Advances in Alzheimer's Disease Care

Josephine Gomes, MD, FACP

Medical Director, Brain Health and Dementia Care Service, University of Louisville Trager Institute Optimal Aging Clinic

Associate Professor Geriatric Medicine

Department of Family and Geriatric Medicine

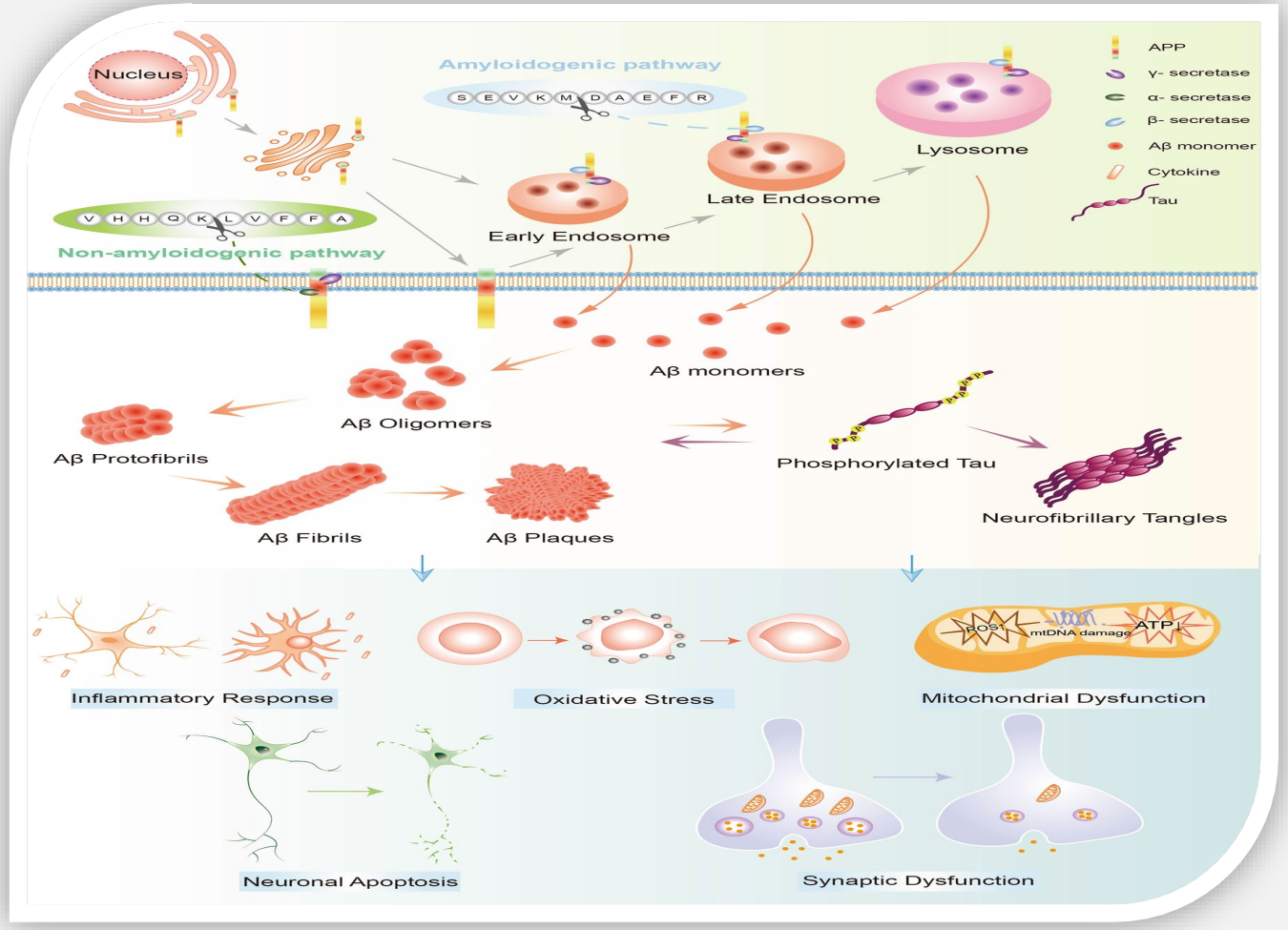
University of Louisville School of Medicine

UNIVERSITY OF LOUISVILLE®

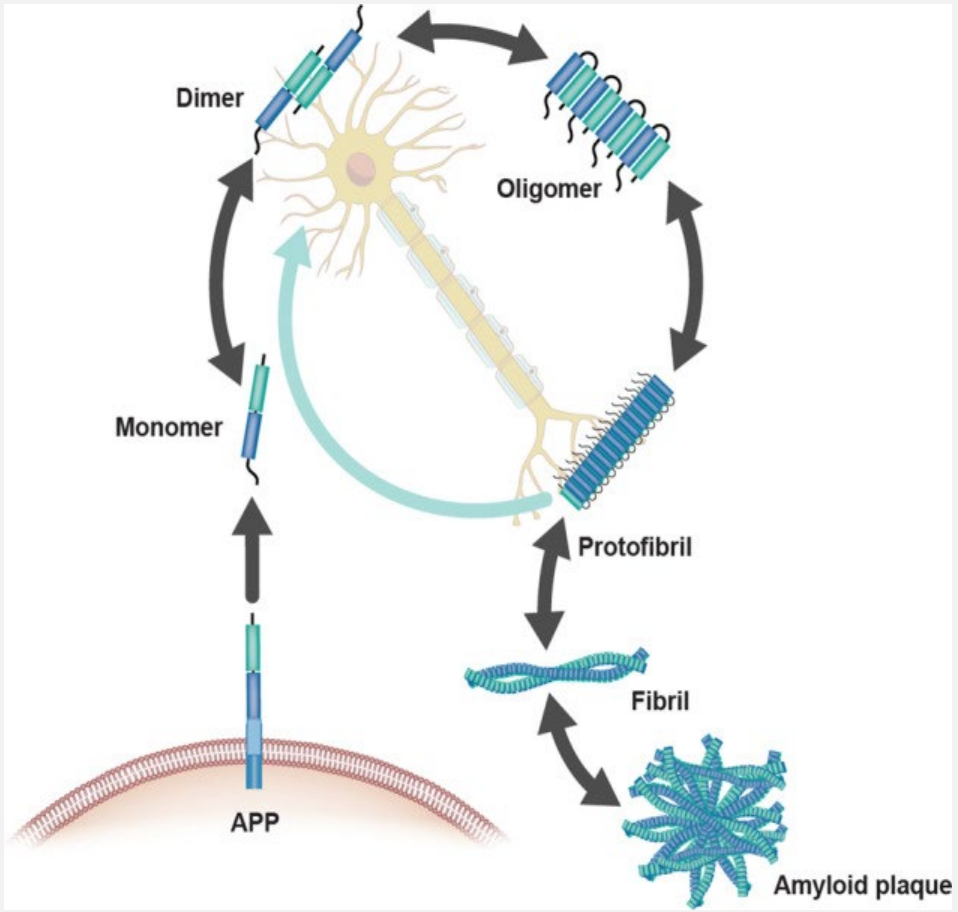
Learning Objectives

- Discuss advances in diagnostic testing
- Review available disease modifying therapies
- Discuss new Care Models

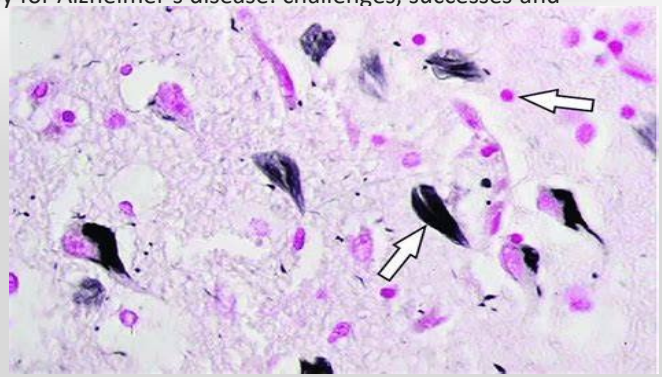
UNIVERSITY OF LOUISVILLE®



Zhang, Y., Chen, H., Li, R. *et al.* Amyloid β-based therapy for Alzheimer's disease: challenges, successes and future. *Sig Transduct Target Ther* **8**, 248 (2023). https://doi.org/10.1038/s41392-023-01484-7



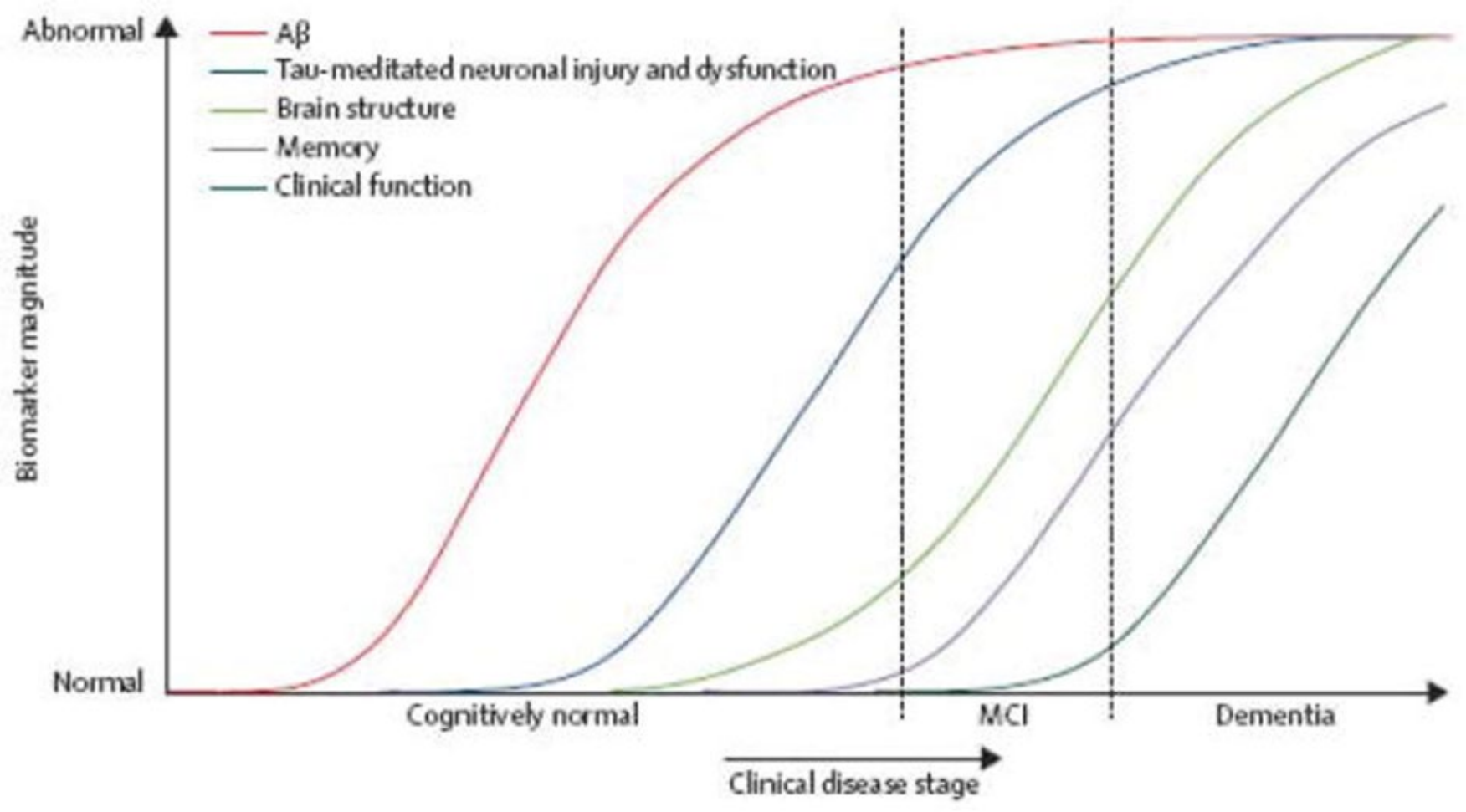
Hampel, H., Hardy, J., Blennow, K. *et al.* The Amyloid-β Pathway in Alzheimer's Disease. *Mol Psychiatry* **26**, 5481–5503 (2021). https://doi.org/10.1038/s41380-021-01249-0



Source: www.alzheimers.org.uk.

UNIVERSITY OF LOUISVILLE®

BIOMARKERS



JACK CR JR, ET AL. LANCET NEUROL. 2013 FEB; 12(2): 207-216

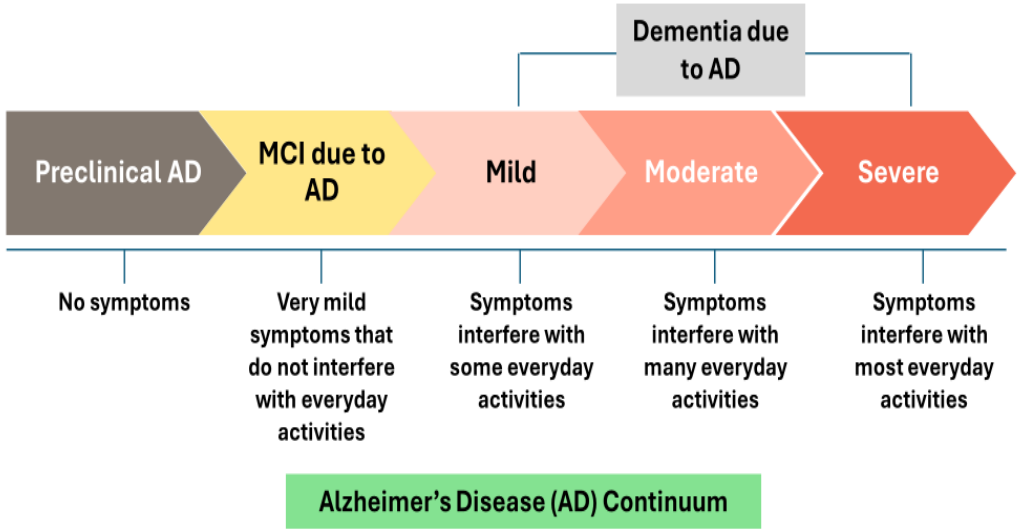
UNIVERSITY OF LOUISVILLE®

BIOMARKERS

	A=Amyloid	T=Tau	N=Neurodegeneration	Considerations
MRI			• Atrophy	• Accessible • High resolution • Nonspecific
CSF	• $A\beta_{42}$ • $A\beta_{42}/A\beta_{40}$ ratio • P-tau/$A\beta_{42}$ ratio	• P-tau	• NFL • T-tau	• Invasive • Inter/Intralab reliability • Amyloid decreases with disease
PET	• Florbetapir F 18 • Florbetaben F 18 • Flutemetamol F 18 • ^{11}C PiB	• Flortaucipir F 18 • ^{18}F MK 6240 • ^{18}F PI 2620 • ^{18}F RO 948	• ^{18}F FDG	• Specific, localizable • Reflects deposition, not turnover • Availability/accessibility issues
Plasma	• $A\beta_{42}$ • $A\beta_{42}/A\beta_{40}$ ratio • $A\beta_{42}$/P-tau ratio	• P-tau	• NFL • T-tau • GFAP	• Noninvasive • Active area of research; many assays still in development

UNIVERSITY OF LOUISVILLE®

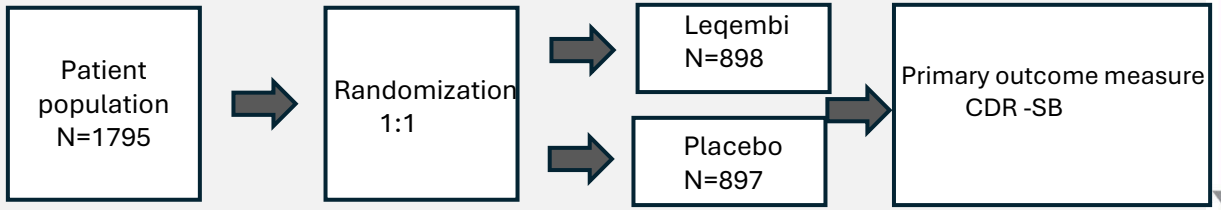
ALZHEIMER'S DISEASE STAGES

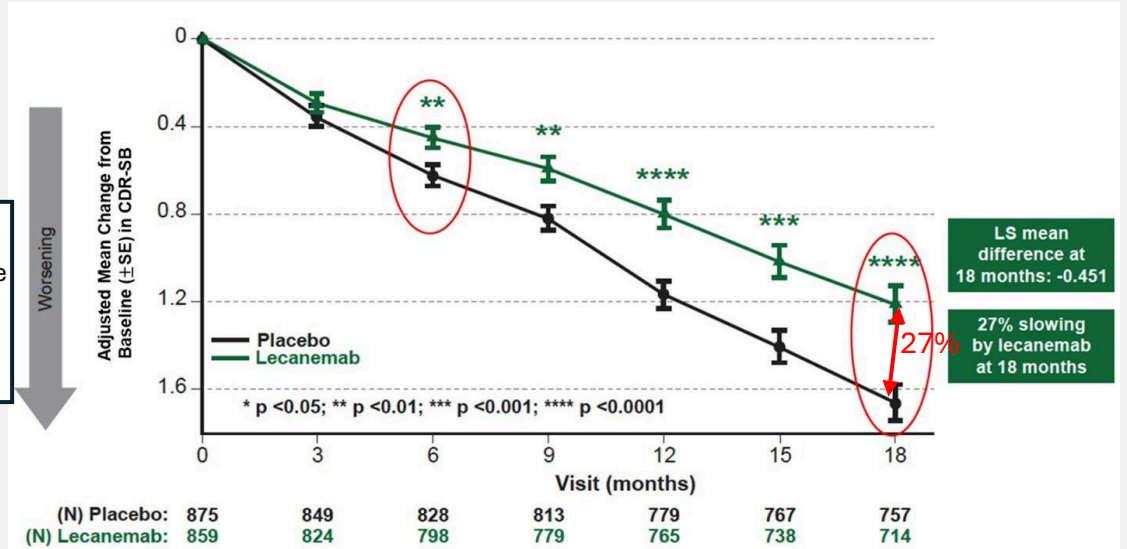


AD=Alzheimer's Disease; MCI=Mild Cognitive Impairment. 1. McKhann GM, et al. *Alzheimer's Dement.* 2011;7(3):263-269. 2. Albert MS, et al. *Allzheimers Dement.* 2011; 7(3):270-279. 3. 2021 Alzheimer's disease facts and figures. *Alzheimers Dement.* 2021;17(3):327-406.

UNIVERSITY OF LOUISVILLE®

Lecanemab Phase 3 (CLARITY AD)



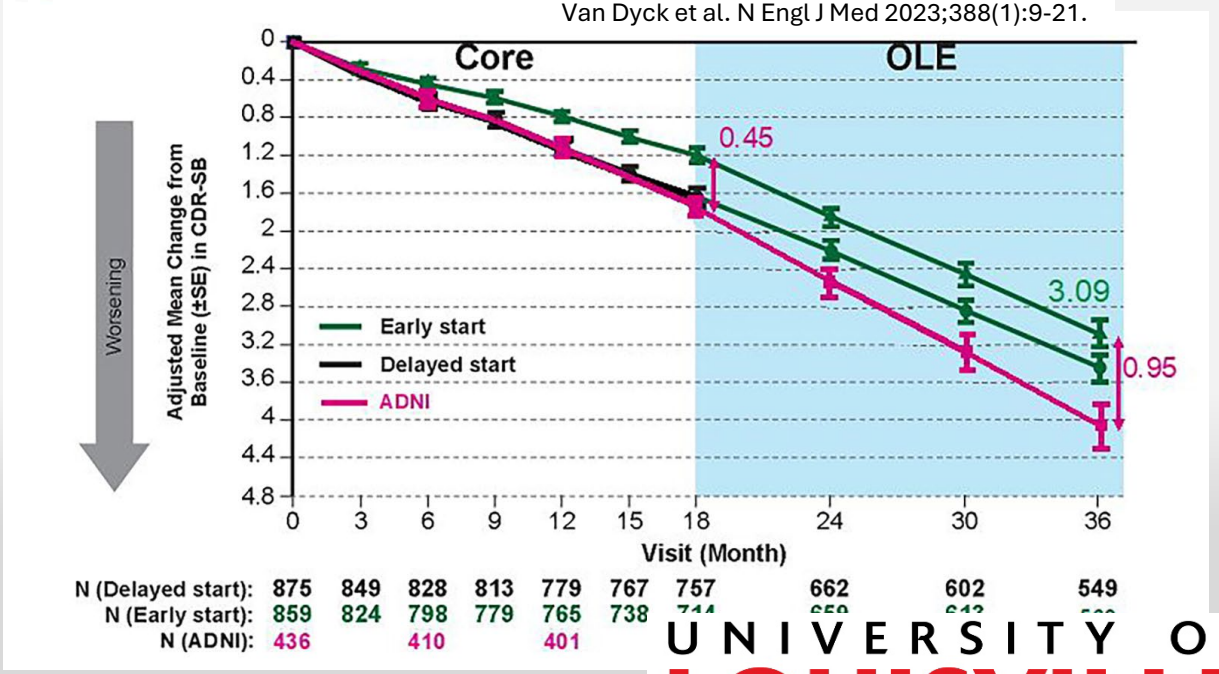


Van Dyck et al. N Engl J Med 2023;388(1):9-21.

Slowing of cognitive and functional decline by 27% ($p<0.001$)

Improvement in all secondary endpoints
- Amyloid plaque clearance was reached at 12 months

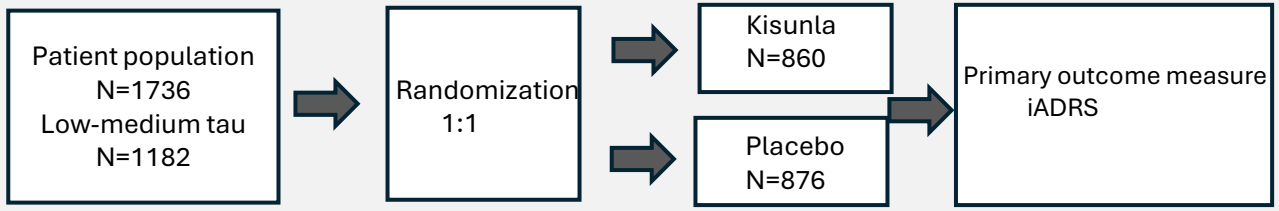
Adverse events (drug/placebo in %)
- Infusion reactions: 26 /7
- ARIA E or ARIA H: 21/9
- ARIA- E : 13/2
- ARIA –H : 17/9
- Symptomatic ARIA : 3%



Presented at AAIC 2024
News Release : 2024 | Eisai Co., Ltd.

UNIVERSITY OF LOUISVILLE

Donanemab Phase 3 (TRAILBLAZER –ALZ2)

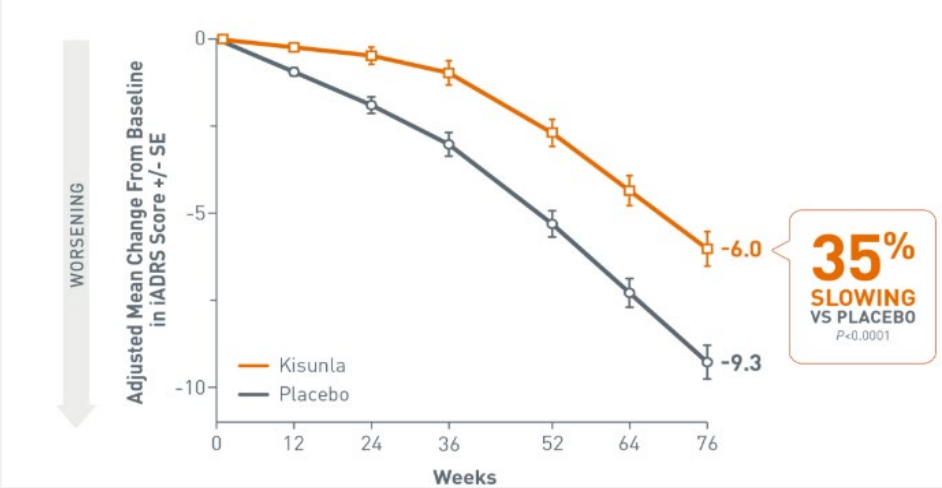


Slowing of cognitive and functional decline by 35% ($p<0.0001$) in low-medium tau group and 22% in the combined population.

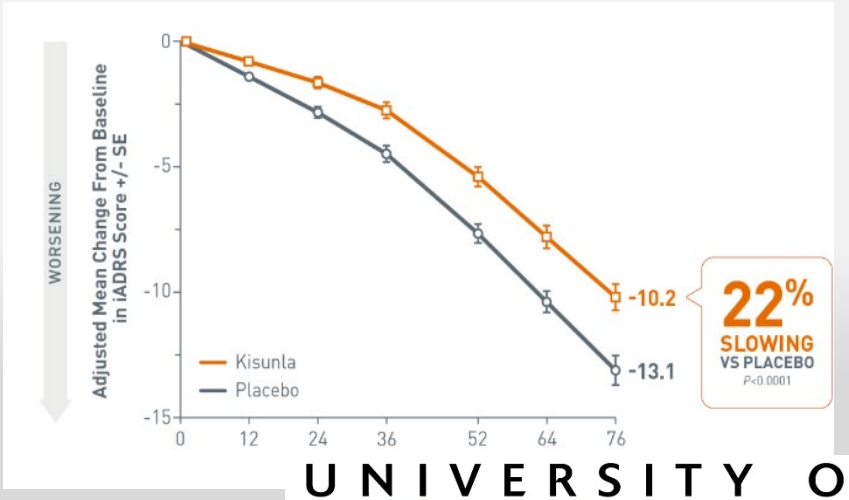
- Amyloid plaque clearance was reached in 17% at 6 months 47% at 12 months and 69% at 18 months.
-Cognitive benefits persisted at 76 weeks for those who were able to stop the drug.

Adverse events (drug/placebo in %)
- Infusion reactions: 9 /0.5
- ARIA- E : 24/2
- ARIA –H : 25/11
- Symptomatic ARIA : 6%

iADRS in Low/Medium Tau Subjects



iADRS in Combined population



Sims JR et al. JAMA 2023;330;(6):512-527

UNIVERSITY OF LOUISVILLE®

INCLUSION CRITERIA

Lecanemab inclusion criteria from CLARITY AD and proposed in the AUR	
Eligibility Criteria Used in the CLARITY AD Pivotal Trial of Lecanemab	**Eligibility Criteria for Lecanemab Treatment From the AUR**
Inclusion Criteria (ie, required criteria for an individual to be considered)	
Diagnosis of MCI or mild AD dementia	Clinical diagnosis of MCI or mild AD dementia[a]
Objective impairment in episodic memory as indicated by at least 1 standard deviation below age-adjusted mean in the WMS-IV LMII	Clinical diagnosis of MCI or mild AD dementia[a]
Positive biomarker for brain amyloid pathology	Positive amyloid PET or CSF studies indicative of AD
50-90 years of age	Physician judgement used for patients outside the 50-90 year age range
MMSE score >22 at screening and baseline and <30 at screening and baseline	MMSE 22-30 or other cognitive screening instrument with a score compatible with early AD
BMI >17 and <35 at screening	Physician judgement used for patients at the extremes of BMI
If receiving an acetylcholinesterase inhibitor (donepezil, rivastigmine, galantamine) or memantine or both must be on a stable dose for at least 12 weeks prior to baseline	Patients may be on cognitive enhancing agents (donepezil, rivastigmine, galantamine, or memantine) for AD; patients may not be on aducanumab
Unless otherwise stated, participants must have been on stable doses of all other (that is, non-AD-related) permitted concomitant medications for at least 4 weeks prior to baseline	Patients may be on standard of care for other medical illnesses (see below for specifics regarding anticoagulation)
Have an identified study partner	Have a care partner or family member(s) who can ensure that the patient has the support needed to be treated with lecanemab
Provide written informed consent	Patients, care partners, and appropriate family members should understand the requirements for lecanemab therapy and the potential benefit and potential harm of treatment

Cummings J, Apostolova L, Rabinovici GD, et al. Lecanemab: appropriate use recommendations. J Prev Alzheimers Dis. 2023;10(3):362-377.

UNIVERSITY OF LOUISVILLE®

EXCLUSION CRITERIA

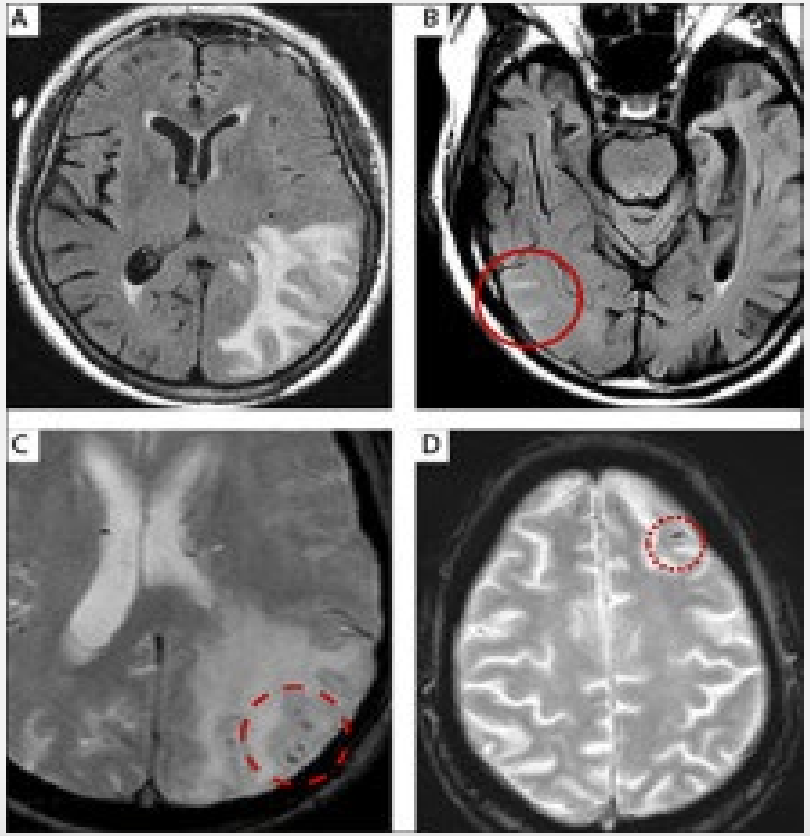
Lecanemab exclusion criteria from CLARITY AD and proposed in the AUR[1]	
Eligibility Criteria Used in the CLARITY AD Pivotal Trial of Lecanemab	**Eligibility Criteria for Lecanemab Treatment From the AUR**
Exclusion Criteria (ie, criteria that render an individual ineligible)	
Any neurological condition that may be contributing to cognitive impairment above and beyond that caused by the participant's AD	Any medical, neurologic, or psychiatric condition that may be contributing to the cognitive impairment or any non-AD MCI or dementia
More than 4 microhemorrhages (defined as 10 mm or less at the greatest diameter); a single macrohemorrhage >10 mm at greatest diameter; an area of superficial siderosis; evidence of vasogenic edema; multiple lacunar infarcts or stroke involving a major vascular territory; severe small vessel; or other major intracranial pathology	More than 4 microhemorrhages (defined as 10 mm or less at the greatest diameter); a single macrohemorrhage >10 mm at greatest diameter; an area of superficial siderosis; evidence of vasogenic edema; more than 2 lacunar infarcts or stroke involving a major vascular territory; severe subcortical hyperintensities consistent with a Fazekas score of 3; evidence of ABRA; CAA-ri; or other major intracranial pathology that may cause cognitive impairment
Evidence of other clinically significant lesions on brain MRI at screening that could indicate a dementia diagnosis other than AD	MRI evidence of a non-AD dementia
History of TIA, stroke, or seizures within 12 months of screening	Recent history (within 12 months) of stroke or TIAs or any history of seizures
Any psychiatric diagnosis or symptoms (example, hallucinations, major depression, or delusions) that could interfere with study procedures in the participant	Mental illness (eg, psychosis) that interferes with comprehension of the requirements, potential benefit, and potential harms of treatment and are considered by the physician to render the patient unable to comply with management requirements
GDS score >8 at screening	Major depression that will interfere with comprehension of the requirements, potential benefit, and potential harms of treatment; patients for whom disclosure of a positive biomarker may trigger suicidal ideation. Patients with less severe depression or whose depression resolves may be treatment candidates
Any immunological disease that is not adequately controlled, or which requires treatment with immunoglobulins, systemic monoclonal antibodies (or derivatives of monoclonal antibodies), systemic immunosuppressants, or plasmapheresis during the study	Any history of immunologic disease (eg, lupus erythematosus, rheumatoid arthritis, Crohn's disease) or systemic treatment with immunosuppressants, immunoglobulins, or monoclonal antibodies or their derivatives
Participants with a bleeding disorder that is not adequately controlled (including a platelet count <50,000 or INR >1.5 for participants who are not on anticoagulant treatment, eg, warfarin)	Patients with a bleeding disorder that is not under adequate control (including a platelet count <50,000 or INR >1.5 for participants who are not on an anticoagulant)
Participants who are on anticoagulant therapy should have their anticoagulant status optimized and be on a stable dose for 4 weeks before screening	Patients on anticoagulants (coumadin, dabigatran, edoxaban, rivaroxaban, apixaban, betrixaban, or heparin) should not receive lecanemab; tPA should not be administered to individuals on lecanemab
Any other medical conditions (example, cardiac, respiratory, gastrointestinal, renal disease) which are not stably and adequately controlled, or which could affect the participant's safety or interfere with the study assessments	Unstable medical conditions that may affect or be affected b therapy

UNIVERSITY OF LOUISVILLE®

Cummings J, Apostolova L, Rabinovici GD, et al. Lecanemab: appropriate use recommendations. J Prev Alzheimers Dis. 2023;10(3):362-377.

ADVERSE REACTIONS

- Infusion Related Reactions
- Amyloid Related Imaging Abnormality (ARIA)
  ARIA-E and ARIA-H

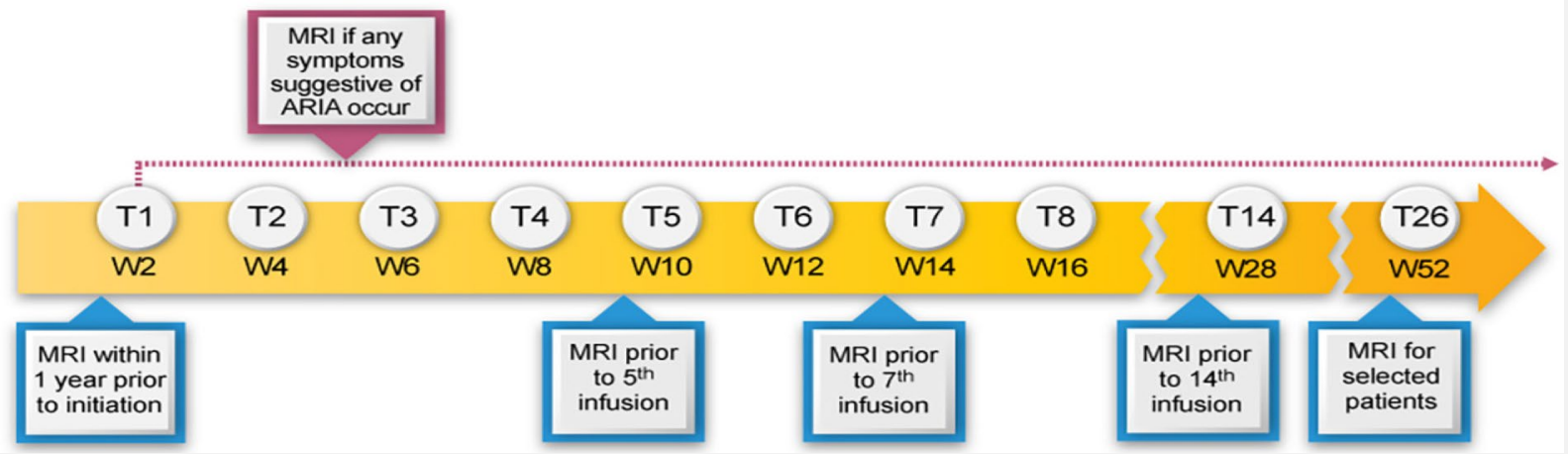


1. BarakosJ, et al. J PrevAlzheimersDis. 2022;9(2):211–220; 2. Cogswell PM, et al. AJNR Am J Neuroradiol. 2022;43(9):E19–E35

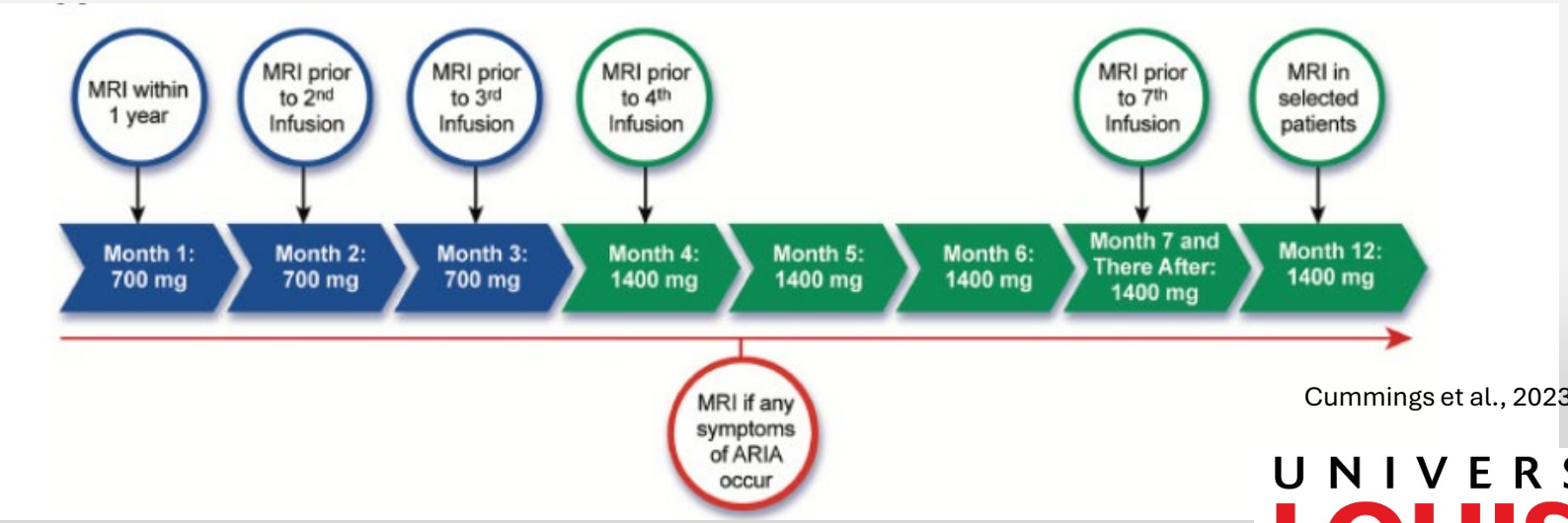
UNIVERSITY OF LOUISVILLE®

MRI TESTING SCHEDULE

Lecanemab



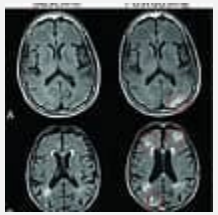
Donanemab



Cummings et al., 2023, Rabinovici et al, 2025

UNIVERSITY OF LOUISVILLE®

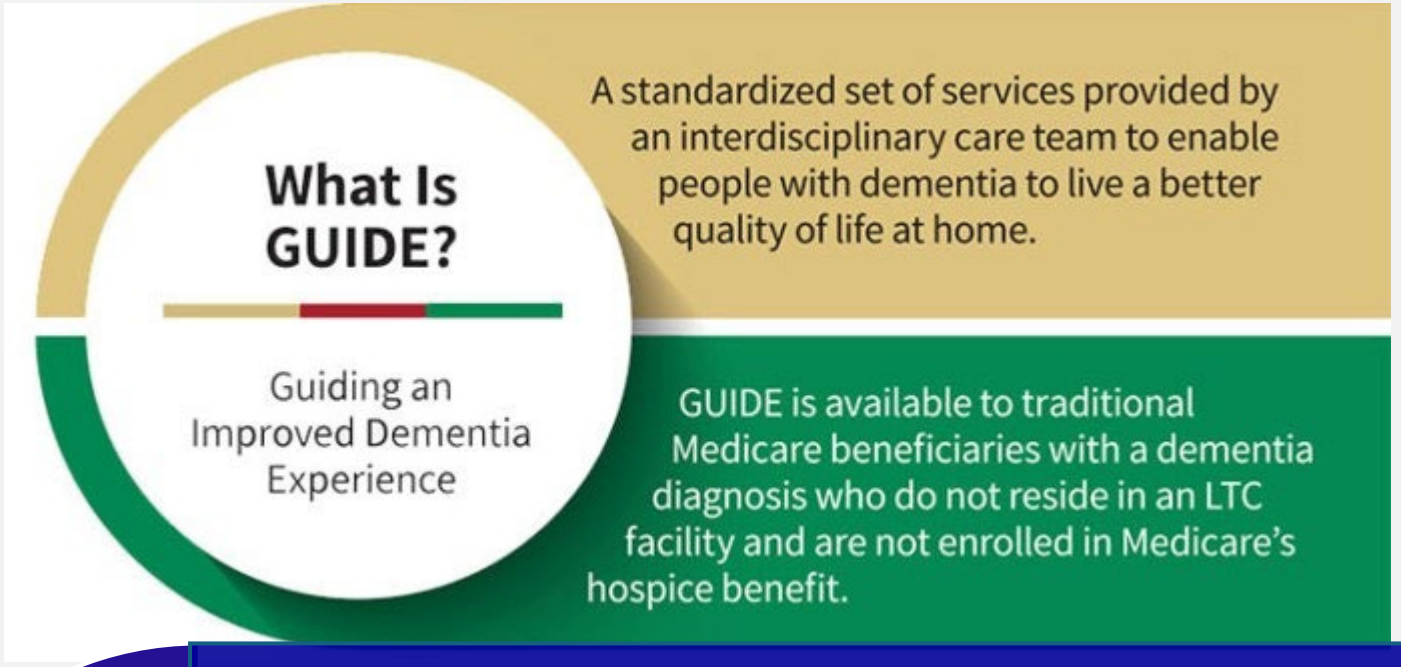
Amyloid Related Imaging Abnormality (ARIA)

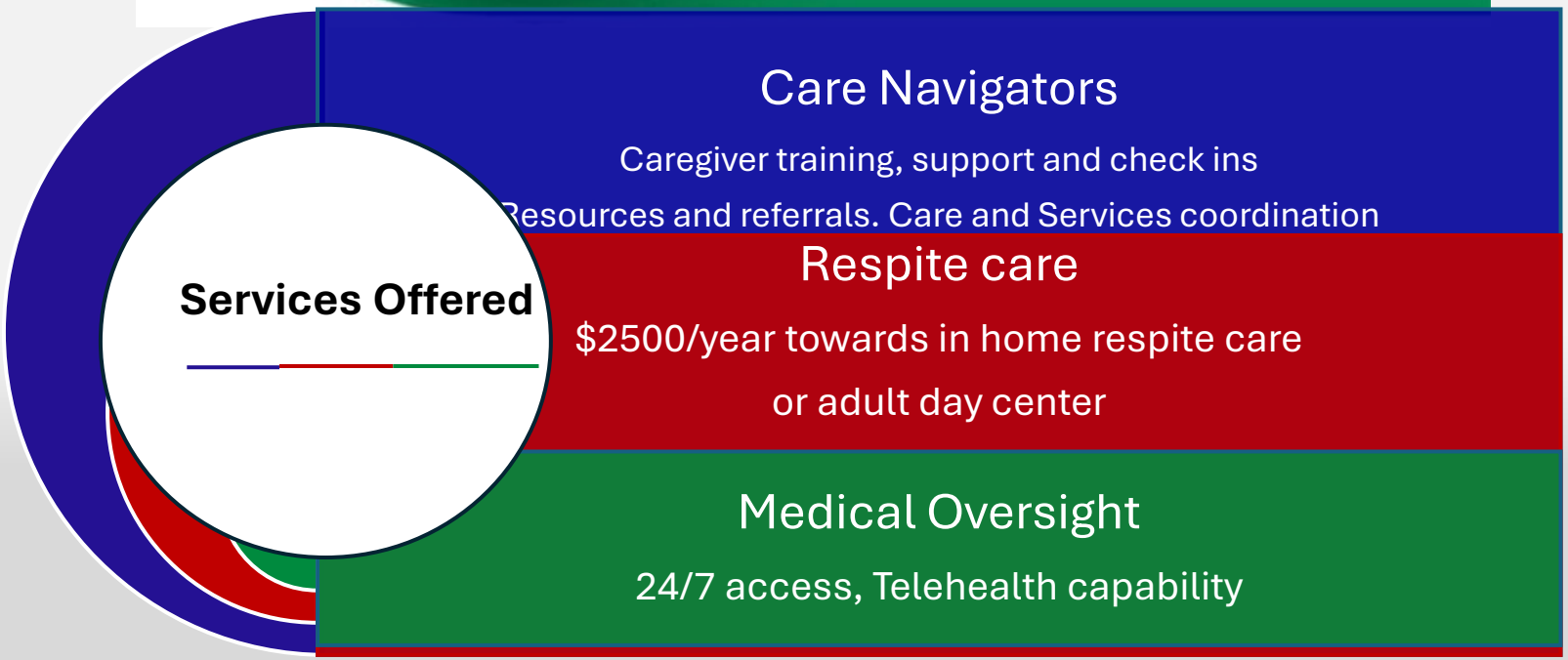


- **Risk Factors**
  - Presence of vascular amyloid and/or cerebral amyloid angiopathy
  - Pre- existing cerebral microhemorrhages
  - APOE e4
  - Anticoagulants
- **Detection**
  - Scheduled MRIs for ARIA surveillance and for symptoms
  - Lecanemab: baseline, before 5th, 7th and 14th dose
  - Donanemab: baseline, before 2nd,3rd, 4th and 7th doses
  - Medicare registry
- **Management**
  - May need to pause or discontinue depending on ARIA severity
  - Corticosteroids/ seizure management

UNIVERSITY OF LOUISVILLE®

GUIDE





UNIVERSITY OF LOUISVILLE®

CASES

CASE 1

78 yo male with history of HTN, presents with repetition, memory loss.
MOCA: 22/30 (2025), 24/30 (2023)
Brain Imaging: Mild microvascular disease
Plasma Biomarkers: Beta amyloid 42/40: 0.127 ptau217: 0.35
Neuropsych: MCI

CASE 2

80 yo female with history of HTN, HLD,OSA, AFIB, COPD on o2
MOCA: 22/30 (2025)
Brain Imaging: Mod volume loss, scattered moderate hypodensities suggestive of moderate microvascular disease.
Plasma Biomarkers: Beta amyloid 42/40: - ptau217: -

CASE 3

78 yo female presents with memory changes, anxiety
MOCA: 21/30 (2025), MMSE - 28/30 (2023)
Brain Imaging: Mild microvascular disease. Small areas of hemosiderin deposition in L occipital lobe
Plasma Biomarkers: Beta amyloid 42/40: 0.146 ptau217: 0.45
ApoE genotype: -
Neuropsych: Amnestic MCI

UNIVERSITY OF LOUISVILLE®

CASES

CASE 4

78 yo female presents with memory changes, anxiety
MOCA: 25/30 (2023)
Brain Imaging: Mild microvascular disease.
Plasma Biomarkers: Beta amyloid 42/40: 0.167 ptau217: -
ApoE genotype: E4/E4
Neuropsych: Amnestic MCI

CASE 5

67 yo female presents with memory changes
MOCA: 19/30 (2025), 20/30 (8/24), 21/30 (12/23)
Brain Imaging: Mild microvascular disease. Mild- mod parenchymal volume loss
Plasma Biomarkers: Beta amyloid 42/40: 0.141 ptau217: -
Amyloid PET: Mod- frequent amyloid neuritic plaque
ApoE genotype: E4/E4
Neuropsych: Amnestic MCI

UNIVERSITY OF LOUISVILLE®