

# Blood and Imaging Biomarkers of Dementia

1/20/26

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# Objectives

Review the definition of a biomarker

Understand the pathophysiology of AD blood biomarkers

Know the impact of blood biomarkers on AD diagnosis and treatment

# Speakers

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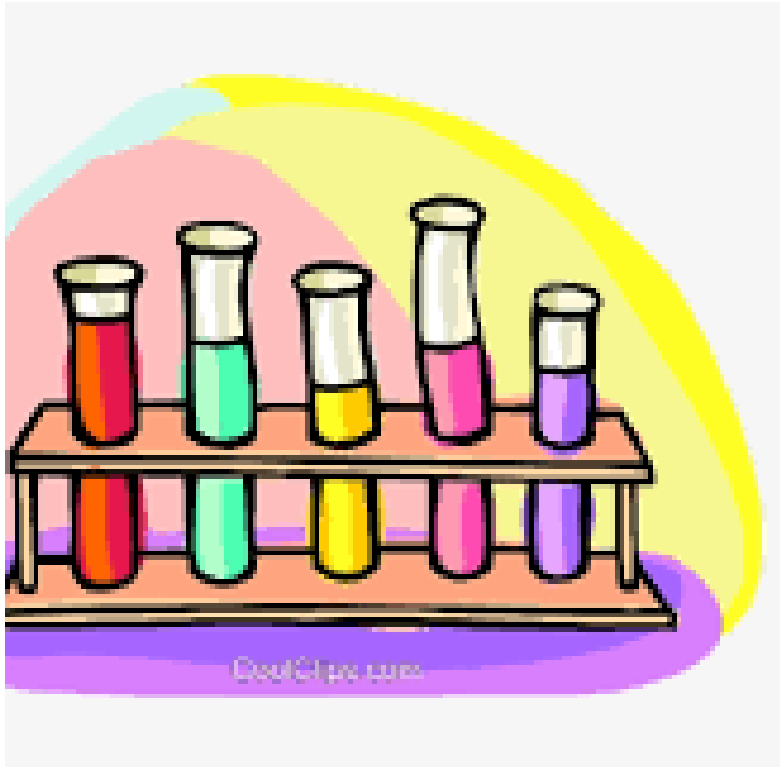
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# Historically AD has been diagnosed clinically and confirmed on autopsy

- For example, the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders) introduced explicit, symptom-based criteria for classifying disorders (1980) including AD:
  - a decline in memory and learning
  - a decline in at least one other cognitive domain (complex attention, executive function, language, perceptual-motor, and social cognition)
  - interference with the activities of daily living because of decline in these cognitive functions

# What is a Biomarker?

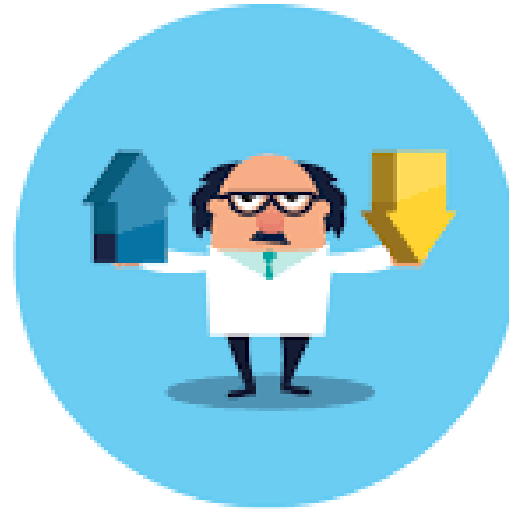


- A measurable substance in an organism whose presence is indicative of some phenomenon such as disease, infection, or environmental exposure
- Used to diagnose diseases, predict risk, monitor disease progression, and guide treatment

# CAN A TEST CORRECTLY IDENTIFY IF A PERSON HAS A DISEASE OR NOT?

## Sensitivity

How well does the test identify people who DO have the disease?

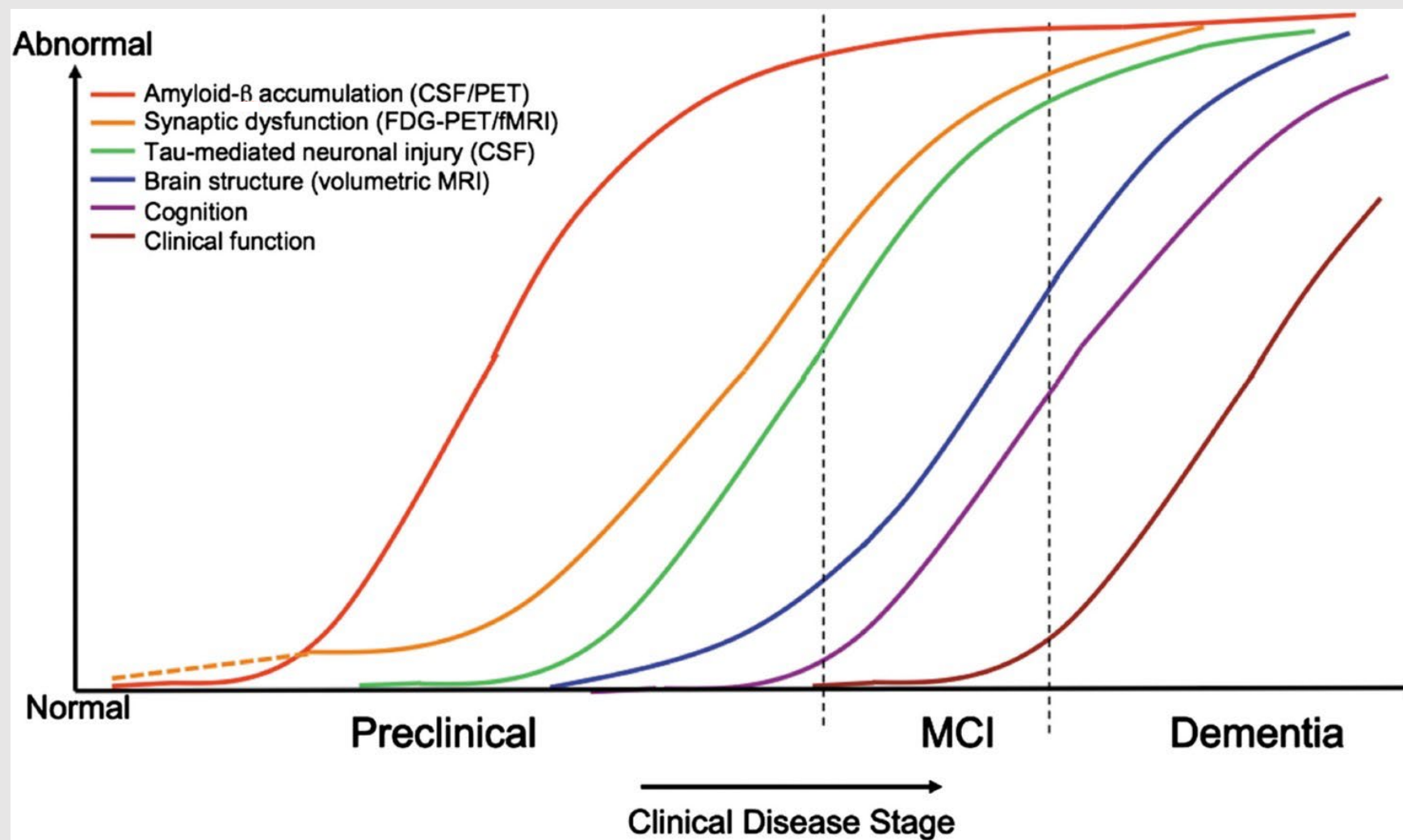


## Specificity

How well does the test identify people who DO NOT have the disease?

There is no single definitive test for Alzheimer's disease, but advances in biomarker technology are improving the time and accuracy of diagnosis.

# Stages of AD Pathology



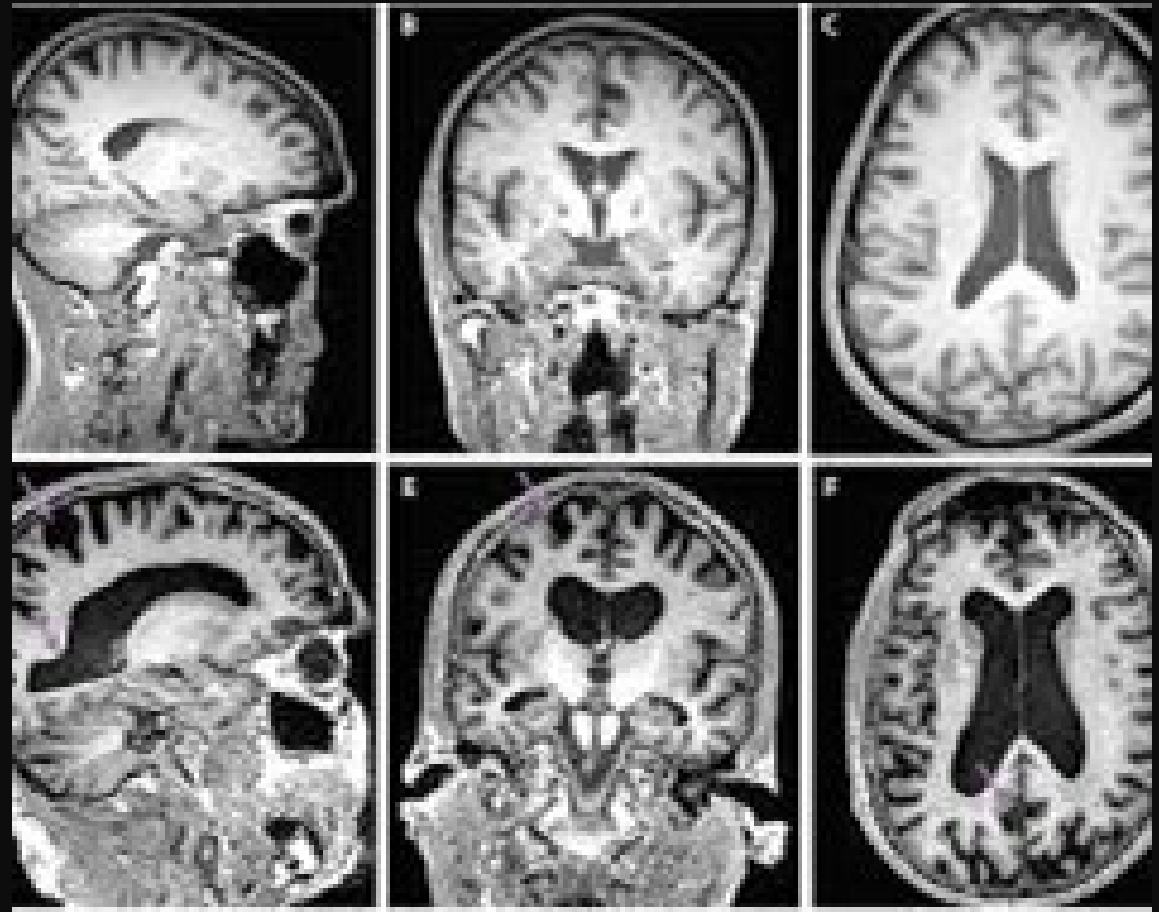
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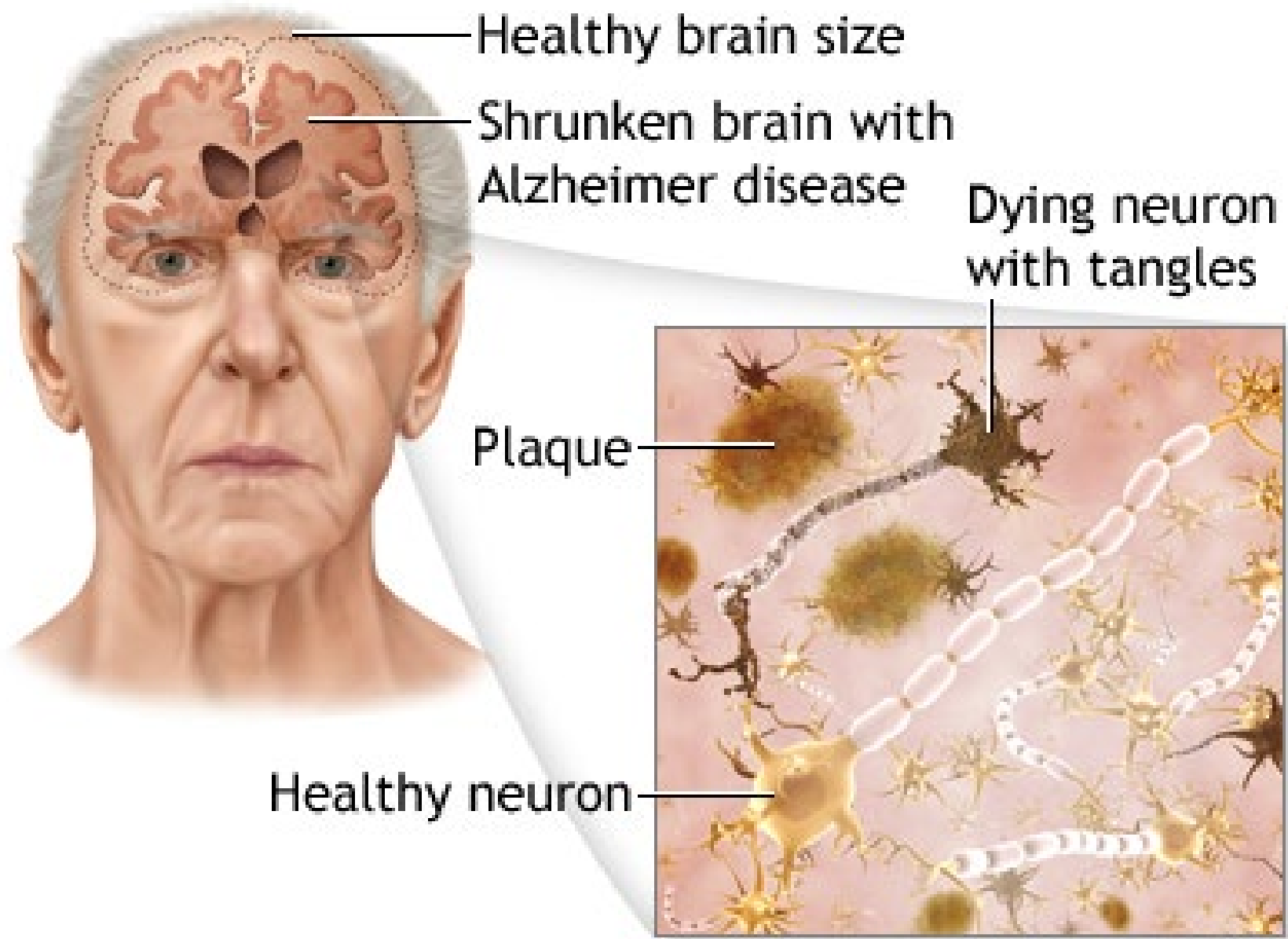
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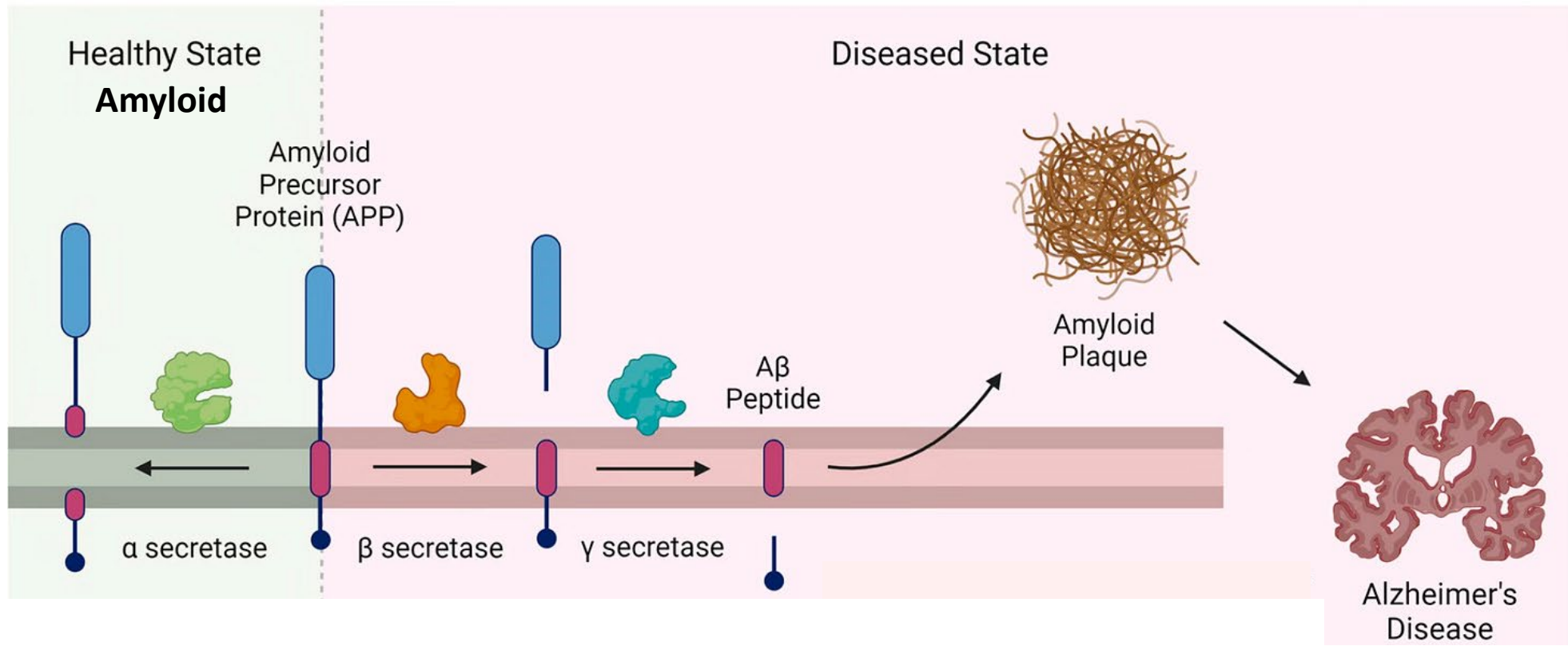
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# Brain Atrophy



PLAQUES & TANGLES



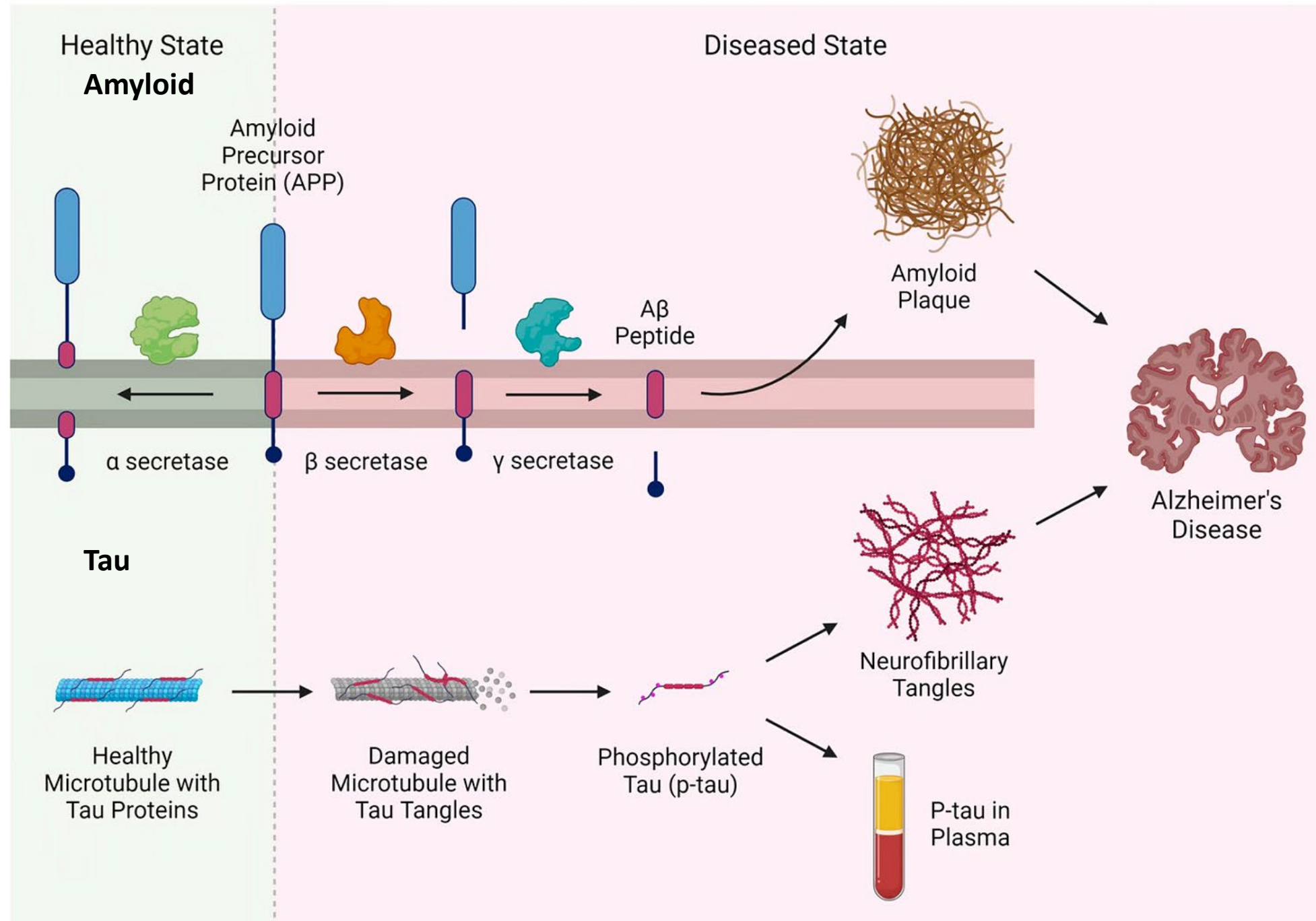


# $\beta$ A in Alzheimer's Disease

- Beta Amyloid 42, from the amyloid precursor protein, is thought to be most toxic, while  $A\beta$ 40 is more common but less aggregative
- Beta Amyloid forms oligomers, then fibrils and then mats called beta sheets
- Aggregation disrupts cell to cell communication
- Aggregation activates immune cells leading to inflammation

# $\beta$ A Plasma Blood Tests

- check for specific forms of beta-amyloid (e.g. A $\beta$ 42/40 ratio)
- perform less invasive testing compared to PET scans or spinal taps with comparable or superior performance
- help distinguish Alzheimer's from other dementias
- indicate if newer amyloid-targeting treatments are appropriate
- Early Sensitivity: ~77.8% to 86%.  
Specificity: ~87.5% to 70% (higher with the ratio than A $\beta$ 42 alone)



# P-tau in Alzheimer's Disease

- Phosphorylation is the addition of a phosphate group to a protein. It is critical for normal cell functions such as cell signaling, energy storage and transfer, glucose metabolism and protein regulation.
- In disease, excessive phosphorylation can occur at over 80 sites. P-tau 217, in particular, has been strongly linked to the formation of neurofibrillary tangles.
- Plasma P-tau 217 has a sensitivity of 95% and specificity of 94% (Lai R, Biomedicines, 2024)
- Plasma P-tau 217 has potential for disease staging (Feizpour et al., Communications Medicine, 2025), including predicting decline in unimpaired individuals (Ossenkoppele et al., Nature Aging, 2025).

# Neurofilament Light Chain

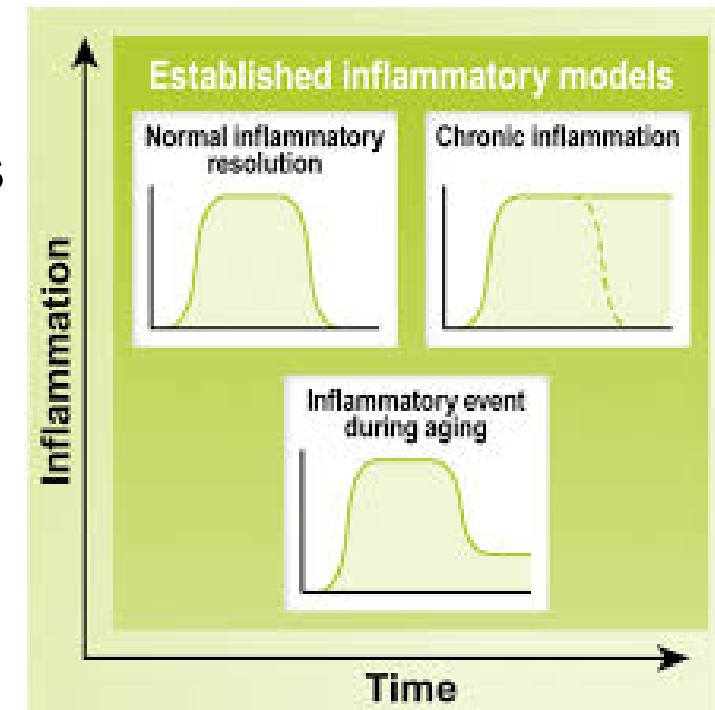
- NfL is another protein present in neurofilaments, which provide neuronal support
- Elevated NfL in CSF or blood is associated with damage to neurons, as well as disease prognosis and risk.
- NfL is not specific, it can occur in AD, MS, ALS and stroke as well as aging and kidney disease. Thus results should be interpreted in the context of other clinical information.

# Neuroinflammation

The **brain's innate immune system is triggered following an inflammatory challenge** such as those posed by injury, infection, exposure to a toxin, neurodegenerative disease, or aging.

A GFAP (Glial Fibrillary Acidic Protein) blood test measures elevated levels of this astrocyte protein in the blood, which signal brain injury or inflammation.

The accumulation of amyloid fibrils elicits immune cell infiltration into tissue and proinflammatory cytokine production.



Newcombe et al., 2018

# Key Biomarker Developments

- **A $\beta$ 42/40 Ratio:** A significant ratio of amyloid beta proteins in the blood strongly correlates with brain amyloid plaques.
- **Phosphorylated Tau (p-tau):** p-tau217 and p-tau231 are emerging as the best indicators for early amyloid accumulation, even before symptoms appear.
- **Combination Biomarkers:** Using multiple markers (like p-tau217 + NfL + GFAP) significantly boosts predictive power for Alzheimer's and general dementia.
- **Neurofilament Light (NfL):** Predicts neurodegeneration and lifespan in late-stage dementia, complementing amyloid/tau markers.

# Major Milestones (2024 – 2025)

- **FDA Clearances:** The first blood tests (Lumipulse pTau217/A $\beta$  ratio and Elecsys pTau181) were cleared by the FDA in 2025 for aiding Alzheimer's diagnosis, particularly for ruling out amyloid pathology in primary care.
- **Improved Accuracy:** These new blood tests rival the accuracy of PET scans and CSF tests for detecting brain amyloid.

## Genetic Markers of AD Risk

- The apolipoprotein E (APOE) gene makes proteins that carry cholesterol and other types of fat in the blood stream.
- The APOE4 allele is the best studied risk-factor gene for late onset AD, and is associated with increased A $\beta$  plaque formation and tau phosphorylation
- About 25% of people have one copy of the APOE4 allele
- 40-65% of people with dementia have at least one copy of the APOE4 allele
- Two copies of the APOE4 allele dramatically increases risk for AD

# Physiological criteria have been adopted

## Biomarker categories:

Core:                   A $\beta$  proteinopathy  
                              Phosphorylated tau

## Non-specific AD Processes:

                              Neuronal injury or degeneration  
                              Inflammation

AD co-pathology       :        Vascular brain injury  
                                      Alpha synuclein

# Objectives

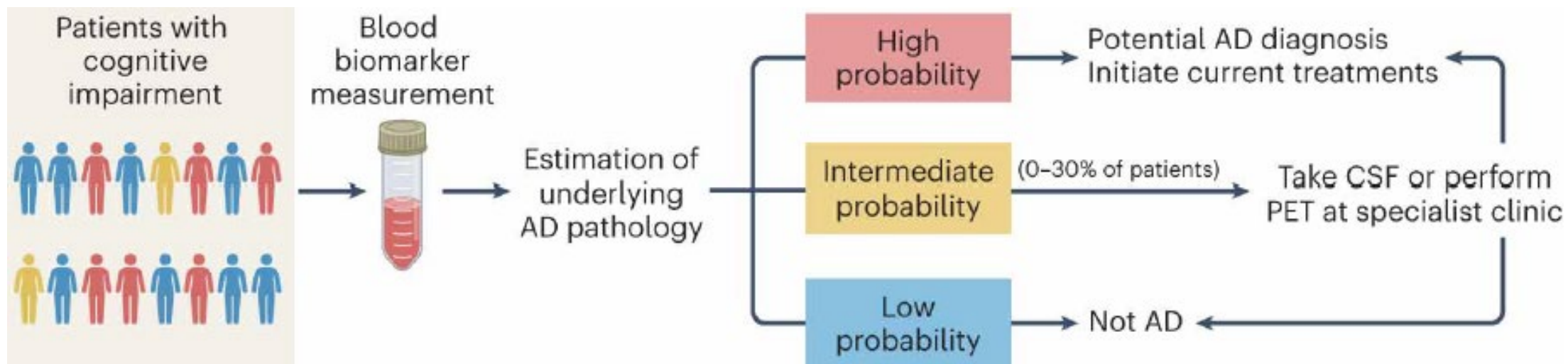
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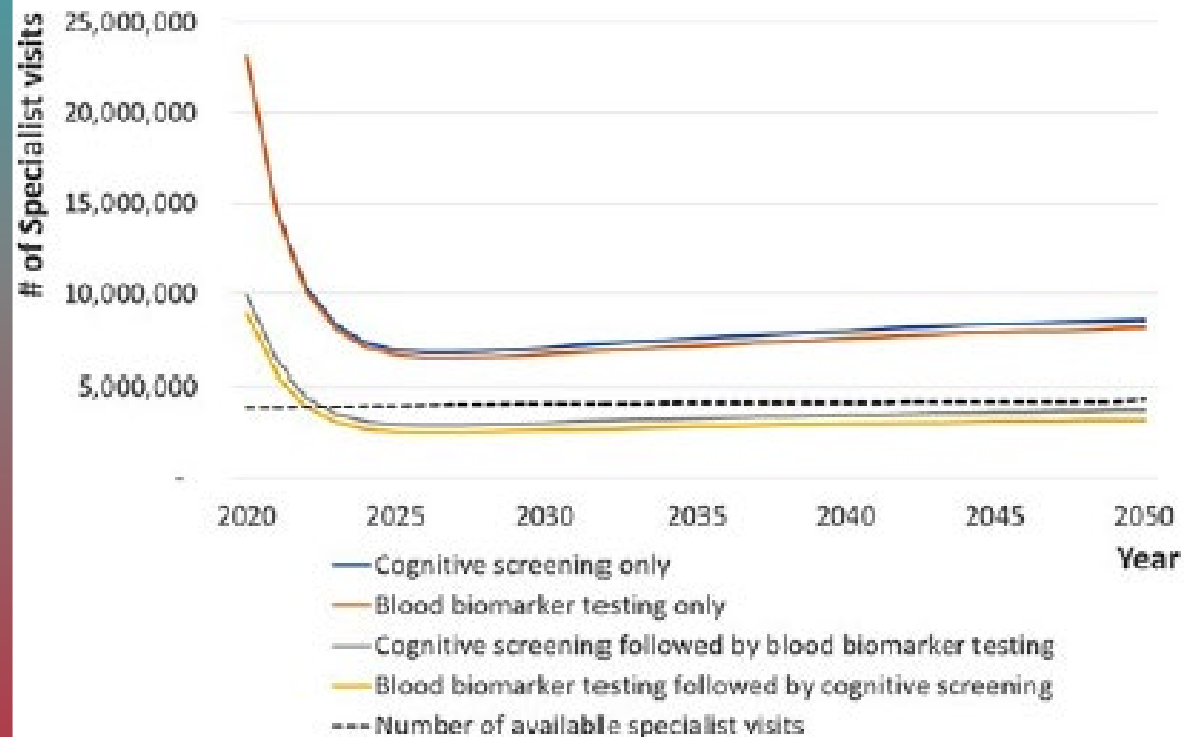
# Potential Clinical Uses of Plasma AD Biomarkers

- Screening in primary care
- Diagnostic step in specialty care
- Monitoring response to therapy



# Potential Impact of Triage on Primary Care

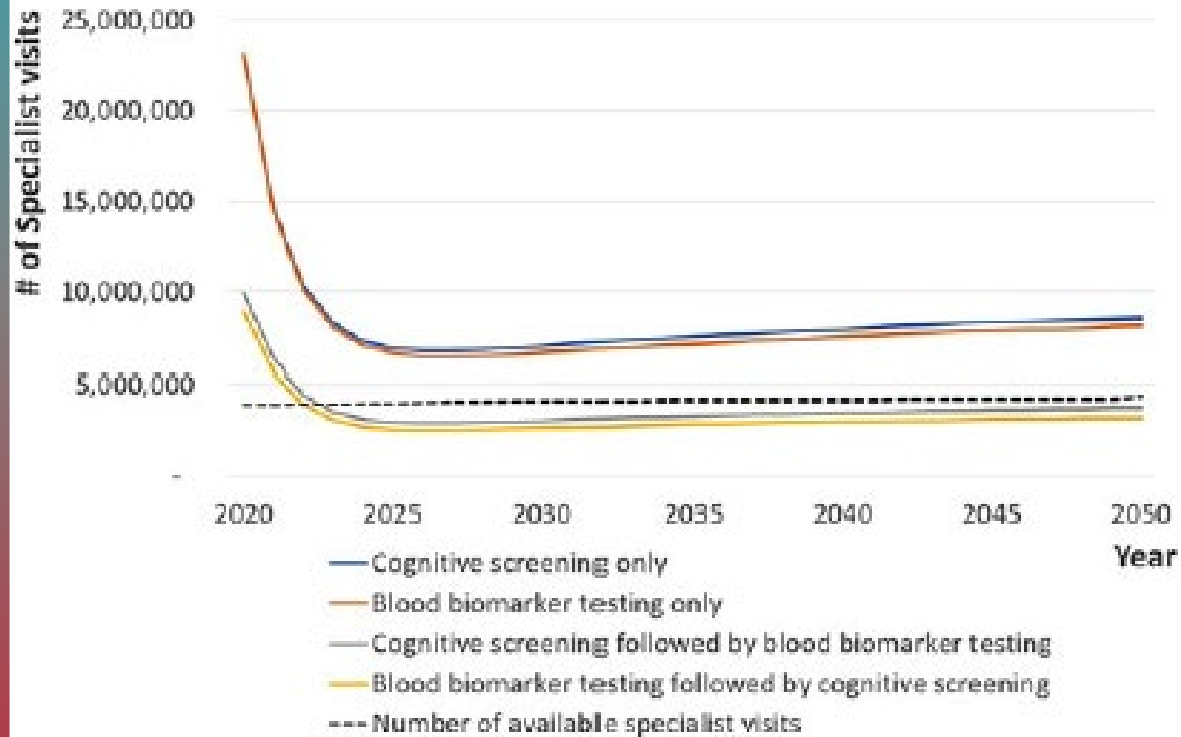
Comparing primary care level triage from the perspective of the U.S. health care system: (1) cognitive test only (Mini Mental State Examination [MMSE]), (2) BBBM test only, (3) MMSE followed by BBBM if positive, and (4) BBBM followed by MMSE if positive.



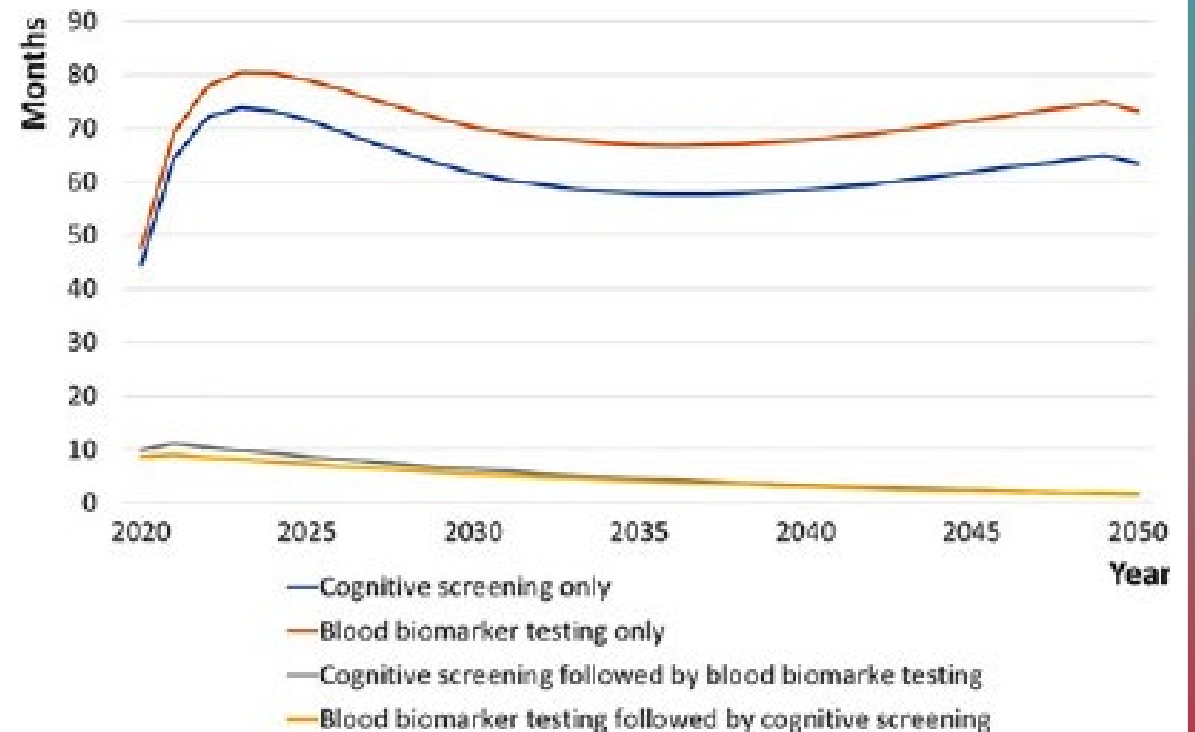
Annual demand for specialist visits

# Potential Impact of Triage on Primary Care

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Annual demand for specialist visits



Annual wait time to complete diagnostic process

# Challenges to Detecting Dementia in Primary Care

- Lack of support/resources
- Degree of comfort performing evaluation
- Concerns about burden to patient
- Doubts about usefulness of diagnosis/perception of limited treatment options
- Time constraints/competing priorities
- Language barriers

# Patient Decision Guide

- This guide describes what information can be provided by a blood test, what to consider when choosing to have a blood test, and how the results are related to AD.
- Provided by AGREEDementia (The Advisory Group on Risk Evidence Education for Dementia), which is a collaborative initiative that facilitates understanding and communication regarding dementia risk information among clinicians, stakeholders, and people at risk, while developing educational materials.
- AGREEDementia (<https://www.agreedementia.org/>) is not affiliated with biomarker companies.
- <https://www.alzbiomarkerhub.org/news-and-research/blood-test-for-alzheimers-disease-decision-guide>





Questions?



# THANK YOU

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website at:

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