to neurodegeneration that occurs in mild and preclinical AD
    - Predictive of decline to dementia in individuals with mild cognitive impairment
- Fluorodeoxyglucose PET
  - $^{18}$F-glucose
  - Type of measurement: Neuronal activity
    - The uptake of $^{18}$F-FDG is a marker for a tissue's metabolism

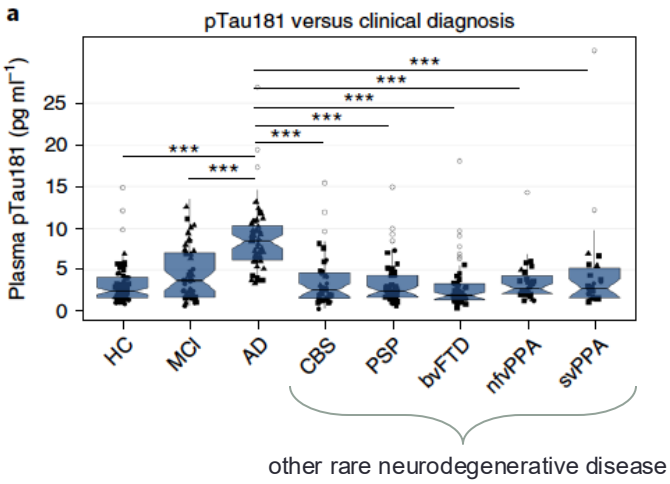
# AD Diagnostics

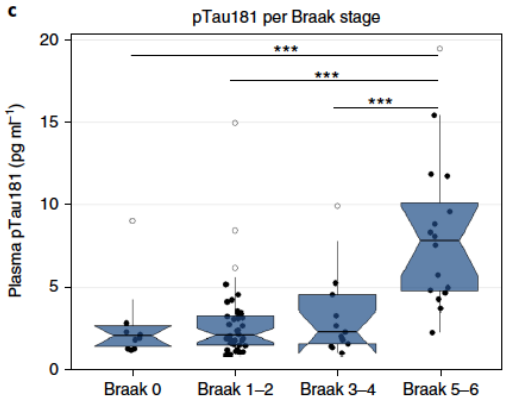
- Blood-based biomarkers

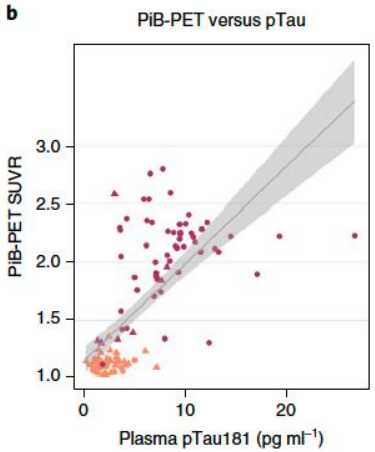


# AD Diagnostics

- pTau181
  - phosphorylated Tau at residue $T_{181}$
  - Specific for AD
  - Correlates well with Braak staging
  - Correlates well PiB-PET



# AD Treatment and Diagnostics Summary

- Open questions:
  - Who to screen and when?
    - Having a biomarker for the disease is not the same as having the disesae
  - Follow-up studies needed, which are costly
    - Clinicians with skilled expertise needed
      - Dementia testing; MRI scanning and interpretation
  - ➢ The past five years have seen an exciting development in treatment and diagnostic options!

- Nevertheless, more studies are still needed!

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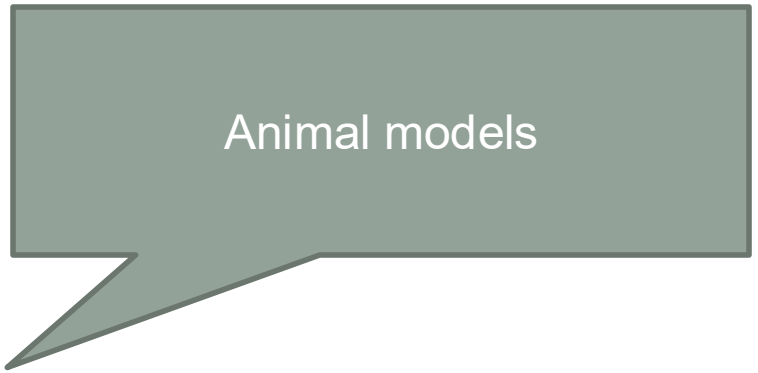
1) Check your knowledge about AD
2) Prevalence and history
3) Symptomatology
4) Pathophysiological hallmarks
   - Tau tangles
   - Amyloid plaques
5) Risk factors
   - Genes
   - Environment
6) Treatment approaches
7) **Diagnostics and biomarkers**

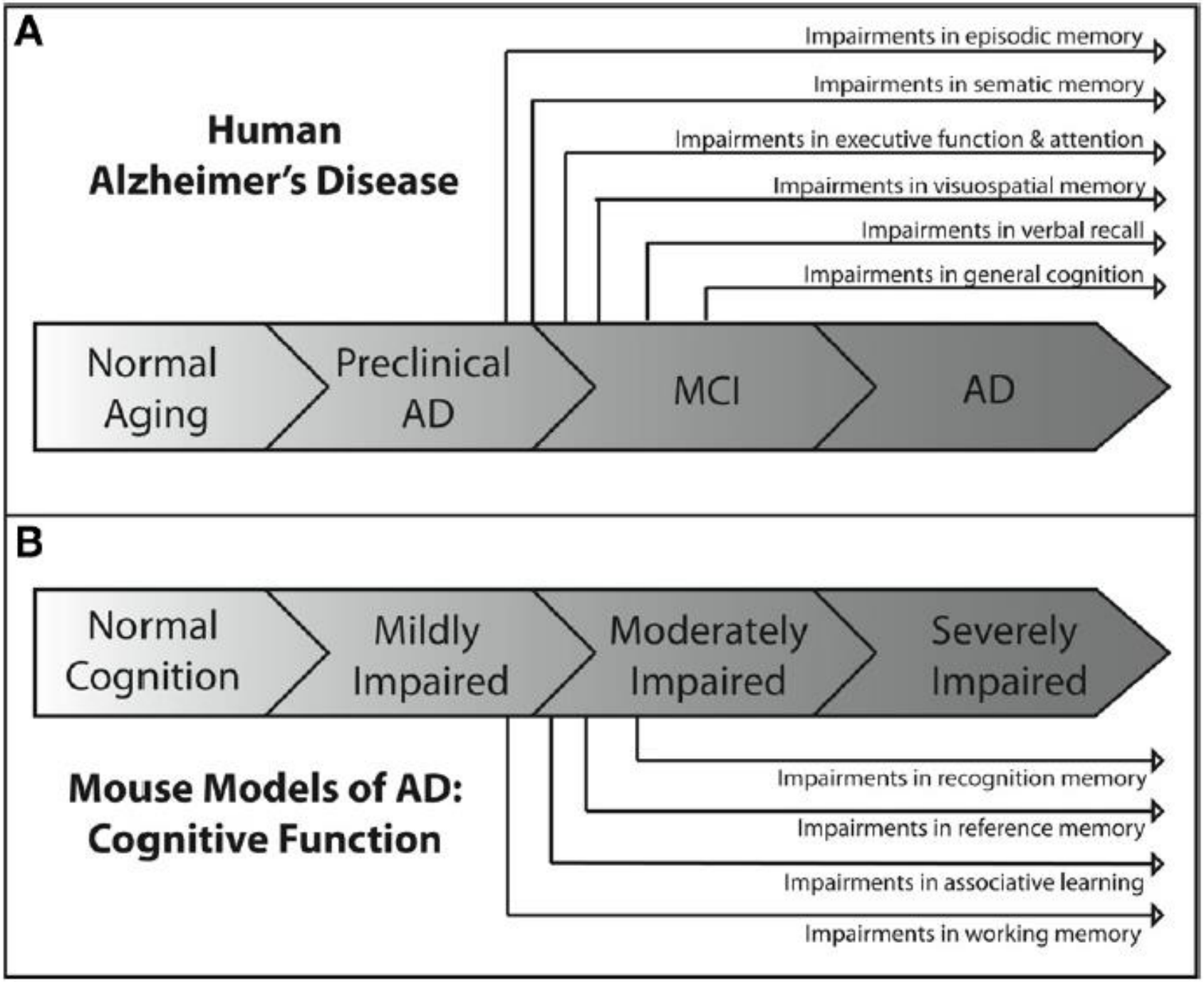


# How to study AD outside humans:

The Jackson Laboratory

JAX® MICE SEARCH

Find your favourite mouse model



# How to study AD outside humans:

frontiers in GENETICS

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## Using mice to model Alzheimer's dementia: an overview of the clinical disease and the preclinical behavioral changes in 10 mouse models

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# Animal models

- Limitations of mouse models:
  - Incomplete recapitulation of the pathology
  - Based on fAD
    - Wild type mice do not develop AD
- Other (animal) models?
  - *C.elegans*
  - *D.melanogaster*
  - Rats
  - Marmosets
  - Brain organoids/cellular culture

# Learning objectives

- Know about
  - Pathophysiological stages of AD – spreading
  - Tau pathophysiology
  - Amyloid cascade
  - Diagnostic tools
  - Treatment options
- Be able to explain
  - Amyloid cascade hypothesis
  - Multiple hit hypothesis
  - Difficulties for finding AD treatments
  - Familial vs sporadic AD
  - Difficulties with animal models of the disease

# Wordle


Familial
Aricept
Anomia
Apraxia
Multiple-Hit
Degeneration
Aphasia
Braak
Acetylcholine
Sporadic
Plaques
Tau
Glutamate
Dementia
ApoE4
Amyloid
Memantine
Amnesia
MMSE
Fibrils
Agnosia
BACE
Reserve
Ab42