Updates in the diagnosis and treatment of Alzheimer's Disease (AD)

Andy Liu, MD, MS

Duke University School of Medicine, Dept of Neurology

Duke-UNC Alzheimer’s Disease Research Center Biomarker Associate Lead

Associate Professor in Neurology and Pathology

January 20th, 2025

Duke University School of Medicine

Duke, UNC & Me

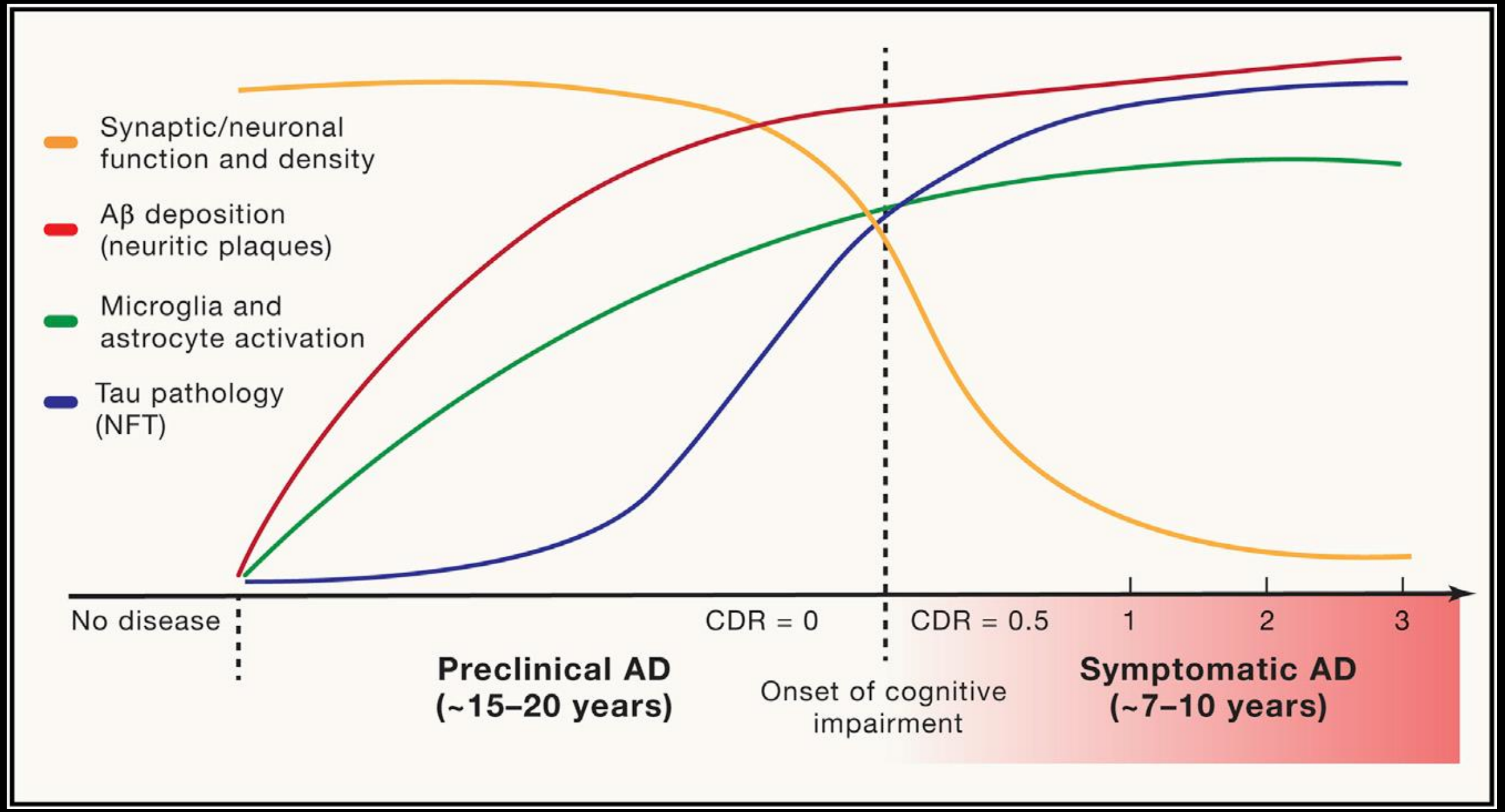
Preventing Alzheimer's Disease Together

Disclosures

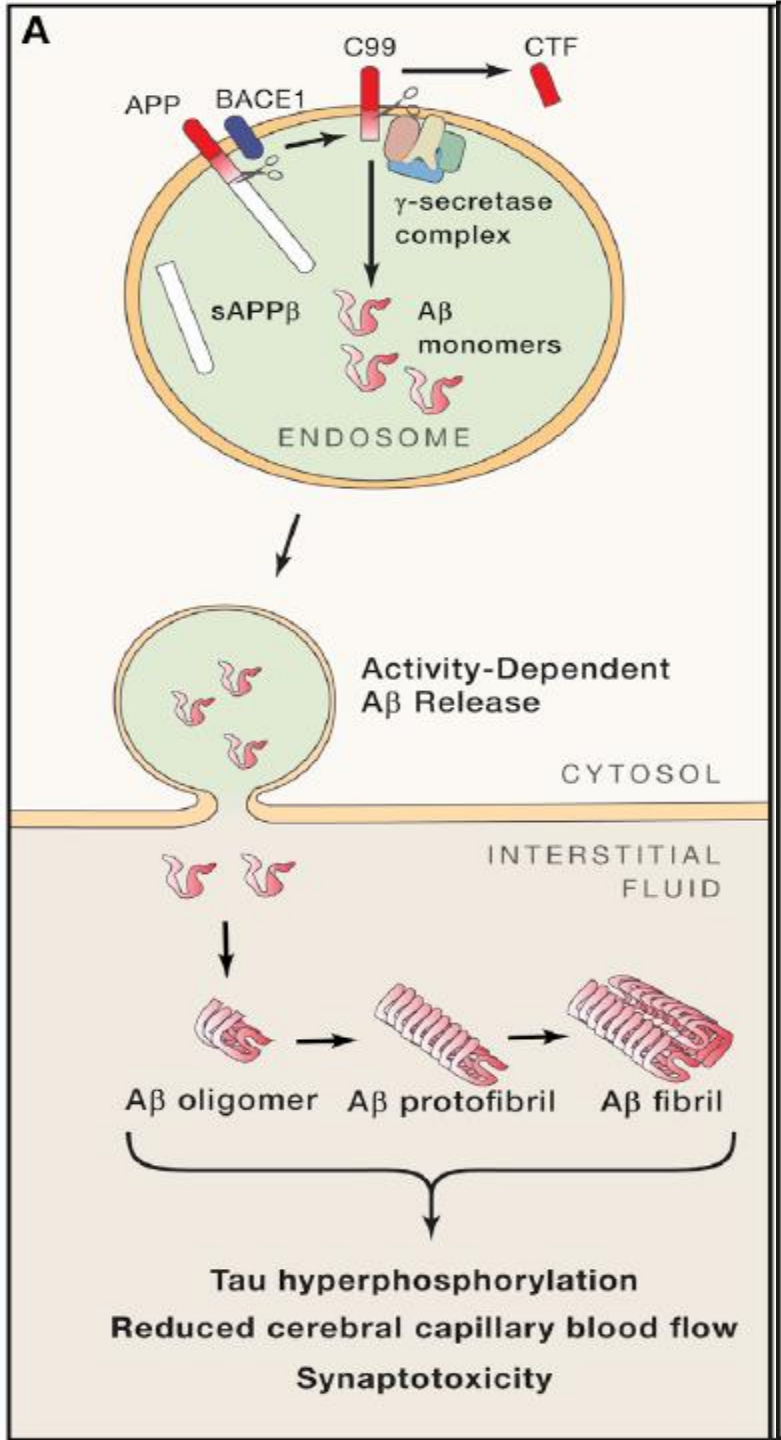
- Lucent consultant, a subsidiary of Quanterix

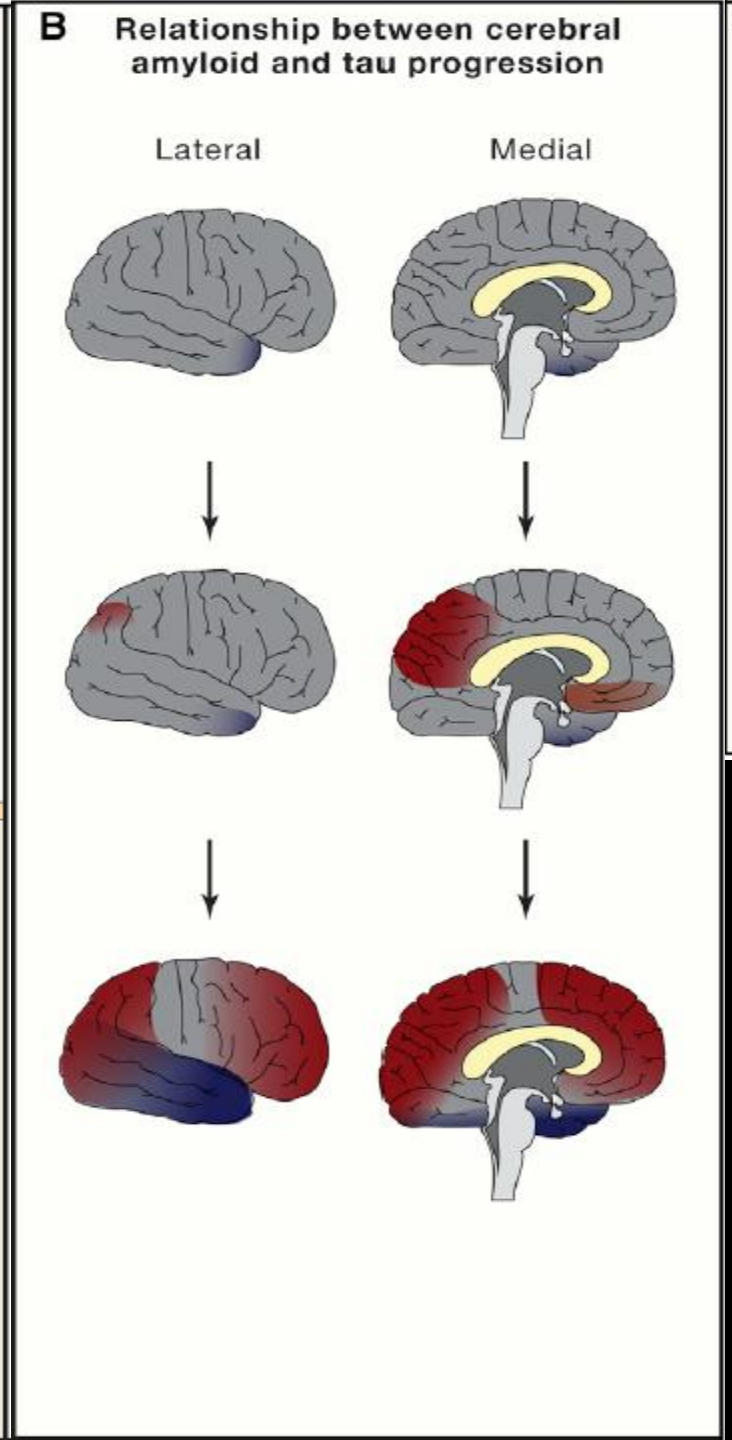
Learning objectives

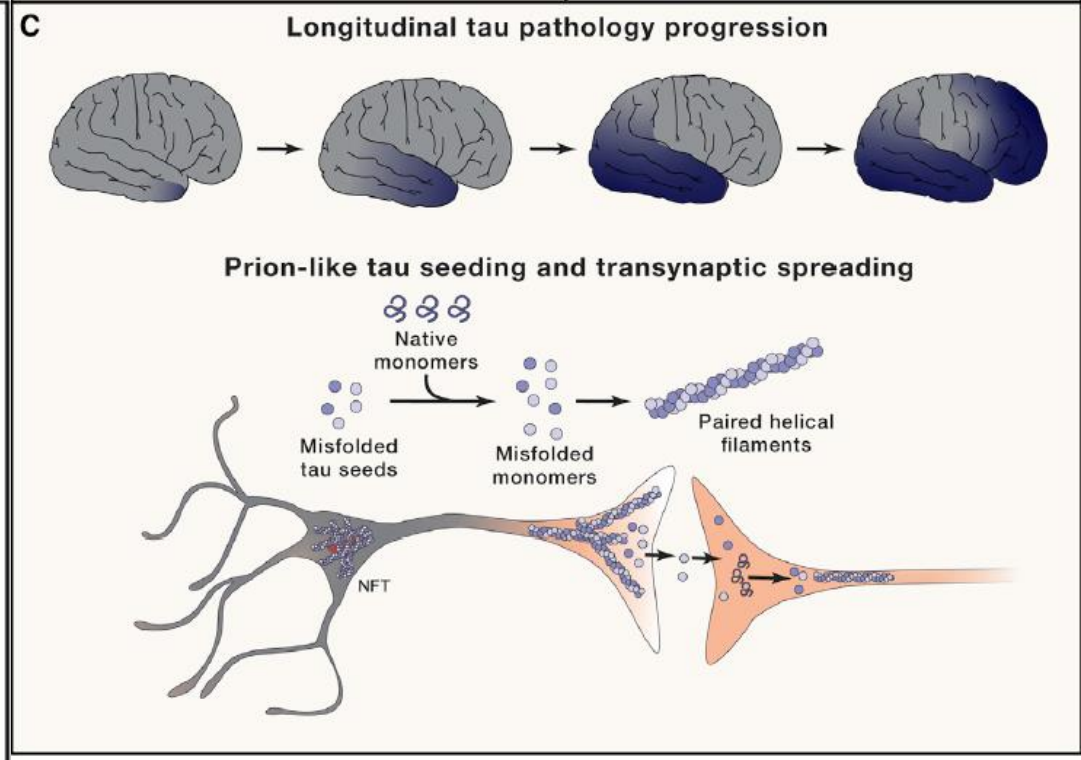
- Explore the updated criteria for diagnosing AD
- Review and interpret AD biomarker results
- Determine appropriate use of anti-amyloids
- Facilitate informed discussions on the risk profile of anti-amyloids



Long et al, 2019







Long et al, 2019

Duke University School of Medicine

Duke, UNC & Me
Preventing Alzheimer's Disease Together

Spectrum of cognitive status

	History	Neuropsychological test results	ADLs & iADLs
Normal Cognition	Normal	Normal	Normal
Subjective Cognitive Impairment (SCI)	Abnormal	Normal	Normal
Mild Cognitive Impairment (MCI)	Abnormal	Abnormal	Normal
Dementia	Abnormal	Abnormal	Abnormal

Updated Diagnostic Criteria for AD 2024

- Alzheimer's Disease is defined biologically, not syndromically
- Combination of core biomarkers are needed
- Positron Emission Tomography, cerebrospinal fluid and plasma biomarkers

Jack et al 2024

Diagnoses using ATNIVS

- A: Amyloid
- T: Tau
- N: Dysfunction, degeneration or injury
- I: Inflammation
- V: Vascular brain injury
- S: α-synuclein

Biomarker category	CSF or plasma analytes	Imaging
Core Biomarkers		
Core 1		
A (Aβ proteinopathy)	Aβ 42	Amyloid PET
T_1: (phosphorylated and secreted AD tau)	p-tau217, p-tau181, p-tau231	
Core 2		
T_2 (AD tau proteinopathy)	MTBR-tau243, other phosphorylated tau forms (e.g., p-tau205), non-phosphorylated mid-region tau fragments[a]	Tau PET
Biomarkers of non-specific 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[a]	

Duke University School of Medicine

Jack et al 2024

Duke, UNC & Me
Preventing Alzheimer's Disease Together

Cerebrospinal fluid (CSF) biomarkers in AD

- Research for CSF AD biomarkers began in the 1990's
- Clinical diagnosis of AD only is 70.9-87.3% sensitive and 44.3-70.8% specific

Zetterberg and Blennow. Molecular Neurodegeneration. 2021, Horie et al. Nature Medicine 2023. Mayeux. NEJM 2024

Cerebrospinal fluid (CSF) biomarkers in AD

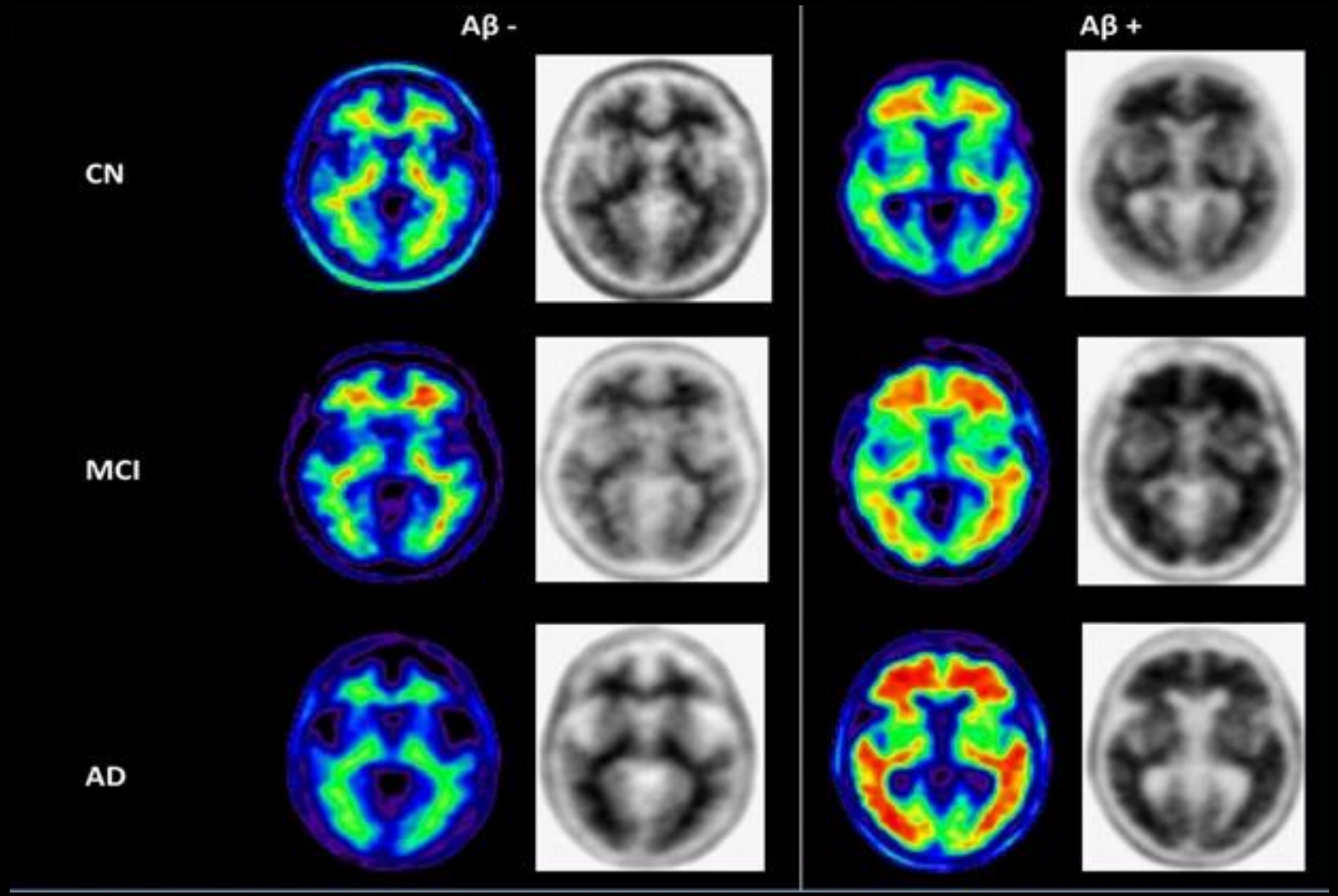
- Amyloid beta-42 (Aβ42), Aβ40, total tau, phosphorylated tau (ptau)-181
- Aβ42 is low in patients with AD pathology
- Aβ42/ Aβ40 ratio is also low in patients with AD pathology
- Total and ptau-181 are high in patients with AD pathology
- Microtubule-Binding Region (MTBR) of tau-243
- Brain derived-Tau

Zetterberg and Blennow. Molecular Neurodegeneration. 2021, Horie et al. Nature Medicine 2023. Mayeux. NEJM 2024

Imaging biomarkers

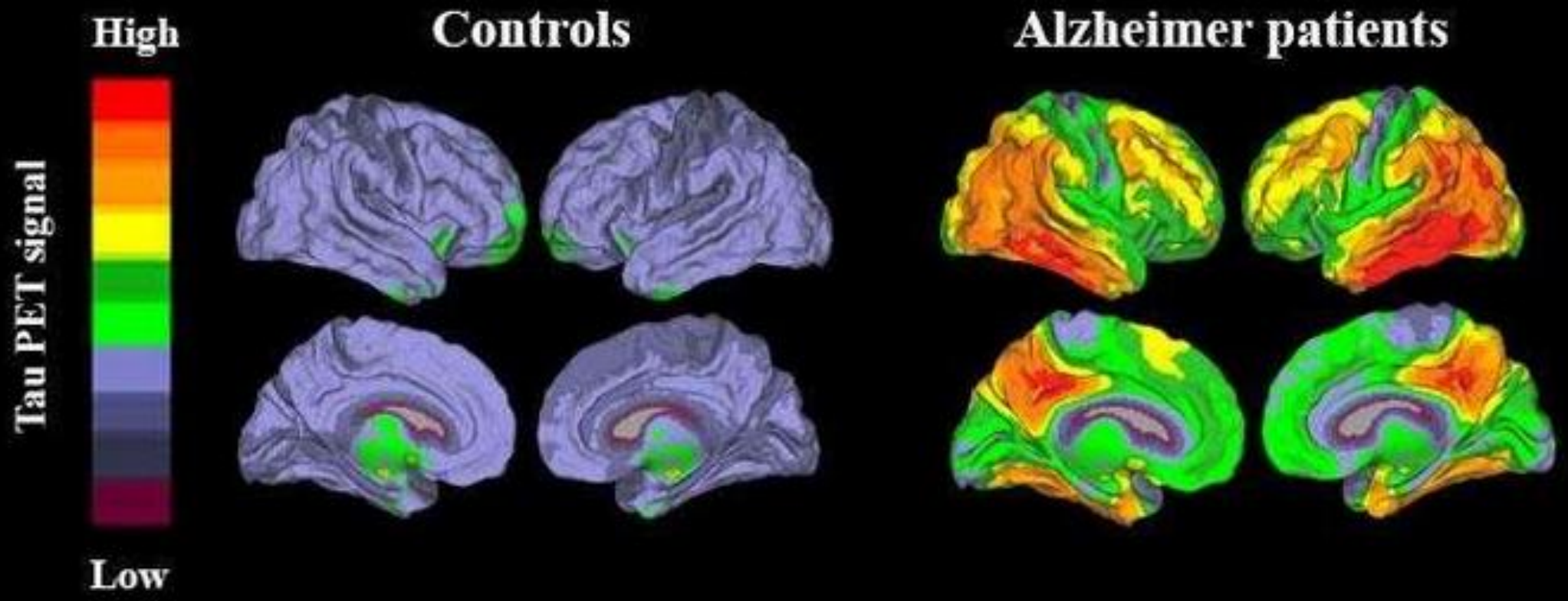
- Amyloid-PET
- Tau-PET
- MRI brain

Amyloid-PET



Doraiswamy et al. Neurology 2014

Tau-PET imaging

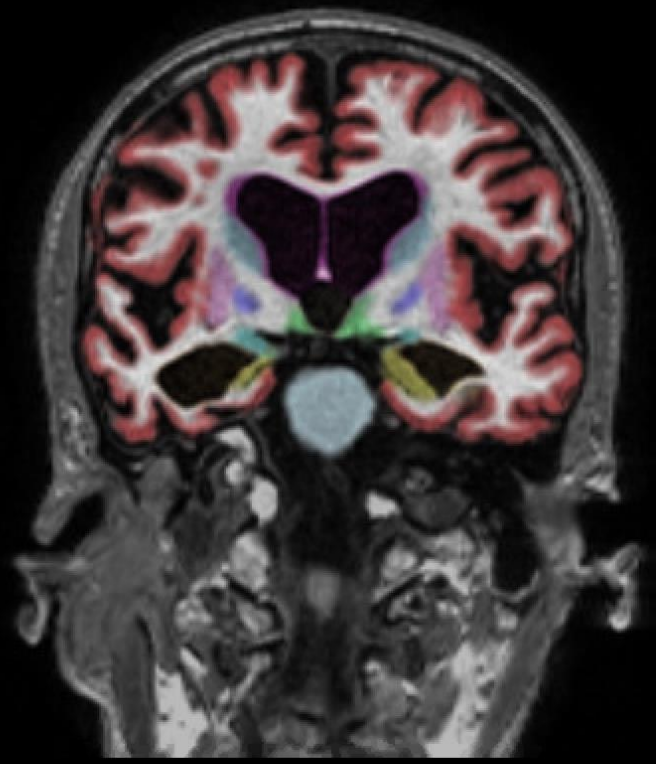


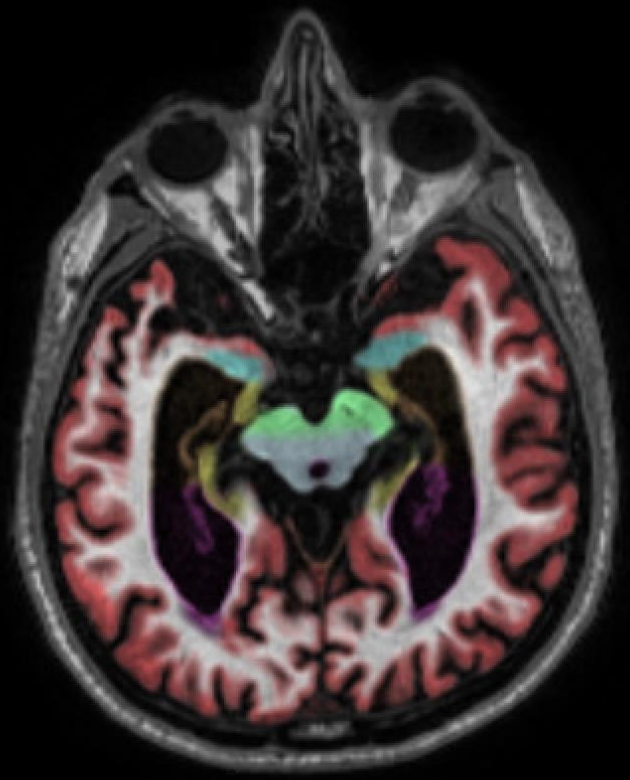
Duke University School of Medicine

Ossenkoppele et al JAMA 2018

Duke, UNC & Me
Preventing Alzheimer's Disease Together

MRI brain

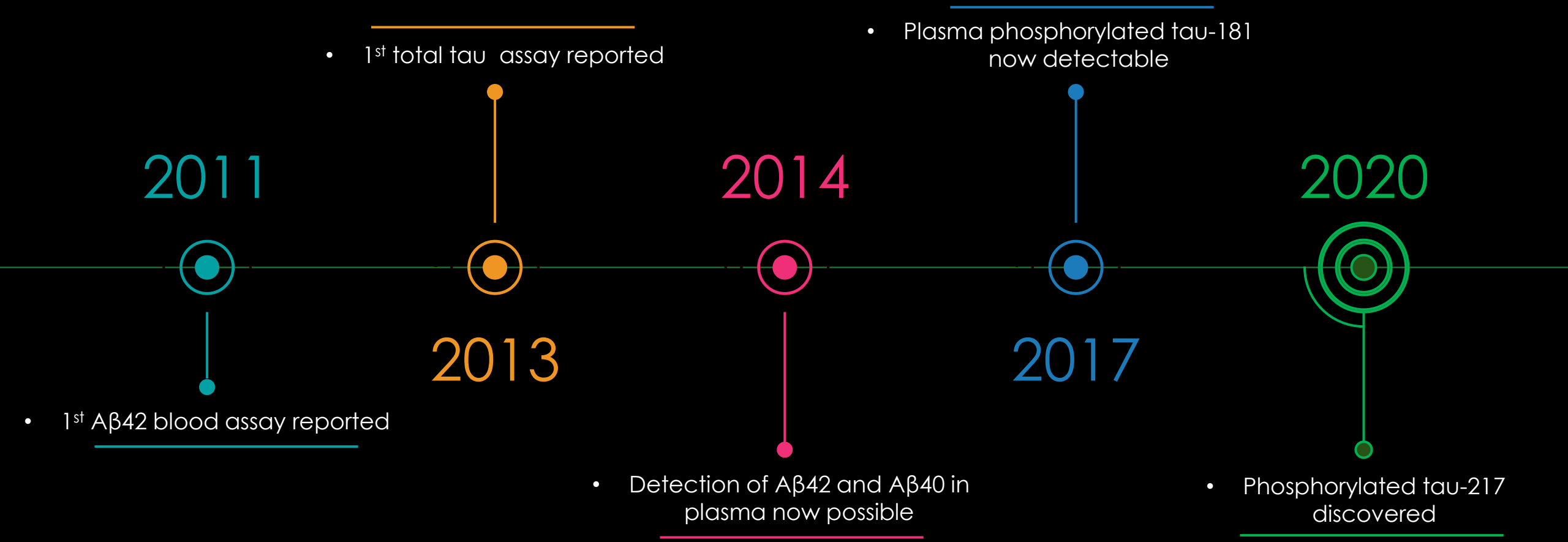




Duke University School of Medicine

Duke, UNC & Me
Preventing Alzheimer's Disease Together

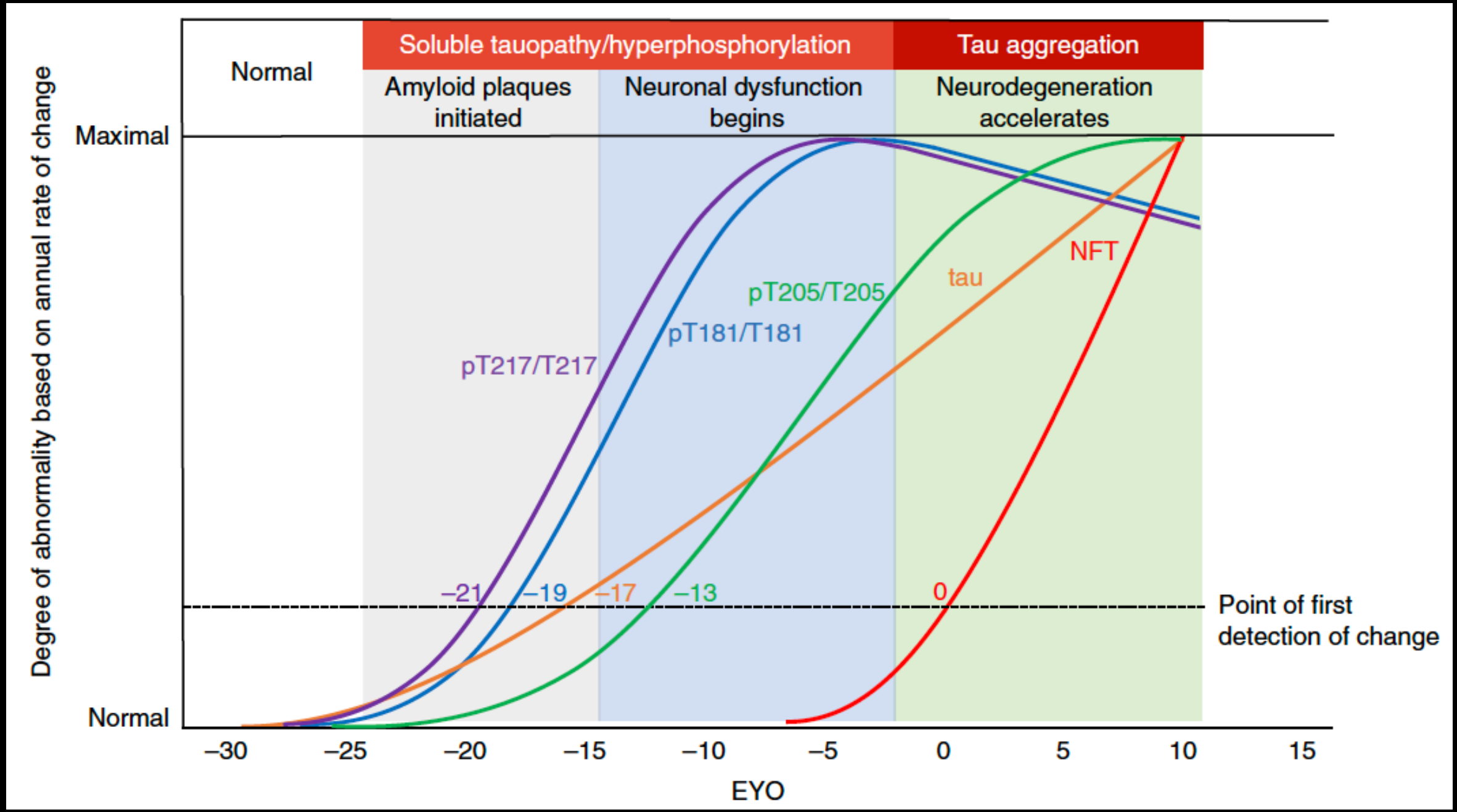
AD blood biomarkers



Zetterberg, H and Blennow, K. Molecular Neurodegeneration 2021

Duke University School of Medicine

Duke, UNC & Me
Preventing Alzheimer's Disease Together



Barthelemy et al 2020

Biological staging

TABLE 3 Biological staging.

	Initial-stage biomarkers (A)	Early-stage biomarkers (B)	Intermediate-stage biomarkers (C)	Advanced-stage biomarkers (D)
PET	Amyloid PET	Tau PET medial temporal region	Tau PET moderate neocortical uptake	Tau PET high neocortical uptake
	$A+T_2-$	$A+T_{2MTL}+$	$A+T_{2MOD}+$	$A+T_{2HIGH}+$
Core 1 fluid	CSF Aβ42/40, p-tau181/Aβ42, t-tau/Aβ42, and accurate[a] Core 1 plasma assays can establish that an individual is in biological stage A or higher, but cannot discriminate between PET stages A–D at present.			

Jack et al 2024

Diagnoses using ATNIVS

- A: Amyloid
- T: Tau
- N: Dysfunction, degeneration or injury
- I: Inflammation
- V: Vascular brain injury
- S: α-synuclein

Biomarker category	CSF or plasma analytes	Imaging
Core Biomarkers		
Core 1		
A (Aβ proteinopathy)	Aβ 42	Amyloid PET
T_1: (phosphorylated and secreted AD tau)	p-tau217, p-tau181, p-tau231	
Core 2		
T_2 (AD tau proteinopathy)	MTBR-tau243, other phosphorylated tau forms (e.g., p-tau205), non-phosphorylated mid-region tau fragments[a]	Tau PET
Biomarkers of non-specific 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[a]	

Duke University School of Medicine

Jack et al 2024

Duke, UNC & Me
Preventing Alzheimer's Disease Together

Clinical staging of Alzheimer's Disease

TABLE 6 Clinical staging for individuals on the Alzheimer's disease continuum.

Stage 0 Asymptomatic, deterministic gene[a]
No evidence of clinical change. Biomarkers in normal range.
Stage 1 Asymptomatic, biomarker evidence only
Performance within expected range on objective cognitive tests.
No evidence of recent cognitive decline or new symptoms.
Stage 2 Transitional decline: mild detectable change, but minimal impact on daily function
Normal performance within expected range on objective cognitive tests.
Decline from previous level of cognitive or neurobehavioral function that represents a change from individual baseline within the past 1 to 3 years, and has been persistent for at least 6 months.
May be documented by evidence of subtle decline on longitudinal cognitive testing, which may involve memory or other cognitive domains but performance still within normal range.
May be documented through subjective report of cognitive decline.
May be documented with recent-onset change in mood, anxiety, motivation not explained by life events.
Remains fully independent with no or minimal functional impact on activities of daily living (ADLs)
Stage 3 Cognitive impairment with early functional impact
Performance in the impaired/abnormal range on objective cognitive tests.
Evidence of decline from baseline, documented by the individual's report or by an observer's (e.g., study partner) report or by change on longitudinal cognitive testing or neurobehavioral assessments.
Performs daily life activities independently but cognitive difficulty may result in detectable functional impact on complex ADLs (i.e., may take more time or be less efficient but still can complete—either self-reported or corroborated by an observer).
Stage 4 Dementia with mild functional impairment
Progressive cognitive and mild functional impairment on instrumental ADLs, with independence in basic ADLs.
Stage 5 Dementia with moderate functional impairment
Progressive cognitive and moderate functional impairment on basic ADLs requiring assistance.
Stage 6 Dementia with severe functional impairment
Progressive cognitive and functional impairment, and complete dependence for basic ADLs.

[a]Individuals with Down syndrome may not be fully independent even in stage 0 because of underlying intellectual disability. In these individuals, decline in functional independence from baseline may be a more appropriate indicator of stage.

Duke University School of Medicine

Jack et al 2024

Duke, UNC & Me
Preventing Alzheimer's Disease Together

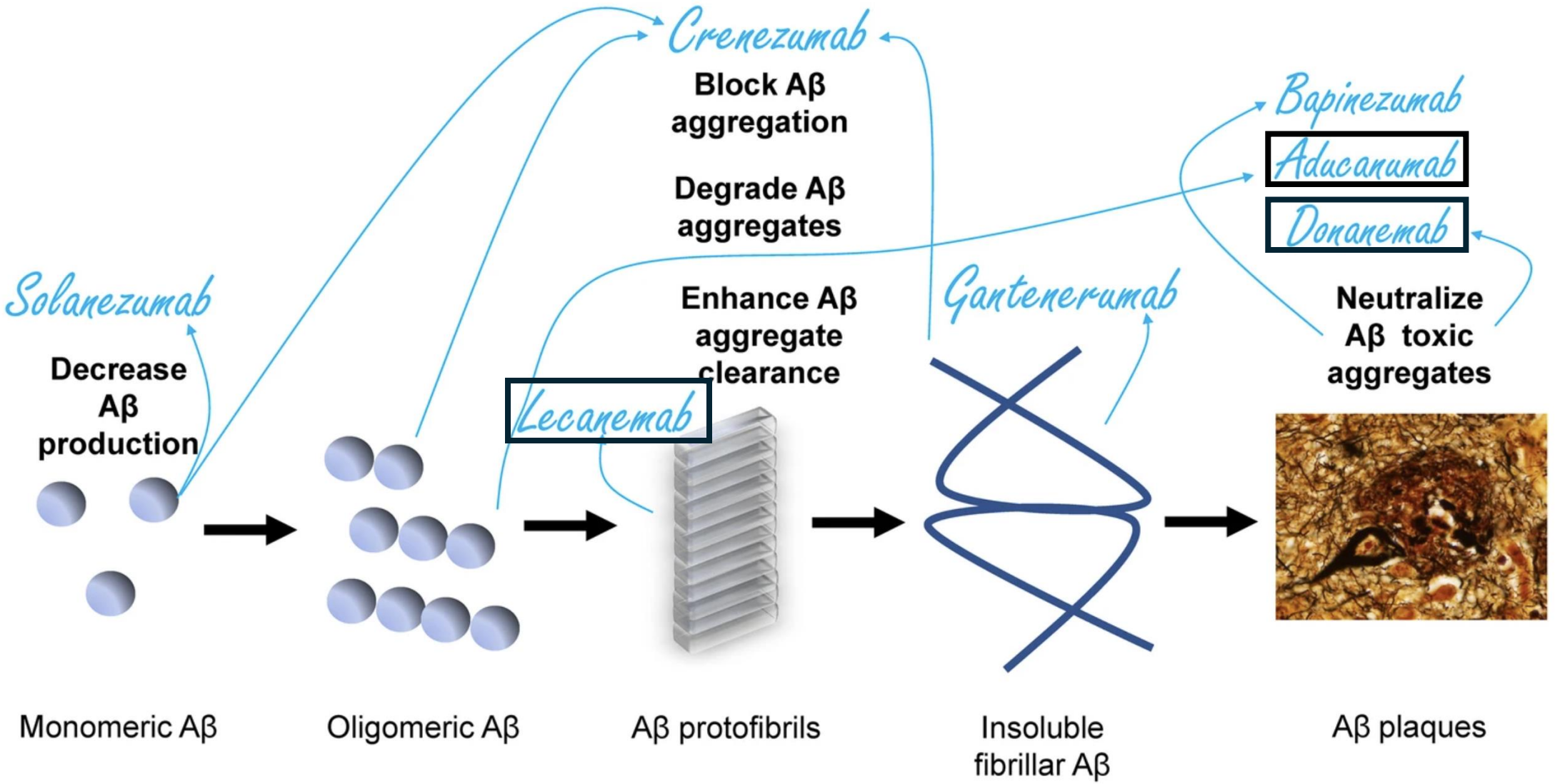
Clinical and Biological staging of AD

TABLE 7 Integrated biological and clinical staging.

	Stage 0	Clinical Stage 1	Clinical Stage 2	Clinical Stage 3	Clinical Stages 4–6
Initial biological stage (A)	X	1A	2A	3A	4-6A
Early biological stage (B)	X	1B	2B	3B	4-6B
Intermediate biological stage (C)	X	1C	2C	3C	4-6C
Advanced biological stage (D)	X	1D	2D	3D	4-6D

Jack et al 2024

From: Anti-Amyloid Immunotherapies for Alzheimer's Disease: A 2023 Clinical Update



Mechanisms of action of different anti-amyloid antibodies in relation to stages of Aβ aggregation

Amyloid Related Imaging Abnormality (ARIA) rates

Drug	Incidence ARIA-E	Incidence ARIA-H	Incidence Any ARIA
Aducanumab: 3, 6 or 10 mg/kg monthly	30.6%	29.9%	60.6%
Lecanemab: 10 mg/kg biweekly	12.6%	17.3%	29.8%
Donanemab: 700mg X3 then 1400 mg monthly (standard dosing)	24.0%	19.7%	36.8%

Haeberlein et al 2022, van Dyck 2022, Sims et al 2023

Amyloid Related Imaging Abnormality (ARIA) rates:

Drug	Incidence ARIA-E	Incidence ARIA-H	Incidence Any ARIA
Aducanumab: 3, 6 or 10 mg/kg monthly	30.6%	29.9%	60.6%
Lecanemab: 10 mg/kg biweekly	12.6%	17.3%	29.8%
Donanemab: Standard dosing	24.0%	19.7%	36.8%
Donanemab: 350mg, 700mg, 1050mg, 1400mg (Modified dosing)	13.7%	20.3%	23.6%

Haeberlein et al 2022, van Dyck 2022, Sims et al 2023, Hong et al 2024

ARIA-E and ApoE genotype status

Drug	Incidence in Noncarriers	Incidence in heterozygotes	Incidence in homozygotes
Lecanemab: 10mg/kg biweekly	6.8%	12.5%	46.1%
Donanemab: standard dosing	15.7%	22.8%	57%
Donanemab: modified dosing	14.6%	17.4%	19%

Criteria for anti-amyloid therapy

1. Clinical staging: Stage 3 (MCI) or stage 4 (mild AD dementia)
2. Review of medications
3. Biological staging: amyloid-PET, CSF AD biomarkers
4. MRI brain
5. ApoE genotyping

Anti-amyloid use at Duke University

- Over 150 patients are currently receiving infusions
- Centralized infusion center
- ED and inpatient neurologist are updated
- Stroke neurologists also updated

Thank you

- Duke University
  - Deborah Rose
  - Jim Burke
  - Joel Morganlander
  - Rich O’Brien
  - Kim Johnson
  - Daniel Parker
  - Sandy Cobb
  - Heba Al-Sahlani
  - Michelle Sanfilippo
- Duke-UNC ADRC
  - Heather Whitson
  - Gwen Garden
  - Heidi Roth

Duke University School of Medicine

Andy.liu@duke.edu

Duke, UNC & Me
Preventing Alzheimer's Disease Together