ASCP 2023

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Emerging Biomarkers for the Assessment of Alzheimer's Disease

Duke Pathology
Duke University School of Medicine

Department of Neurology
Duke University School of Medicine

Emerging Biomarkers for the Assessment for Alzheimer's Disease

ASCP 2023 annual meeting

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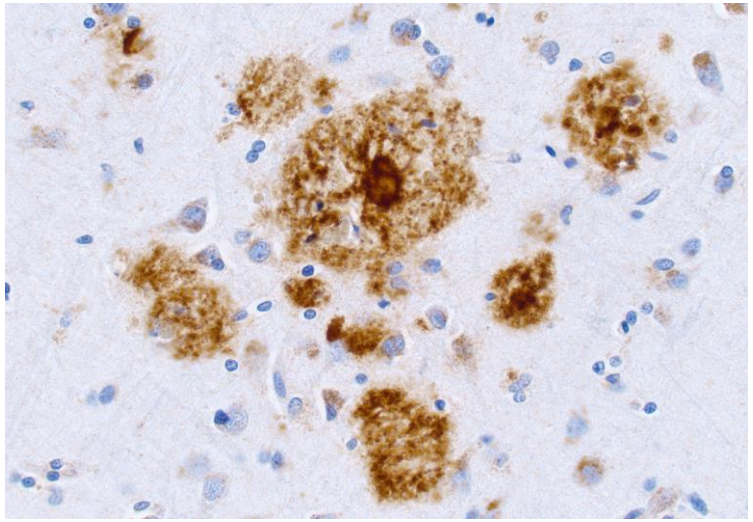
Disclosure:

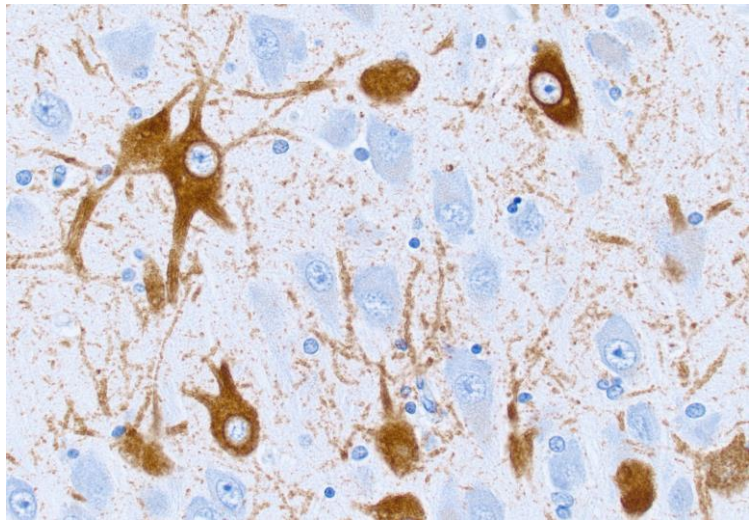
- “I have no financial relationships with ineligible companies to disclose”

Towards a biological construct of AD

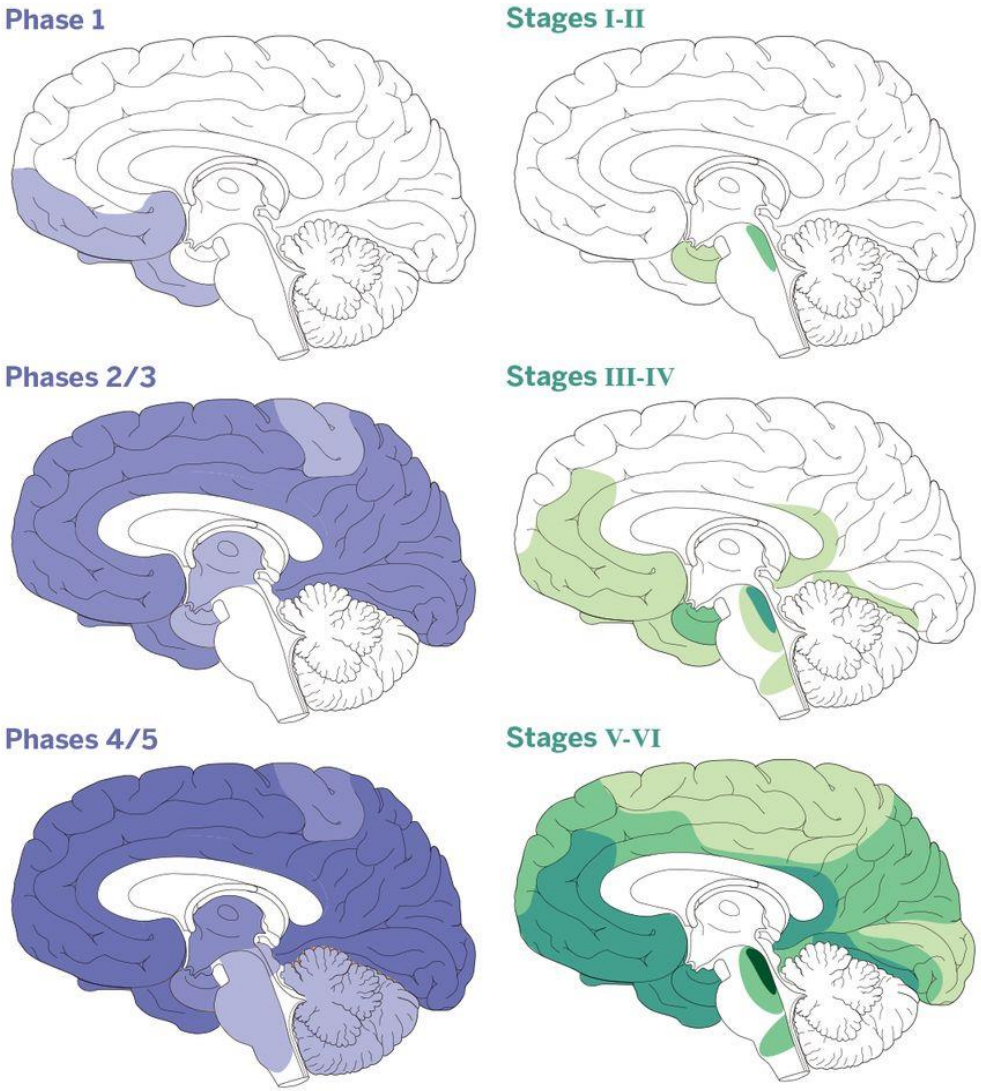
- **Alzheimer's disease is a clinical-pathologic entity characterized by a multi-domain amnestic syndrome, and confirmed at death by the presence of Alzheimer's disease neuropathologic changes**



Amyloid plaques



Neurofibrillary tangles



Plaques NFT

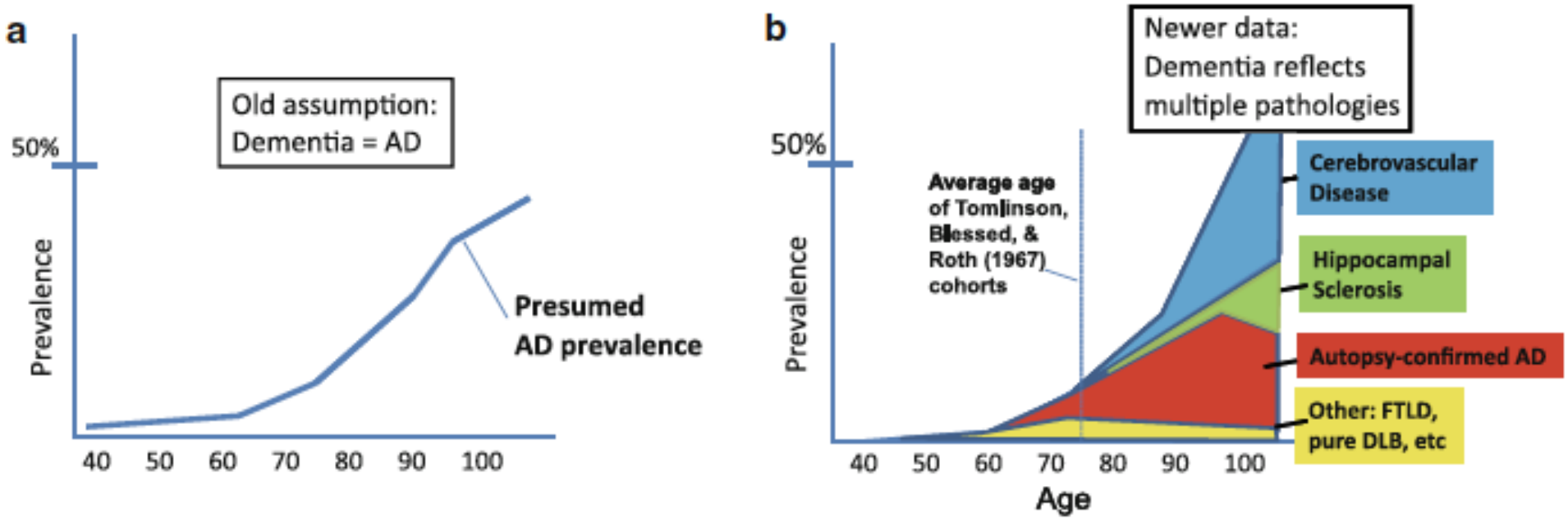
The extent to which clinical syndromes can be explained by AD neuropathologic change is determined by the extent of amyloid plaque (Thal phase) and neurofibrillary tangle(Braak stage) pathology

Towards a biological construct of AD

However,

- **The relationship between clinical presentation and neuropathology is not straightforward**
- **The need to define “preclinical stage” Alzheimer’s disease**
- **The need to identify patients for disease-modifying therapies and enroll in clinical trials**
- **The need to understand early changes of AD**

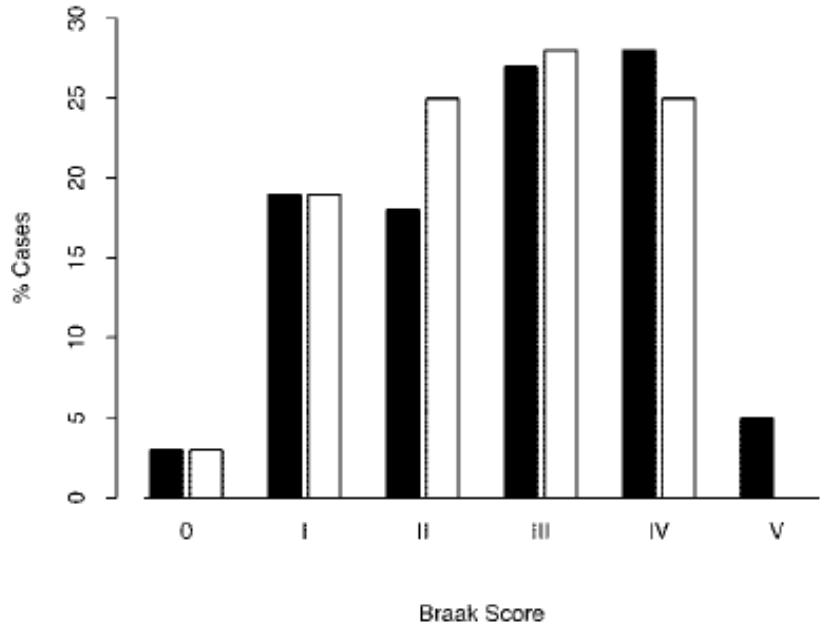
10-30% of individuals diagnosed with AD dementia by experts do not show AD neuropathologic change at autopsy



(Nelson PT et al., *Acta Neuropathol*, 2011)

Contribution of co-pathologies (Lewy body disease, cerebrovascular disease, TDP-43 pathology)?

30-40% of cognitively unimpaired elderly persons have AD neuropathologic changes at autopsy.



Braak Score		
0	3 (3.1)	1 (2.8)
I	19 (19.4)	7 (19.4)
II	18 (18.4)	9 (25.0)
III	26 (26.5)	10 (27.8)
IV	27 (27.6)	9 (25.0)
V	5 (5.1)	0
VI	0	0

(Bennett PT et al., *Neurology*, 2006)

Need to identify patients who would benefit from disease-modifying therapies and enroll in clinical trials.

Monoclonal antibody (RCT)	Trial endpoint (weeks)	Number of trial participants	Amyloid negative in treatment group at end (%)[a]	Dose	Cognitive benefit compared to placebo	ARIA-E (% treatment greater than placebo)	ARIA-H (% treatment greater than placebo)	Aβ target
Solanezumab (Expedition 1,2)[69]	80	2,052	-	400 mg	No	0.5	−0.7	Soluble monomer
Crenezumab (CREAD 1,2)[70]	102	1,619	-	60 mg/kg	No	0.1	0.5	Soluble oligomers
Gantenerumab (Graduate 1,2)[134]	116	1,965	27	1,020 mg	No	-	-	Insoluble fibrils
Aducanamab (EMERGE)[64]	78	1,638	48	10 mg/kg[b]	Yes	33.0	13.0	Insoluble fibrils
Aducanamab (ENGAGE)[64]	78	1,647	31	10 mg/kg[b]	No	33.0	13.0	Insoluble fibrils
Donanemab (TRAILBLAZER-ALZ 2)[4]	76	1,736	76	700 mg first 3 doses, 1,400 mg	Yes	21.9	17.8	Plaque-associated Aβ
Lecanemab (Clarity AD)[3]	78	1,734	81	10 mg/kg	Yes	10.9	6.3	Protofibrils

(Self and Holtzman, *Nat Med*, 2023)

Poll question #1

What are some examples of AD biomarkers currently used for AD diagnosis (imaging or fluid)?

Biomarker grouping by AT(N) framework

A: Amyloid

CSF Aβ42 or Aβ42/Aβ40 ratio (Elecsys®, Lumipulse®)

Amyloid PET (Amyvid™, Neuraceq™, and Vizamyl™)

T: Tau

CSF phopho-tau181 (Elecsys®, Lumipulse®)

CSF PET (flortaucipir)

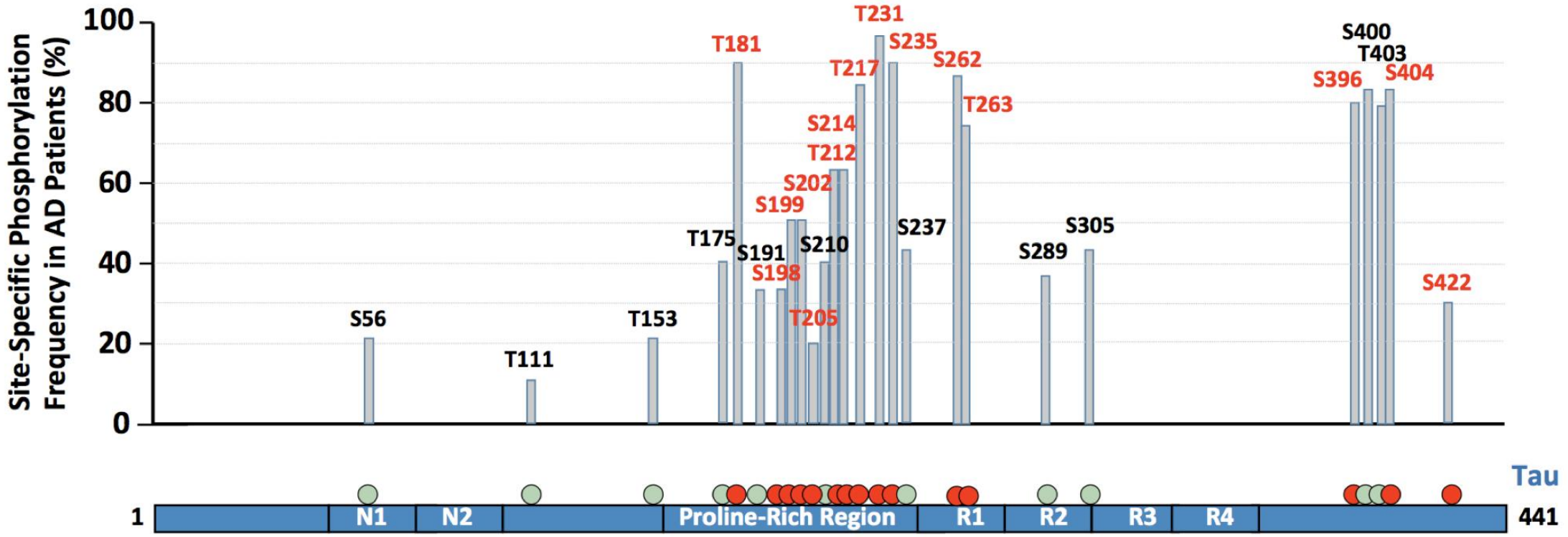
N: Neurodegeneration or neuronal injury

CSF total tau (Elecsys®, Lumipulse®)

Anatomic MRI

FDG PET

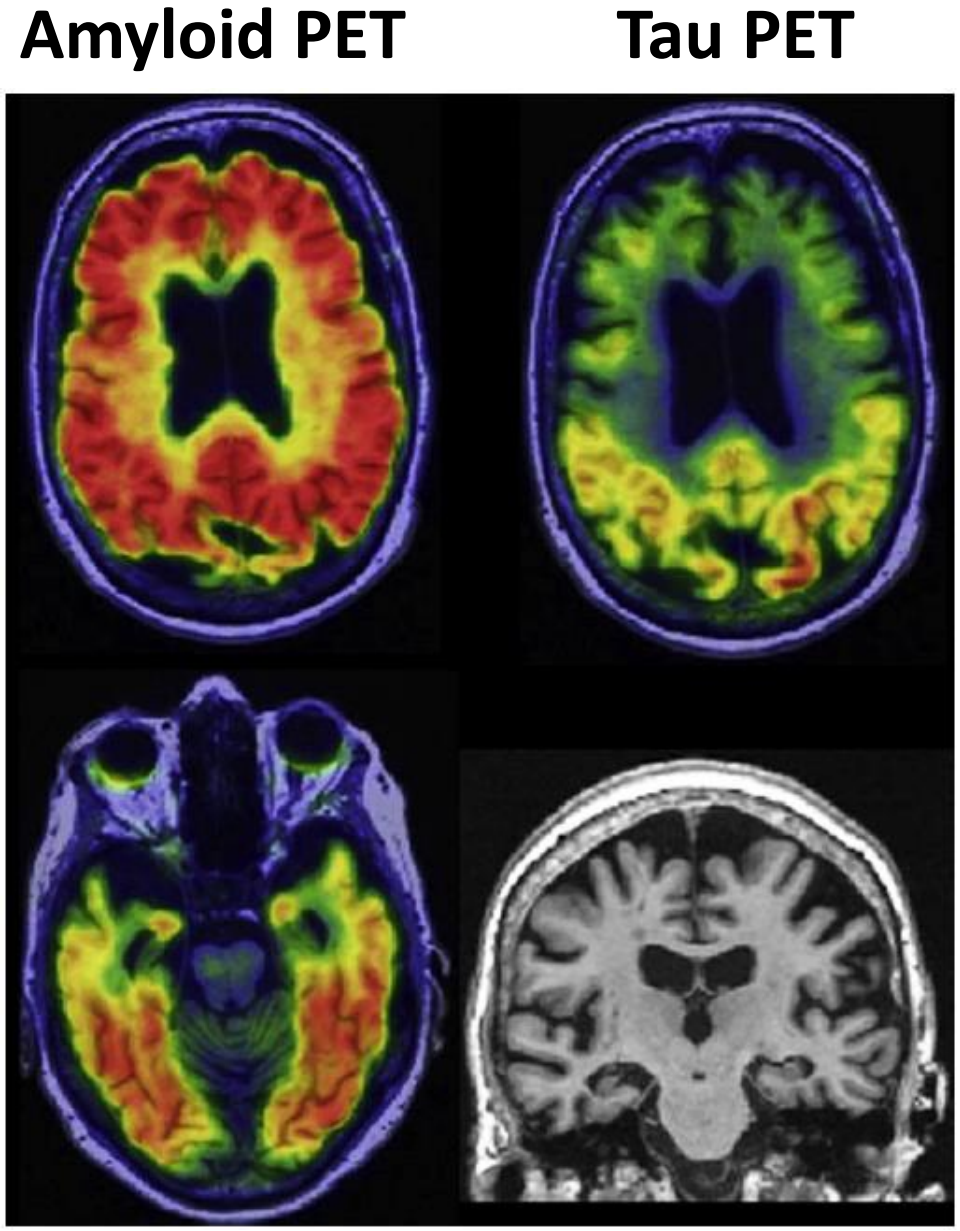
Tangles consist of hyperphosphorylated tau



AT(N) profiles	Biomarker category	
A-T-(N)-	Normal AD biomarkers	
A+T-(N)-	Alzheimer's pathologic change	Alzheimer's continuum
A+T+(N)-	Alzheimer's disease	
A+T+(N)+	Alzheimer's disease	
A+T-(N)+	Alzheimer's and concomitant suspected non Alzheimer's pathologic change	
A-T+(N)-	Non-AD pathologic change	
A-T-(N)+	Non-AD pathologic change	
A-T+(N)+	Non-AD pathologic change	

Combinations of A, T, and N biomarkers define categories along the "Alzheimer's continuum" as well as non-AD pathological changes

(Jack CR et al., *Alz Dement*, 2018)



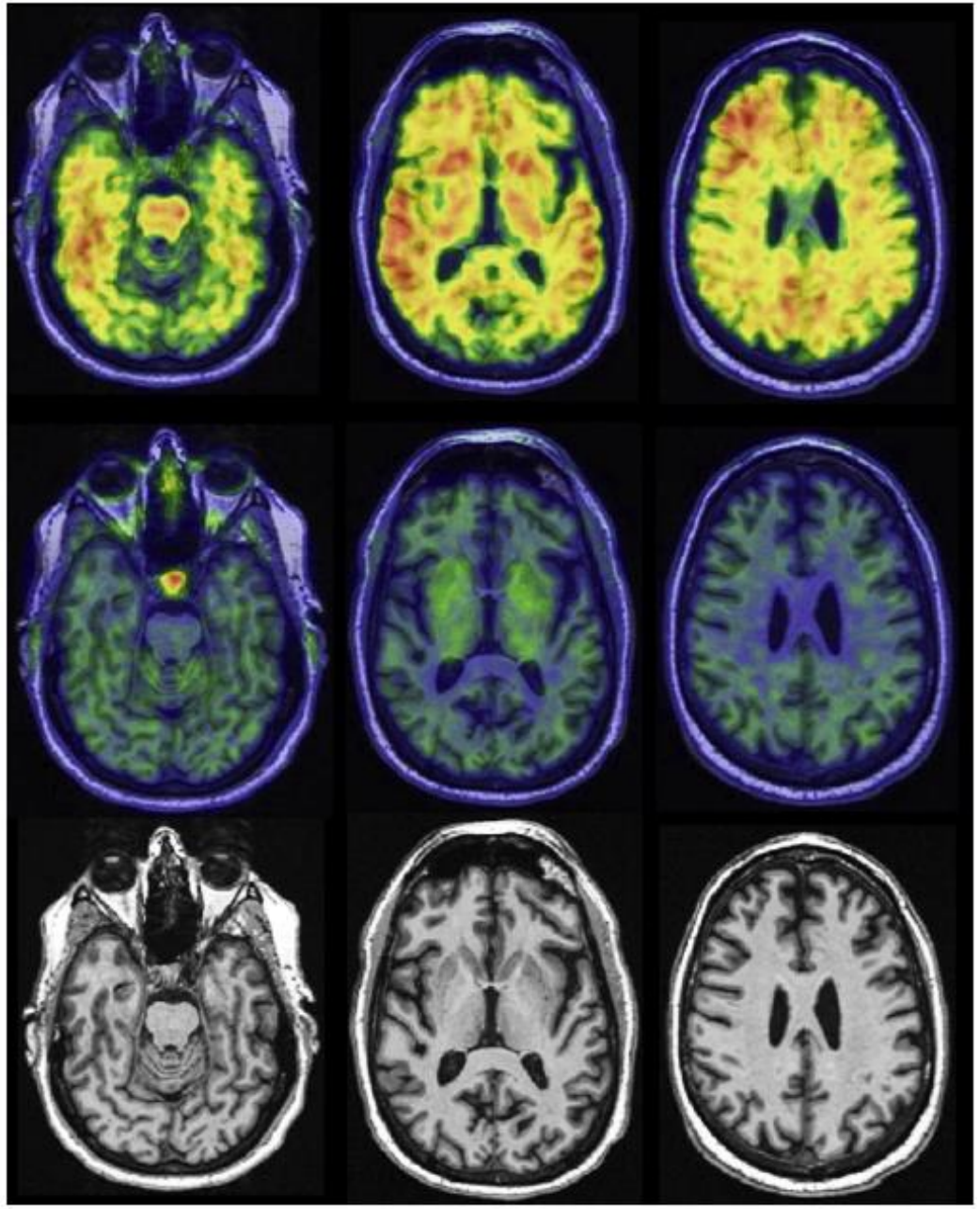
- **Abnormal amyloid PET**
- **Abnormal tau PET**
- **Atrophy on MRI**
- **A+T+(N)+ → Alzheimer's disease**

(Modfied from Jack CR et al., *Alz Dement*, 2018)

Amyloid PET

Tau PET

MRI



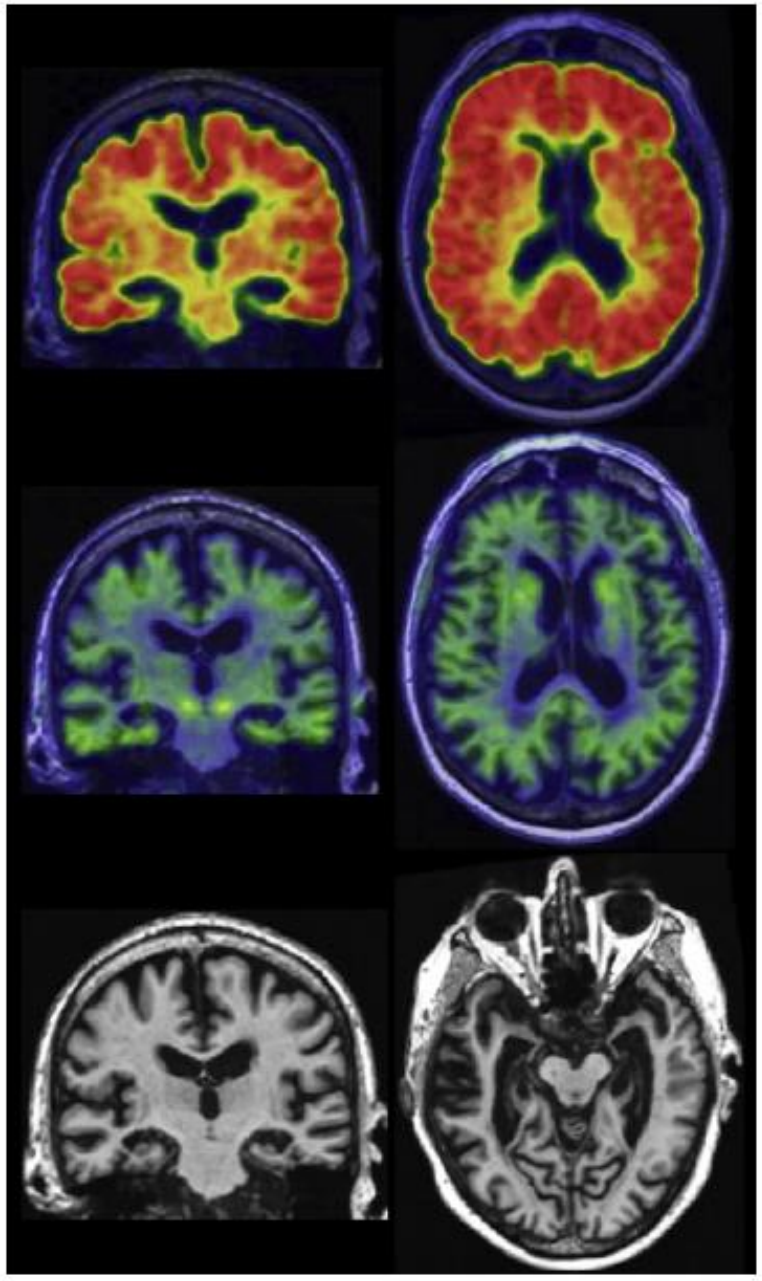
- **Abnormal amyloid PET**
- **Normal tau PET**
- **No atrophy on MRI**
- **A+T-(N)- → Alzheimer's pathologic change**

(Modfied from Jack CR et al., *Alz Dement*, 2018)

Amyloid PET

Tau PET

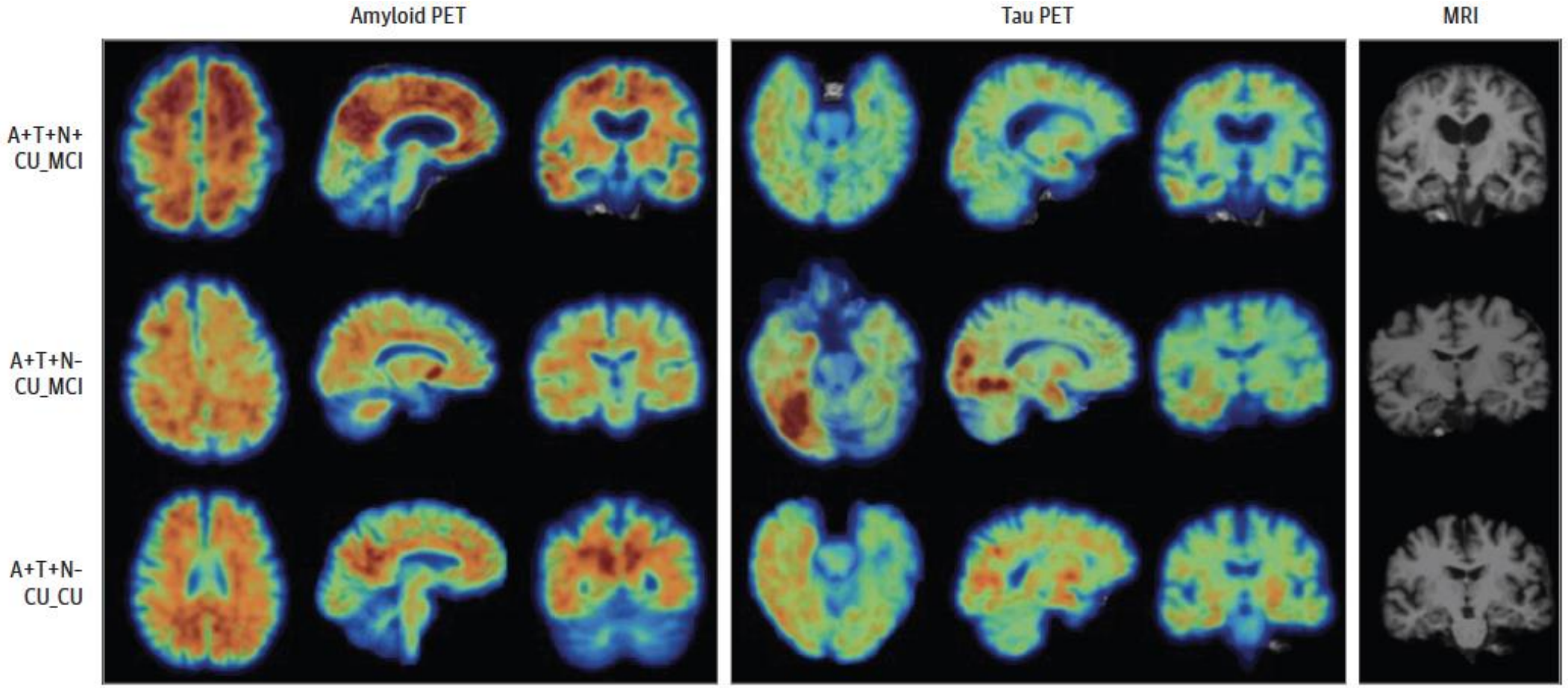
MRI



- **Abnormal amyloid PET**
- **Normal tau PET**
- **Atrophy on MRI**
- **A+T-(N)+ → Alzheimer's with concomitant non-Alzheimer's pathologic change eg. LATE**

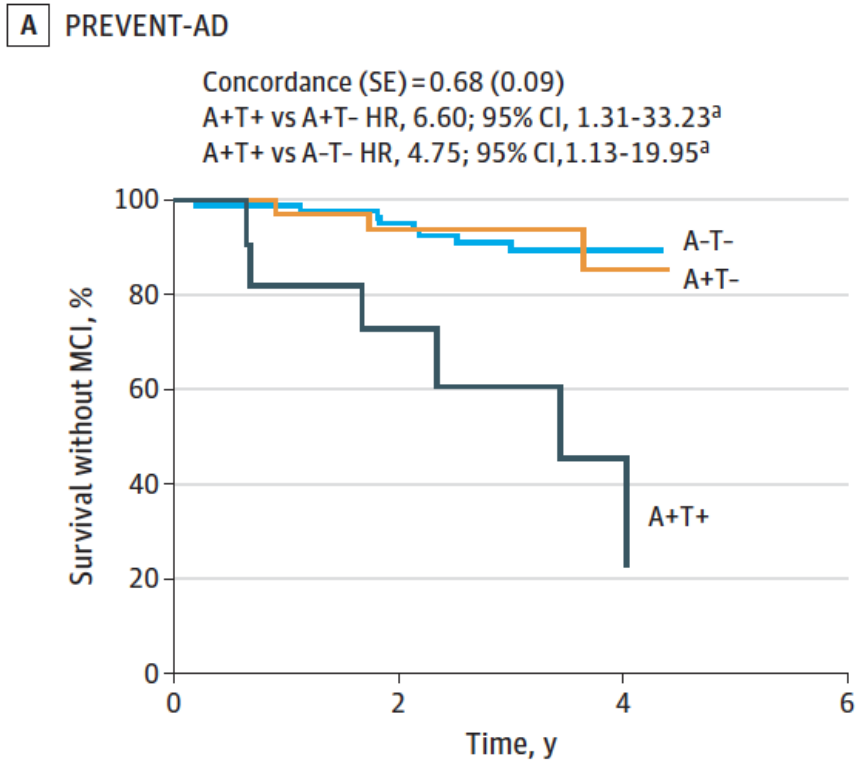
(Modfied from Jack CR et al., *Alz Dement*, 2018)

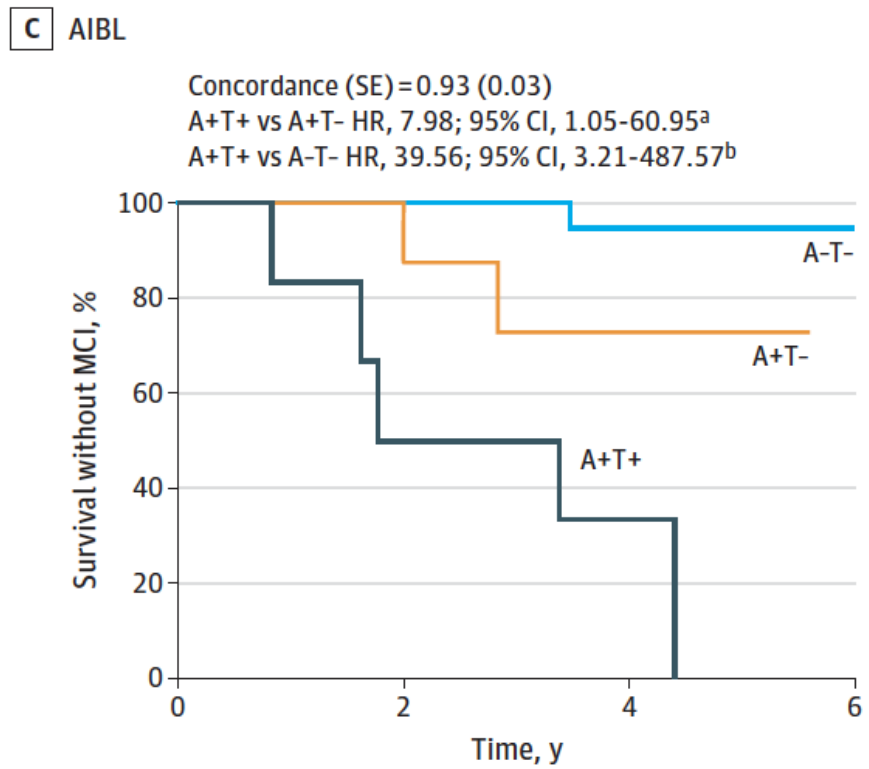
Imaging biomarkers predict cognitive decline



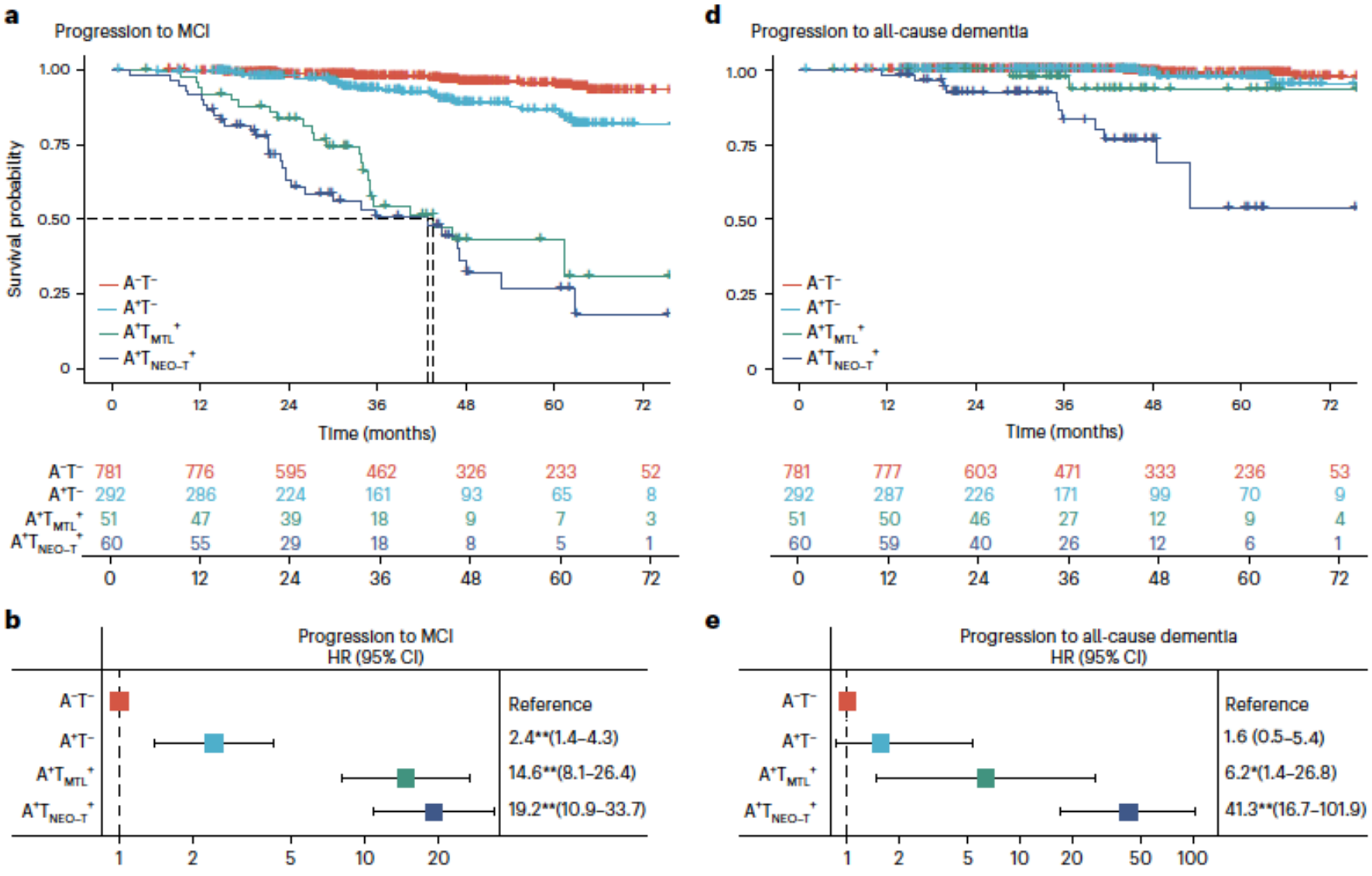
(Strikwerda-Brown C et al., *JAMA Neurol*, 2022)

Imaging biomarkers predict cognitive decline





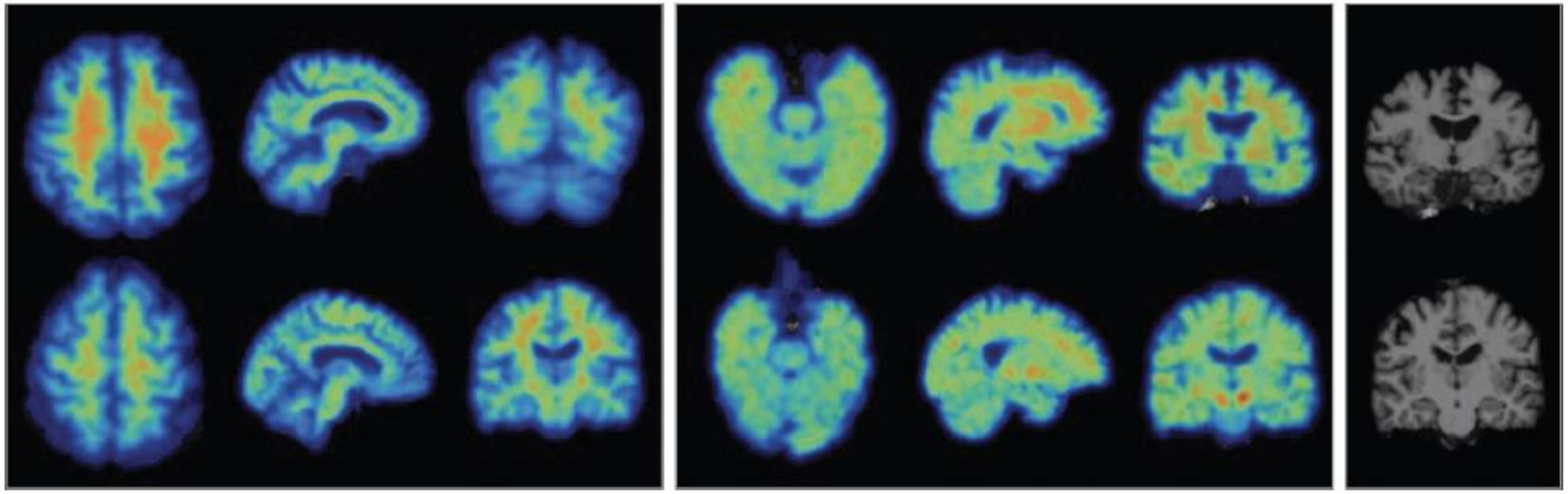
(Strikwerda-Brown C et al., *JAMA Neurol*, 2022)



(Ossenkoppele R et al., *Nat Med*, 2022)

Limitations of imaging biomarkers

- Expensive
- Requires substantial technical infrastructure
- Use radioactive tracers



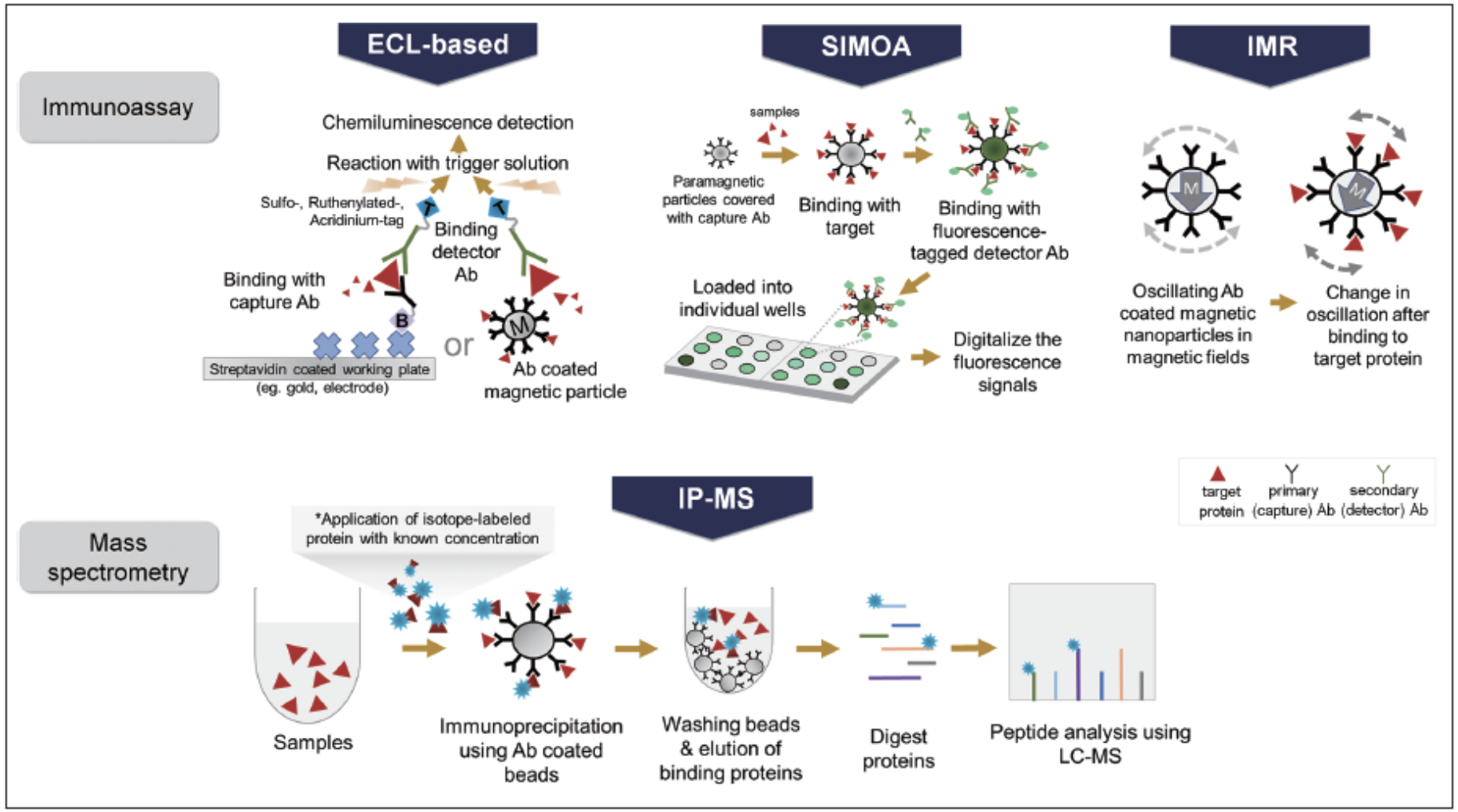
Imaging vs fluid biomarkers

- Imaging measures represent the magnitude of abnormal protein deposition or damage accumulated over time, and thus reflects neuropathologic load

- Fluid biomarkers reflect the balance between abnormal protein production and clearance at a given time point

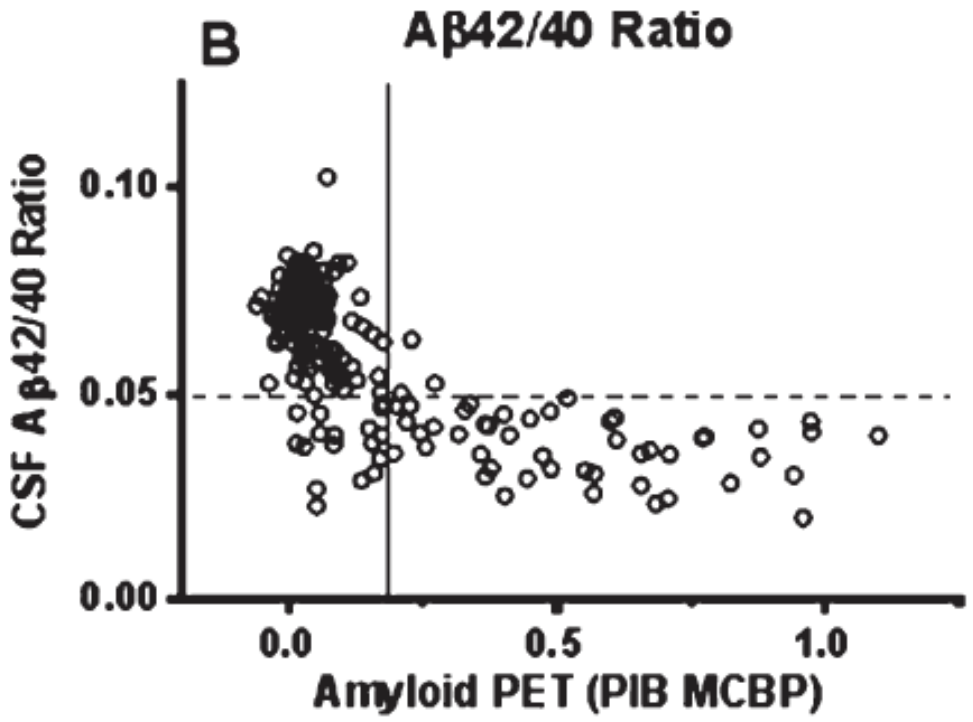
- Imaging and fluid biomarkers can show discordance eg. CSF phospho-tau plateaus in later-stage AD, but tau PET signal continues to increase

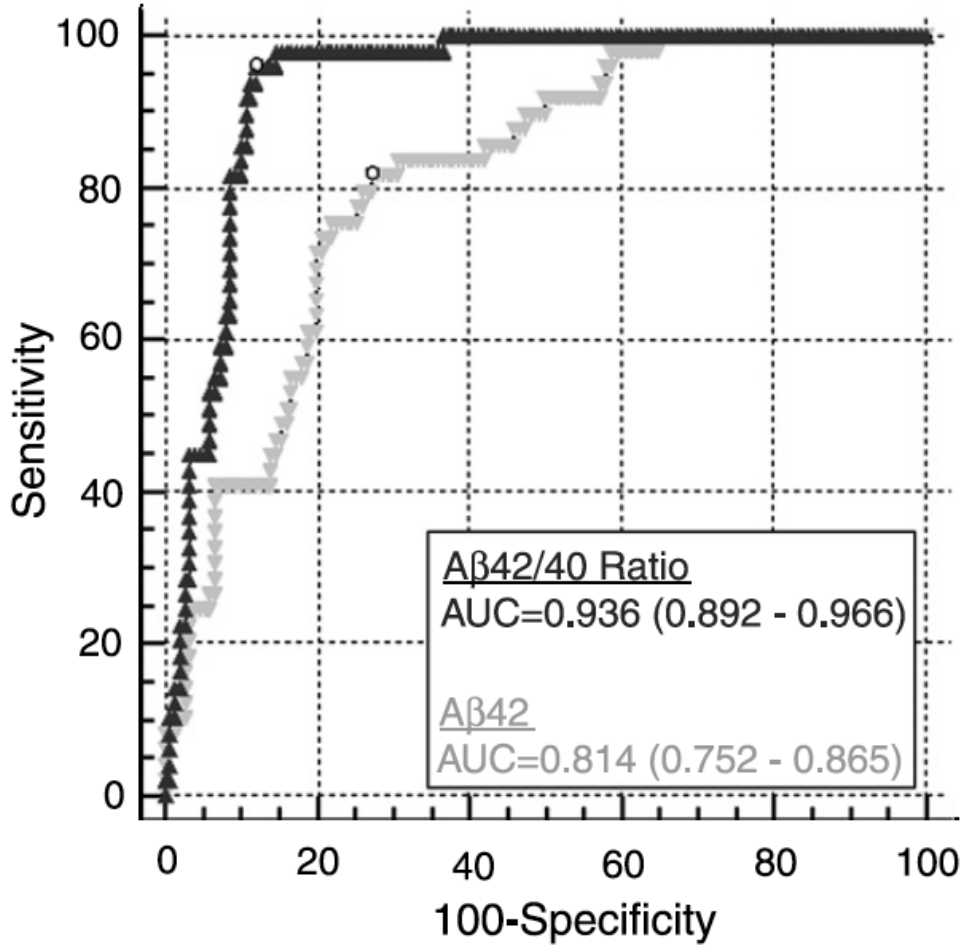
Ultrasensitive biomarker detection methods



(Park SA et al., *JCN*, 2022)

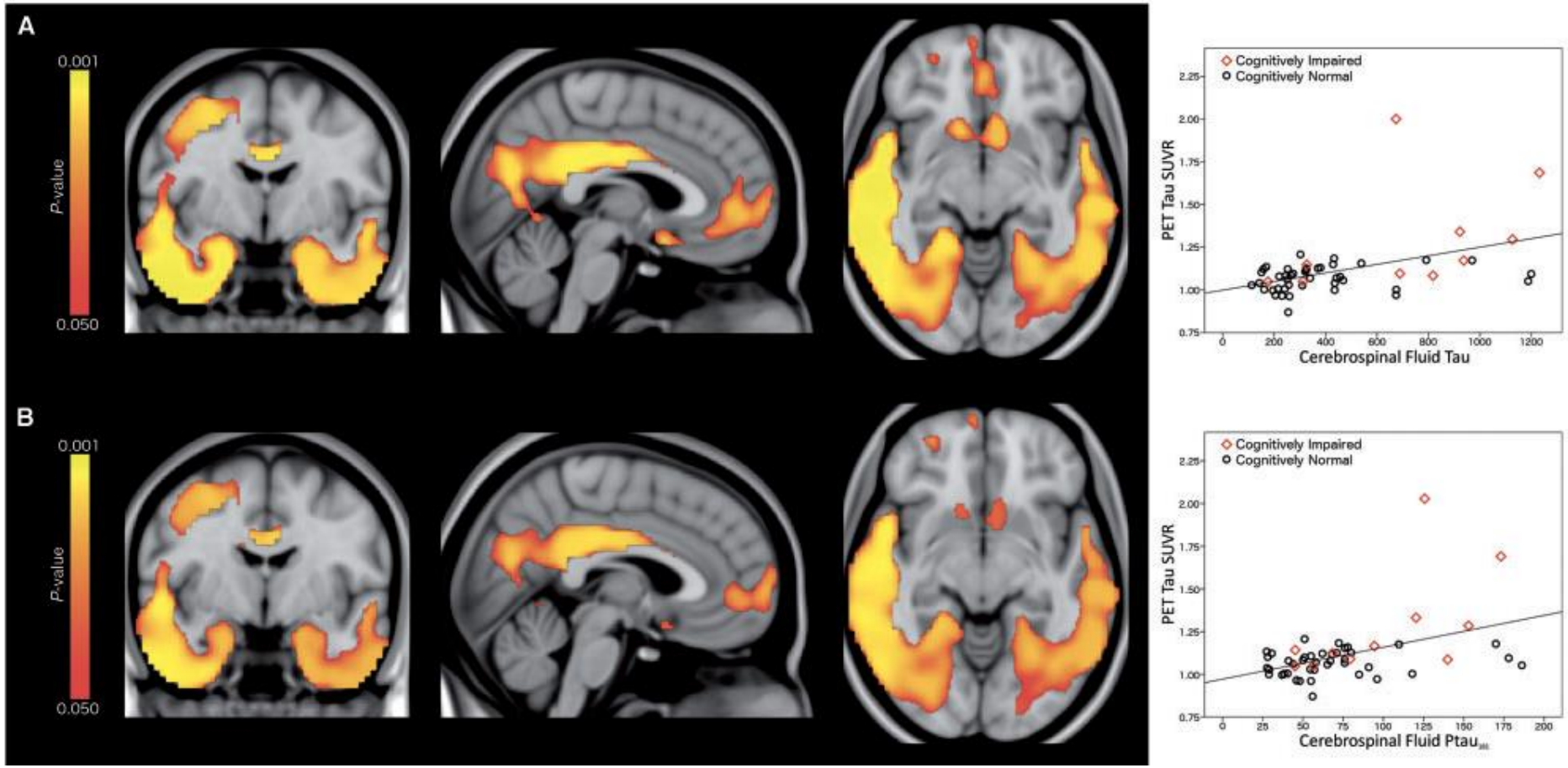
CSF Aβ42/ Aβ40 ratio correlates with amyloid PET





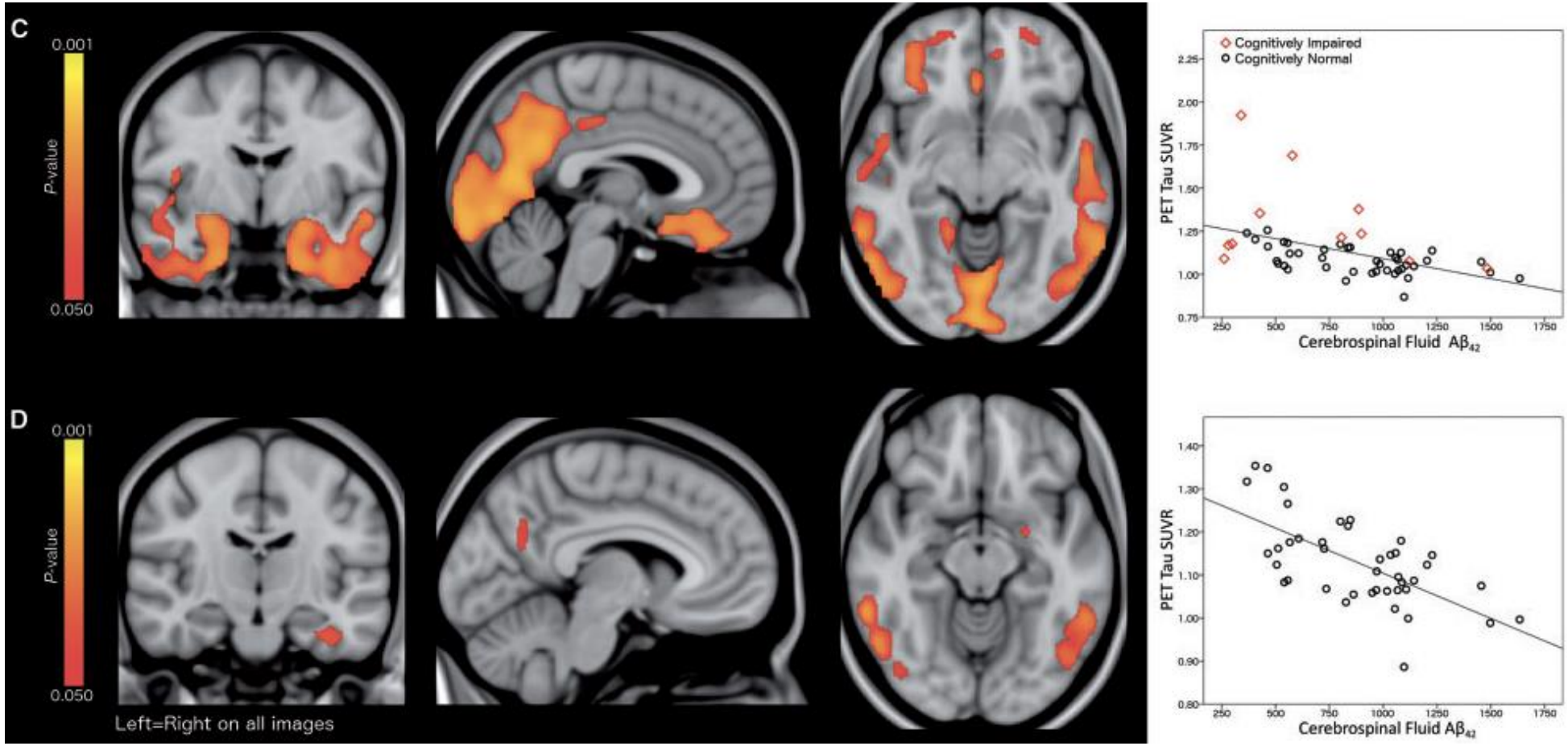
(Lewczuk P et al., *JAD*, 2017)

CSF total tau and phophos-tau correlate with tau PET



(Gordon BA et al., *Brain*, 2016)

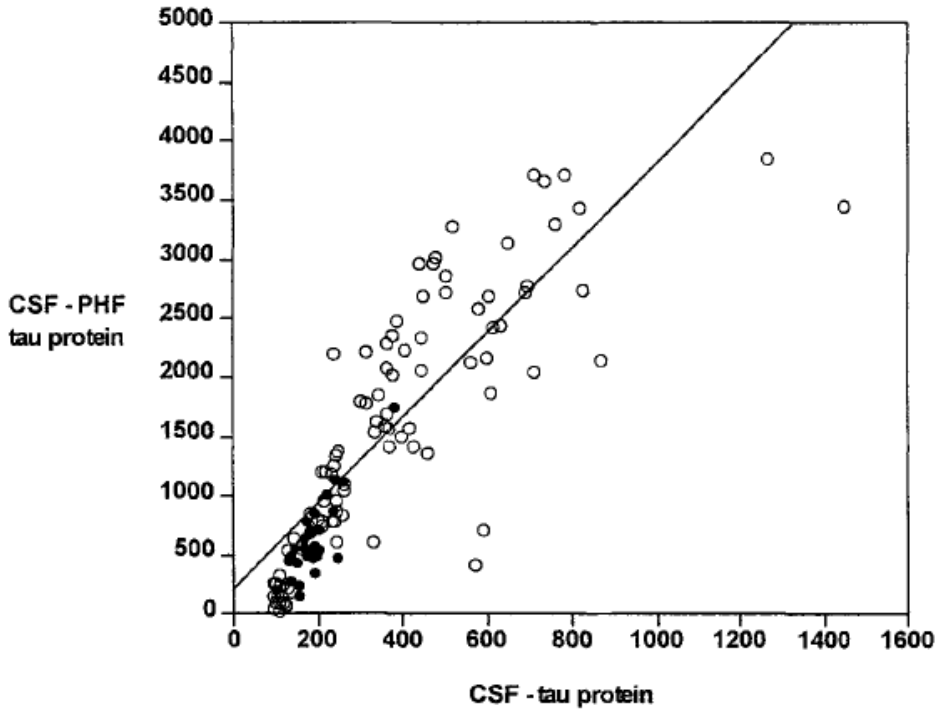
CSF Aβ42 also correlate with tau PET

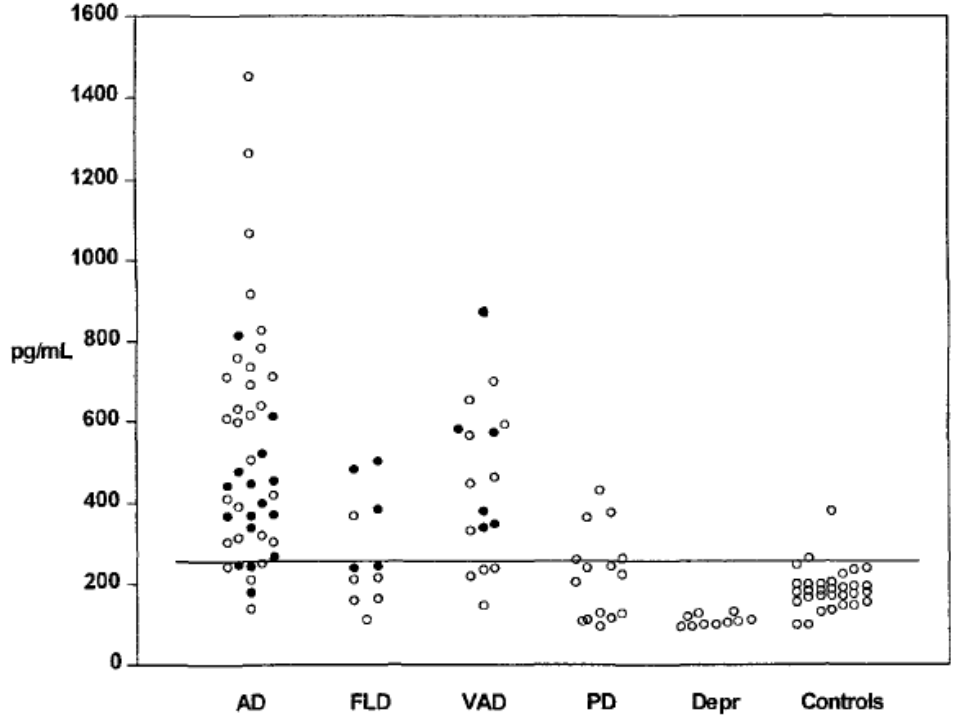


(Gordon BA et al., *Brain*, 2016)

CSF total tau is a measure of neurodegeneration

- CSF total tau (t-tau) correlates almost perfectly with CSF phospho-tau (p-tau)
- But t-tau is not a specific marker for neurofibrillary tangles

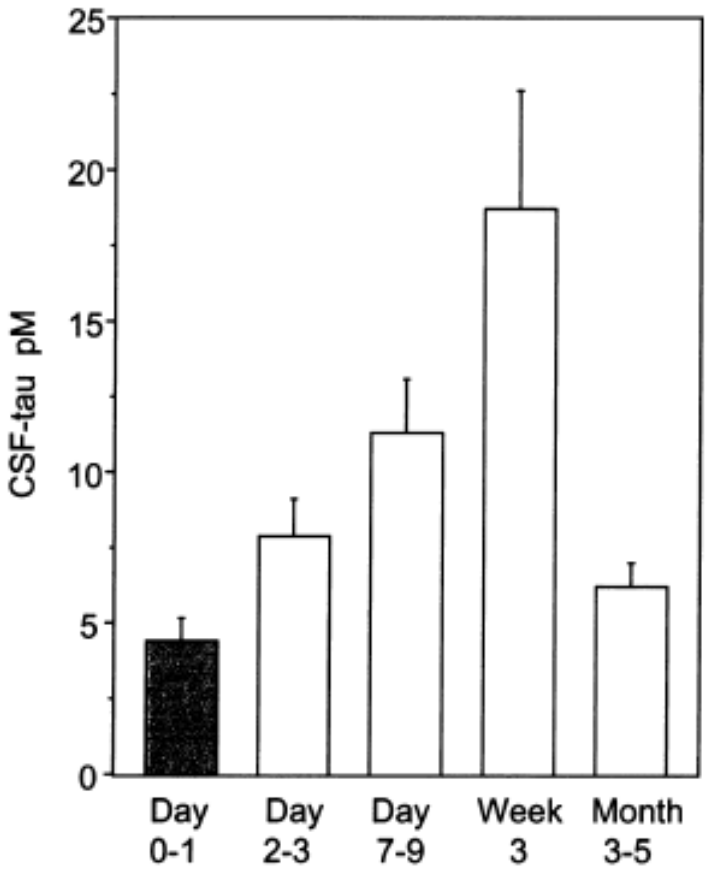


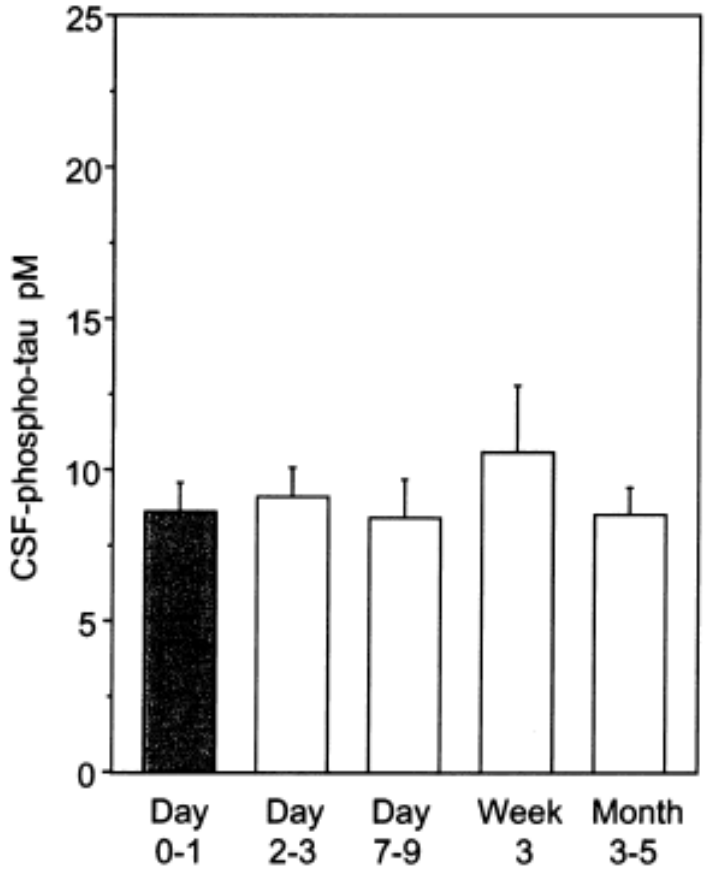


(Blennow K et al., *Mol Chem Neuropahol*, 1995)

CSF t-tau is a measure of neurodegeneration

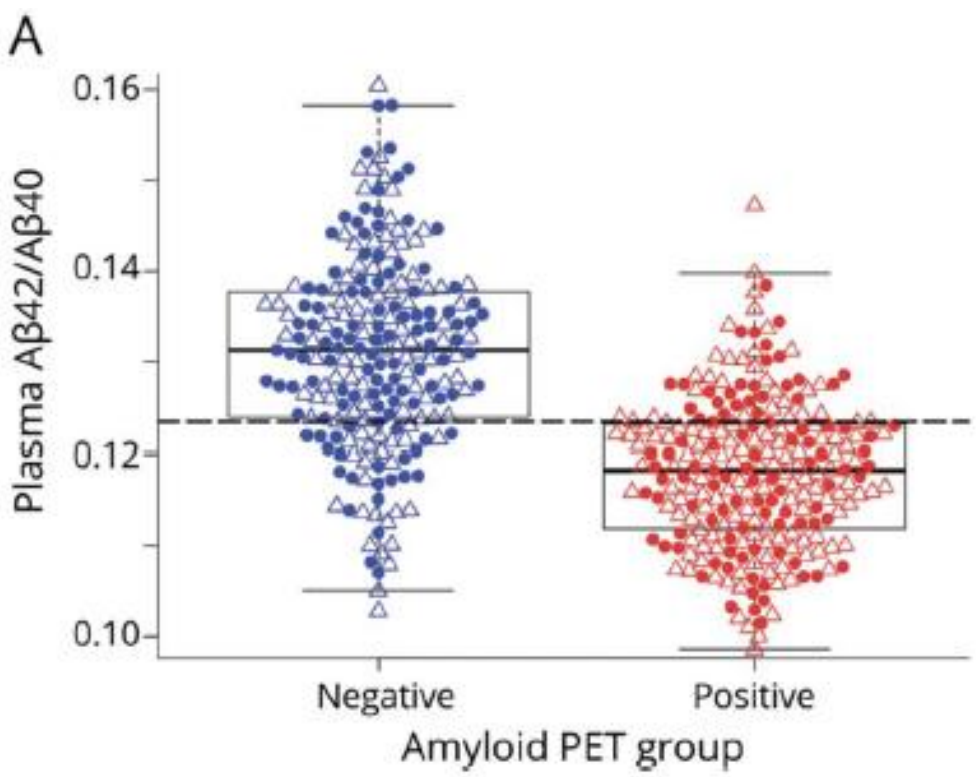
- CSF t-tau, but not p-tau, shows transient increase in stroke

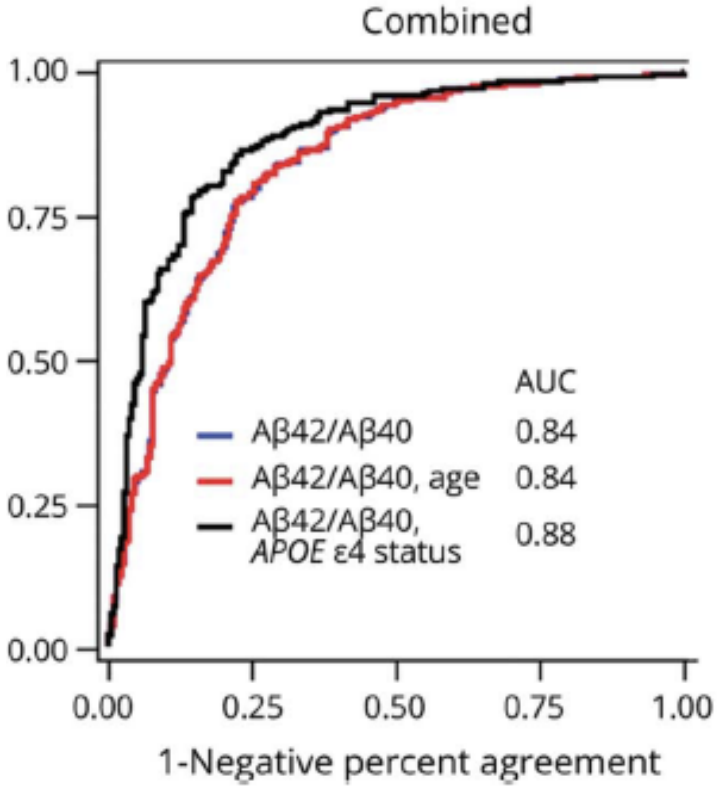




(Hesse C et al., *Neurosci Lett*, 2001)

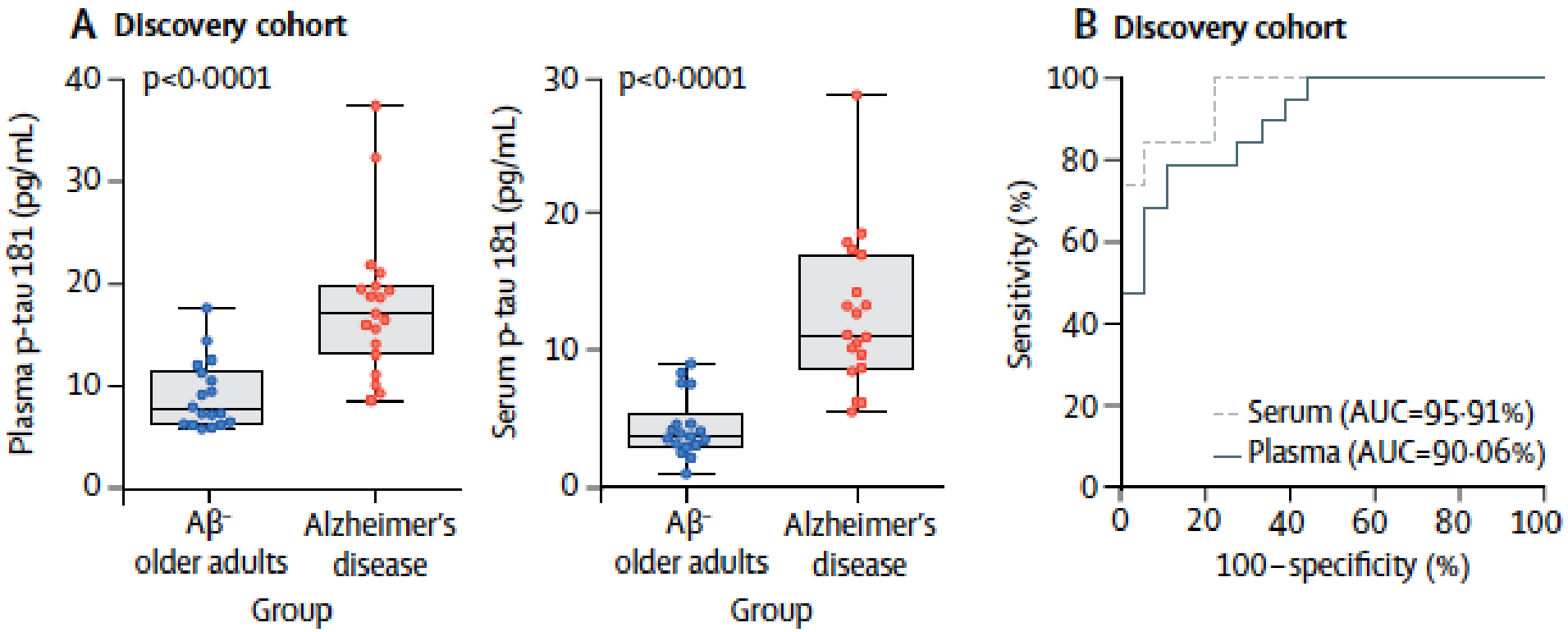
Development of plasma biomarkers: Aβ42





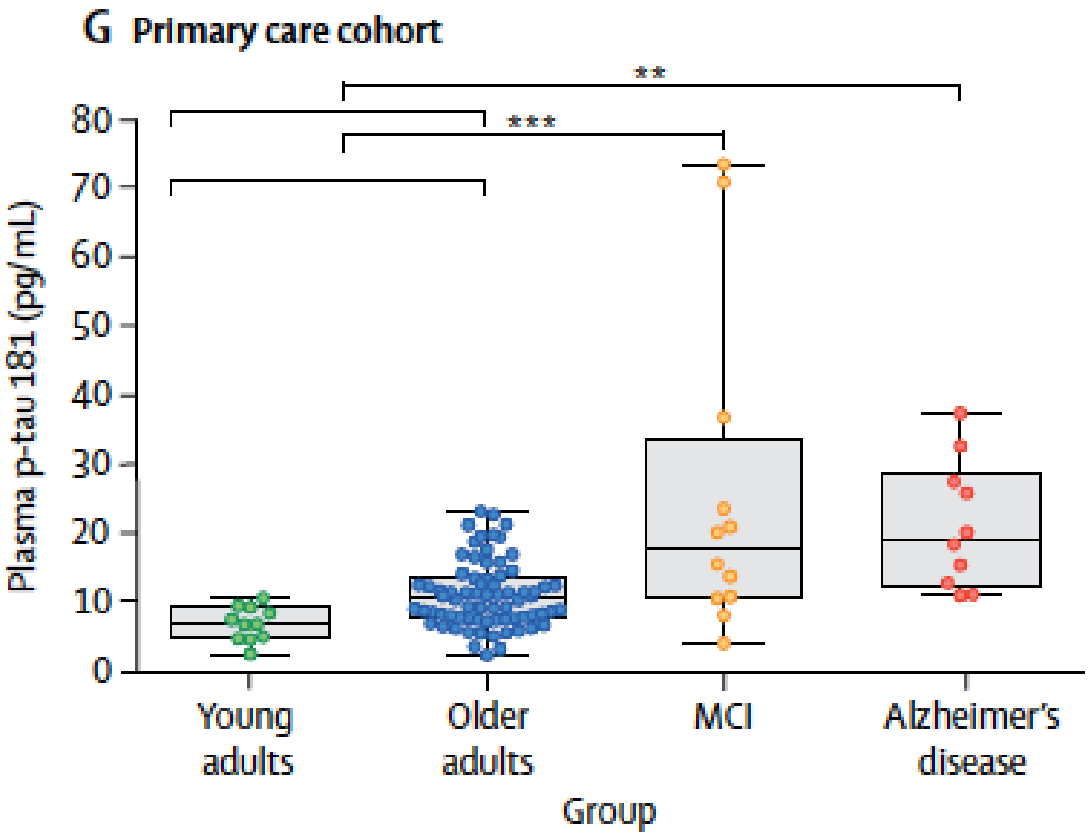
(Li Y et al., *Neurology*, 2022)

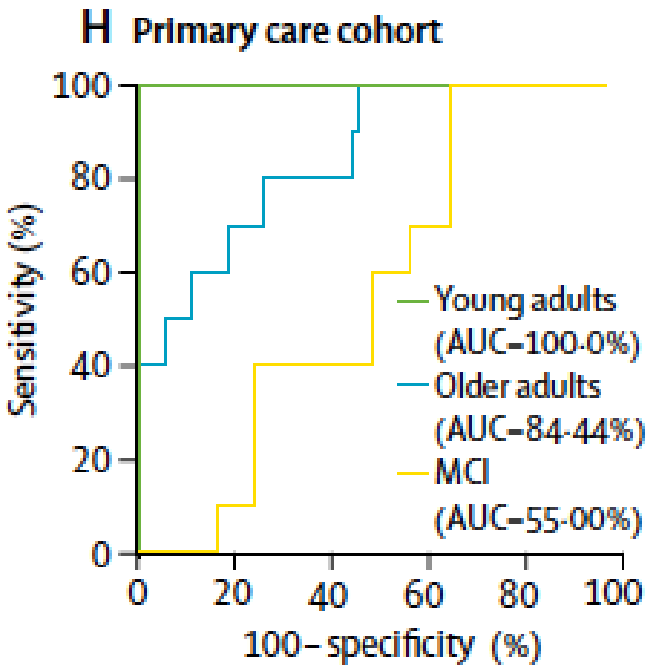
Development of plasma biomarkers: p-tau181



(Karikari T et al., *Lancet Neurology*, 2020)

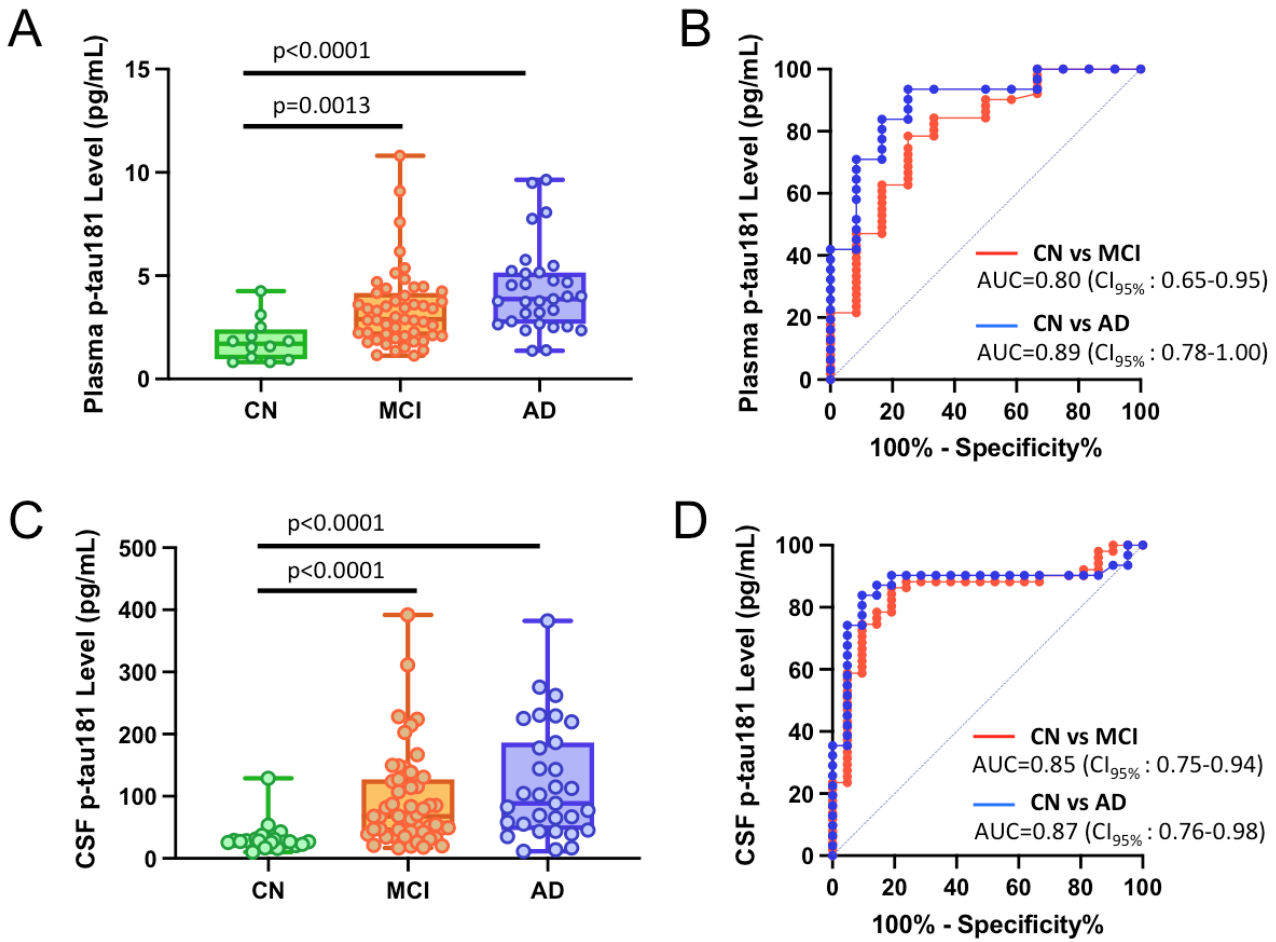
Development of plasma biomarkers: p-tau181





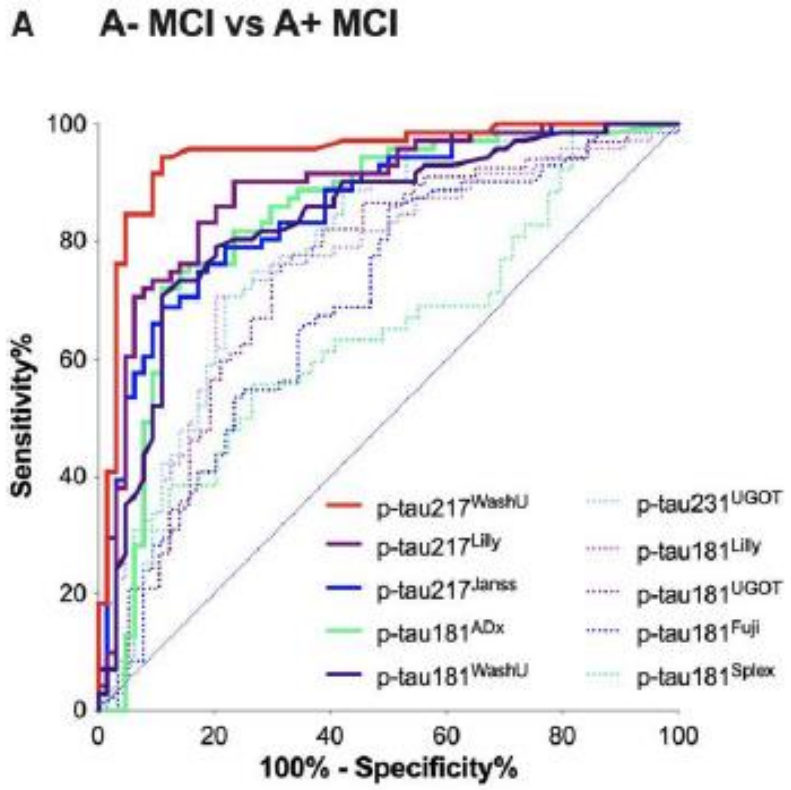
(Karikari T et al., *Lancet Neurology*, 2020)

Development of plasma biomarkers: p-tau181



Unpublished data, collaboration with Ling Wu, Bin Xu, and Andy Liu

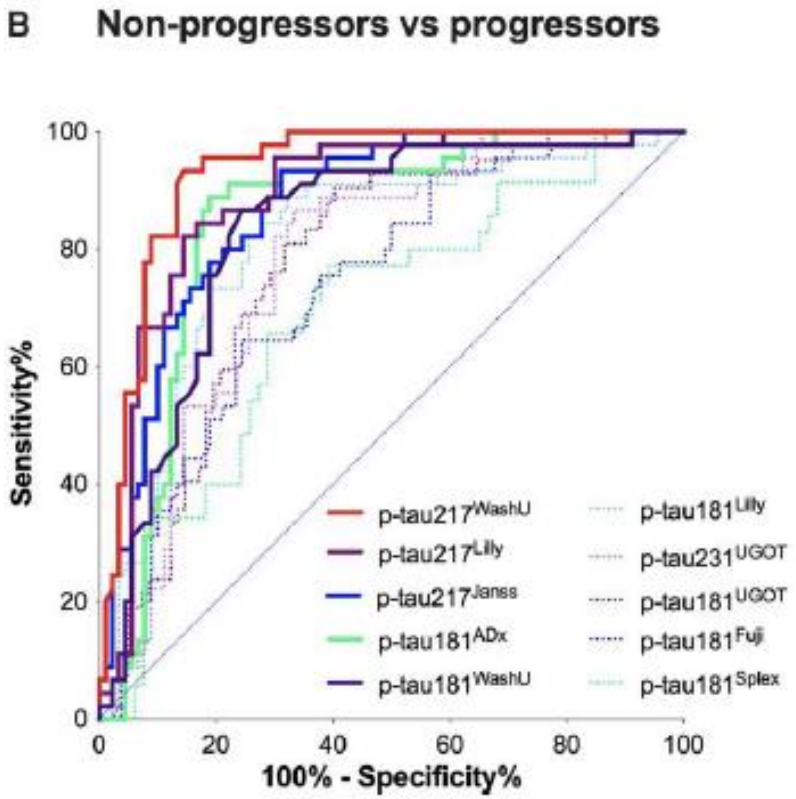
Comparison of 10 plasma p-tau biomarkers



P-tau217 WashU: Mass spectrometry
P-tau217 Lilly: Mass spectrometry
P-tau217 Janss: SIMOA
P-tau181 ADx: SIMOA
P-tau181 WashU: Mass spectrometry
P-tau231 UGot: SIMOA
P-tau181 Lilly: Mass spectrometry
P-tau181 UGot: SIMOA
P-tau181 Fuji: Lumipulse immunoassay
P-tau181 Splex: Splex immunoassay

(Janelidze S et al., *Brain*, 2023)

Comparison of 10 plasma p-tau biomarkers



P-tau217 WashU: Mass spectrometry
P-tau217 Lilly: Mass spectrometry
P-tau217 Janss: SIMOA
P-tau181 ADx: SIMOA
P-tau181 WashU: Mass spectrometry
P-tau231 UGot: SIMOA
P-tau181 Lilly: Mass spectrometry
P-tau181 UGot: SIMOA
P-tau181 Fuji: Lumipulse immunoassay
P-tau181 Splex: Splex immunoassay

(Janelidze S et al., *Brain*, 2023)

Recommendations for blood biomarkers

- Blood biomarkers recommended for screening in clinical trials or specialized memory clinics, but need to be confirmed by PET or CSF biomarkers whenever possible

- Additional studies required to establish best plasma biomarker combinations vs PET or CSF biomarker
- Additional studies required to examine potential confounders, such as peripheral neuropathies, BMI, kidney disease etc.
- Need more real-world studies in diverse and representative populations

Core biomarkers per AT(N) framework

A: Amyloid

CSF Aβ42 or Aβ42/Aβ40 ratio (Elecsys®, Lumipulse®)

Amyloid PET (Amyvid™, Neuraceq™, and Vizamyl™)

T: Tau

CSF phopho-tau181 (Elecsys®, Lumipulse®)

CSF PET (flortaucipir)

N: Neurodegeneration or neuronal injury

CSF total tau (Elecsys®, Lumipulse®)

Anatomic MRI

FDG PET

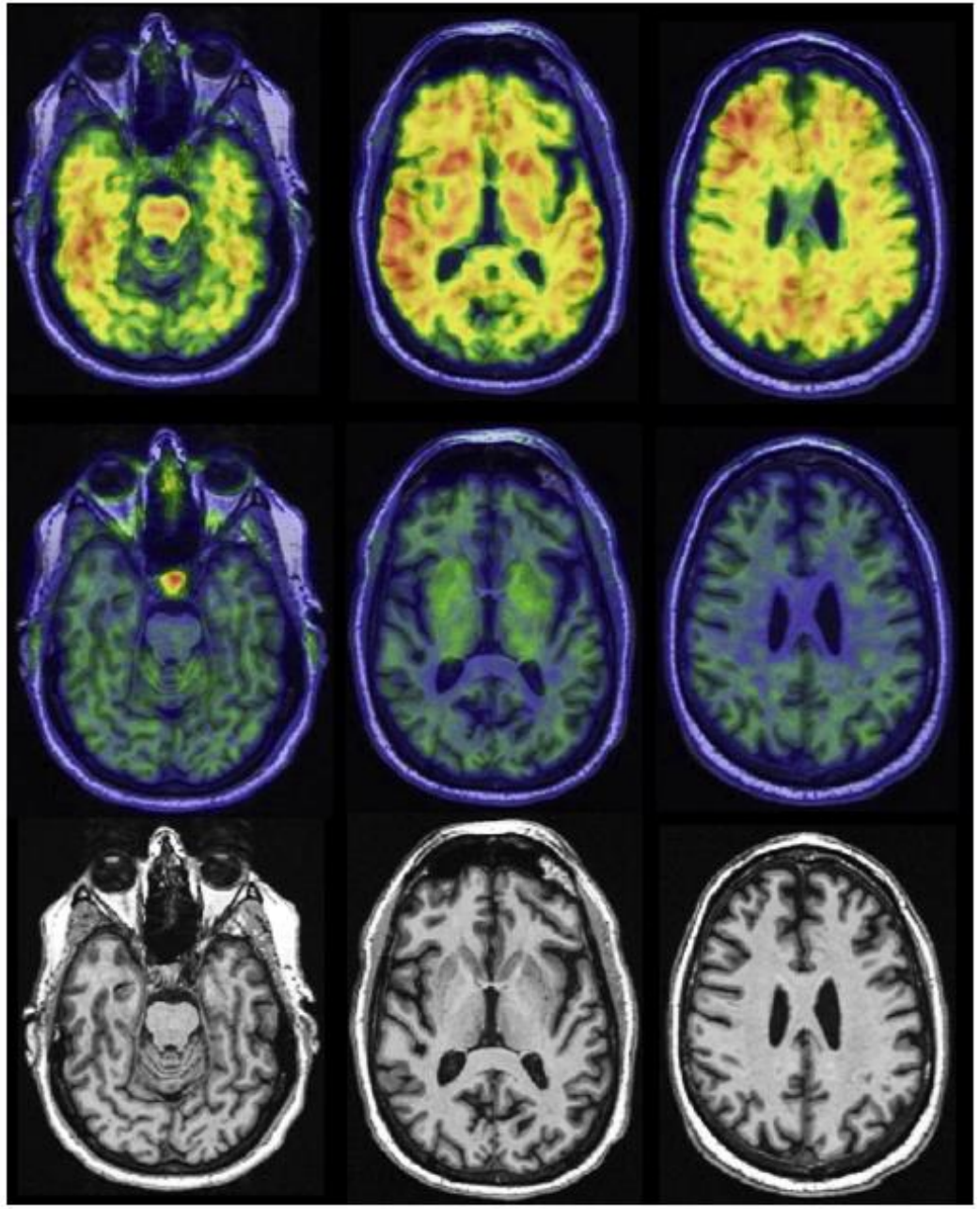
Poll question #2

A cognitively normal 65-year-old man shows abnormal amyloid PET, normal CSF p-tau181, and normal CSF t-tau. What is your diagnosis?

Amyloid PET

Tau PET

MRI



- **Abnormal amyloid PET**
- **Normal tau PET**
- **No atrophy on MRI**
- **A+T-(N)- → Alzheimer's pathologic change**

(Modfied from Jack CR et al., *Alz Dement*, 2018)

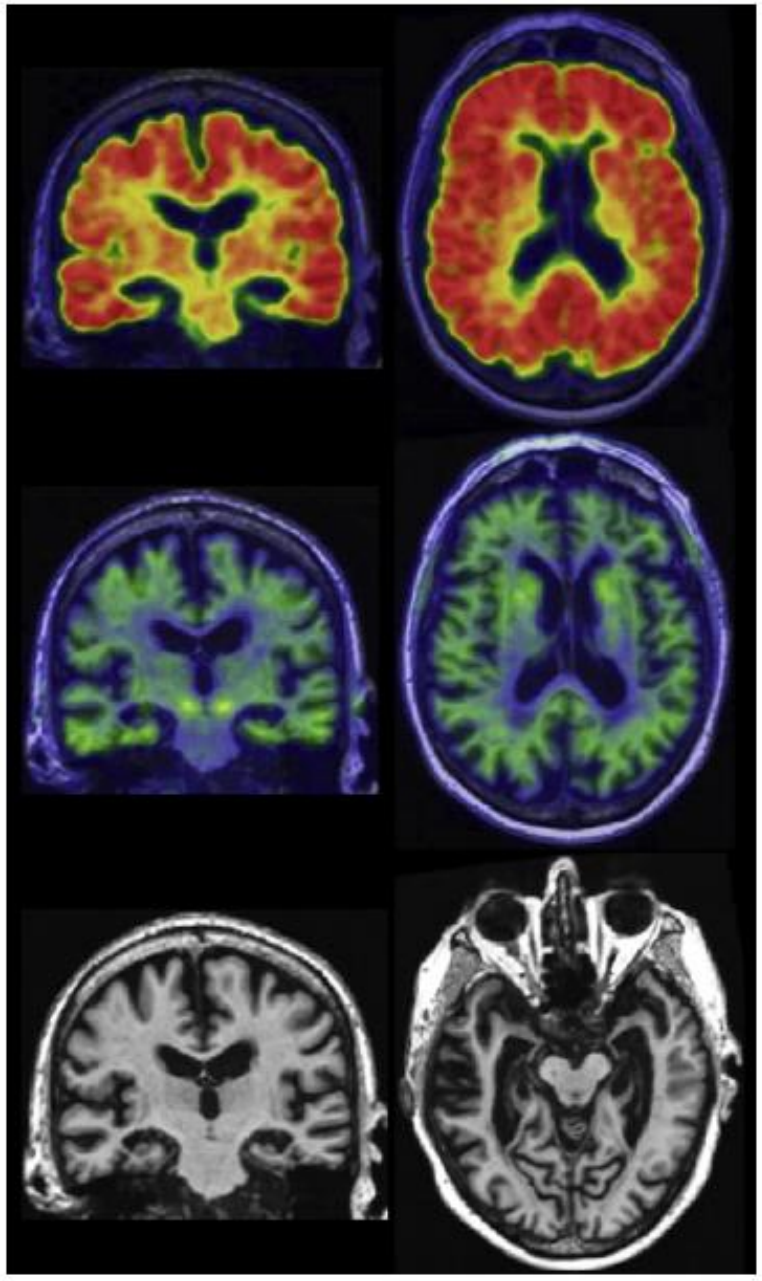
Poll question #3

A 91-year-old woman with severe amnestic dementia shows low CSF Aβ42/40 ratio, normal CSF p-tau181, and severe medial temporal lobe atrophy on anatomical MRI. What is your diagnosis?

Amyloid PET

Tau PET

MRI



- **Abnormal amyloid PET**
- **Normal tau PET**
- **Atrophy on MRI**
- **A+T-(N)+ → Alzheimer's with concomitant non-Alzheimer's pathologic change eg. LATE**

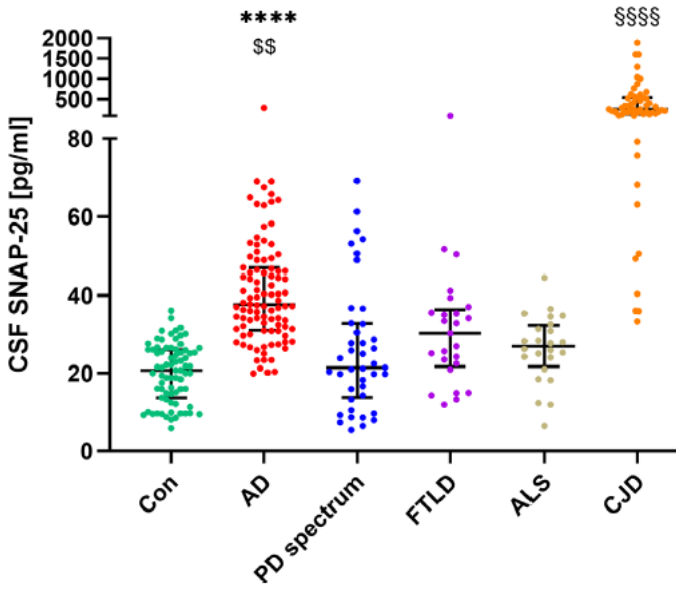
(Modfied from Jack CR et al., *Alz Dement*, 2018)

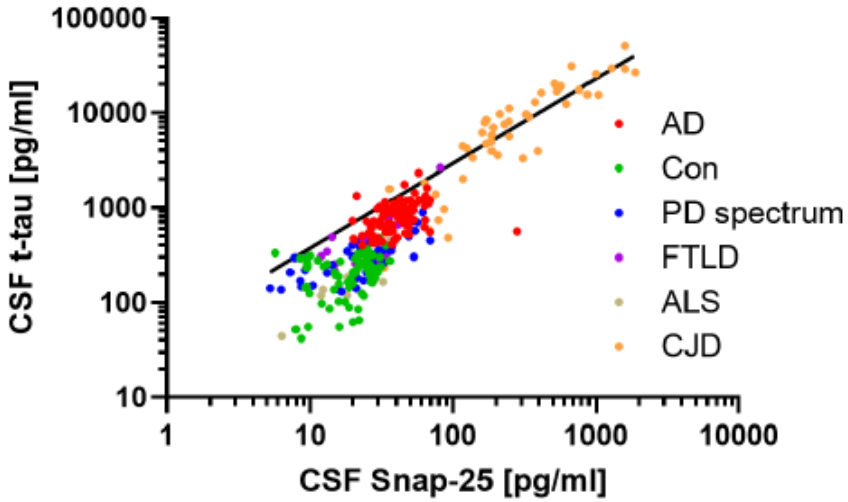
Poll question #4

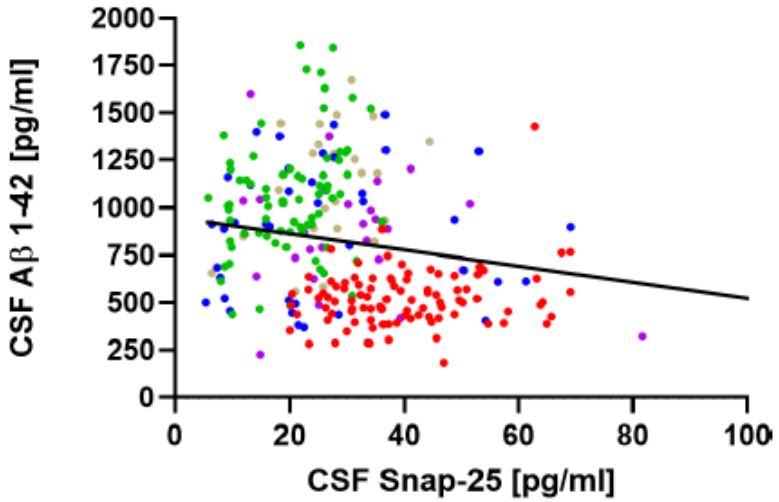
Which of the following are not considered core AD biomarkers?

Other biomarkers: synapse loss

SNAP-25 is a member of the SNARE proteins important for fusion of synaptic vesicles to the presynaptic membrane

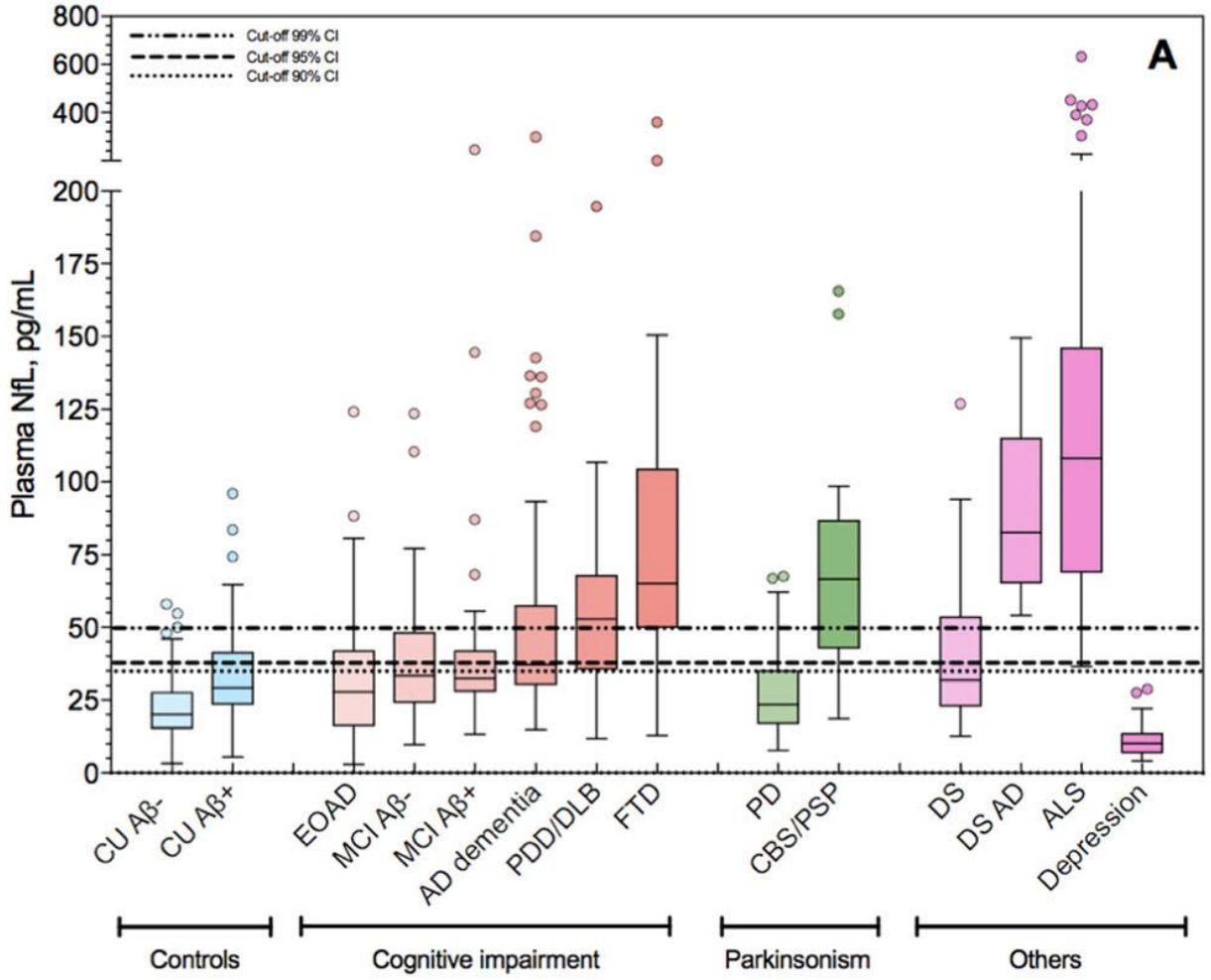






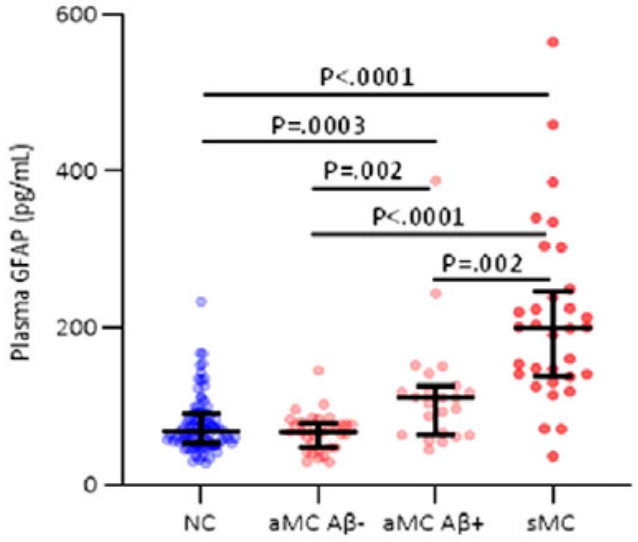
(Halgebeuer S et al., *J Neurol Neurosurg*, 2022)

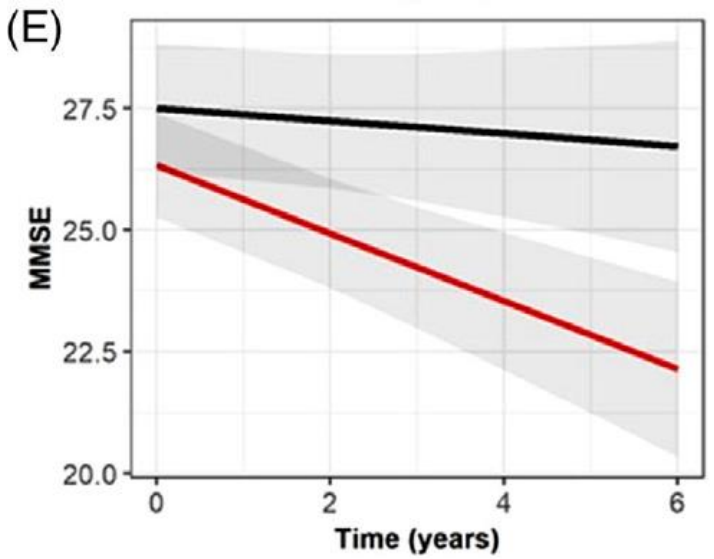
Other biomarkers: neuronal injury

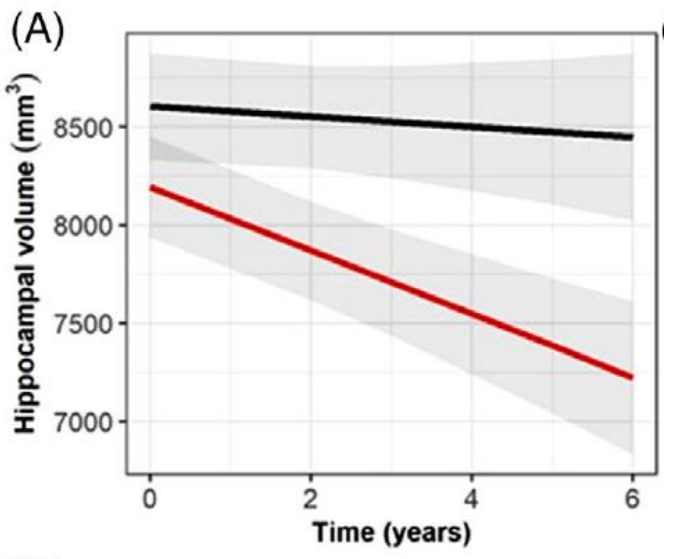


(Ashton NJ et al., *Nat Comm*, 2021)

Other biomarkers: neuroinflammation

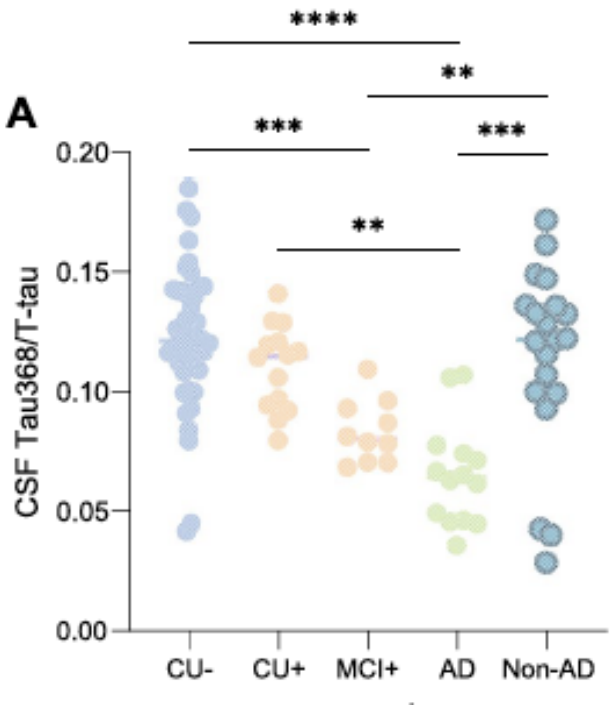




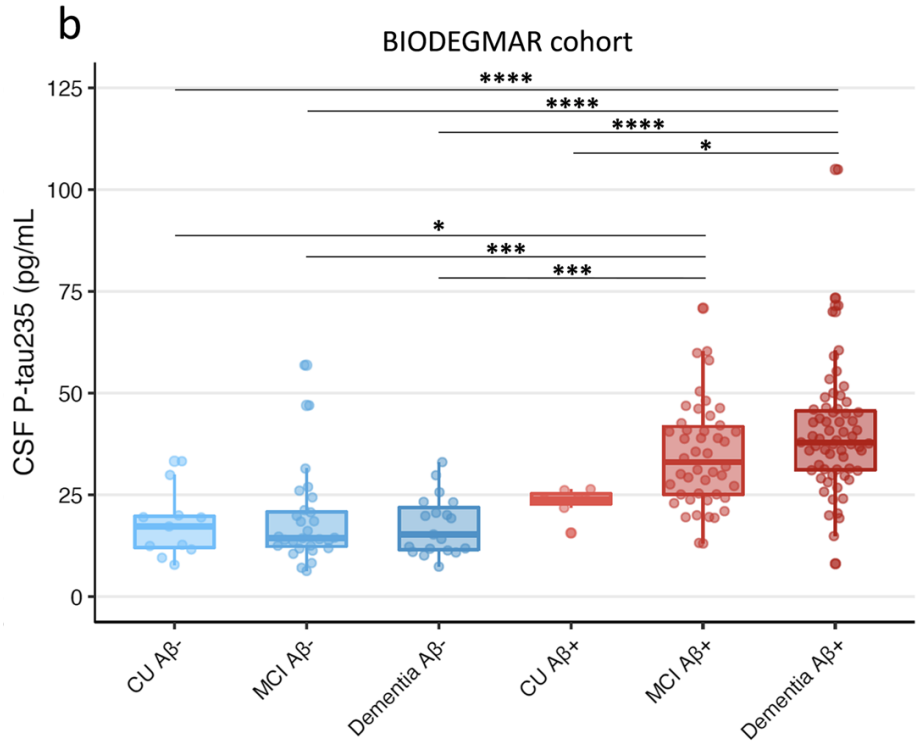


(Chatterjee P et al., *Alzheimers Dement*, 2022)

Ongoing search for better tau biomarkers

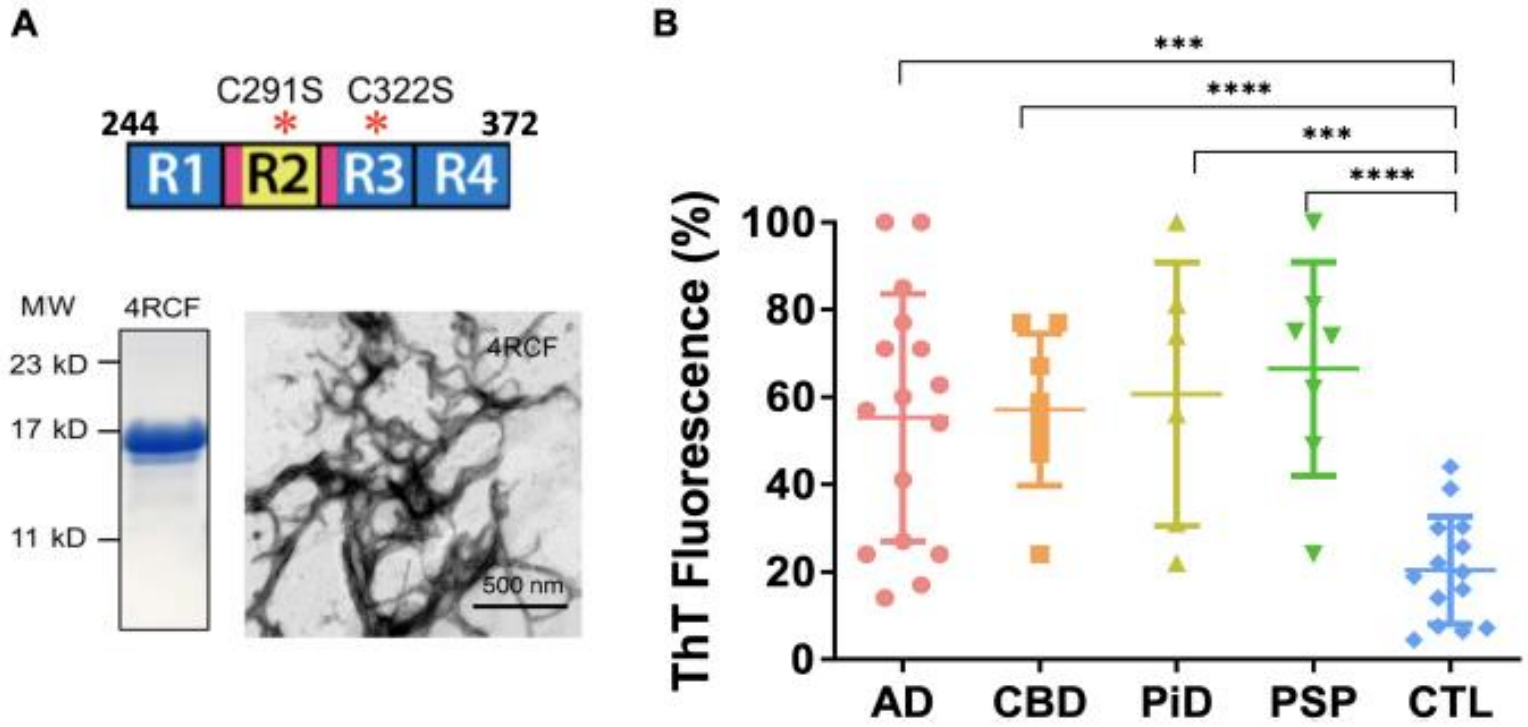


(Simren J et al., *Alzheimers Res Ther*, 2022)

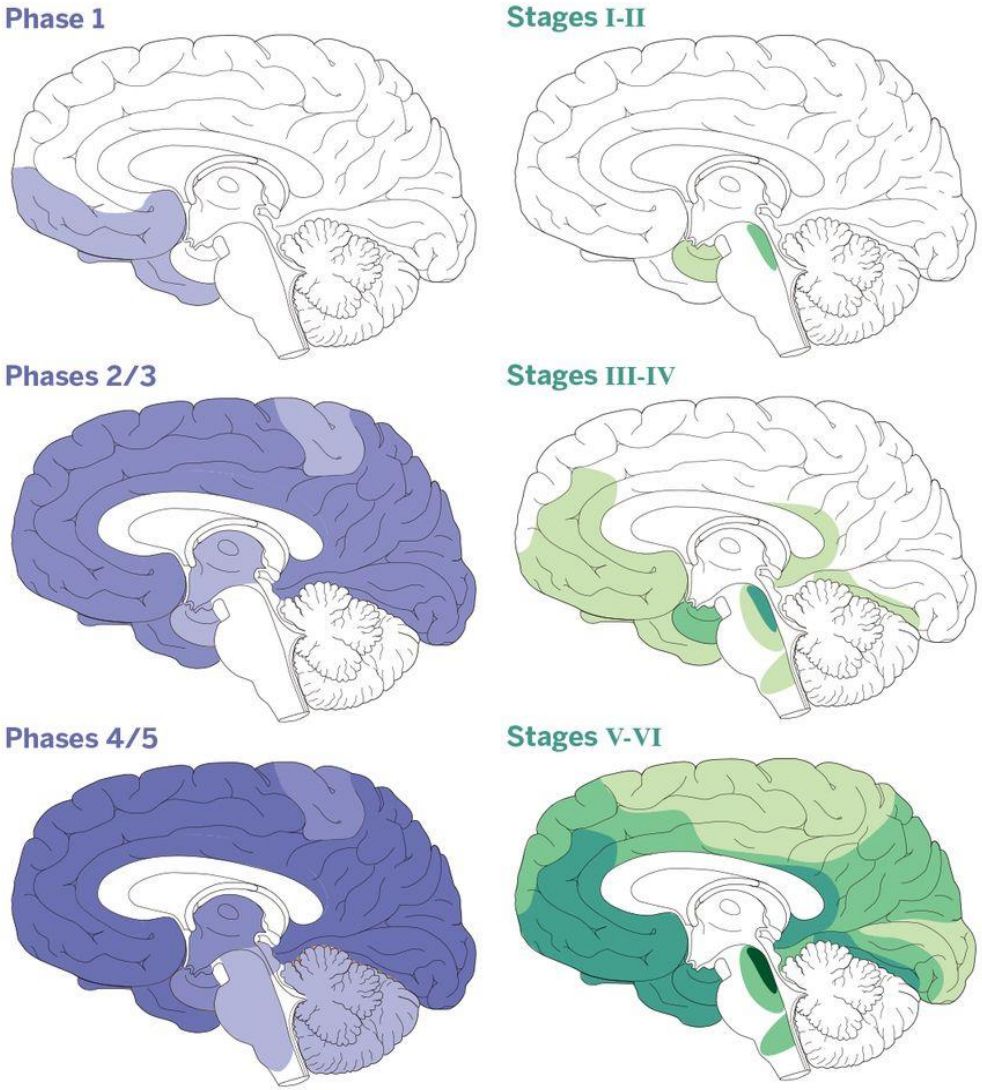


(Lantero-Rodriguez J et al., *Alzheimers Res Ther*, 2022)

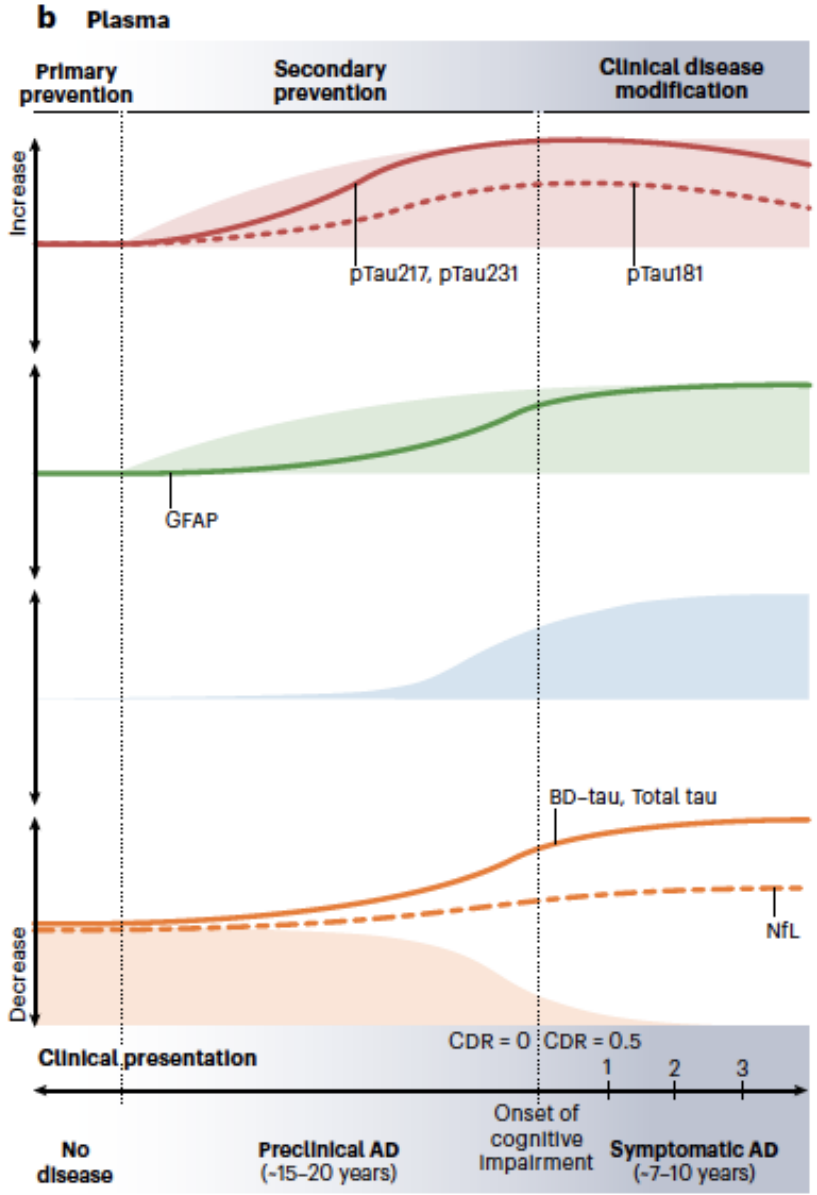
Other ultrasensitive detection methods: RT-QuIC



(Wu L et al., *Frontiers Ageing Neurosci*, 2022)



Plaques **NFT**



(Wade and Holtzman., *Nat Med*, 2023)

Future challenge: mixed pathology of dementia

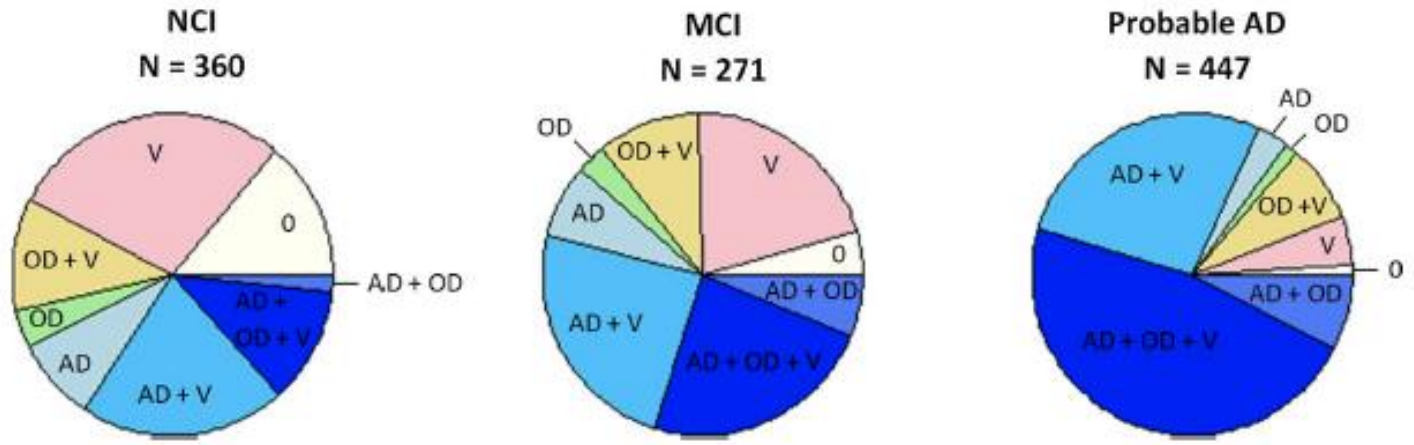


Table 2 Prevalence of mixed pathologies in ROS/MAP

Pathology	Clinical diagnosis		
	No cognitive impairment ($n = 360$)	Mild cognitive impairment ($n = 271$)	Probable AD ($n = 447$)
No vascular* or other degenerative**	50 (13.89%)	12 (4.43%)	4 (0.89%)
Vascular only	102 (28.33%)	57 (21.03%)	22 (4.92%)
Other degenerative only (no AD)	14 (3.89%)	8 (2.95%)	6 (1.34%)
Other degenerative (no AD) + vascular	41 (11.39%)	28 (10.33%)	35 (7.83%)
AD only	30 (8.33%)	20 (7.38%)	14 (3.13%)
AD + vascular	75 (20.83%)	65 (23.99%)	122 (27.29%)
AD + other degenerative	6 (1.67%)	17 (6.27%)	34 (7.61%)
AD + other degenerative + vascular	42 (11.67%)	64 (23.62%)	210 (46.98%)

(Kapasi et al., *Acta Neuropathol,* 2017)

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