ALZHEIMER'S DISEASE

An update on Diagnosis and Therapeutics

STAAB 2025

NO RELEVANT DISCLOSURES

“One of the hardest things you will ever have to do, my dear, is to grieve the loss of a person who is still alive.” Unknown

OBJECTIVES

- Update physicians on diagnosis, terminology, and approved anti-amyloid treatments for Alzheimer's disease (AD).
- A quick review the current indications and appropriate patient selection for these therapies.
- Inform physicians caring for patients with MCI and mild Alzheimer's disease, how current Anti amyloid therapies may affect their patients future care and treatment, and problems patients may experience.
- Provide a review of this topic to aid in clinicians' discussion with family members and patients regarding the diagnosis of Alzheimer's disease, and treatment.
- Focus primarily on Mild cognitive impairment and mild Alzheimer's disease as patients with these diagnosis are going to be the primary use of these new therapies.
- Spoiler alert we are probably 15-20 years too late!

WHAT WE ARE NOT TALKING ABOUT

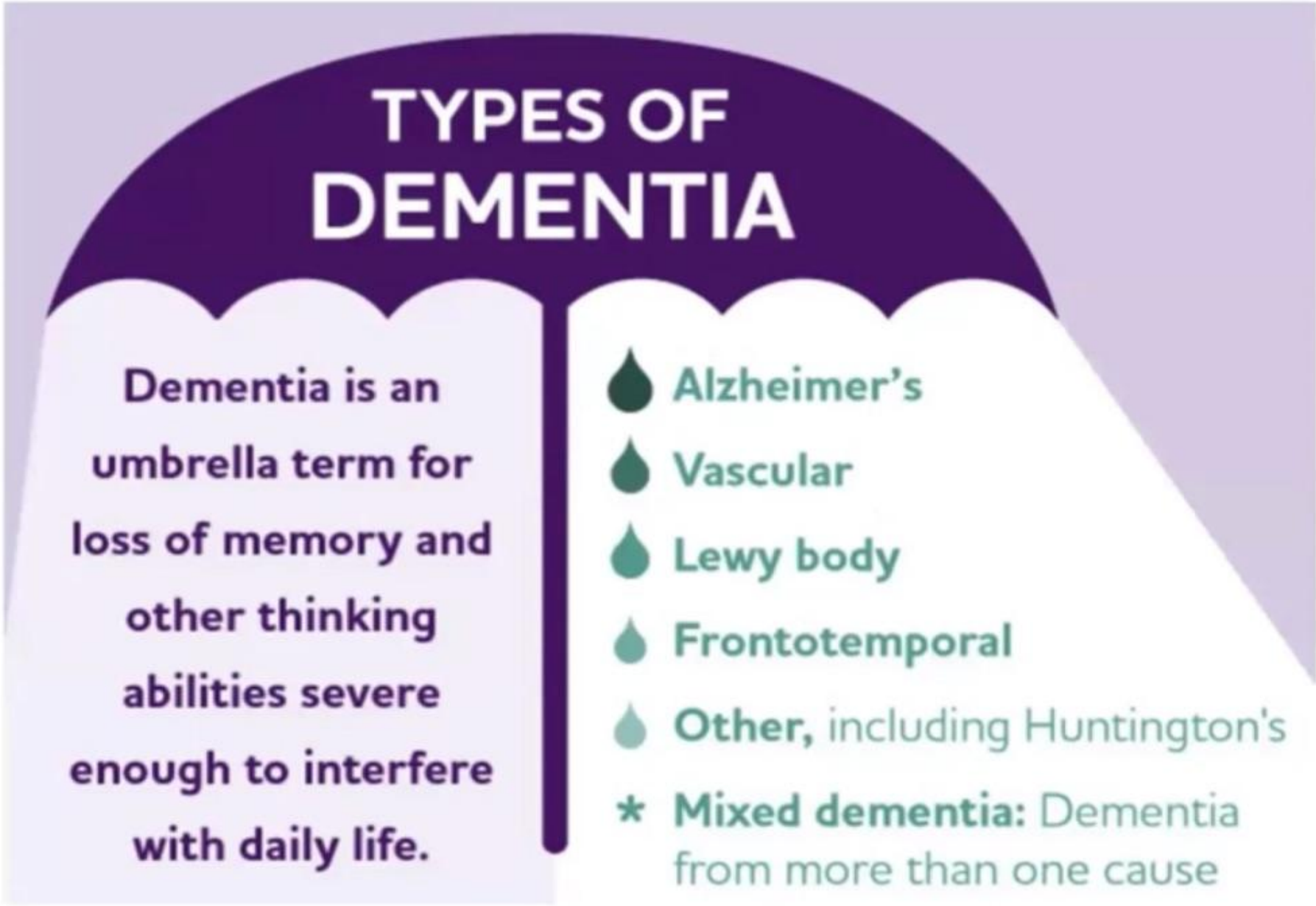
- I will not try and convince you to use these medications. The pivotal studies leading to approval of these agents will not be the focus of this discussion. Patients will be on them! You will be asked about them!
- We will not be discussing medications such as cholinesterase therapies and memantine for Alzheimer's disease.
- Dementia's other than Alzheimer’s disease.
- Behavioral problems in patient with Alzheimer's disease.
- Medications, or nutraceuticals that are not approved for Mild cognitive impairment and mild Alzheimer’s disease.
- Lifestyle modifications, which absolutely have a beneficial effect on the natural history of Alzheimer’s disease.
- Rapidly progressive dementia

INTRODUCTION

- There are approximately 6.7 million people who are living with Alzheimer's disease in the United states. Worldwide 100 million people have Alzheimer's disease.
- Alzheimer's disease is an epidemic it's frequently referred to as type 3 diabetes.
- The incidence of Alzheimer's disease doubles every five years after age 65 from approximately 5% between the ages of 65 and 74 to 32% in individuals over the age of 85.
- Alzheimer's disease is 5th leading cause of death in people 65 years or older.
- A typical 70-year-old person with Alzheimer's disease can expect to spend 40% of their remaining life with severe dementia.
- There are approximately 187 active trials involving 141 agents that are under investigation for Alzheimer's disease. Most of these target amyloid, Tau and neuroinflammation, none are anticipated to achieve FDA approval before 2026.

OKLAHOMA ALZHEIMER'S STATISTICS

- Number of people 65 and older with AD 70,500
- Percent of adults over 65 with AD 10.8%
- Number of ED visits per 1000 people with dementia 1,692
- Hospital readmission rate in patients with dementia 21.6%
- Number of deaths from AD 1,580 per year.
- Per Capita Medicare spending on people with Dementia in 2023 dollars- 32,584.



Source: Alzheimer's Association

Brain degeneration is often associated with abnormal protein accumulation

Reagan	Gehrig	Ali	Guthrie
AD	ALS/FTD	PD	HD
Aβ, Tau	many proteins	synuclein	polyglutamine

DIAGNOSIS OF ALZHEIMER'S DISEASE

- Prior to the development of amyloid targeted therapies (ATT) for MCI and mild Alzheimer's disease, symptomatic medications were used but didn't affect the natural history of the disease.
- Since the approval of amyloid targeted therapies, the way we evaluate and diagnose patients with Mild cognitive impairment and early Alzheimer's disease is evolving from a clinical diagnosis to a biomarker diagnosis.
- The use of these newer medications require biomarker proof.

DIAGNOSIS OF ALZHEIMER'S DISEASE

- In the clinic situation the concept of mild cognitive impairment has become an important decision point in the evaluation of patients that are candidates for amyloid targeted therapies.
- Besides the clinical aspects, information obtained from family members, biomarkers, are now an essential part of the evaluation, if patients are considered for ATT.

MONDAY MORNING 8:00 AM

72-year-old retired Astronomy professor presents to your clinic because family members have noticed that he has word finding problems, and memory problems, for about a year. The patient doesn't think it's a significant problem.

Patient has a history of hypertension diabetes, both well controlled for years He has a family history of Alzheimer's disease.

Physical examination is nonfocal there are no spontaneous features of Parkinson's disease.

No behavioral change, or significant depression was reported.

The patient is only here because his daughter is worried about him and made him come to this appointment.

How do you want to proceed?

How do we check this out to the patients and family satisfaction?

WORK UP OF A PATIENT WITH A COGNITIVE COMPLAINT

- History and physical, **medication history** etc.
- Bedside cognitive testing such as MOCA, SLUMS, FMMS exam, Depression scale (GDS).
- Activities of daily living (ADL) questionnaire, such as the AD 8 or functional activities questionnaire.
- Imaging- MRI brain is preferred with appropriate sequences, CT brain, as a minimum.
- Laboratory studies that include at a minimum B12, thyroid function test specifically TSH and T4 if indicated.

Functional Activities Questionnaire

Administration

Ask informant to rate patient's ability using the following scoring system:

- Dependent = 3
- Requires assistance = 2
- Has difficulty but does by self = 1
- Normal = 0
- Never did [the activity] but could do now = 0
- Never did and would have difficulty now = 1

1.	Writing checks, paying bills, balancing checkbook	
2.	Assembling tax records, business affairs, or papers	
3.	Shopping alone for clothes, household necessities, or groceries	
4.	Playing a game of skill, working on a hobby	
5.	Heating water, making a cup of coffee, turning off stove after use	
6.	Preparing a balanced meal	
7.	Keeping track of current events	
8.	Paying attention to, understanding, discussing TV, book, magazine	
9.	Remembering appointments, family occasions, holidays, medications	
10.	Traveling out of neighborhood, driving, arranging to take buses	
	TOTAL SCORE:	

Evaluation

Sum scores (range 0-30). Cut-point of 9 (dependent in 3 or more activities) is recommended to indicate impaired function and possible cognitive impairment.

Pfeffer, R.I., Kurosaki, T.T., Harrah, C.H. Jr., Chance, J.M., & Filos, S. (1982). Measurement of functional activities in older adults in the community. *Journal of Gerontology, 37*(3), 323-329.

The Ascertain Dementia 8 Questionnaire[a,b]

Questions administered to a reliable informant

1 Is there repetition of questions, stories, or statements?

2 Are appointments forgotten?

3 Is there poor judgment (eg, buying inappropriate items, poor driving decisions)?

4 Is there difficulty with financial affairs (eg, paying bills, monitoring banking statements)?

5 Is there difficulty in learning or operating appliances (eg, television remote, microwave oven)?

6 Is the correct month or year forgotten?

7 Is there decreased interest in hobbies and usual activities?

8 Is there overall a problem with thinking and/or memory?

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[a] Modified with permission from Galvin JE, et al, Neurology.[67]

[b] The Ascertain Dementia 8 questionnaire is an eight-question screening tool to detect mild cognitive impairment or very mild dementia in older adults. Positive responses to two or more Ascertain Dementia 8 questions were associated with a high (87%) positive predictive value for impairment (versus no impairment) in research participants (who were 55 years old and older) enrolled within a longitudinal cohort study of memory and aging at a single center.[67]

- The patient’s MOCA was 27/30, (>26 is normal). The geriatric depression scale was 1/15 which suggest the patient is not depressed.(>5 is probable depression)
- The patient's functional activities questionnaire filled out by the family was a 3/30. (>9 suggests problems with activities of daily living)
- The laboratory studies done were unremarkable, the patient's medications were not felt to be contributory the patient had well controlled hypertension and diabetes for years. No history of seizures, cerebral vascular event or significant head trauma.

- MRI brain was age appropriate. No prior areas of ischemia or prior hemorrhage were commented on. Specifically, there's no structural explanation for the cognitive complaints.
- What's this patient's diagnosis?

MILD COGNITIVE IMPAIRMENT (MCI)

- In short MCI is a cognitive state between normal cognition and dementia. The distinction between age-related cognitive decline and mild cognitive impairment is gray.
- MCI is divided into amnestic MCI (aMCI) and non amnestic MCI (naMCI). Single domaine and Multiple domain.
- MCI refers to individuals that are impaired but don't meet the criteria for a major neurocognitive disorder.
- These patients have a memory complaint that is also noted by reliable informants, mild objective impairment of cognitive function, and function well, with preserved activities of daily living.
- They don't meet criteria for dementia (major neurocognitive disorder).

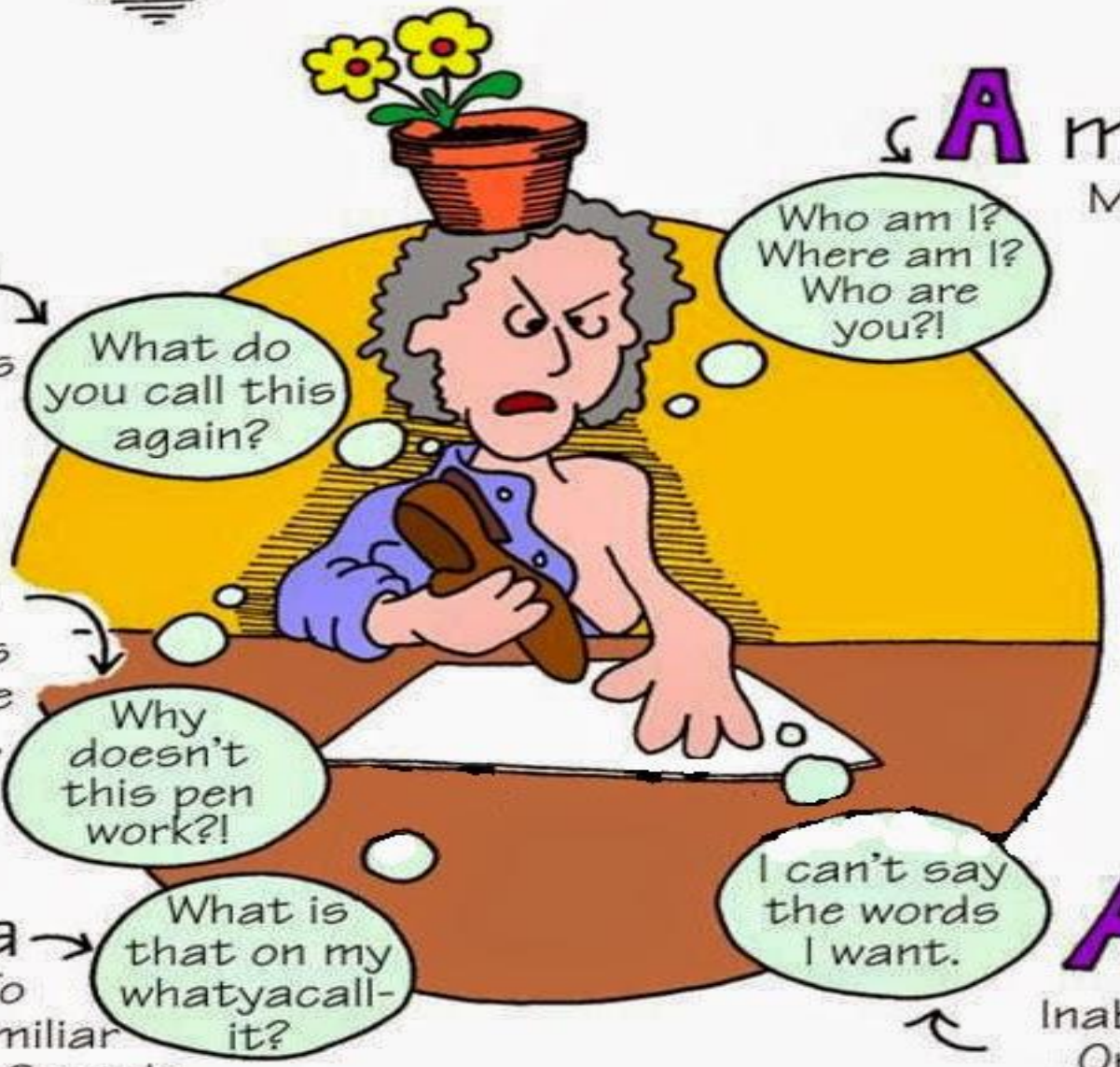
MILD COGNITIVE IMPAIRMENT (MCI) DSM-5 MILD NEUROCOGNITIVE DISORDER

- These patients may have Some cognitive deficits apparent on testing but not to a level diagnostic of dementia (MMSE 24-29), (MOCA >26)
- Minimal if any functional impairments. Normal AD8 and FAQ.
- 13-15% per year progression to Alzheimer's disease but not all progress and some may improve.
- Risk factors for progression include amnestic type MCI, hippocampal atrophy on MRI and APO E4 homozygosity.
- Ultimately this is a clinical diagnosis that considers the expected level of cognitive function against the persons performance on cognitive testing.
- Most patients haven't had cognitive testing to show or demonstrate a clear deterioration and therefore cannot confidently be diagnosed with mild cognitive impairment versus normal aging. We assume they were unaffected before being evaluated for a cognitive complaint.

MILD COGNITIVE IMPAIRMENT (MCI), DEMENTIA OR NORMAL AGEING?

	MCI	Dementia	Normal Ageing
Occasional memory lapses *(forgetting an appointment or task, losing train of thought mid-conversation, repeating questions)*	✓	✓	✓
Slight difficulty concentrating, understanding complex conversations or following instructions	✓	✓	✓
Frequent & more severe memory slips and trouble concentrating & comprehending, such as forgetting common words or names of a good friend, common words, making monthly payments, etc	✓	✓	
Facing challenges completing familiar tasks such as cooking a simple dish, finding the way home, or even getting dressed.		✓	
Apparent mood, behaviour, or personality changes *(becoming aggressive, reckless, rude, or withdrawn)*		✓	

5 As to Alzheimer Diagnosis



Amnesia
Memory Loss...

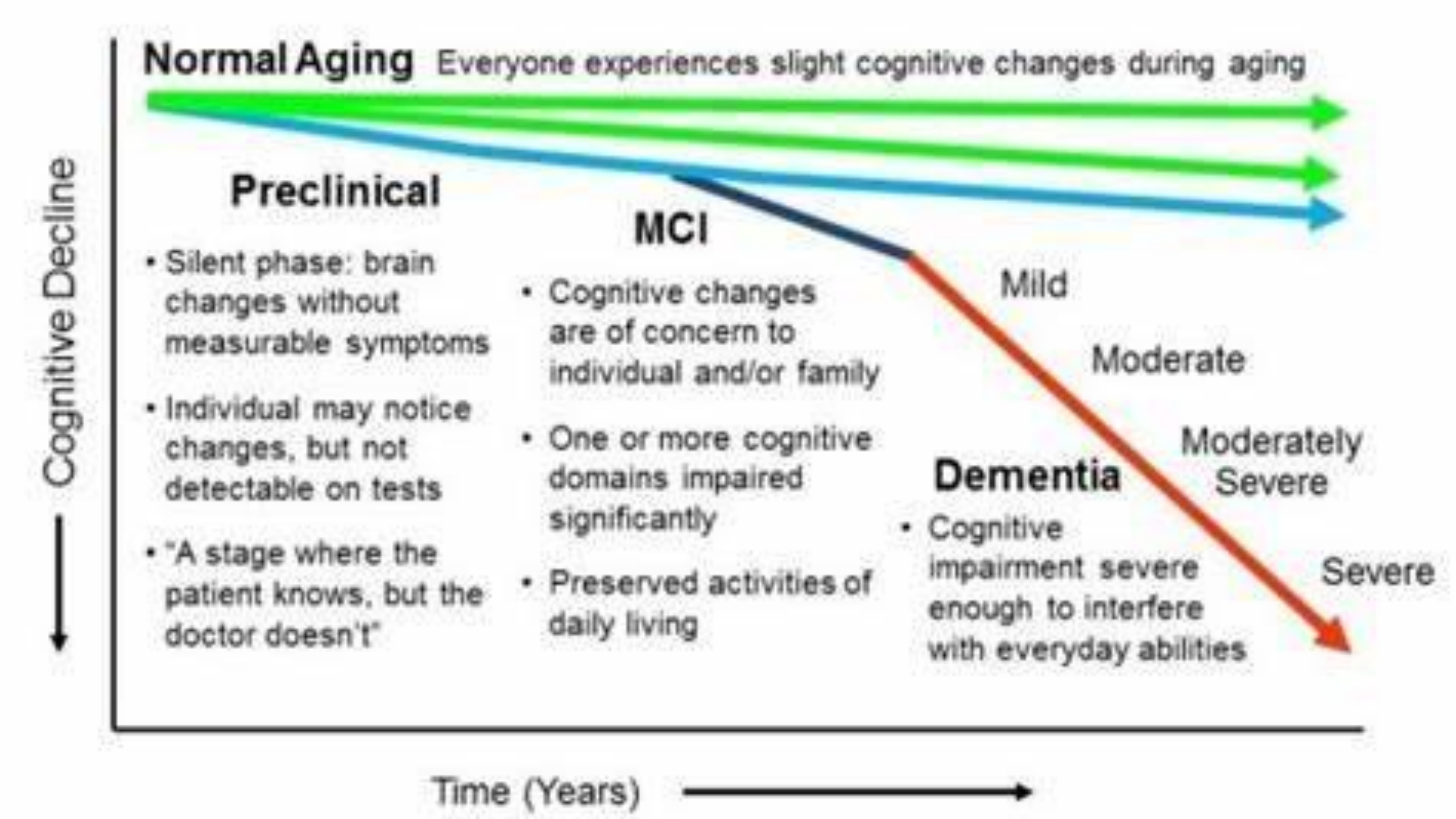
Anomia
Inability To Remember Names of Things...

Apraxia
Misuse Of Objects Because Of Failure To Identify Them...

Agnosia
Inability To Recognize Familiar Objects, Tastes, Sounds, And Other Sensations...

Aphasia
Inability To Express Oneself Through Speech...

Judgment
Concentration
Attention


Normal Aging
Everyone experiences slight cognitive changes during aging
Preclinical
• Silent phase: brain changes without measurable symptoms
• Individual may notice changes, but not detectable on tests
• "A stage where the patient knows, but the doctor doesn't"
MCI
• Cognitive changes are of concern to individual and/or family
• One or more cognitive domains impaired significantly
• Preserved activities of daily living
Dementia
• Cognitive impairment severe enough to interfere with everyday abilities
Mild
Moderate
Moderately Severe
Severe
Cognitive Decline
Time (Years)

Alzheimer's Disease Progresses Through Distinct Stages

Dementia/Alzheimer's

Symptoms

Mild

- Memory loss
- Language problems
- Mood swings
- Personality changes
- Diminished judgment

Moderate

- Behavioral, personality changes
- Unable to learn/recall new info
- Long-term memory affected
- Wandering, agitation, aggression, confusion
- Require assistance w/ADL

Severe

- Gait, incontinence, motor disturbances
- Bedridden
- Unable to perform ADL
- Placement in long-term care needed

- The diagnosis is MCI, what next?
- Does this patient have Alzheimer's disease?
- Are there any disease modifying therapies for Alzheimer's disease?
- The patient's family ask about medications that they've heard about that were recently approved for Alzheimer's disease?
- Is this patient a candidate for those medications?
- If so, are the indicated?

- To qualify for amyloid targeted therapies patients must have a diagnosis of mild cognitive impairment, or mild Alzheimer's disease.
- Patient's must have **biomarker evidence** of Alzheimer's disease, either CSF, or molecular imaging.
- Patients must not have contraindications to amyloid targeted therapies (see next slide)
- APO-E genotyping, for risk stratification of amyloid targeted therapies.
- Patient and family need to commit to infusion therapies either every two weeks or every four weeks, in addition serial neuroimaging and surveillance for complications of amyloid imaging abnormalities (ARIA).

Contraindications to the use of amyloid-targeted therapies for Alzheimer disease

Contraindications – These conditions increase the risk of adverse effects of anti-amyloid therapy

- *APOE* ε4 homozygotes*
- Moderate to severe dementia (CDR score >1)
- Non-Alzheimer disease pathologies as the cause of cognitive impairment or dementia
- Bleeding disorders (eg, platelets <50,000 or INR >1.5)
- Anticoagulant therapy (warfarin, heparin, DOAC) or dual antiplatelet therapy*
- History or MRI finding suggestive of:
  - CAA-related inflammation/amyloid beta-related angiitis
  - Prior cerebral hemorrhage (ICH >10 mm)
  - High-risk vascular malformation
  - Any stroke or TIA within the last year
  - Cerebral infarction due to large artery occlusion (cardiogenic embolism or atherothromboembolism)
  - Multiple lacunar strokes (>2)
  - Multiple microhemorrhages (>4)
  - Superficial siderosis
  - Vasogenic edema
  - Brain tumor other than meningioma or arachnoid cyst
  - Active/unresolved CNS infection
  - Severe subcortical hyperintensities (Fazekas score of 3)
- Systemic treatment with immunosuppressants, immunoglobulins, or monoclonal antibodies that suppress the immune system or their derivatives
- Active autoimmune or immunologic disease
- Pregnancy
- BMI >35 or <17
- Inability to comply with MRI monitoring

Relative contraindications – Having one or more of these conditions can increase the risk and/or decrease the benefits of anti-amyloid therapy

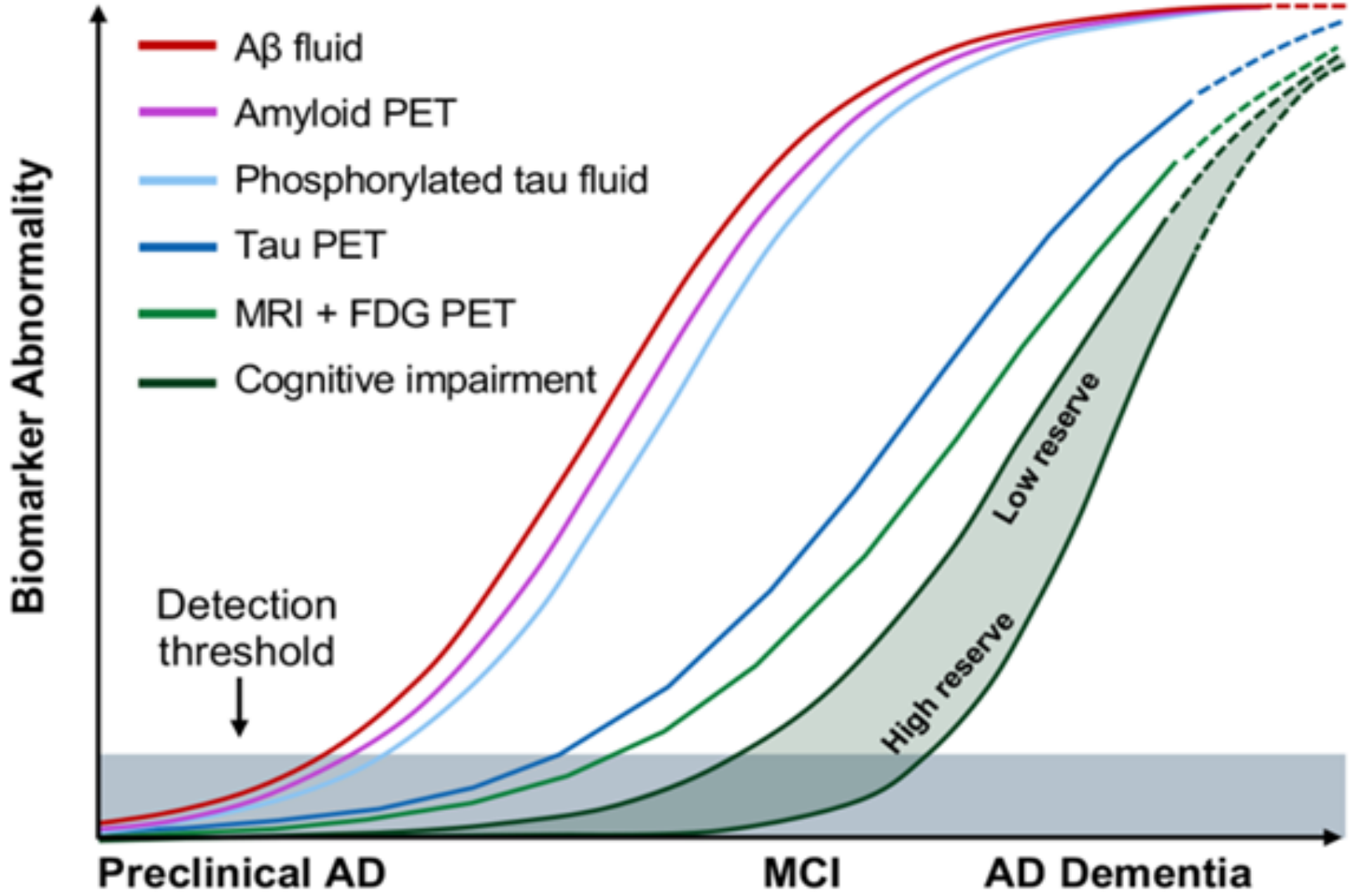
- Unstable medical or psychiatric condition
- Major depression, uncontrolled (GDS-15 score >8)
- Seizures within the previous 12 months
- Cerebral contusion
- Encephalomalacia
- Brain aneurysm
- Breastfeeding

Some of the contraindications listed here are being reevaluated as more patients are treated with these therapies. At present, we adhere fairly closely to these in order to minimize risk to our patients.

APOE ε4: apolipoprotein E epsilon 4; BMI: body mass index; CAA: cerebral amyloid angiopathy; CDR: clinical dementia rating; CNS: central nervous system; DOAC: direct oral anticoagulant; ICH: intracerebral hemorrhage; GDS: Geriatric Depression Scale; INR: International Normalized Ratio; MRI: magnetic resonance imaging; TIA: transient ischemic attack.

* Some clinicians consider these as relative contraindications and treat these patients after risk/benefit discussions with the patient and care partners.

Temporal Evolution of AD Biomarkers and Cognitive Impairment[1]



1. Jack Jr CR et al. *Lancet Neurol*. 2022;10:866-869.

Updated Biomarker Categorization From the Revised Criteria for Diagnosis and Staging of AD (2024)[1]

Biomarker Category	CSF or Plasma Analytes	Imaging
Core 1 Biomarkers		
A (Aβ proteinopathy)	Aβ42	Amyloid PET
T_1 (phosphorylated and secreted AD tau)	P-tau217, P-tau181, P-tau231	—
Core 2 Biomarkers		
T_2 (AD tau proteinopathy)	P-tau205, MTBR-243, nP-tau fragments	Tau PET
Biomarkers of Nonspecific Processes Involved in AD Pathophysiology		
N (injury, dysfunction, or degeneration of neuropil)	NfL	Anatomic MRI, FDG PET
I (inflammation) astrocytic activation	GFAP	—
Biomarkers of Non-AD Copathology		
V (vascular brain injury)	—	Infarction on MRI or CT, WMH
S (α-synuclein)	αSyn-SAA	—

1. Jack Jr CR et al. *Alzheimers Dement*. 2024 Jun 27 [Epub ahead of print].

Advantages and Limitations of Three Modalities of AD Biomarkers

Modality	Advantages	Limitations
PET scan[1-5] Amyloid PET, tau PET	• Associated with changes in management of patients with MCI and dementia • Long history of use and standardized interpretation • Multiple FDA-approved tracers • Reflects spatial distribution and amount of pathology • Medicare will now cover amyloid PET	• Costly without coverage and still difficult to get reimbursed by Medicare in many locations • Limited capacity and availability • Invasive (radiation)
CSF[6-9] Aβ42/40, T-tau/Aβ42, P-tau181/Aβ42	• Widely available • Reimbursed by CMS for certain diagnoses • Long history of use and standardized interpretation • Multiple FDA-approved tests • Can be performed by a radiologist, neurologist, or advanced practice provider	• Test characteristics vary by method (sampling and measurement) • Invasive (lumbar puncture) • Contraindications • Post LP complications
Plasma[10-18] The following tests are available as single analytes or in combination panels: P-tau217, Aβ42/Aβ40, P-tau181, *APOE*4, NfL	• CLIA certified • Minimally invasive • Widely accessible • Can be ordered by any provider • Analytically validated	• Not yet FDA approved • Not reimbursed by CMS • Test performance varies by assay and measurement method • Relatively new; lacking validation in a general population

1. Wong DF et al. *J Nucl Med*. 2010;51:913-920. 2. Rabinovici GD et al. *JAMA*. 2019;321:1286-1294. 3. Jie CVM et al. *Pharmaceuticals*. 2021;14:110. 4. Chávez-Fumagalli MA et al. *J Alzheimer's Dis Rep*. 2021;5:15-30. 5. https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&NCAId=308. 6. Duits FH et al. *Alzheimers Dement*. 2016;12:154-163. 7. Bittner T et al. *Alzheimers Dement*. 2016;12:517-526. 8. Janelidze S et al. *Ann Clin Transl Neurol*. 2016;3:154-165. 9. Canevelli M et al. *Front Aging Neurosci*. 2019;11:282. 10. Qu Y et al. *Neurosci Biobehav Rev*. 2021;128:479-486. 11. Li Y et al. *Neurology*. 2022;98:e688-e699. 12. Jack CR et al. *Alzheimer's Dement*. 2024;1-27. 13. Pleen J et al. *Practical Neurology*. 2024;23:27-42. 14. Hampel H et al. *Neuron*. 2023;111:2781-2799. 15. https://www.labcorp.com/providers/neurology/neurodegenerative-diseases/alzheimers-disease. 16. https://testdirectory.questdiagnostics.com/test/home?specialty=Geriatrics%2FAge%20Management. 17. https://www.lucentdiagnostics.com/about-lucentad-providers/. 18. https://precivityad.com/.

Commercially Available Biomarkers for AD[1-9]

Test Name (Developer)	Biomarker Modality	Biomarkers	Assay Platform	Regulatory Status
Florbetapir (Lilly)	Amyloid PET	Amyloid plaques	N/A	FDA-approved
Florbetaben (Life Molecular Imaging)	Amyloid PET	Amyloid plaques	N/A	FDA-approved
Flutemetamol (GE Healthcare)	Amyloid PET	Amyloid plaques	N/A	FDA-approved
Flortaucipir (Lilly)	Tau PET	Tau aggregates	N/A	FDA-approved
Elecsys AD (Roche)	CSF	P-tau181/Aβ42, T-tau/Aβ42	Elecsys	FDA-approved
Lumipulse G (Fujirebio)	CSF	Aβ42/40	Lumipulse	FDA-approved
AD-Detect (Quest Diagnostics)	Plasma	P-tau217, p-tau181, Aβ42/40, ApoE isoform	CLEIA, LC-MS/MS	CLIA-certified
ALZpathDx (ALZpath, Quanterix)	Plasma	P-tau217	Simoa	CLIA-certified & FDA breakthrough
LucentAD (Lucent Diagnostics)	Plasma	P-tau217	Simoa	CLIA-certified
Amyloid Plasma Panel (Roche, Lilly)	Plasma	P-tau217, Aβ42/Aβ40, P-tau181, APOE4	Elecsys	Breakthrough device
Phosphorylated Tau 217 (Labcorp)	Plasma	P-tau217	Lumipulse CLEIA	CLIA-certified
Phospho-Tau 217 (Mayo Clinic)	Plasma	P-tau217	CLEIA	CLIA-certified
PrecivityAD, PrecivityAD2 (C2N)	Plasma	Aβ42/Aβ40, APOE4, P-tau217/nP-tau217	IP-LC-MS/MS	CLIA/breakthrough

1. https://testdirectory.questdiagnostics.com/test/test-guides/TS_AD_Detect_Ptau217Plasma/quest-ad-detect-phosphorylated-tau217-p-tau217-plasma?p=td. 2. https://www.quanterix.com/advancing-alzheimers-disease-pathology-detection-with-simoa-alzpath-p-tau217-assay/. 3. https://www.lucentdiagnostics.com/wp-content/uploads/2024/05/04.07_LucentAD_White_Paper.pdf. 4. https://www.labcorp.com/tests/484390/phosphorylated-tau-217-ptau-217-plasma. 5. https://precivityad.com/precivityad2-hcp. 6. https://diagnostics.roche.com/us/en/news-listing/2024/roche-granted-fda-breakthrough-device-designation-ptau217-blood-test-support-earlier-alzheimers-disease-diagnosis.html. 7. https://www.mesoscale.com/en/products_and_services/services/s-plex/tau_pt217_and_pt181_services. 8. Pleen J et al. *Practical Neurology*. 2024;23:27-42. 9. Hampel H et al. *Neuron*. 2023;111:2781-2799.

Are Plasma Biomarkers Ready for Prime Time?[1-5]

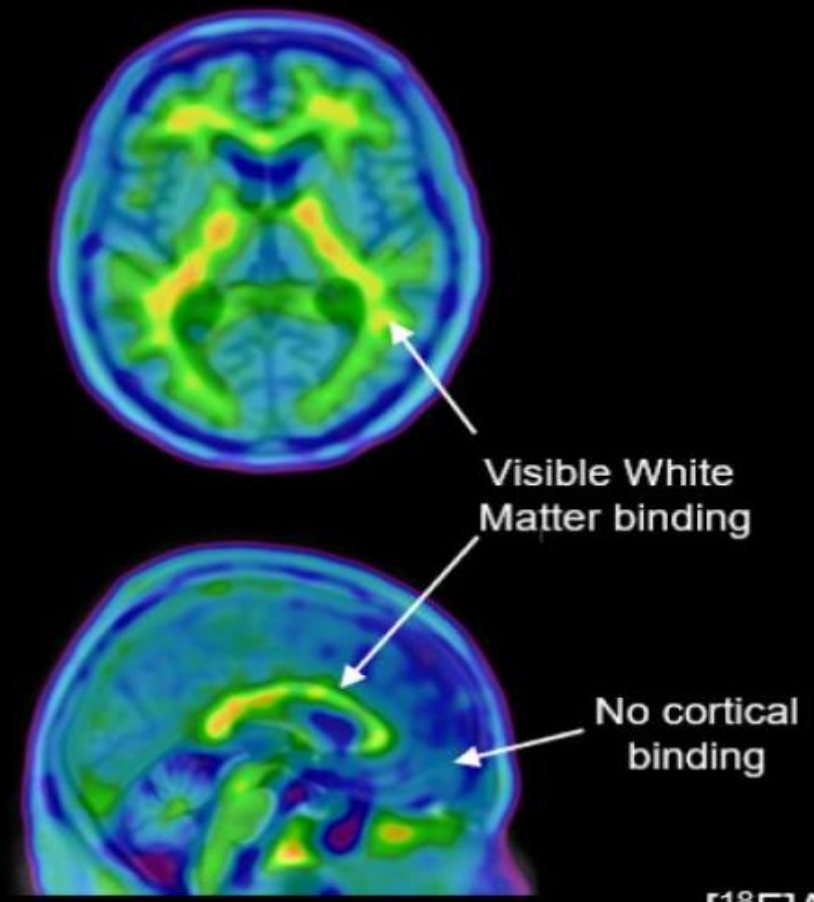
- Plasma tests should have performance equivalent to FDA-approved CSF tests
  - **≥90% sensitivity and ≥90% specificity** (amyloid status)

Plasma P-tau217 tests are the only plasma assays achieving overall accuracy that exceeds 90%

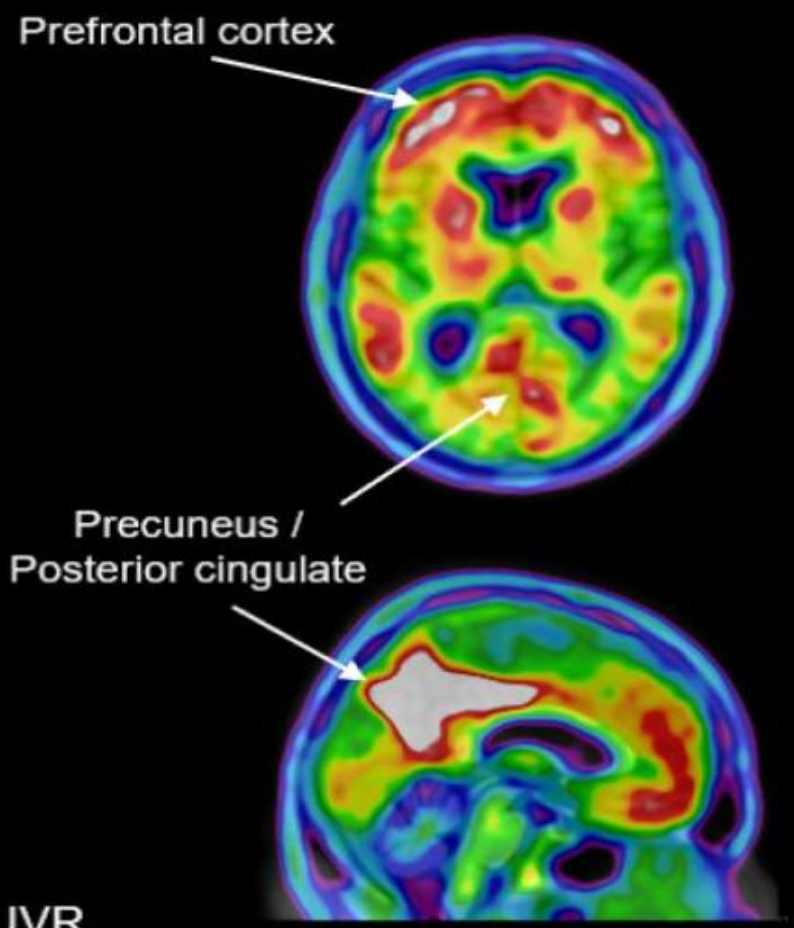
1. Schindler SE et al. *Nat Rev Neurol*. 2024;20:426-439. 2. Rissman RA et al. *Alzheimers Dement*. 2024;20:1214-1224. 3. Janelidze S et al. *Brain*. 2023;146:1592-1601. 4. Palmqvist S et al. *JAMA*. 2024 Jul 28 [Epub ahead of print]. 5. Jack Jr CR et al. *Alzheimers Dement*. 2024 Jun 27 [Epub ahead of print].

So, in our patient we elected to do Molecular imaging Amyloid PET, instead of CSF or Plasma testing.

Amyloid-PET negative



Amyloid-PET positive



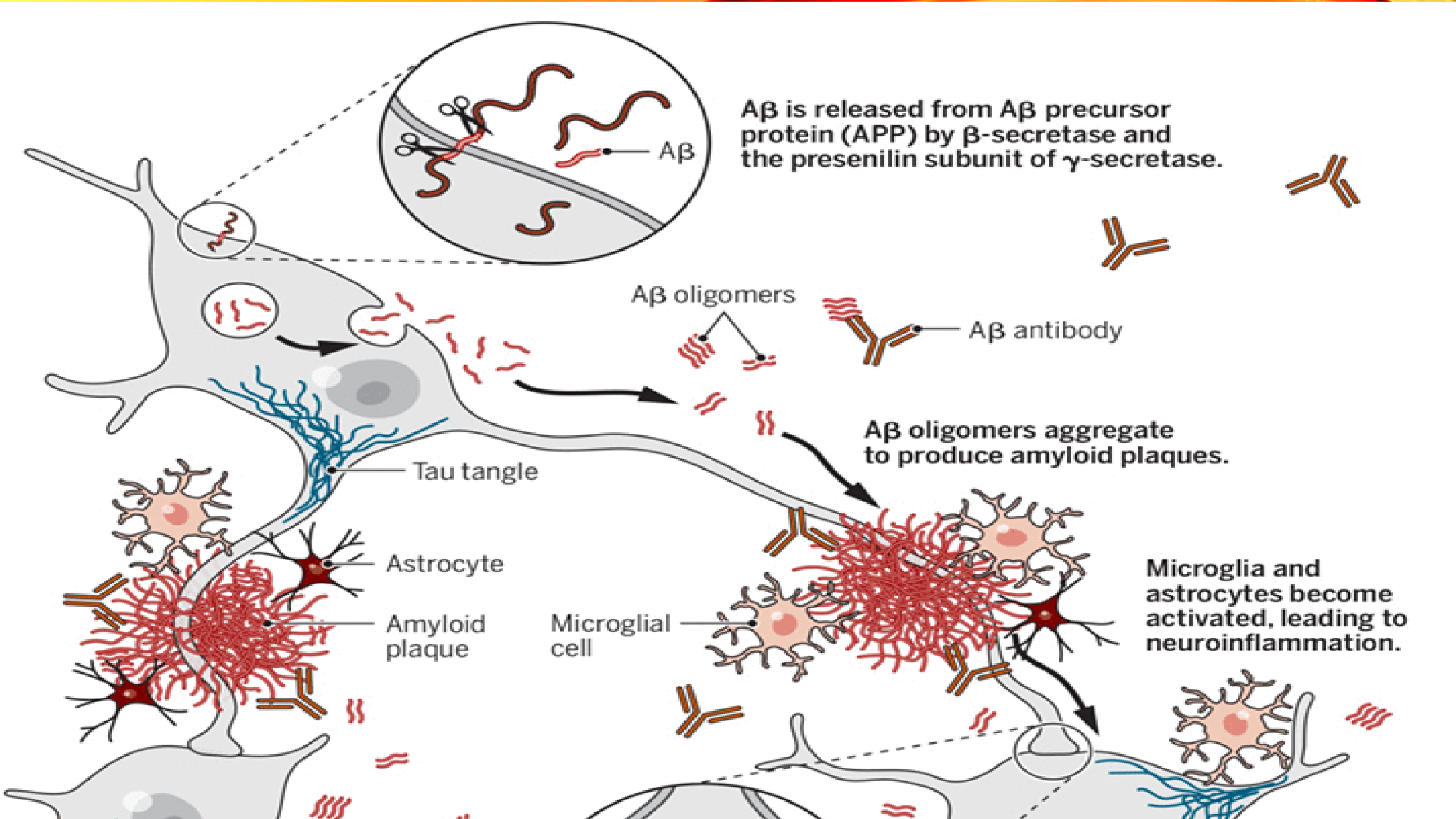
[^{18}F]AZD4694 SUVR

min max

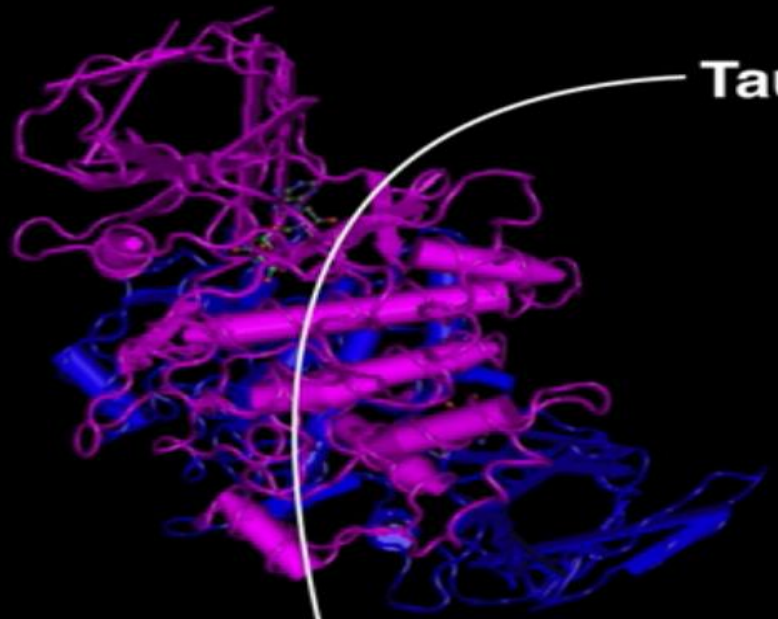
RECENT REGULATORY MILESTONES

- **Aduhelm,** Aducanumab (2021): First FDA-approved anti-amyloid therapy. Now off the market. Controversial evidence of efficacy.
- **Leqembi,** Lecanemab (2023): Confirmed benefits for early-stage Alzheimer's disease.
- **Kisunla,** Donanemab (2024) Confirmed benefits for early-stage Alzheimer's.

WHAT DO THESE MEDICINES DO, HOW DO THEY WORK, WHY IS IT IMPORTANT?

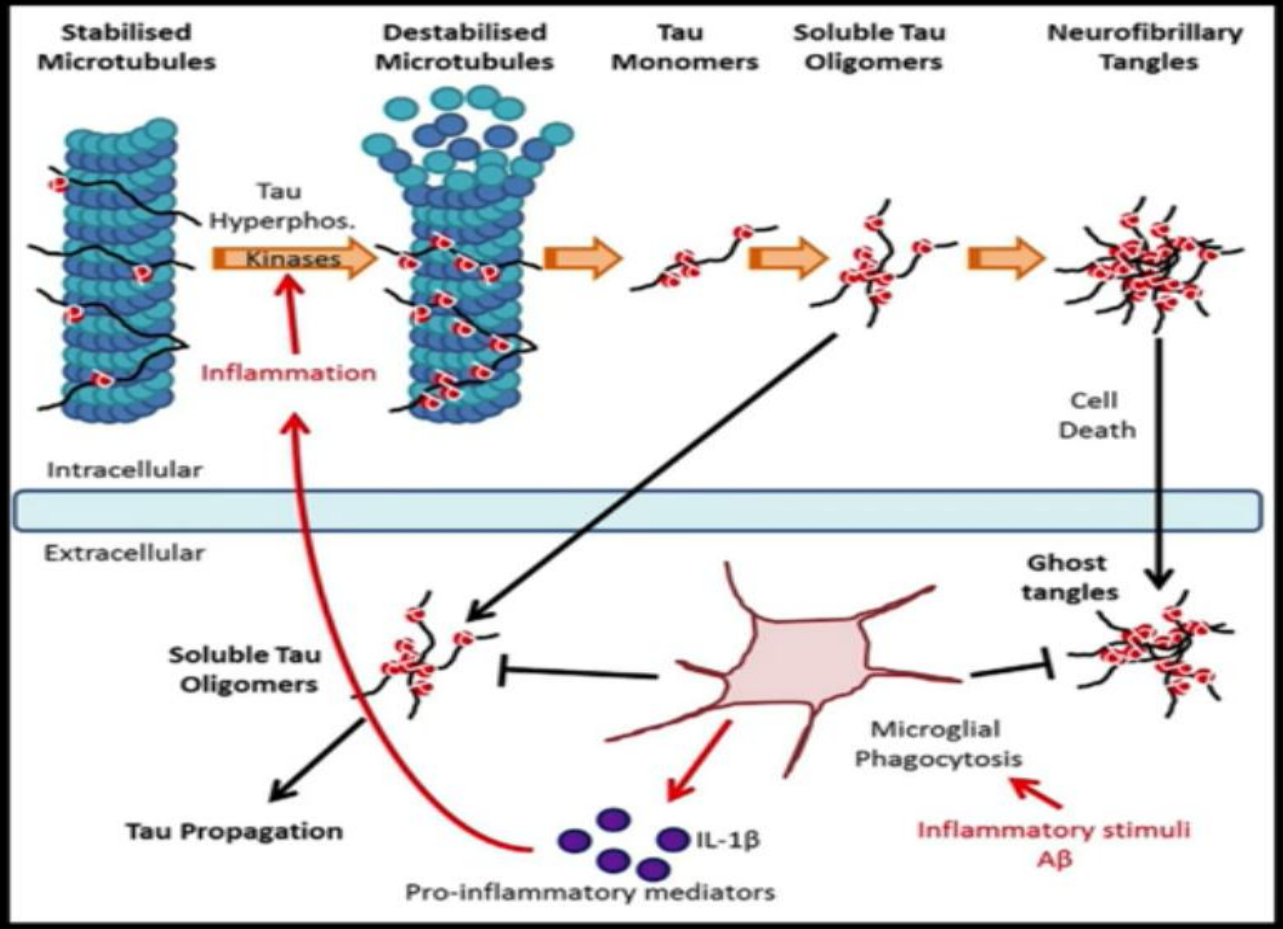

Aβ
Aβ is released from Aβ precursor protein (APP) by β-secretase and the presenilin subunit of γ-secretase.
Aβ oligomers
Aβ antibody
Tau tangle
Aβ oligomers aggregate to produce amyloid plaques.
Astrocyte
Amyloid plaque
Microglial cell
Microglia and astrocytes become activated, leading to neuroinflammation.

Prions: The *Tau* Hypothesis in Alzheimer's Disease



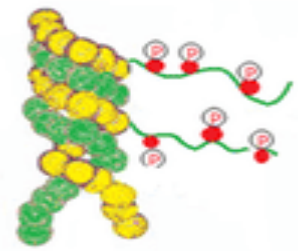
$Tau\text{-}O\text{-}PO_3^{2-}$

Tau Protein Kinases

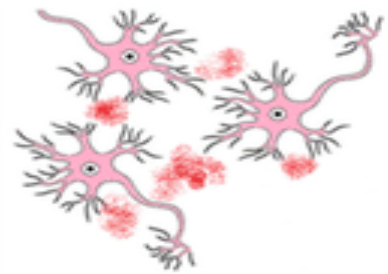


Hyperphosphorylated Tau → Microtubule Catastrophe → Tau Oligomerization → Neurofibrillary Tangles →

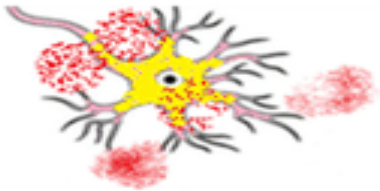
MITOCHONDRIAL DYSFUNCTION



TAU HYPER-PHOSPHORYLATION

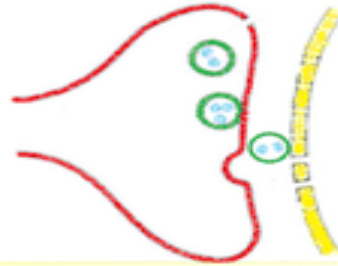


AMYLOID PLAQUES



NEURO-INFLAMMATION

ALZHEIMER'S DISEASE

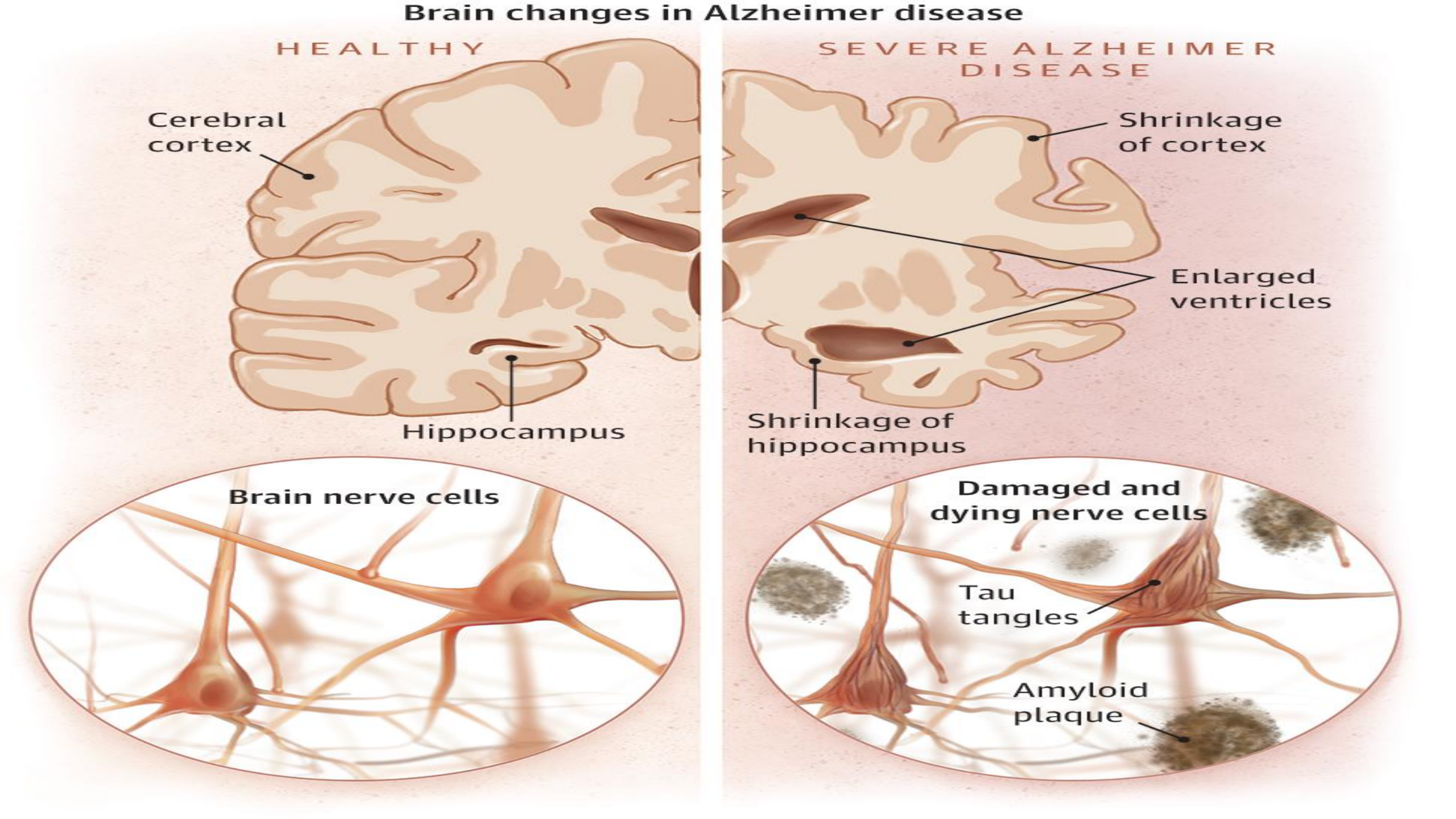


CHOLINERGIC INSUFFICIENCY

OXIDATIVE STRESS

HORMONAL IMBALANCE

Brain changes in Alzheimer disease



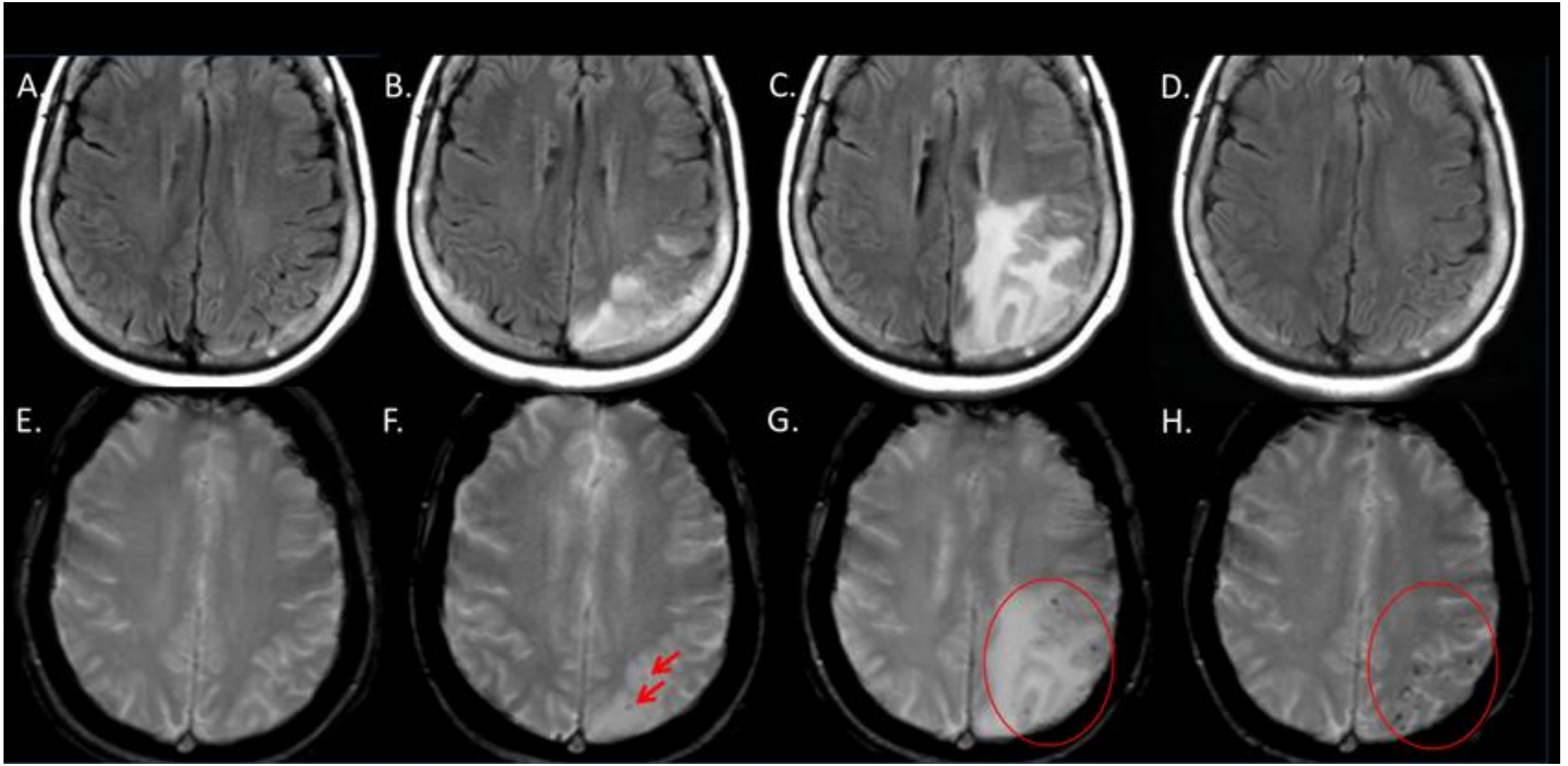
PATHOLOGY

- In short Alzheimer's disease progresses across decades with one of the central features being aggregation and accumulation of amyloid beta plaques and subsequently triggering inflammation and the formation of neurofibrillary tangles, (Tau accumulation.)
- The current medications approved only address amyloid beta only!
- Anti-Tau therapies are in development. Tau imaging is available.

COST:

- Lequembi –Lecanemab-(January 2023) - $26,500.00 per year
- Kinsunla-Donanemab- (July 2024) – $32,000.00 per year
- Aduhelm-Aducanumab- (June 2021) – No longer being produced, was around $56,000.00
- Amyloid PET- $10,000.00 per scan.
- CSF testing – $1,000.00-$1,500.00

- So, our patient has decided to go on an anti amyloid therapy or amyloid targeted therapy. The patient had an amyloid PET imaging that was positive. APO E genetic testing was 3/4. There were no contraindications.
- Patient had been doing well for approximately 3 months then started developing some symptoms specifically headache and stroke-like symptoms, right hemiparesis, right visual field loss, aphasia.
- Patient presents to a local hospital 1 hour after symptoms started.
- Did this patient have an acute stroke? Does this patient need thrombolytics?


A.
B.
C.
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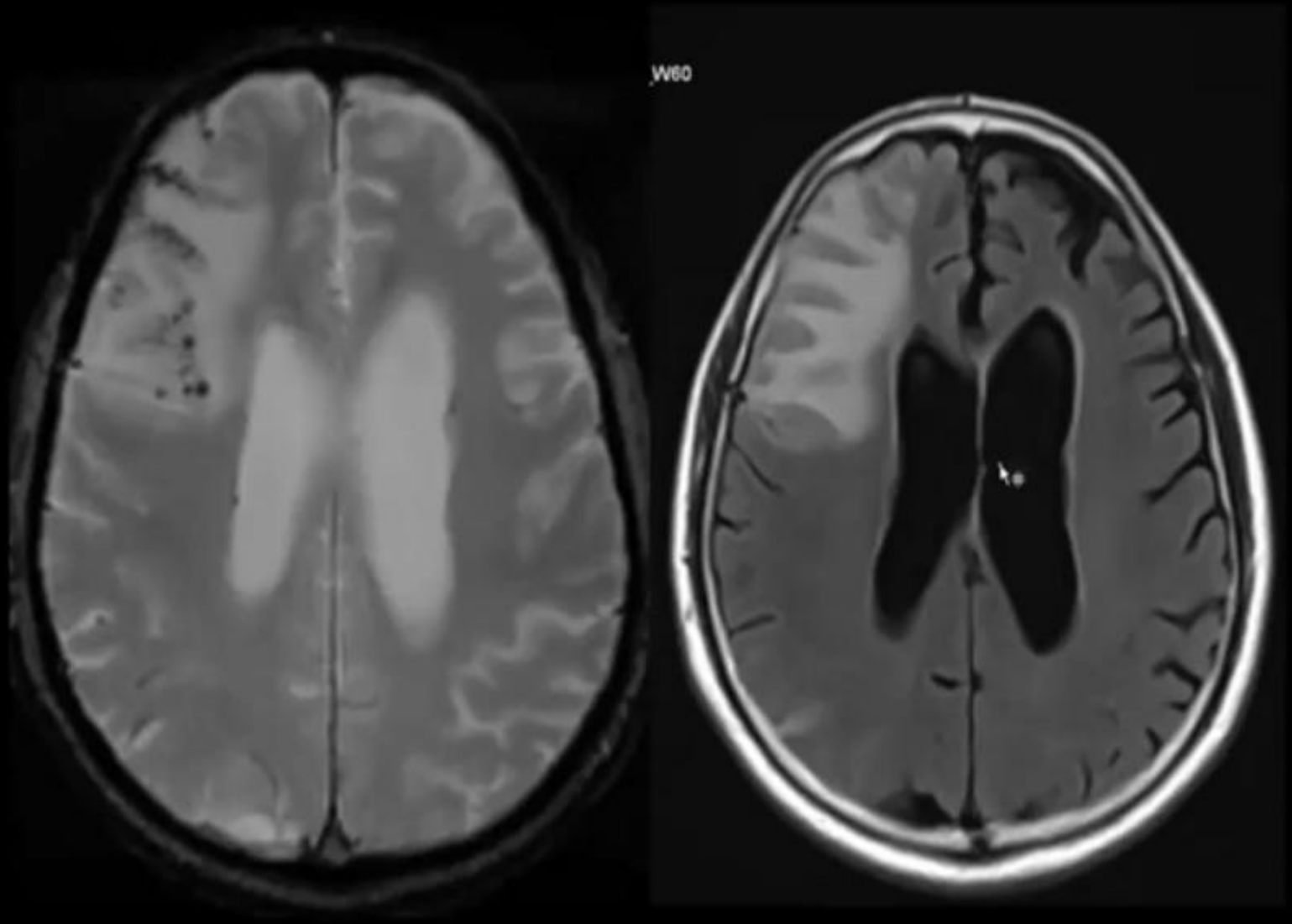
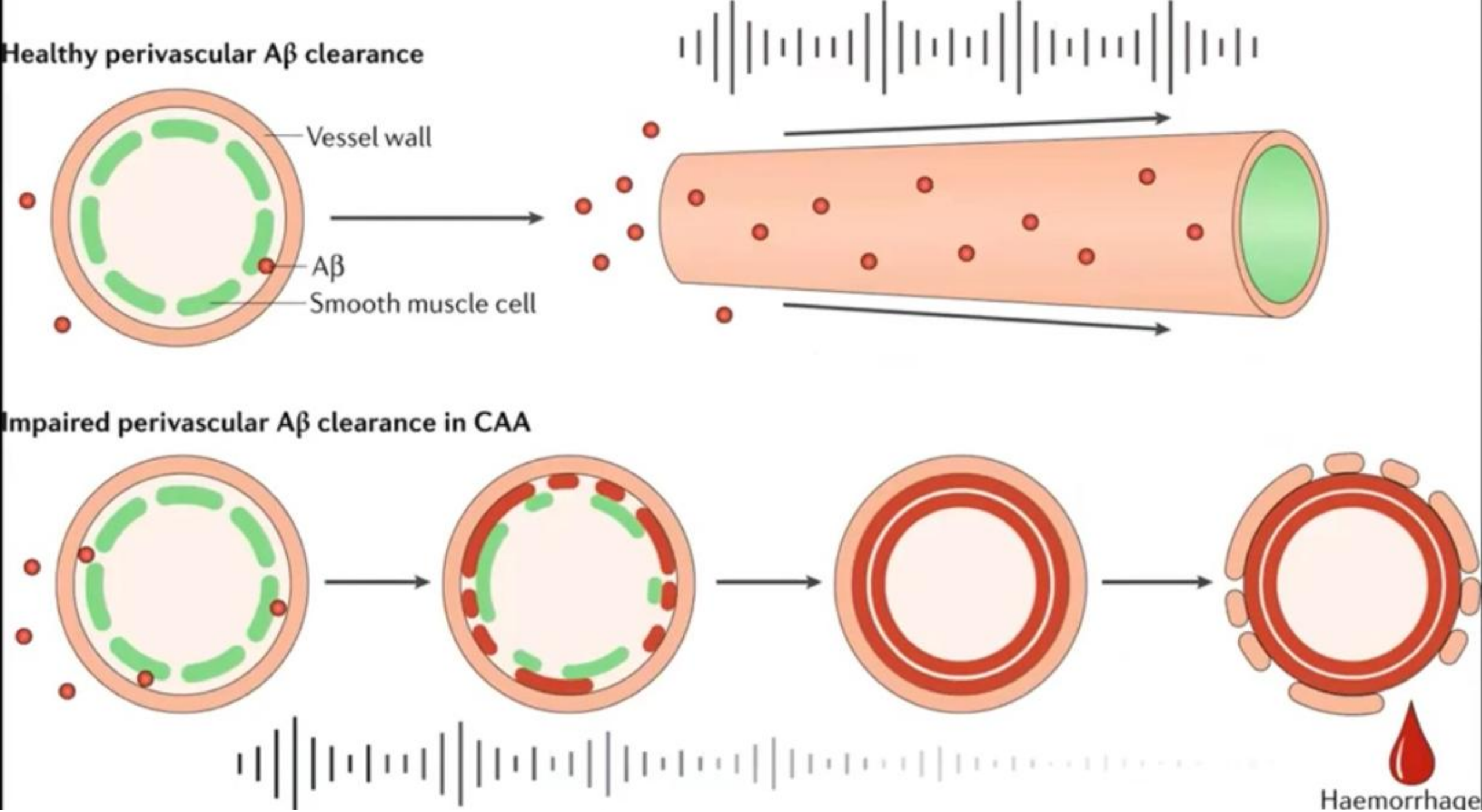
ARIA: Amyloid Related Imaging Abnormality



ARIA-E: Effusions, edema
ARIA-H: Hemorrhage

Risk factors include ApoE4 genotype

Baseline MRI findings of >5 MCH and/or cerebral infarction generally exclusionary for most clinical trials.


Healthy perivascular Aβ clearance
Vessel wall
Aβ
Smooth muscle cell
Impaired perivascular Aβ clearance in CAA
Haemorrhage

SYMPTOMS OF ARIA

- In most cases, ARIA is found on MRI imaging during monitoring and is asymptomatic.
- The symptoms of ARIA are nonspecific and include headache, confusion, nausea, vomiting, visual disturbances, neuropsychiatric symptoms, dizziness, fatigue, or gait disturbances.
- Infrequently, severe neurological symptoms occur (e.g., encephalopathy, focal neurological symptoms, seizures, and status epilepticus)

WHAT DO I NEED TO BE WATCHING FOR IN MY PATIENTS!

- symptoms of ARIA-E and ARIA-H. (see previous slide)
- Patients must have MRI imaging if patient is symptomatic. CT will never show ARIA, unless it is a large hemorrhage.
- What medications do I need to avoid? Anti-coagulants, t-PA, TNKase,(Tenecteplase)
- If a patient presents to acute care with ARIA symptoms and has a diagnosis of mild cognitive impairment or mild Alzheimer's disease, and they are on an IV medication every two weeks, or every four weeks as an outpatient, for Alzheimer's disease, MRI is the only modality that will separate ARIA from an acute stroke. Please note avoid thrombolytics with these patients.

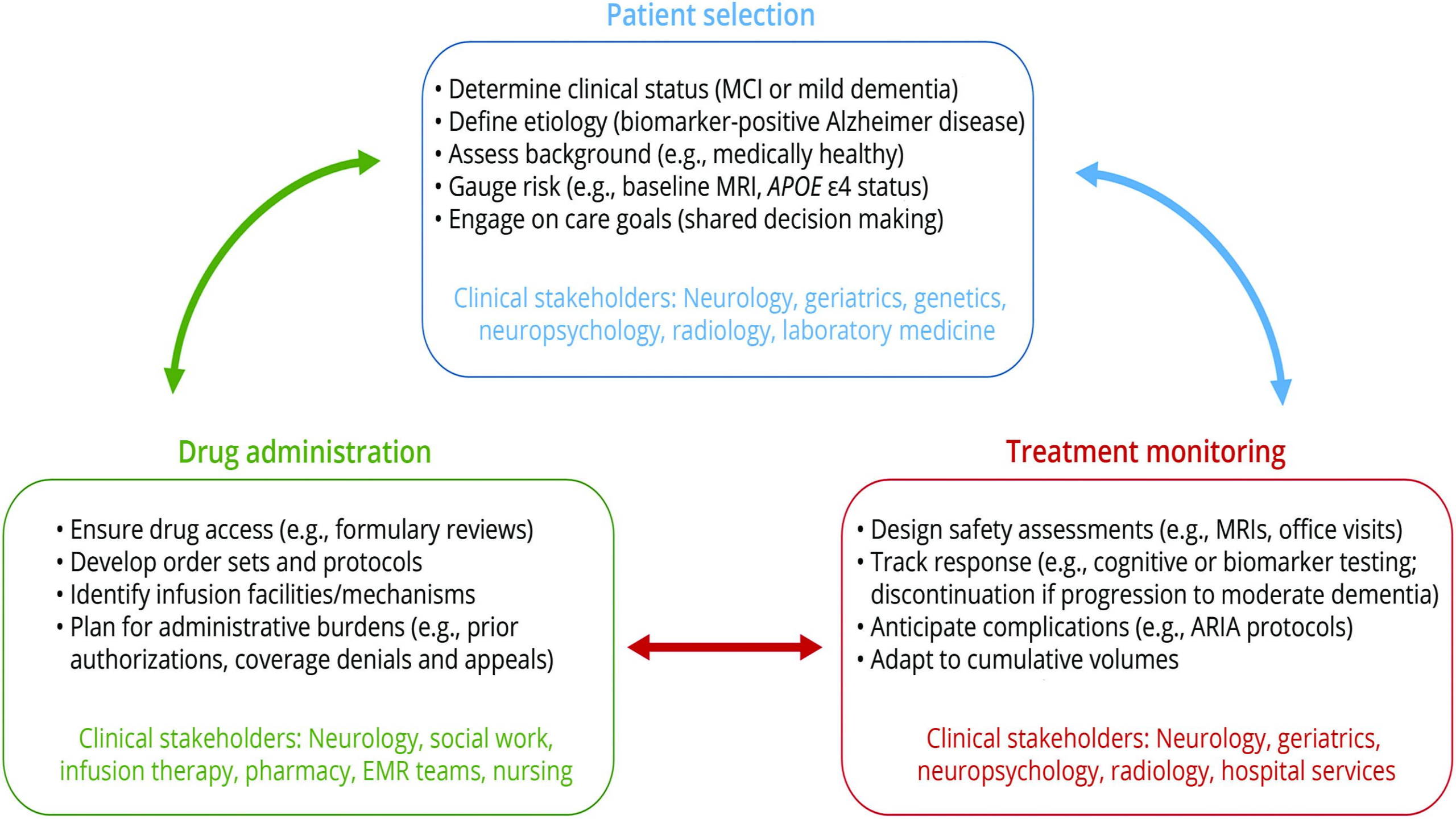
Clinical Stages of Alzheimer's Disease[1,2]

Preclinical AD	**Stage 1:** Clinically asymptomatic, biomarker evidence only
	Stage 2: Normal performance in expected range on cognitive tests, but decline from previous level of cognitive function, without functional impairment
Mild Cognitive Impairment	**Stage 3:** Objective cognitive impairment without functional impairment
Alzheimer's Dementia	**Stage 4 (Mild dementia):** Progressive cognitive and mild functional impairment on instrumental ADLs with independence in basic ADLs
	Stage 5 (Moderate dementia): Progressive cognitive and moderate functional impairment requiring assistance on basic ADLs
	Stage 6 (Severe dementia): Progressive cognitive and severe functional impairment causing dependence for basic ADLs

Screening for preclinical AD is not currently recommended outside of clinical trials

Amyloid-targeting therapies are approved for patients with MCI or mild dementia who also have positive AD biomarkers

1. Jack Jr CR et al. *Alzheimers Dement*. 2024 Jun 27 [Epub ahead of print]. 2. Jack Jr CR et al. *Alzheimers Dement*. 2018;14:535-562.


Patient selection
• Determine clinical status (MCI or mild dementia)
• Define etiology (biomarker-positive Alzheimer disease)
• Assess background (e.g., medically healthy)
• Gauge risk (e.g., baseline MRI, *APOE* ε4 status)
• Engage on care goals (shared decision making)
Clinical stakeholders: Neurology, geriatrics, genetics, neuropsychology, radiology, laboratory medicine
Drug administration
• Ensure drug access (e.g., formulary reviews)
• Develop order sets and protocols
• Identify infusion facilities/mechanisms
• Plan for administrative burdens (e.g., prior authorizations, coverage denials and appeals)
Clinical stakeholders: Neurology, social work, infusion therapy, pharmacy, EMR teams, nursing
Treatment monitoring
• Design safety assessments (e.g., MRIs, office visits)
• Track response (e.g., cognitive or biomarker testing; discontinuation if progression to moderate dementia)
• Anticipate complications (e.g., ARIA protocols)
• Adapt to cumulative volumes
Clinical stakeholders: Neurology, geriatrics, neuropsychology, radiology, hospital services

BARRIERS IN ALZHEIMER'S TREATMENT

- Late diagnosis limits intervention options, the current anti amyloid therapies are indicated very early in Alzheimer's disease and probably would be best utilized years before the diagnosis.
- Complex disease pathology (amyloid plaques, tau tangles, neuroinflammation).
- Limited efficacy of existing therapies, these therapies are a small step forward.

CHALLENGES AND OPPORTUNITIES

- Integration of biomarkers for early diagnosis.
- Combination therapies targeting multiple pathways.
- Collaboration between academia and industry.
- Personalized medicine approaches.

CONCLUSION:

- A new class of medications for the treatment of patients with mild cognitive impairment and mild dementia secondary to Alzheimer's disease have been approved and are currently in use.
- Complications from these medications may occur and are directly related to the anti amyloid effects of these medications. Bleeding and swelling.
- Anticoagulant medications and anti thrombolytic medications are contraindicated in these patients acutely if given close monitoring is recommended.
- The challenge in evaluating patients in the office or in the hospital is complicated by patient's medications, IV medications, may not be listed on there home medications.
- CT scan of the brain will not show these abnormalities and therefore patients must have MRI to identify these complications.

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