Blood-Based Biomarkers for Alzheimer's Disease and Related Disorders' Neuropathology in Clinical Research and Clinical Practice

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Disclosures

I have the following relevant financial relationships to disclose:

Consulting/Advisory Boards

Allyx Therapeutics, Inc.
BioVie
Bob's Last Marathon
Foster & Eldredge
Jocasta Neuroscience
Merck
ProSelect Insur Co
Quince Therapeutics / Cortexyme, Inc. (DSMB)
Sage Therapeutics, Inc.
Sanofi
Vandria

AANP

Learning Objectives

At the end of this activity, learners should be able to:

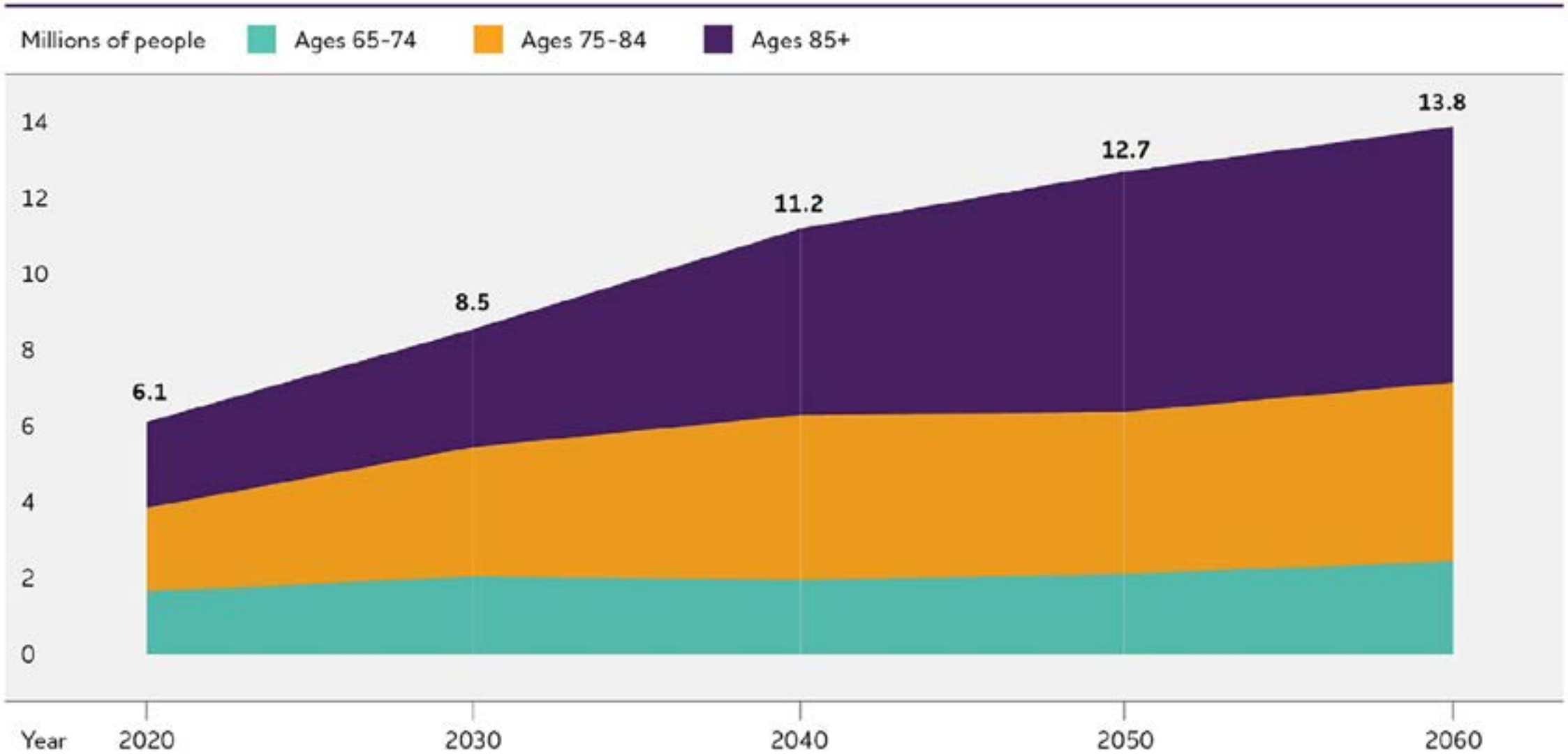
1. Describe the development and validation of blood-based biomarkers for detecting amyloid, tau and associated neurodegenerative pathology in the brain.

2. Discuss how Alzheimer's disease blood-based biomarkers may be useful in diagnosis, prognosis, staging and tracking of disease progression or treatment response.

3. Describe the potential (and limitations) of blood-based biomarkers to provide mechanistic insights into Alzheimer's disease and related neurodegenerative dementias.

AANP

Alzheimer's Disease Prevalence in US



Alzheimer's Association, 2024 Alzheimer's disease facts and figures, Alz Demen'24

Diagnosis of Alzheimer's Disease c.1984 - 2024

Table 1. Criteria for clinical diagnosis of Alzheimer's disease

I. The criteria for the clinical diagnosis of PROBABLE Alzheimer's disease include:

dementia established by clinical examination and documented by the Mini-Mental Test,[1] Blessed Dementia Scale,[2] or some similar examination, and confirmed by neuropsychological tests;

deficits in two or more areas of cognition;

progressive worsening of memory and other cognitive functions;

no disturbance of consciousness;

onset between ages 40 and 90, most often after age 65; and

absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.

II. The diagnosis of PROBABLE Alzheimer's disease is supported by:

progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia);

impaired activities of daily living and altered patterns of behavior;

family history of similar disorders, particularly if confirmed neuropathologically; and

laboratory results of:

normal lumbar puncture as evaluated by standard techniques,

normal pattern or nonspecific changes in EEG, such as increased slow-wave activity, and

evidence of cerebral atrophy on CT with progression documented by serial observation.

III. Other clinical features consistent with the diagnosis of PROBABLE Alzheimer's disease, after exclusion of causes of dementia other than Alzheimer's disease, include:

plateaus in the course of progression of the illness;

associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physical outbursts, sexual disorders, and weight loss;

other neurologic abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder;

seizures in advanced disease; and

CT normal for age.

IV. Features that make the diagnosis of PROBABLE Alzheimer's disease uncertain or unlikely include:

sudden, apoplectic onset;

focal neurologic findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness; and

seizures or gait disturbances at the onset or very early in the course of the illness.

V. Clinical diagnosis of POSSIBLE Alzheimer's disease:

may be made on the basis of the dementia syndrome, in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, in the presentation, or in the clinical course;

may be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be *the* cause of the dementia; and

should be used in research studies when a single, gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.

VI. Criteria for diagnosis of DEFINITE Alzheimer's disease are:

the clinical criteria for probable Alzheimer's disease and

histopathologic evidence obtained from a biopsy or autopsy.

VII. Classification of Alzheimer's disease for research purposes should specify features that may differentiate subtypes of the disorder, such as:

familial occurrence;

onset before age of 65;

presence of trisomy-21; and

coexistence of other relevant conditions such as Parkinson's disease.

McKhann et al., Neurology, 1984

Alzheimer's Dement. 2024;20:5143–5169.
RESEARCH ARTICLE

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup

Clifford R. Jack Jr.[1] | J. Scott Andrews[2] | Thomas G. Beach[3] | Teresa Buracchio[4] | Billy Dunn[5] | Ana Graf[6] | Oskar Hansson[7,8] | Carole Ho[9] | William Jagust[10] | Eric McDade[11] | Jose Luis Molinuevo[12] | Ozioma C. Okonkwo[13] | Luca Pani[14] | Michael S. Rafii[15] | Philip Scheltens[16] | Eric Siemers[17] | Heather M. Snyder[18] | Reisa Sperling[19] | Charlotte E. Teunissen[20] | Maria C. Carrillo[18]

BOX 1: Fundamental principles

It is necessary to separate syndrome (clinically identified impairment) from biology (etiology).

Alzheimer's disease (AD) is defined by its biology with the following implications.

AD is defined by its unique neuropathologic findings; therefore, detection of AD neuropathologic change by biomarkers is equivalent to diagnosing the disease.

AD exists on a continuum. The disease is first evident in vivo with the appearance of disease-specific Core biomarkers while people are asymptomatic. Pathophysiologic mech-

MEDPAGETODAY

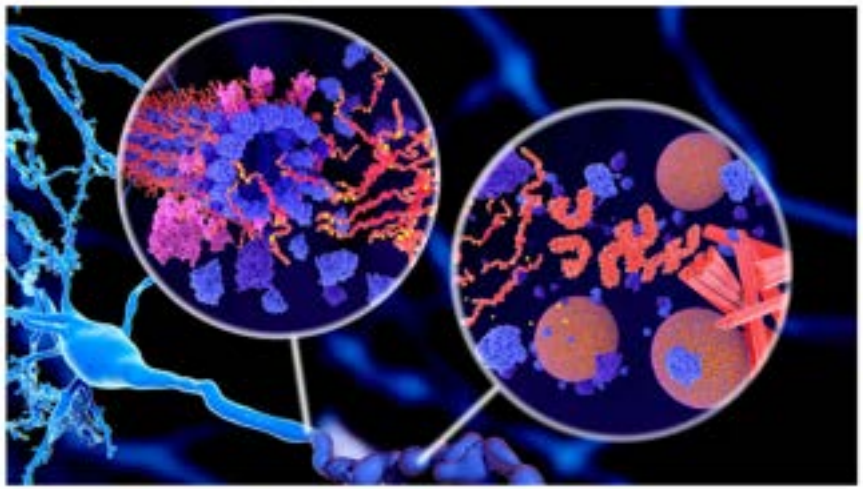
Neurology > Alzheimer's Disease

Alzheimer's Gets a New Definition

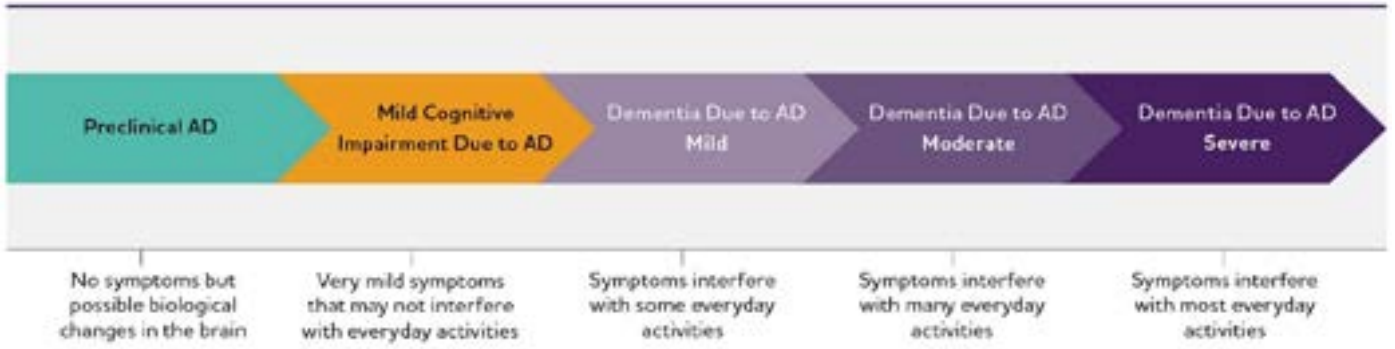
— Controversial criteria for diagnosis are based on biomarkers

by Judy George, Deputy Managing Editor, MedPage Today
July 1, 2024

Last Updated July 2, 2024



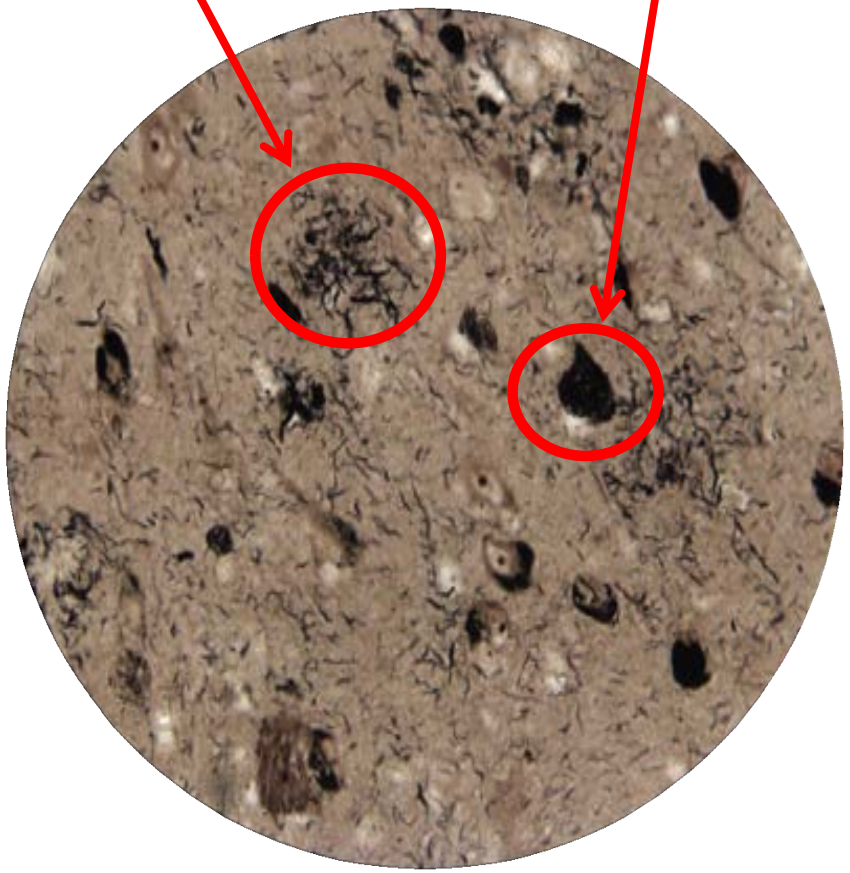
Clinical Syndromes of AD



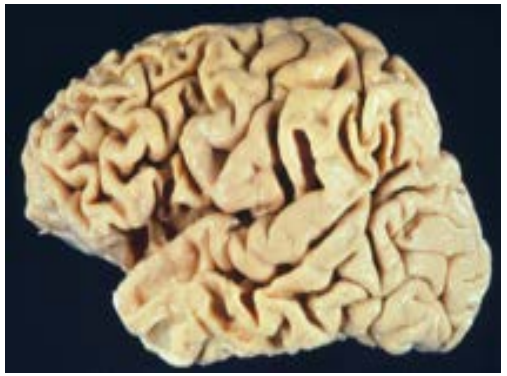
Alzheimer's Association, 2024 Alzheimer's disease facts and figures, Alz Demen'24

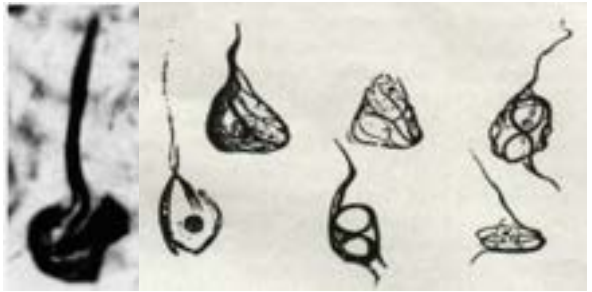
Alzheimer's Disease
"Plaques" and "Tangles"

Auguste D



Alois Alzheimer

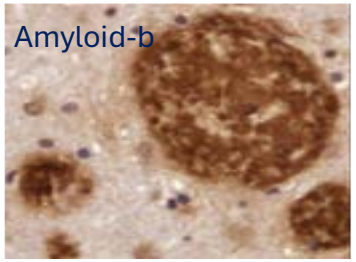


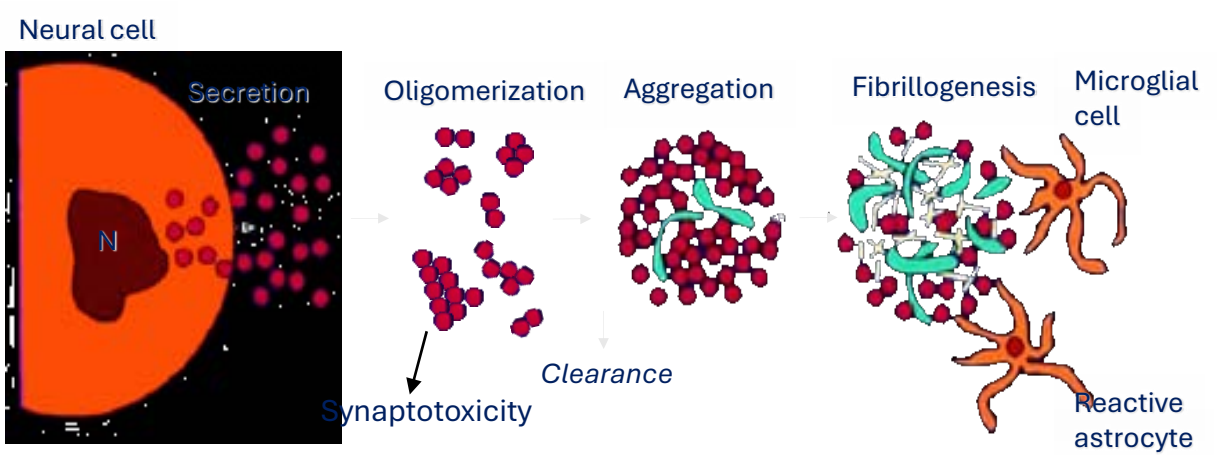


A. Alzheimer, 1911

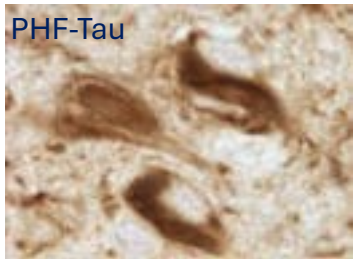
Signature Lesions of Alzheimer's Disease

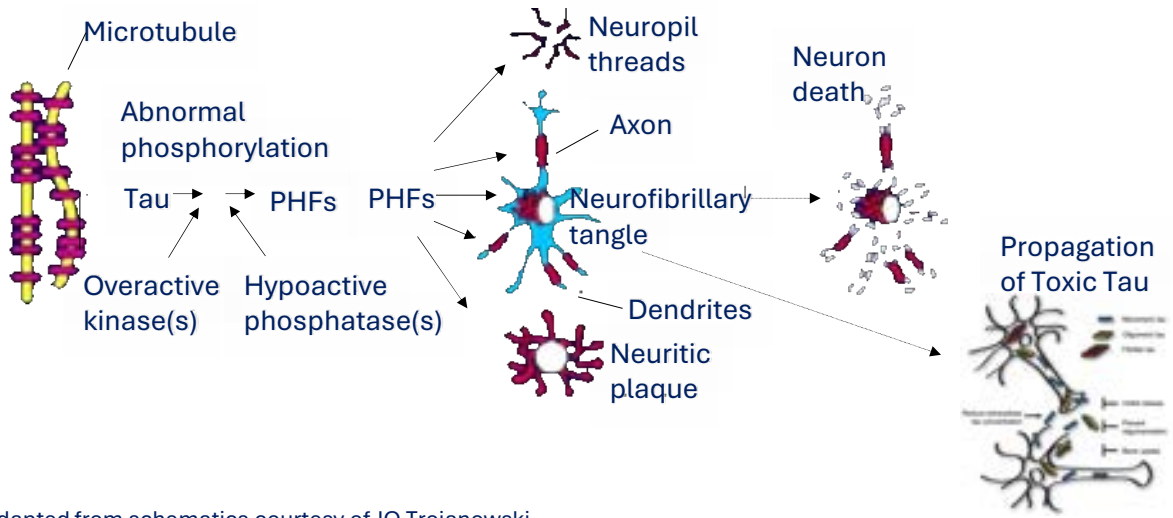
Amyloid-β Neuritic Plaques





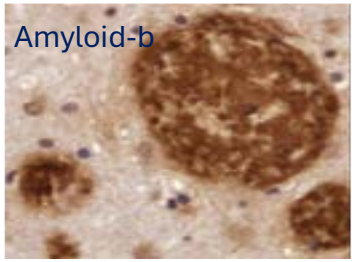
PHF-Tau Neurofibrillary Tangles



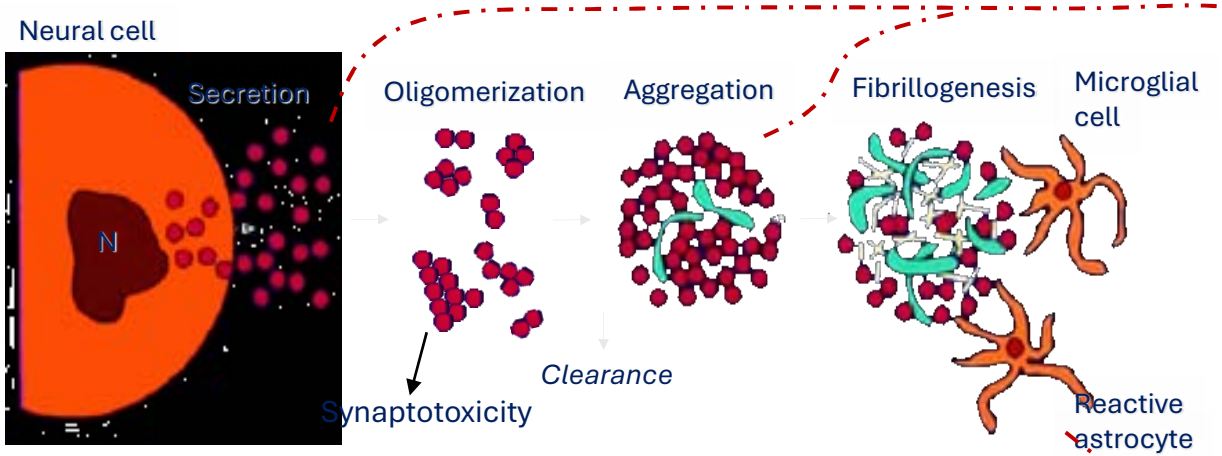


Adapted from schematics courtesy of JQ Trojanowski

Signature Lesions of Alzheimer's Disease



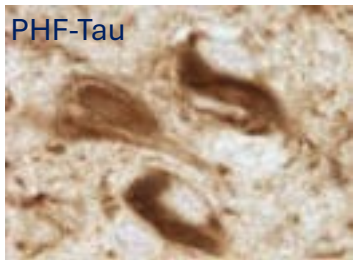
Amyloid-β Neuritic Plaques



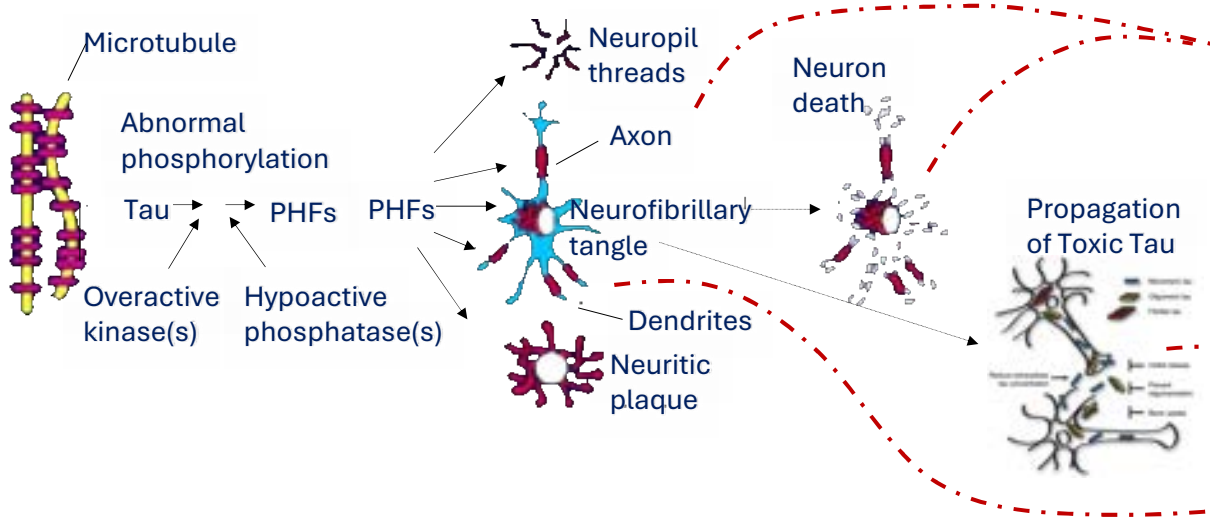
Key Blood-Based Biomarkers

Amyloid-β
$A\beta_{42}$, $A\beta_{40}$

Glial Fibrillary Acidic Protein
GFAP



PHF-Tau Neurofibrillary Tangles



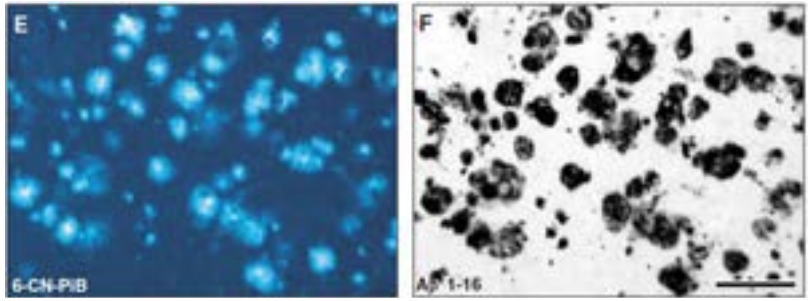
Neurofilament-light
NfL

Phospho-Tau^{217}, $^{\#\#\#}$
BD-Tau

Adapted from schematics courtesy of JQ Trojanowski

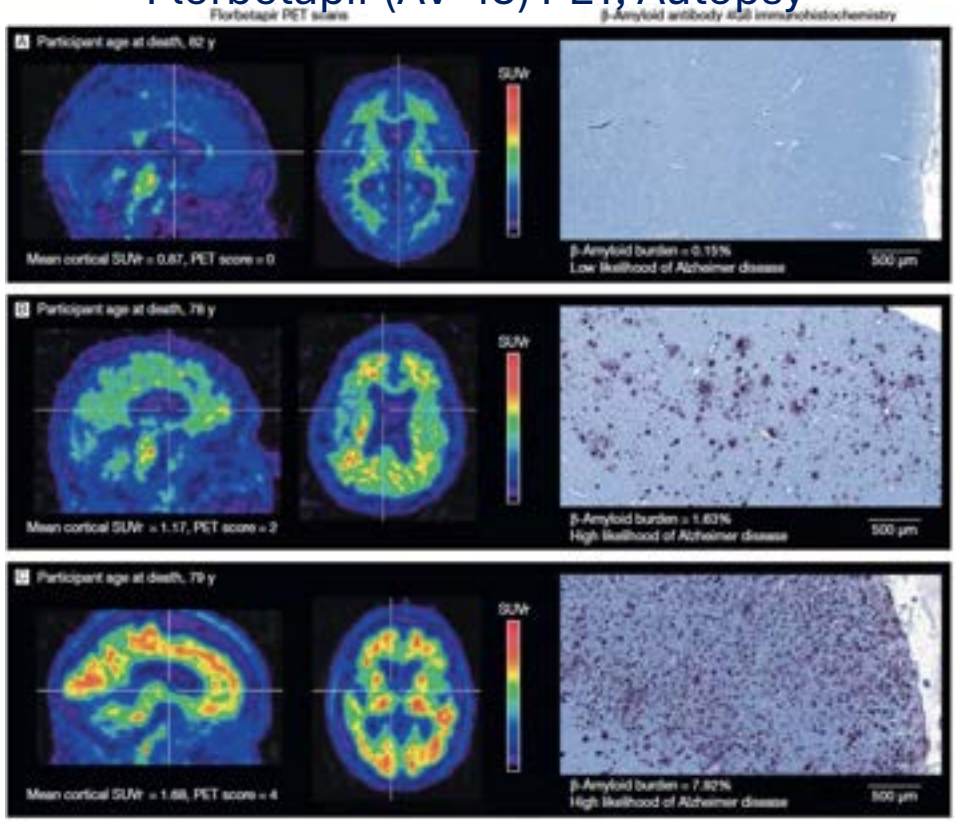
Autopsy & Amyloid-β PET

Binding of PiB to Amyloid-β Plaques



MD Ikonomovic et al., Brain'08

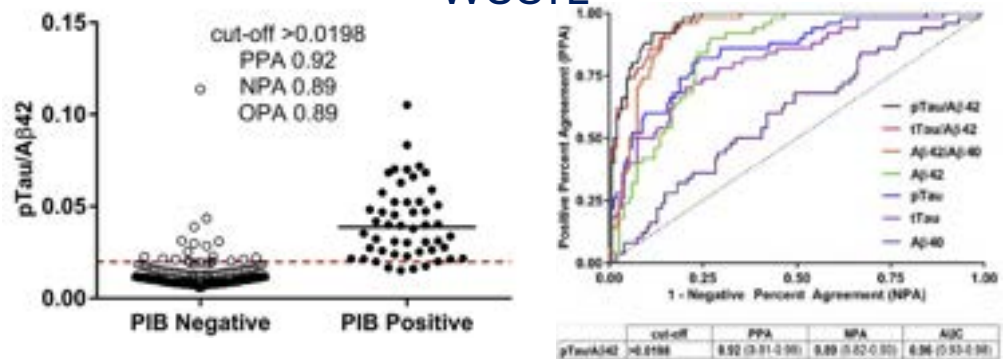
Florbetapir (AV-45) PET, Autopsy



CM Clark et al., JAMA'11

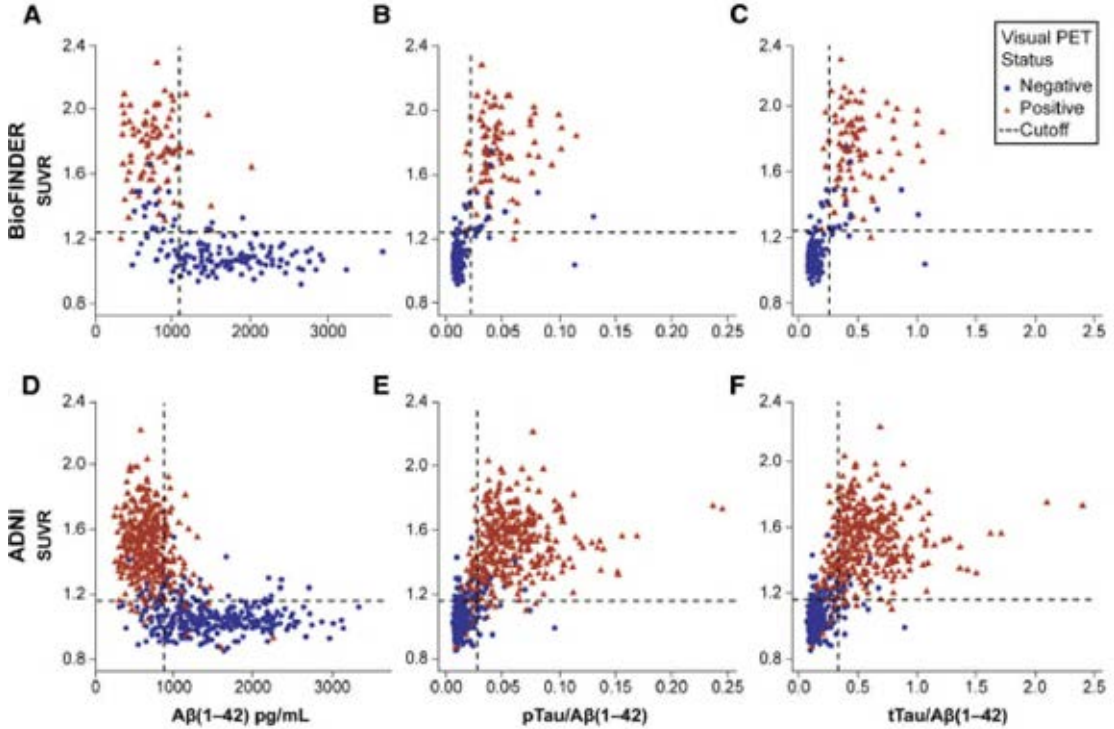
Aβ PET & CSF Aβ Concordance

WUSTL



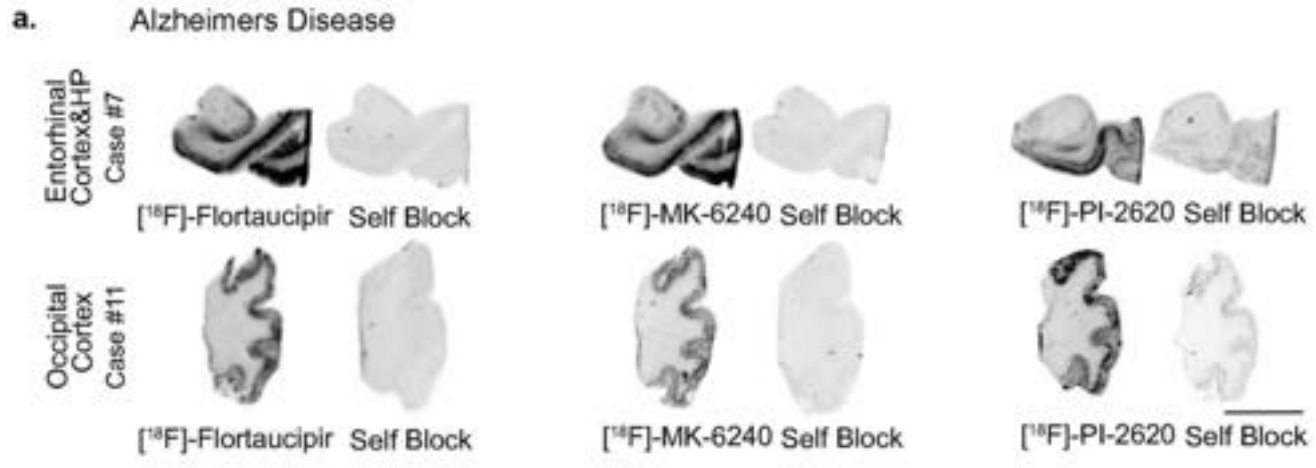
SE Schidler et al., Alz Dement'18

BiofFINDER and ADNI

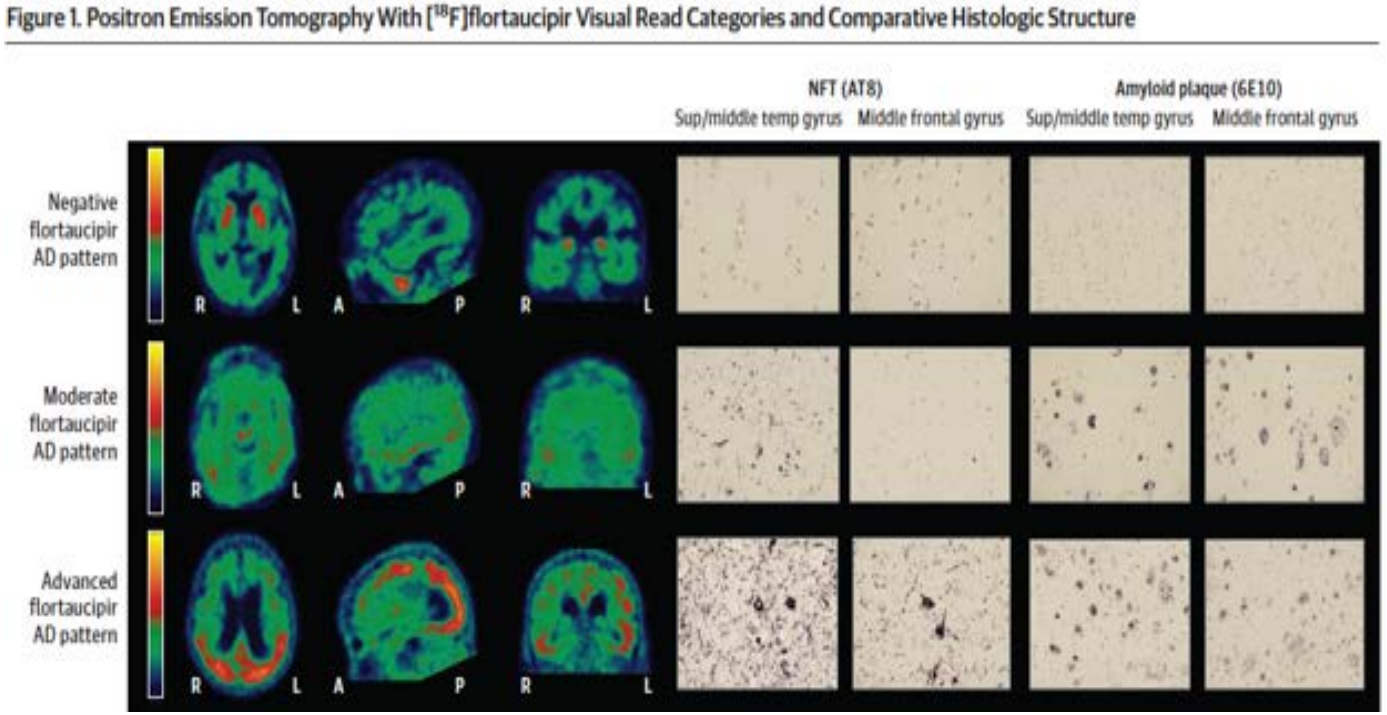


O Hansson et al. Alz Dement'18

Autopsy & Tau PET Concordance



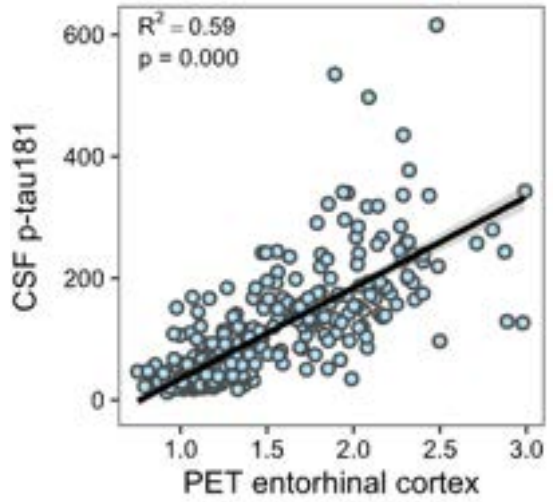
C Aguero et al, ACTA Neuropathol 2024

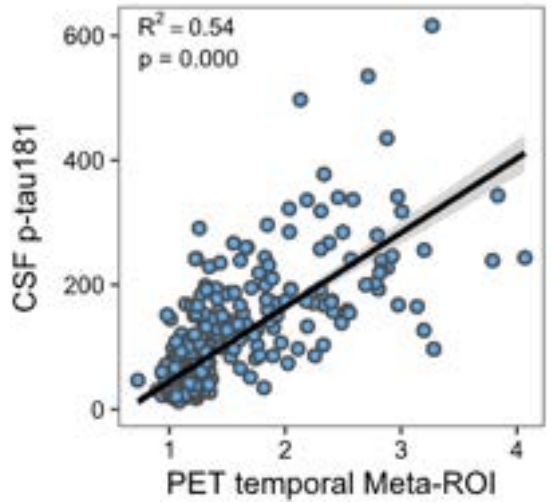


Fleisher et al. JAMA Neurology'20

Tau PET & CSF pTau^{181} Concordance

BioFINDER-2

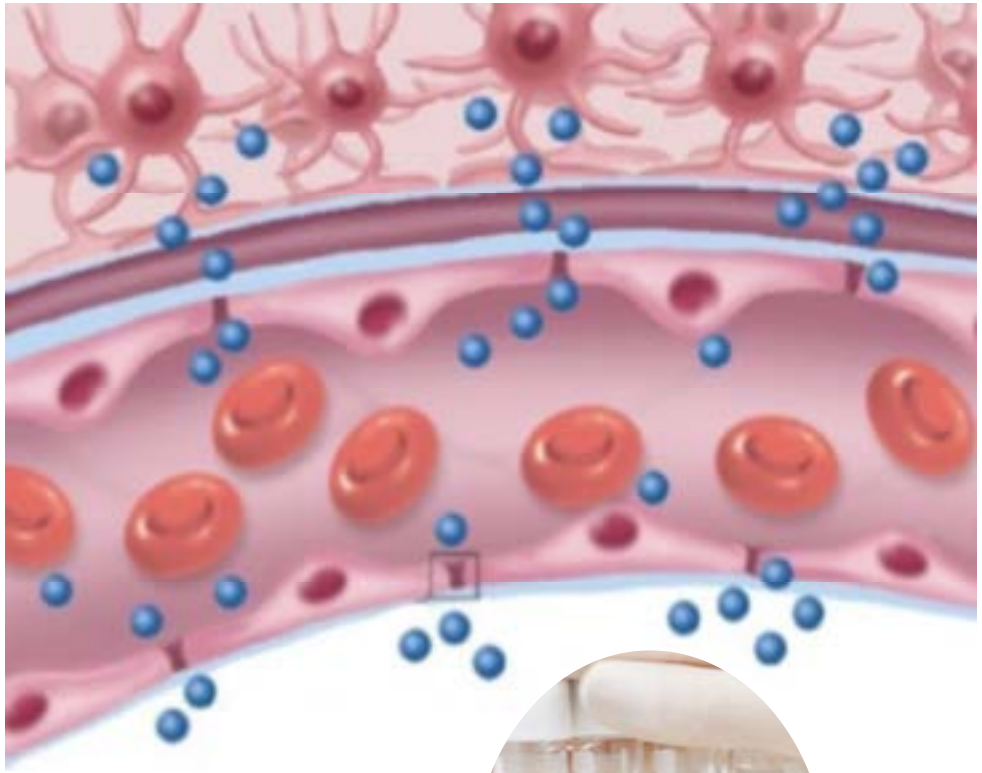




R Ossenkoppel et al., EMBO Molec Med'21

Blood-based Biomarkers of CNS Health and Disease Challenges in Analytical Chemistry

Blood Brain Barrier



adapted from Focused Ultrasound Society

$A\beta_{1-42}$ / $A\beta_{1-40}$ in AD Diagnosis

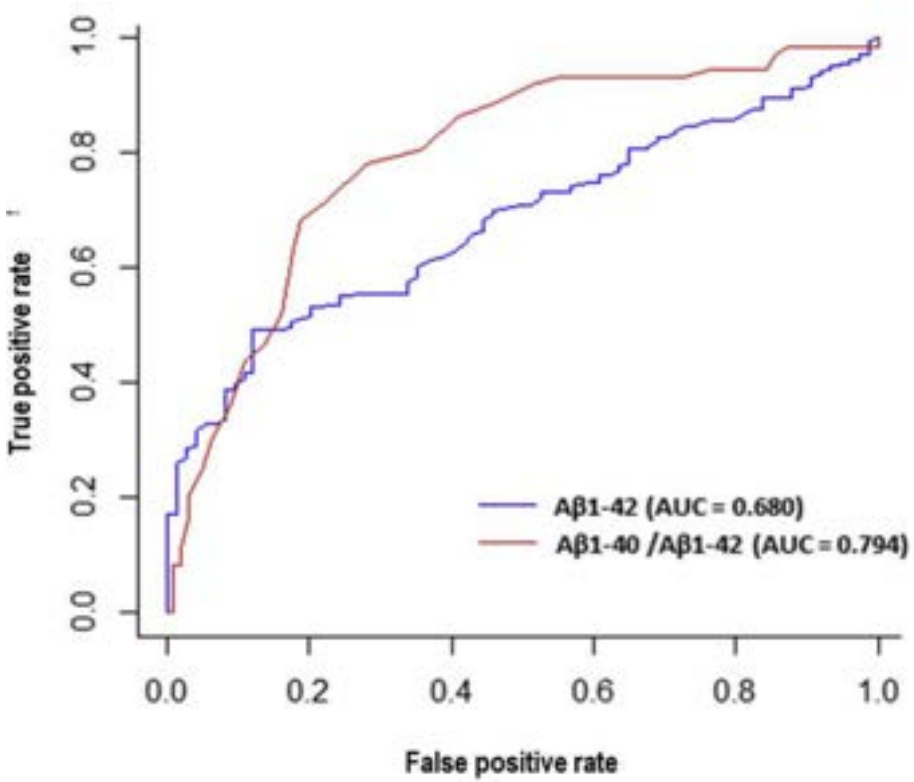
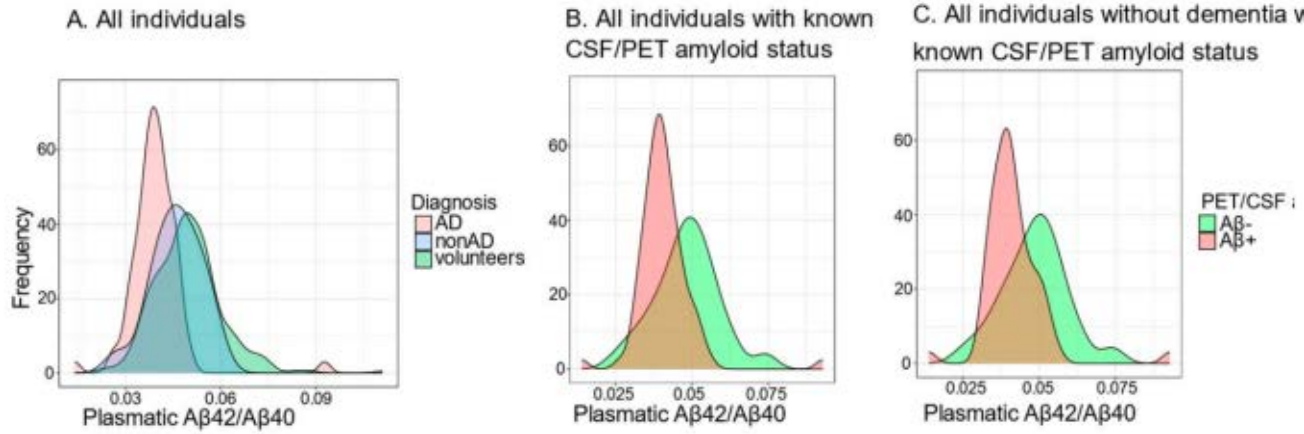


Table 1
Demographic and clinical data of subjects at timepoint 1

	Positive Aβ-PET status (N = 73)	Negative Aβ-PET status (N = 203)	Statistics (df), *P* value*
Sex (F/M)	47/27	123/80	$\chi^2 = 0.19$ (1), $P = .67$
Age (years)	77.3; SD 3.2	76.6; SD 3.4	$F = -1.5$ (275), $P = .13$
APOE ε4 (n/p)	46/27	176/27	$\chi^2 = 18.5$ (1), $P < .001$
$A\beta_{1-42}$ (pg/mL)	15.1; SD 4.0	18.4; SD 5.8	$F = 5.2$ (188, 4), $P < .001$
$A\beta_{1-40}$ (pg/mL)	295.5; SD 75.4	301.9; SD 87.8	$F = 0.5$ (274), $P = .58$
$A\beta_{1-40}/A\beta_{1-42}$	19.4; SD 3.3	16.7; SD 5.2	$F = -4.0$ (274), $P < .001$
Mean Aβ-PET SUVR	1.07; SD 0.27	0.608; SD 0.05	$F = -11.7$ (74, 8), $P < .001$



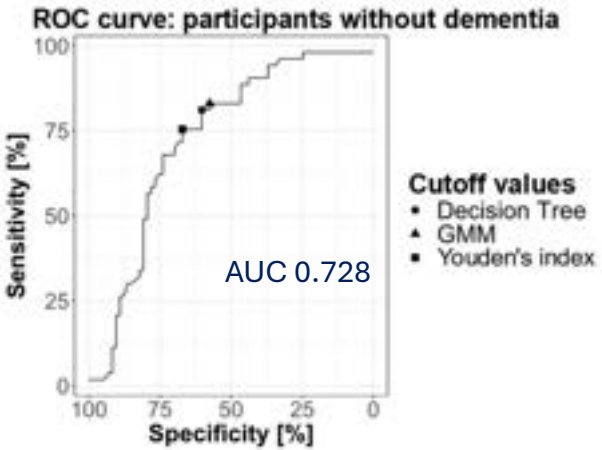


Table 2. Characteristics of all participants with confirmed amyloid status from CSF/PET analysis, and of participants without dementia with confirmed amyloid status. SD: standard deviation.

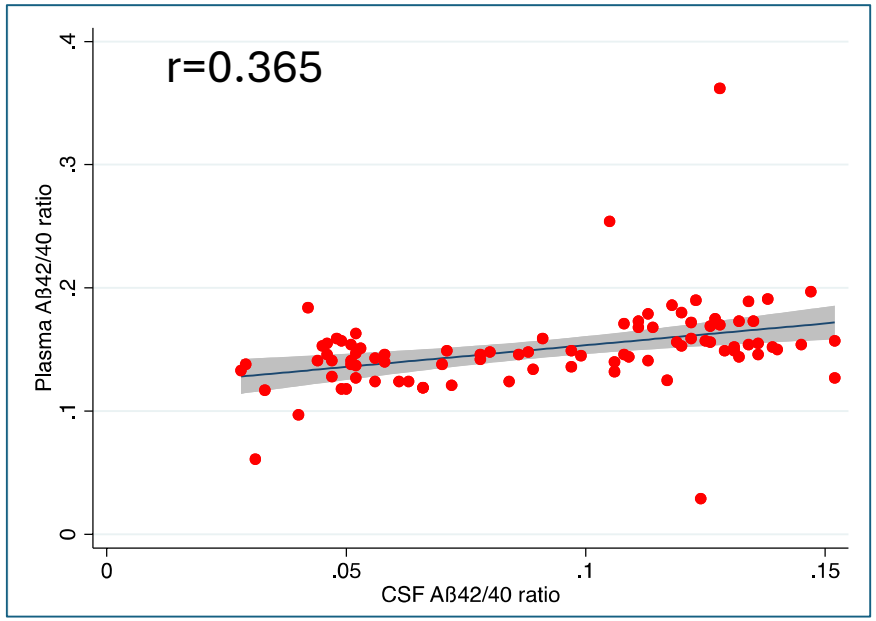
	All Participants		Non-Demented Participants	
	CSF/PET Aβ+	CSF/PET Aβ−	CSF/PET Aβ+	CSF/PET Aβ−
n	74	77	53	73
Age: mean (SD)	70.8 (8.11)	67.8 (8.67)	70.9 (7.32)	67.5 (8.63)
MMSE: mean (SD)	24.6 (4.57)	27.8 (2.15)	27.06 (1.62)	28.15 (1.54)
APOE *: n ε4− /n ε4+ (% ε4− /% ε4+)	20/47 (30%/70%)	49/23 (68%/32%)	15/36 (30%/70%)	48/21 (70%/30%)
Gender: male/female	33/41	35/42	24/29	32/41
Non-demented/ demented	53/21	73/4	–	–
Volunteers	13	53	13	53
AD patients	60	9	39	7
Non-AD patients	1	15	1	13
Measure of amyloid:				
CSF	54	24	37	21
[18F]flutemetamol PET	17	51	15	51
[11C]PIB PET	3	2	1	1

A Vergallo et al., Alz Dement'19

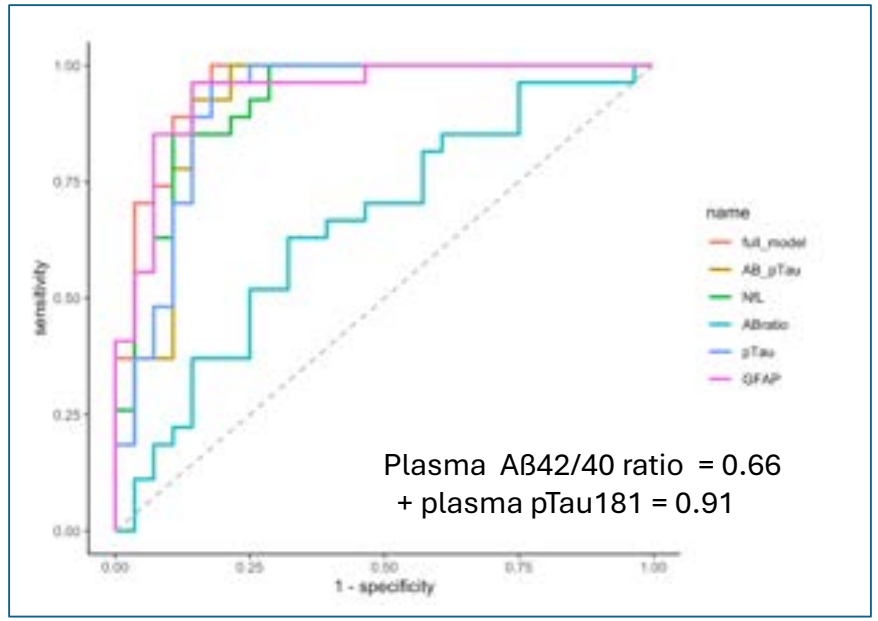
L Colmant et al Int J Mol Sci'24

Plasma Amyloid-ß42/40 ratio performance

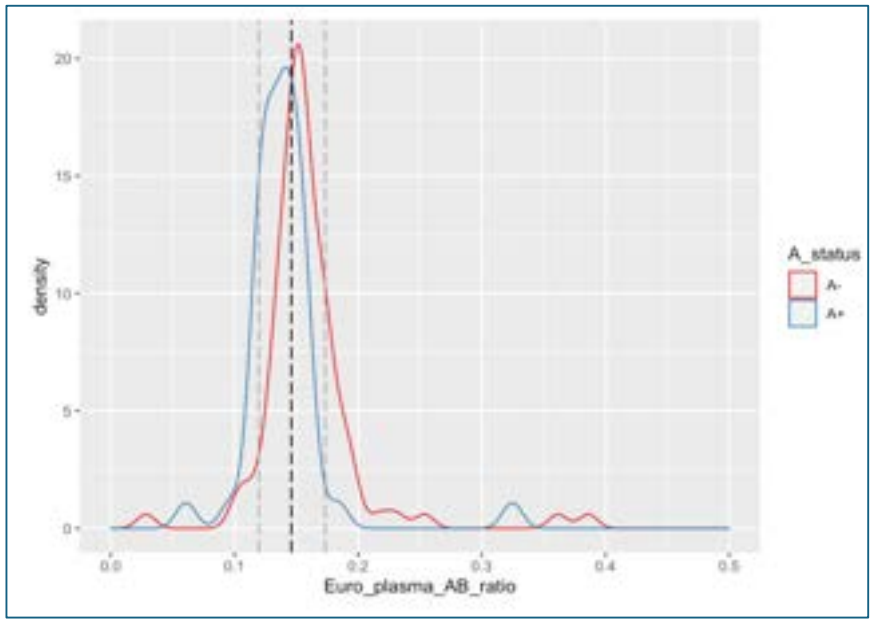
Correlation plasma and CSF Aß42/40 ratio



AUC for differentiating pos vs neg CSF Aß42/40 ratio



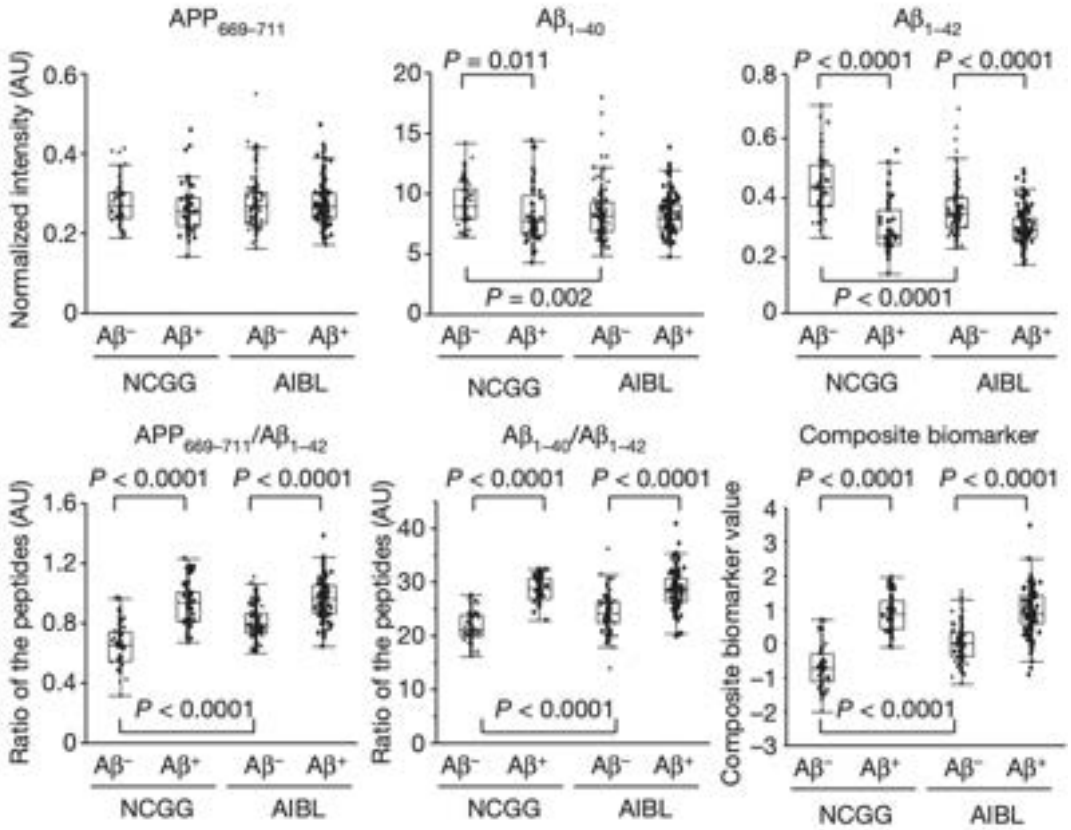
Distribution of plasma Aß42/40 ratio in CSF Aß+/- subjects



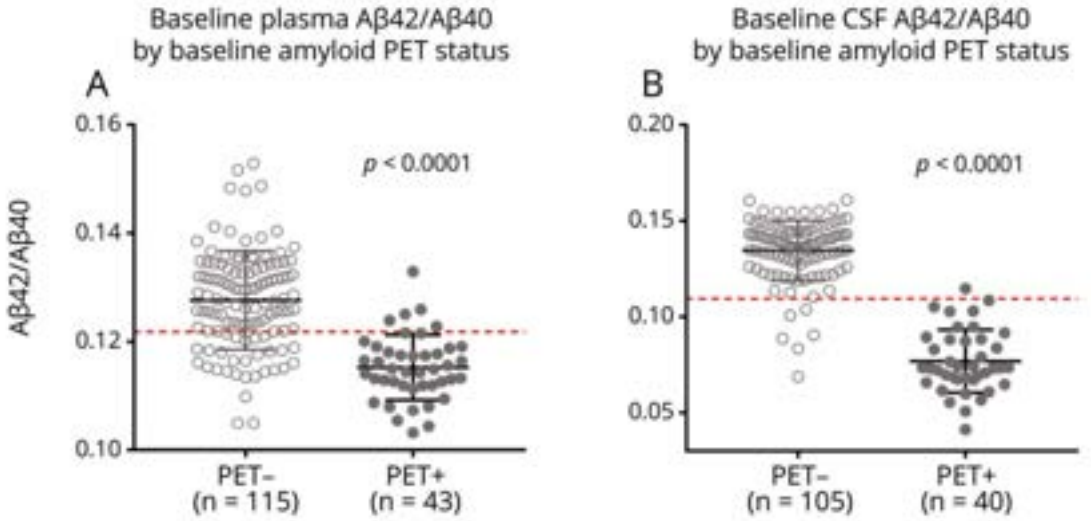
Carlyle, Kivisåkk et al, unpublished

$A\beta_{1-42}$ / $A\beta_{1-40}$ in AD Diagnosis (IP-MS)

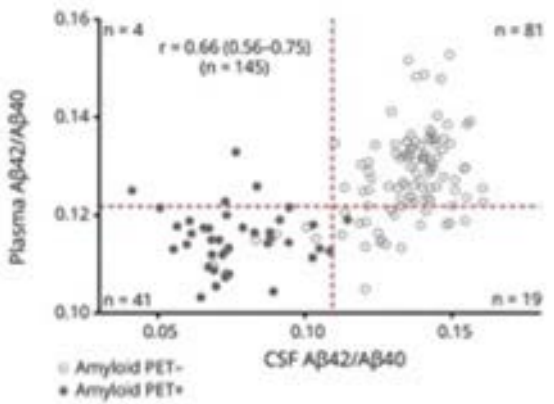
Japan NCGG, AIBL (Shimadzu)

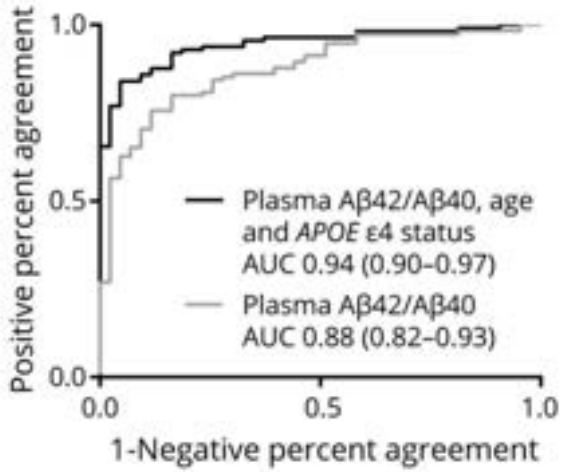


WUSTL (C2N)



Plasma – CSF Correlation





Nakamura et al., Nature '18

SE Schindler et al., Neurology'19

Reasons Mass Spectrometry Surpasses Immunoassays for Plasma Aβ42/40 Analysis

Key Limitations of Immunoassays

- Antibody Epitope Bias – Misses truncated/modified Aβ isoforms
- Matrix Interference – High background from plasma proteins
- Lower Precision – Less sensitive to small Aβ42/40 differences
- Inconsistent Ratio Calculation – High variability in low range

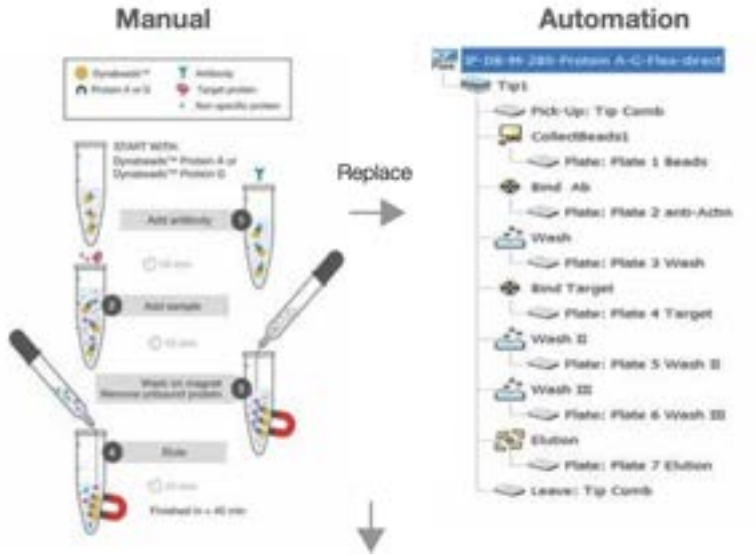
Advantages of Mass Spectrometry

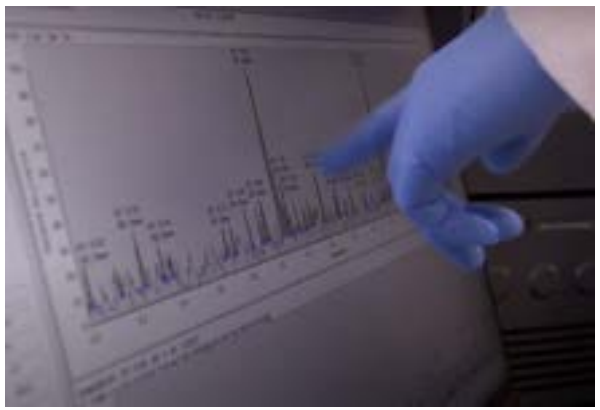
- High Specificity & Sensitivity – Detects exact Aβ isoforms
- Robust to Interference – Extracts Aβ from complex matrix
- Higher Predictive Accuracy – AUC ~0.85–0.90 vs. ~0.65–0.75
- Quantitative & Reproducible – Ideal for clinical qualification

Implication for AD Diagnostics

- Mass spec preferred for Aβ42/40 in trials & diagnostics
- Immunoassays remain useful but need strict validation

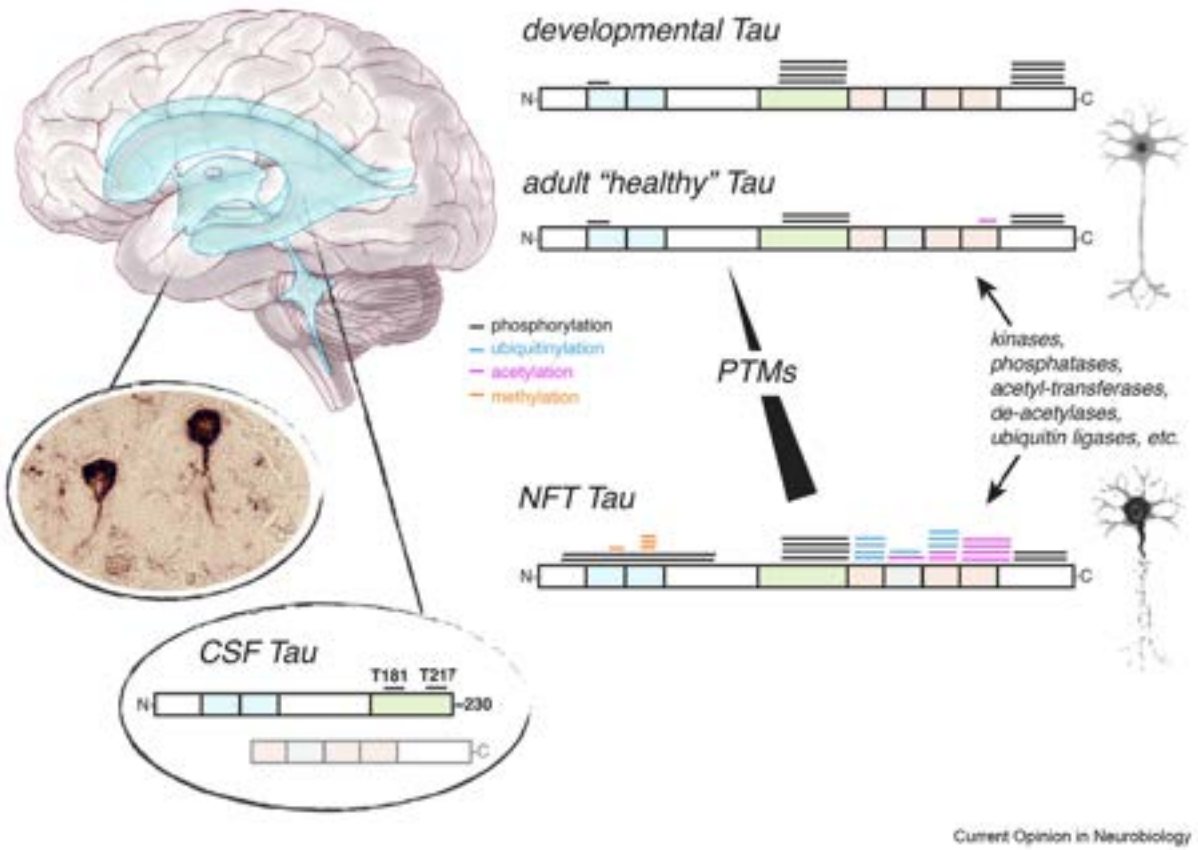
Immunoprecipitation - Mass Spectrometry

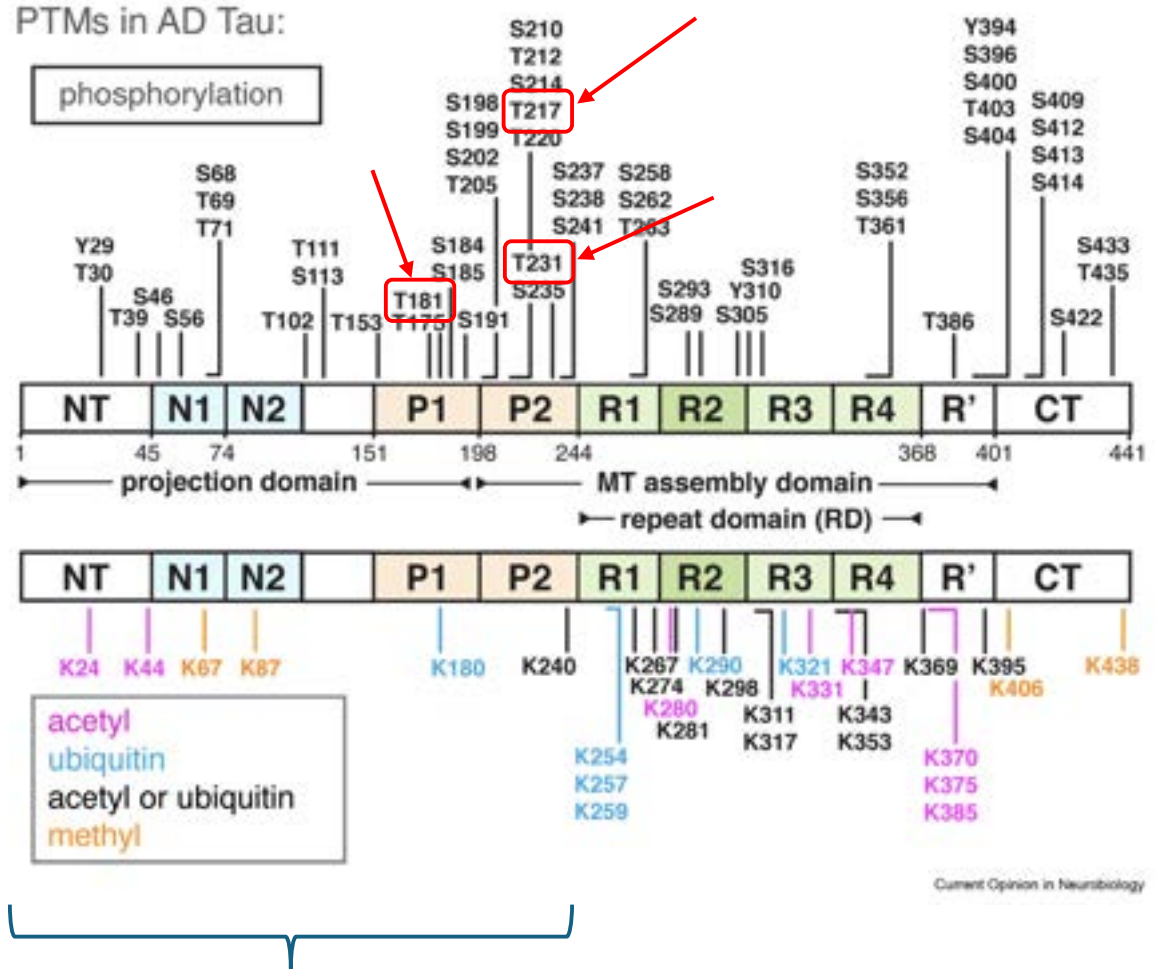




Schindler SE et al. Neurology. 2019

Tau
Post-Translational Modifications in AD

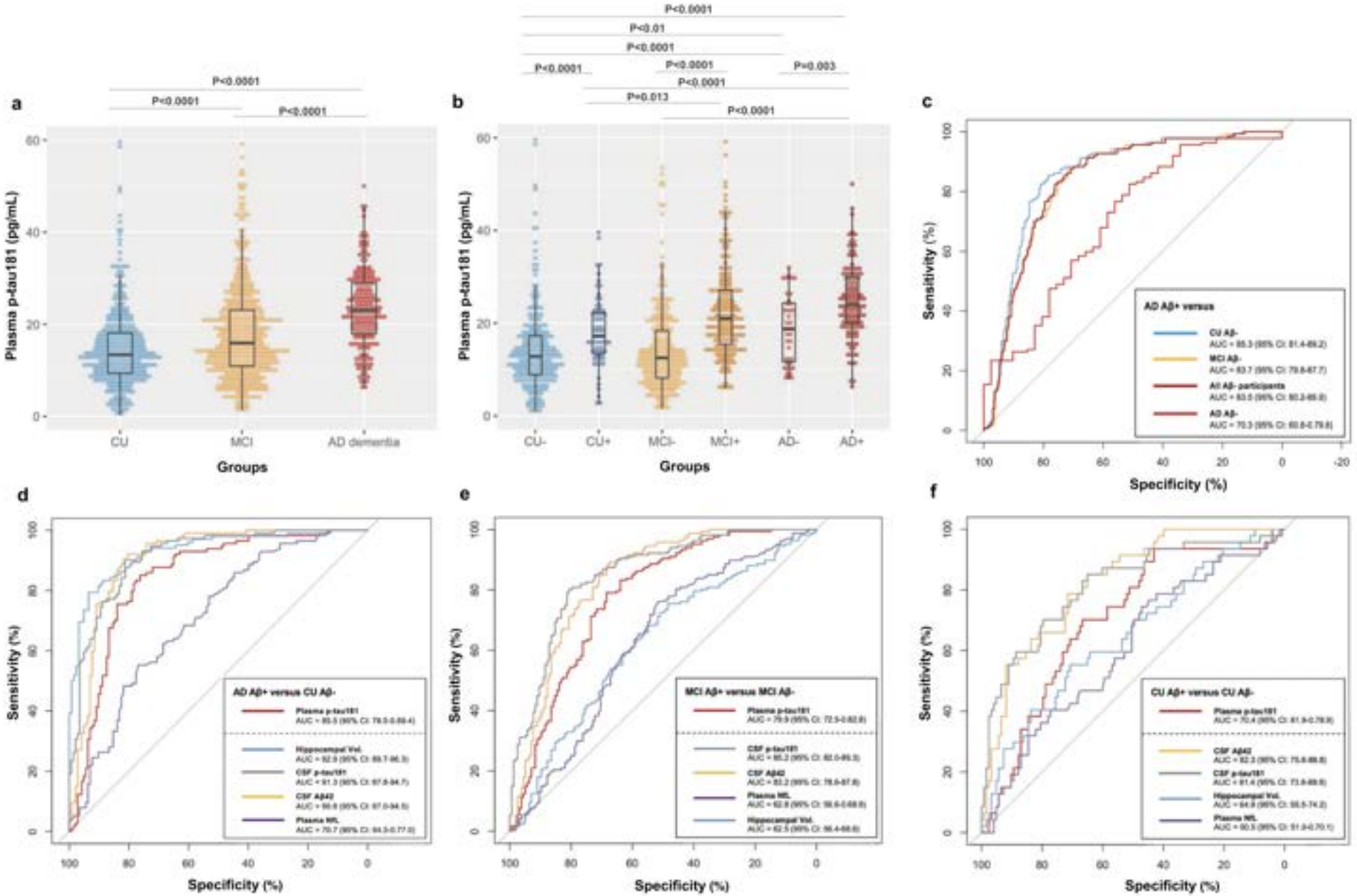




Predominant fragments in CSF

S Wegmann et al. Current Opinion Neurobiology'21

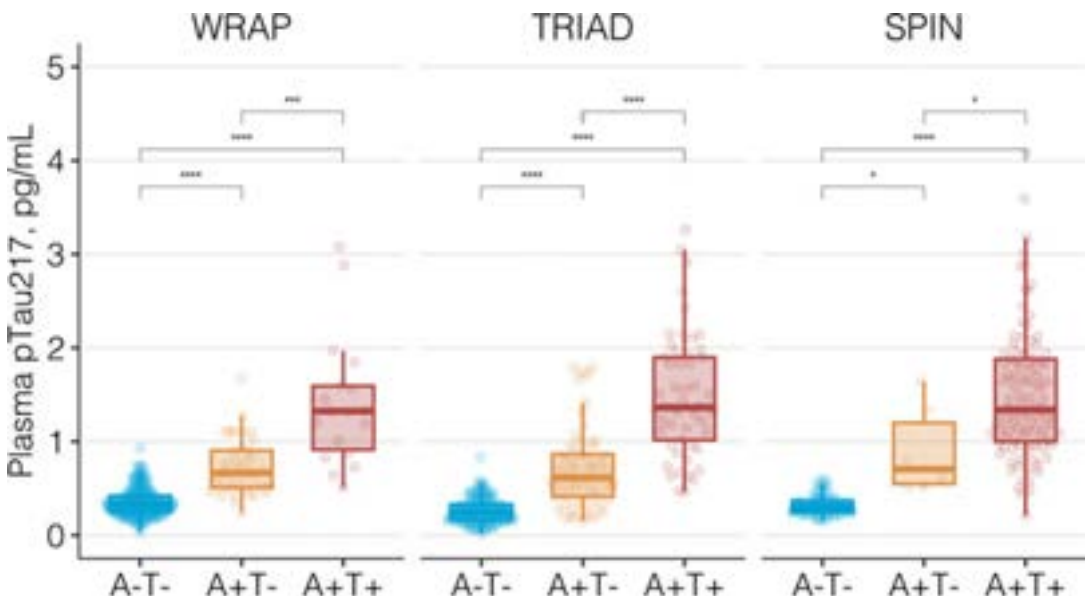
Plasma pTau181 for AD Diagnosis in ADNI

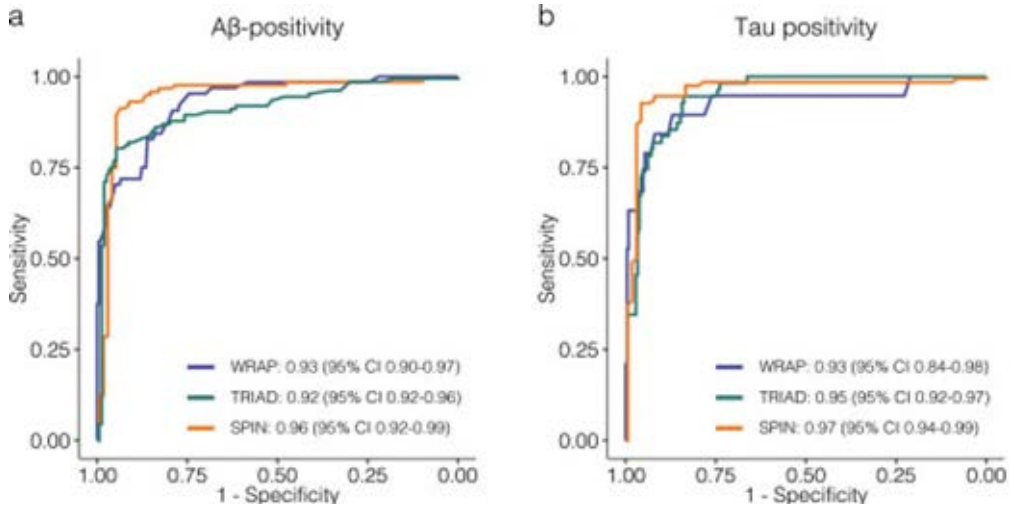


Karikari et al, Molec Psychiatry 2021

Plasma pTau217 for AD Diagnosis

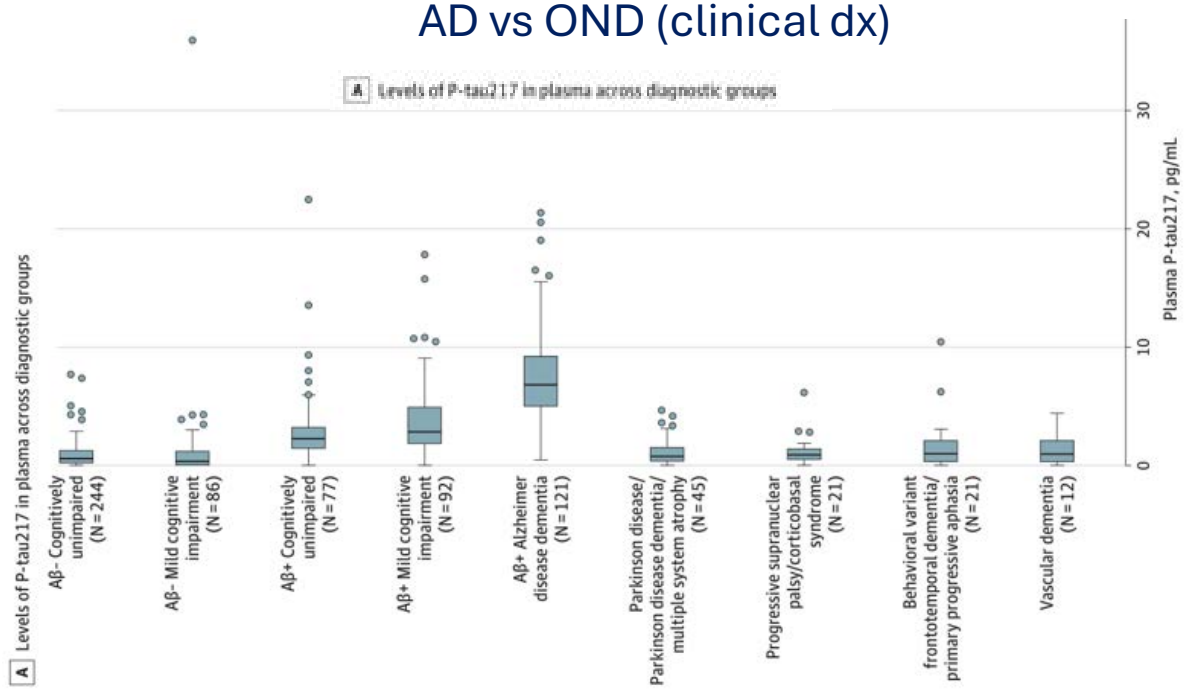
ALZPath (n=786)

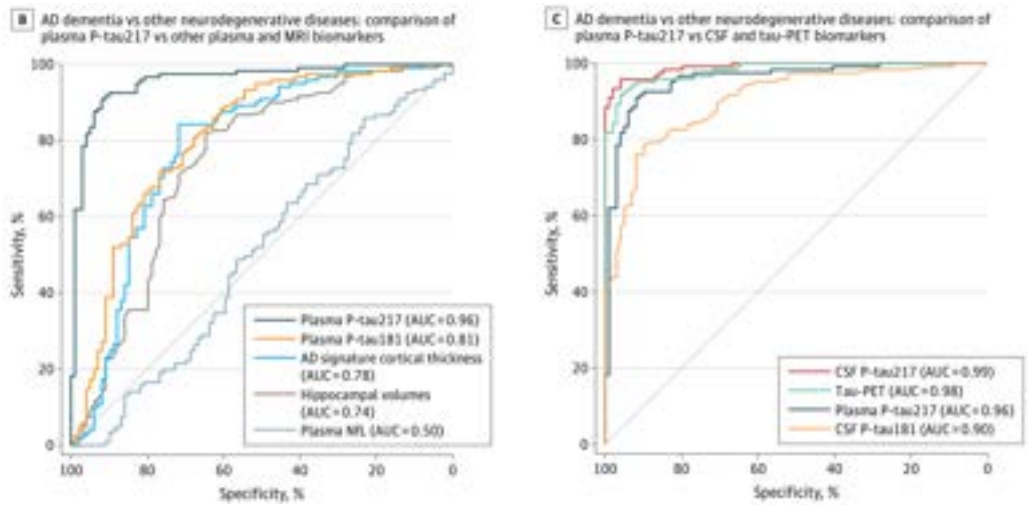




Ashton et al, JAMA Neurol 2024

BioFINDER (n=699)
AD vs OND (clinical dx)





Palmquist et al., JAMA 2020

Plasma pTau (MSD S-plex) for AD Diagnosis with Major Biomarker (Npath, PET, CSF)

MADRC Research Cohort

n	1088
Age	70.6 (10.7)
Sex	F 56.1%, M 43.9%
URG	111 (11.0%)
Educ	<16: 32.6% 16+: 67.3%
BBMs	3366 (pTau + other)

Cog Status (based on CDR)

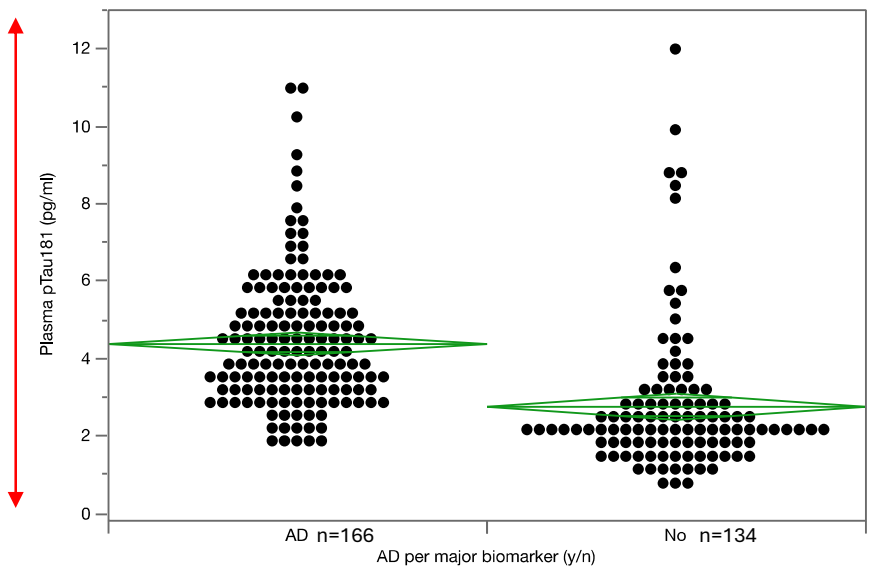
NCI	320
MCI	452
Dem	315

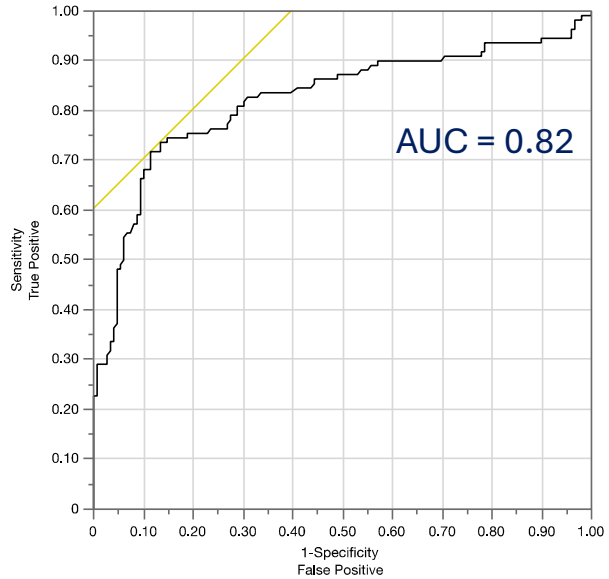
Major Biomarkers

Autopsy	243
CSF	64
PET (Aβ,Tau)	78

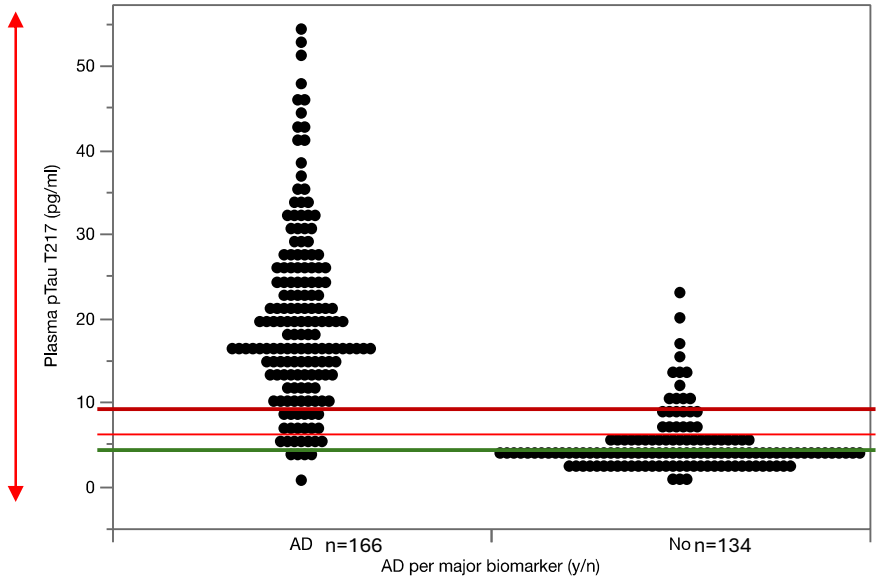
MASSACHUSETTS Alzheimer's Disease Research Center

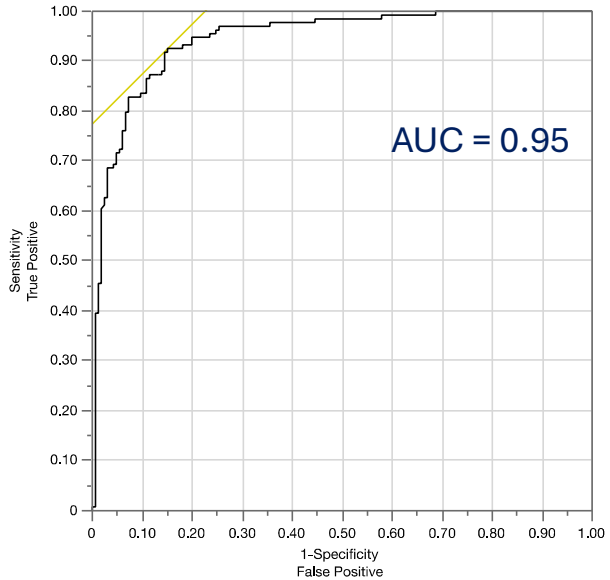
pTau181



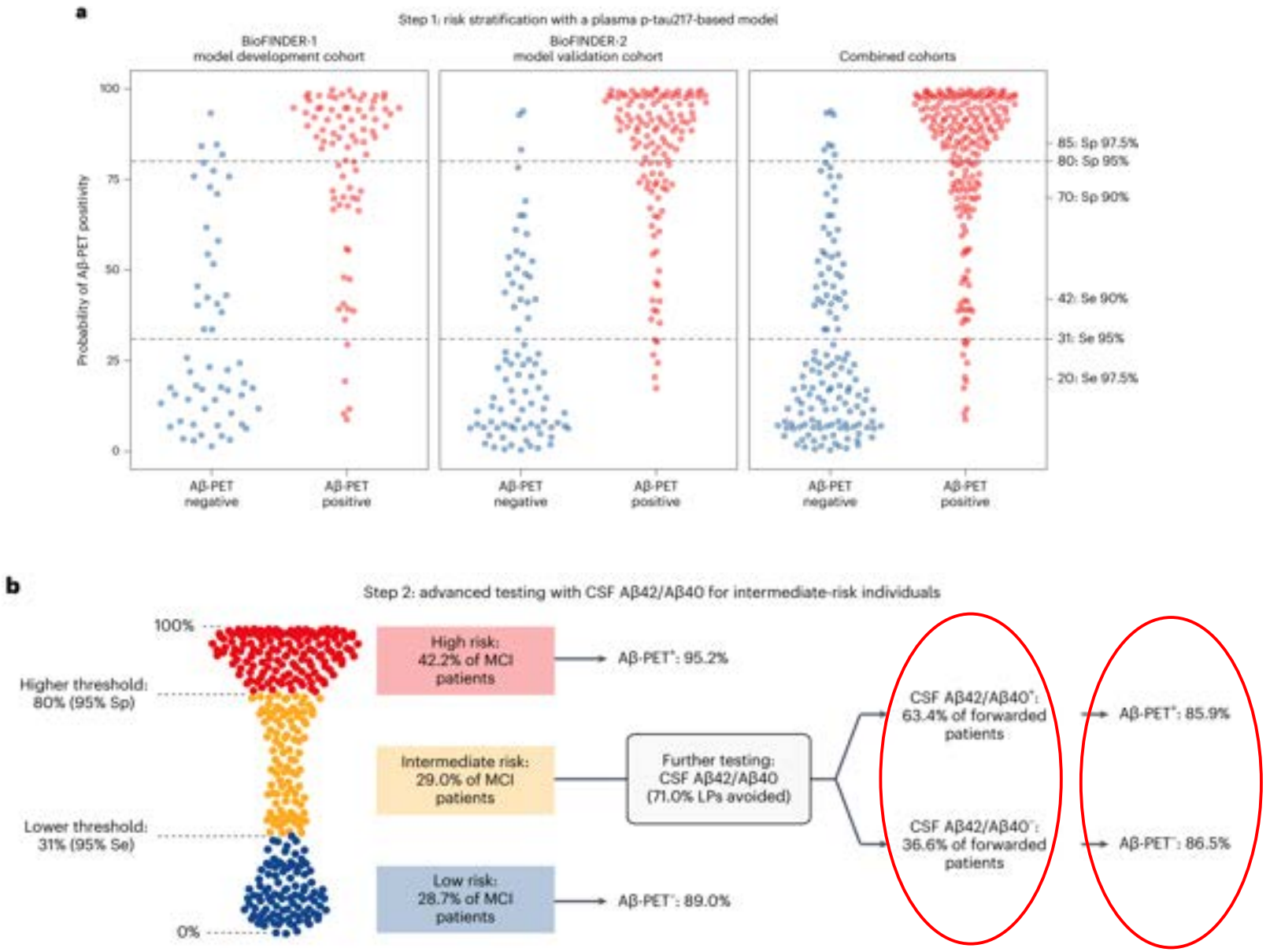


pTau217



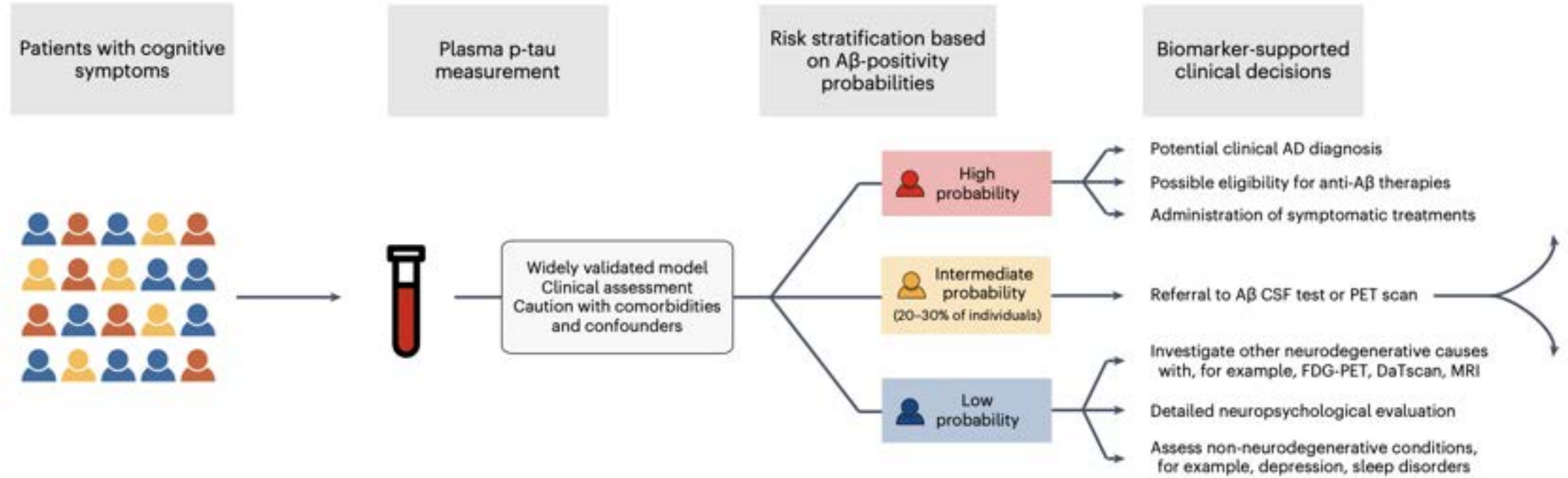


A Two-Step Workflow for Use of Plasma pTau217 in AD Diagnosis



WS Brum et al, Nat Aging 2023

A Two-Step Workflow for Use of Plasma pTau217 in AD Diagnosis

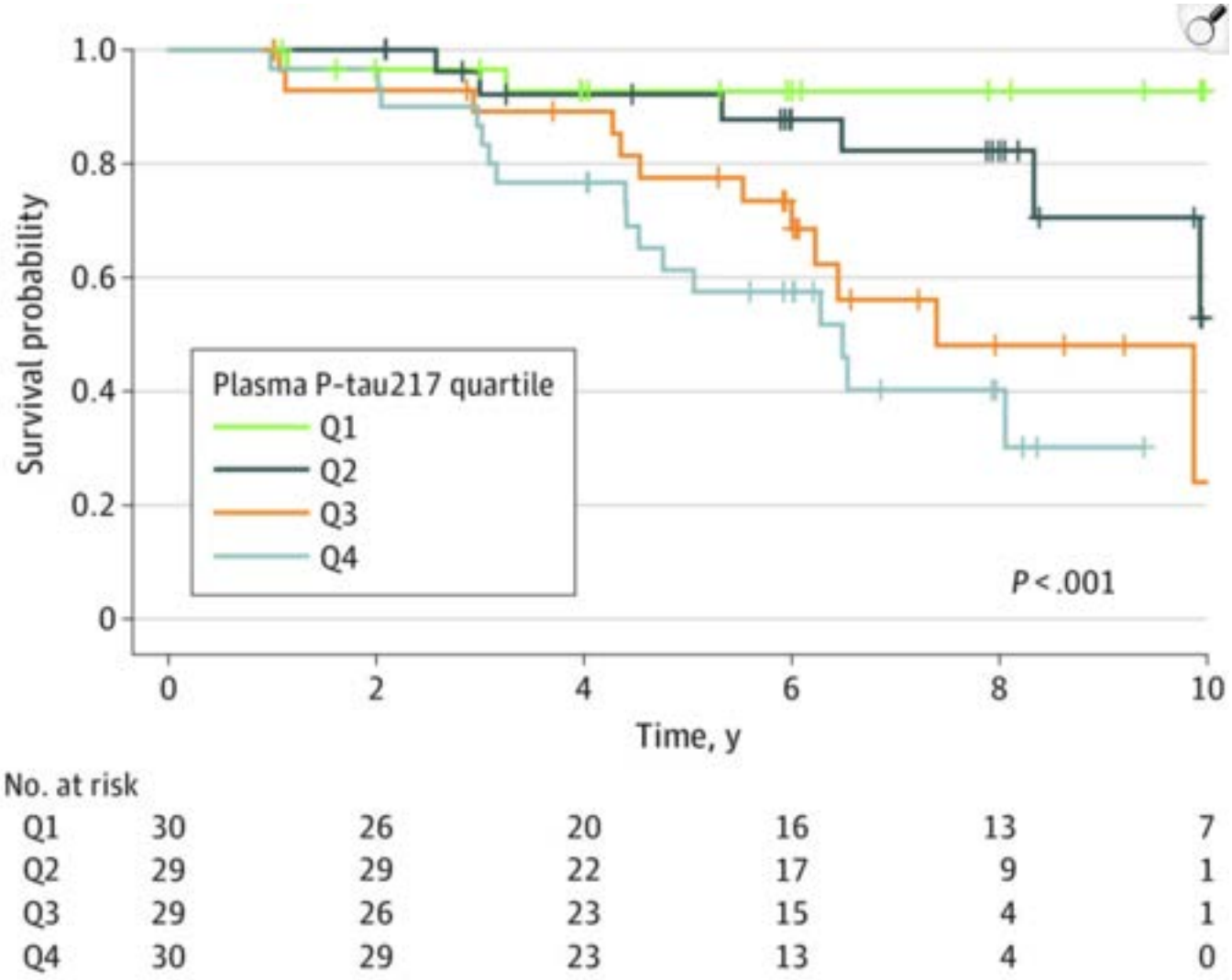


WS Brum et al, Nat Aging 2023

pTau217 and Prognosis in Preclinical AD (Aβ+)
BioFINDER and WRAP

Table 1. Participant Demographic Characteristics.

Characteristic	Participants, No. (%)			
	BioFINDER-1 cohort[a]		WRAP cohort	
	Aβ-negative (n = 286)	Aβ-positive (n = 119)	Aβ-negative (n = 107)	Aβ-positive (n = 52)
Age, mean (SD), y[b]	71.8 (5.6)	73.0 (5.4)	62.0 (6.6)	64.4 (4.6)
Sex				
Female	172 (60.1)	72 (60.5)	70 (65.4)	34 (65.4)
Male	114 (39.9)	47 (39.5)	37 (34.6)	18 (34.6)
Years of education, mean (SD)	12.4 (3.5)	12.2 (4.2)	16.3 (2.7)	16.5 (2.0)
APOE4 status				
Negative	229 (80.1)[c]	48 (40.3)	67 (62.6)	18 (34.6)
Positive	53 (18.5)[c]	71 (59.7)[c]	40 (37.4)	34 (65.4)
Subjective cognitive impairment				
No	185 (64.7)	63 (52.9)	NA	NA
Yes	101 (35.3)	56 (47.1)	NA	NA
MMSE[d]				
Baseline score				
Mean (SD)	28.9 (1.4)	28.5 (1.3)	29.4 (1.0)	29.5 (0.8)
Median (IQR)	29.0 (28.0-30.0)	29.0 (28.0-29.5)	30.0 (29.0-30.0)	30.0 (29.0-30.0)
Follow-up time, mean (SD), y	5.8 (2.3)	5.6 (2.1)	6.1 (1.4)	5.7 (1.5)
No. of visits, median (IQR)	4 (4-6)	5 (4-6)	4 (3-4)	3 (3-4)
mPACC[e]				
Baseline score, mean (SD)	−0.16 (0.80)	−0.79 (1.36)	−0.07 (0.64)	−0.16 (0.76)
Follow-up time, mean (SD), y	5.5 (2.5)	5.0 (2.5)	6.2 (1.4)	5.7 (1.5)
No. of visits, median (IQR)	4 (3-5)	4 (3-4)	3 (3-4)	3 (3-4)
Plasma, mean (SD), ng/L[f]				
P-tau217	0.17 (0.06)	0.30 (0.16)	0.23 (0.06)	0.41 (0.17)
P-tau231	10.40 (5.43)	20.30 (8.55)	NA	NA
P-tau181	2.86 (0.90)	4.00 (1.50)	NA	NA
GFAP	0.09 (0.06)	0.12 (0.05)	NA	NA
NFL	2.46 (1.39)	2.87 (1.72)	NA	NA
CSF, mean (SD), ng/L[f]				
P-tau217	5.94 (3.09)	24.10 (21.60)	NA	NA
P-tau181	17.60 (5.25)	28.90 (12.90)	NA	NA
GFAP	12.50 (4.66)	14.90 (5.12)	NA	NA
NFL	140.10 (69.40)	190.40 (133.80)	NA	NA
Aβ42/40	0.095 (0.015)	0.045 (0.011)	NA	NA
PiB PET, mean (SD), CL[g]	NA	NA	4.78 (6.49)	62.10 (33.00)



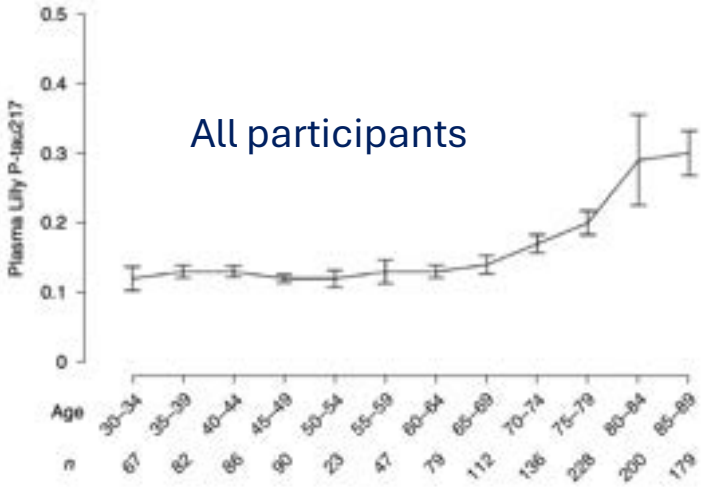
N Mattson-Calgren et al., JAMA Neurol'23

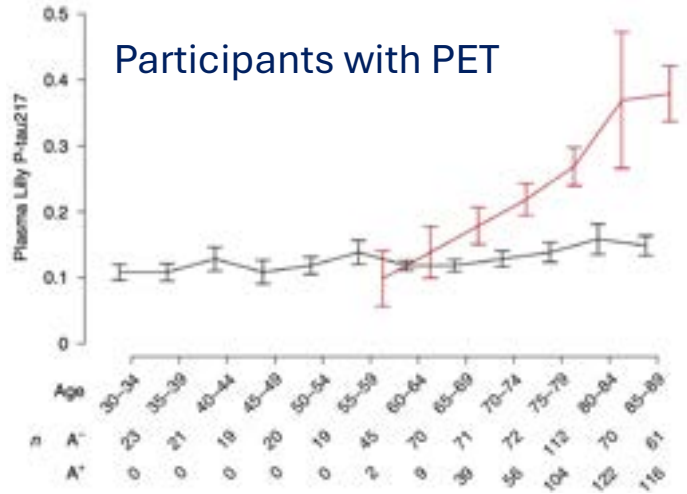
pTau217 in a Community Sample - Mayo Clinic Study of Aging

Participant Characteristics

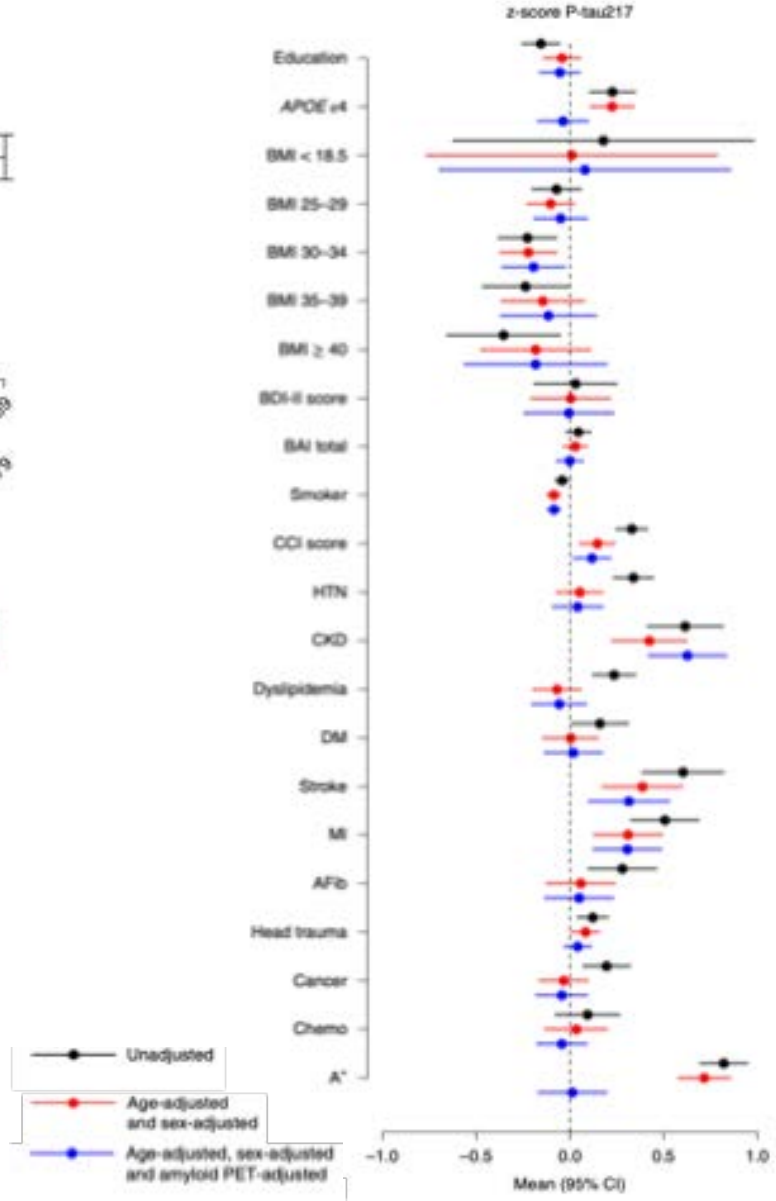
All	n = 1329	(Age 73.2, Male 54.9%)
CU	n = 1161	(Age 70.9, Male 54.2%)
MCI	n = 153	(Age 80.8, Male 57.5%)
Dem	n = 15	(Age 83.5, Male 86.7%)

Age





Co-morbidities



Adapted from Mielke et al., Nat Med'22

AAC

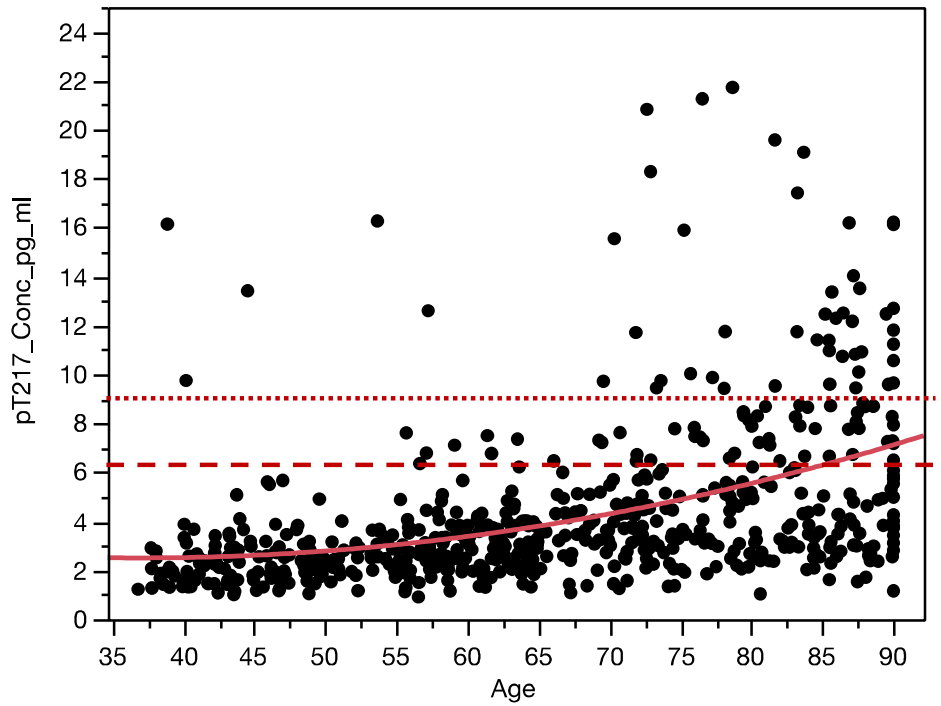
AGING ADULT BRAIN CONNECTOME

U19AG073585

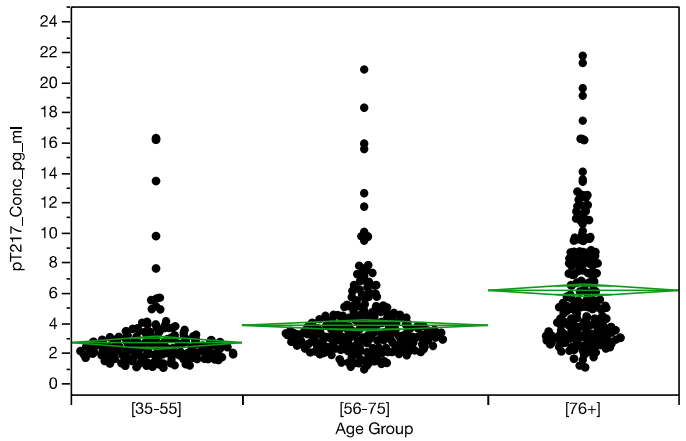
AABC-HCPA with Blood

n	902
Age	66.7 (15.5)
Sex	F 54.7%, M 45.3%
Race	
Asian	5.4%
Black/AfAm	14.1%
Multi/Other	4.4%
White	74.5%
NOS	1.5%
Ethnicity (Hispanic/Latine)	
H/L	11.3%
Not H/L	88.2%
NOS	0.4%
Age Categories	
[36-55]	251 (27.9%)
[56-75]	345 (38.3%)
[75-90+]	305 (33.9%)

pTau217

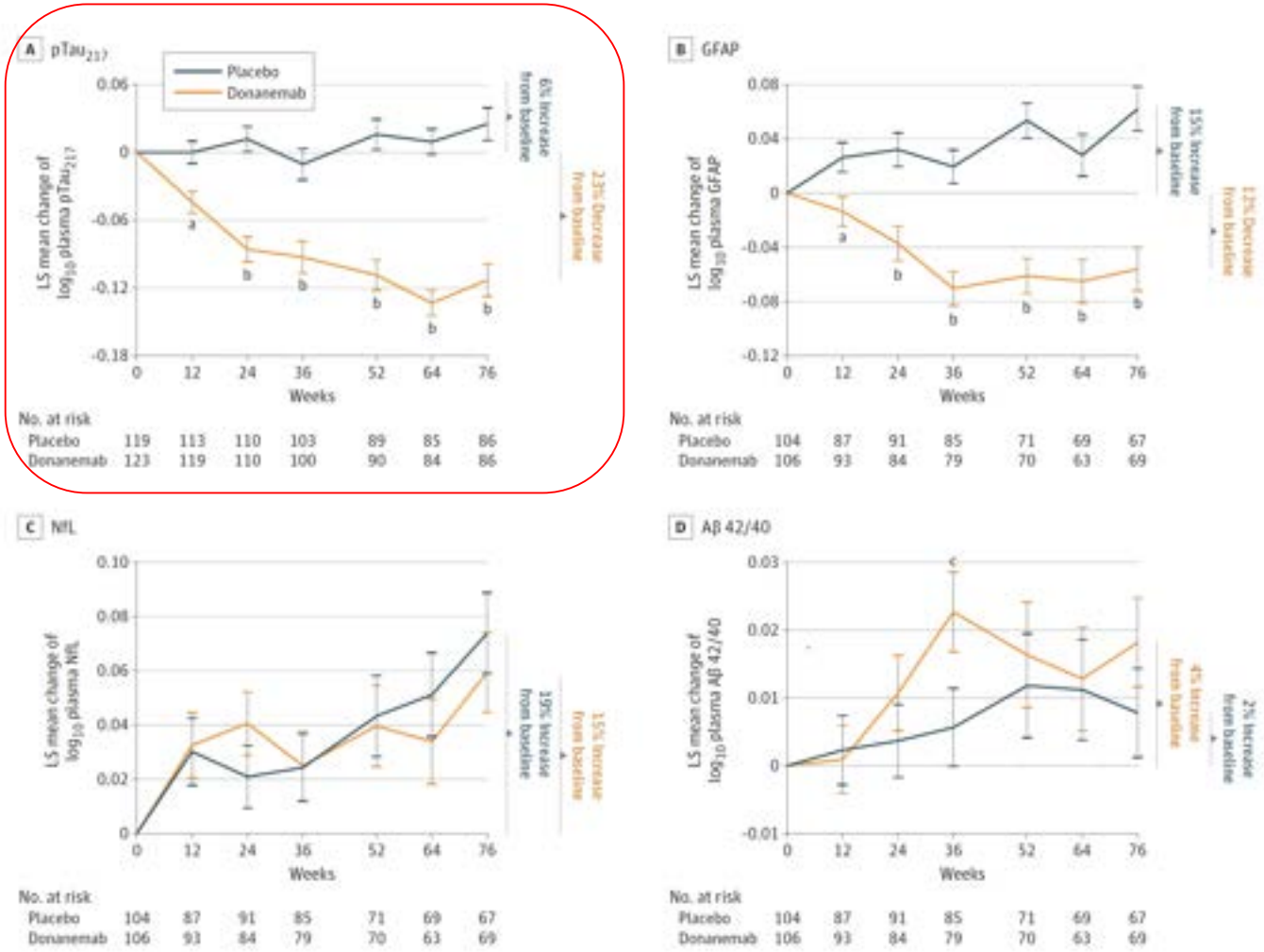


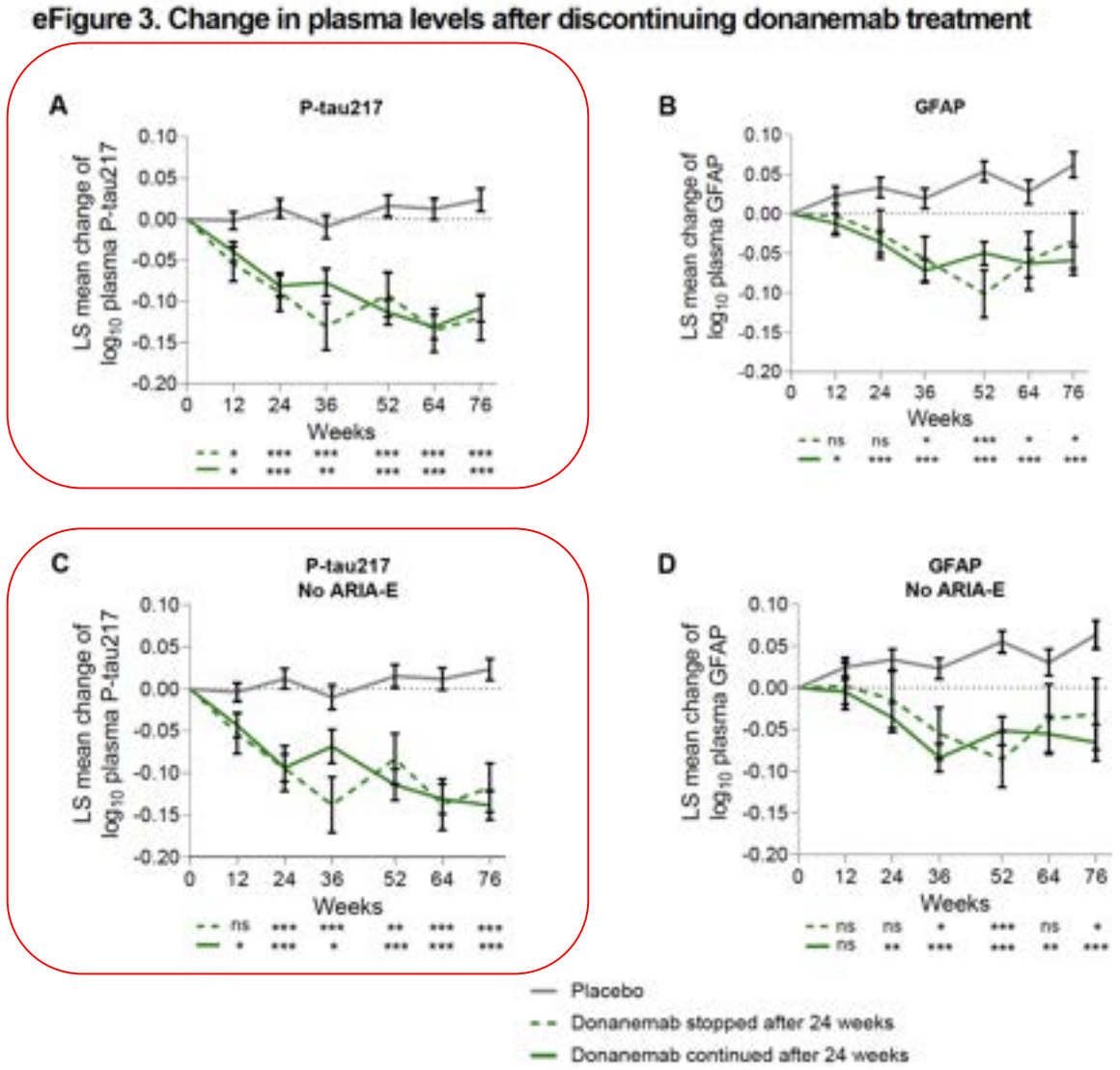
Adult Age Categories



Kivisakk/Arnold Preliminary analyses

Blood-based Biomarkers in Anti-Amyloid Immunotherapy
Donanemab -- TRAILBLAZER ALZ (Ph2)



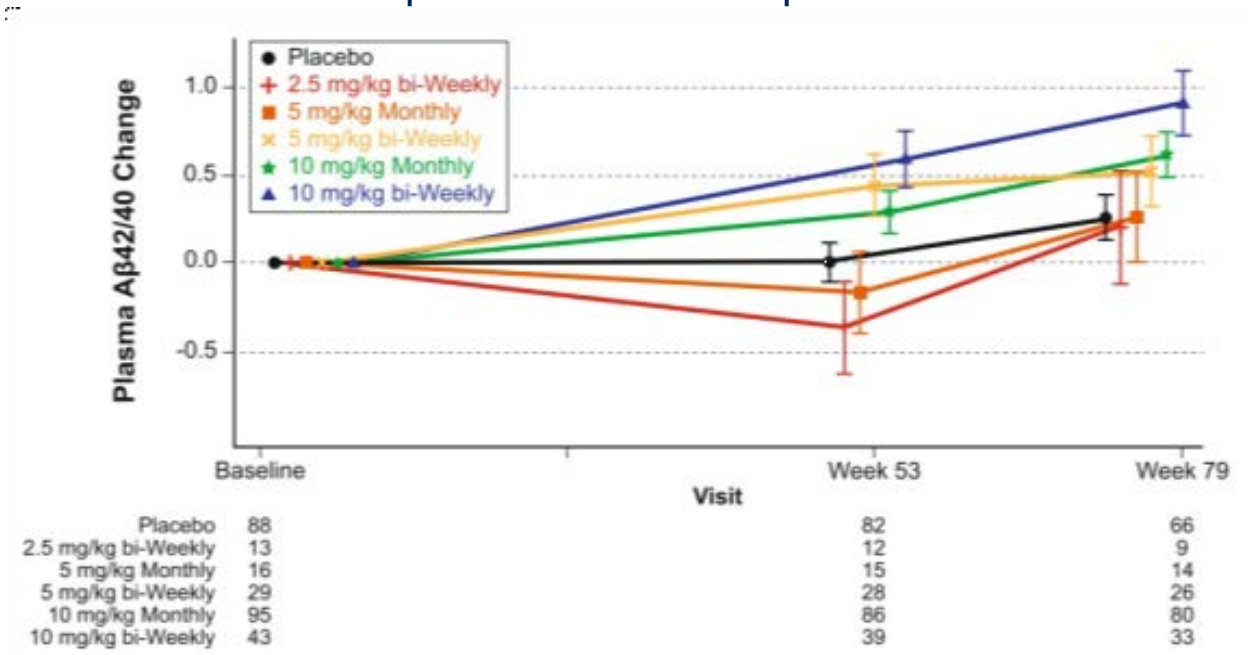


M Pontecorvo, JAMA Neurol 2022

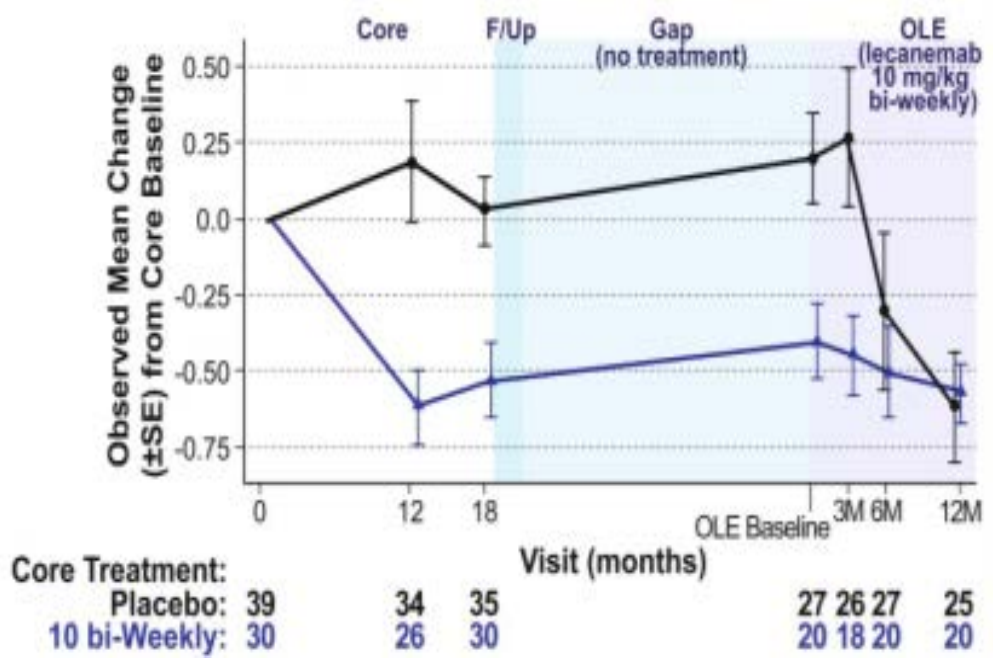
Blood-based Biomarkers in Anti-Amyloid Immunotherapy
Lecanemab -- Study 201

Phase 2 POC "Study 201": n=856 → 247 PBO, 609 LEC → 180 OLE (10 mg/kg)

pTau181 Dose Response



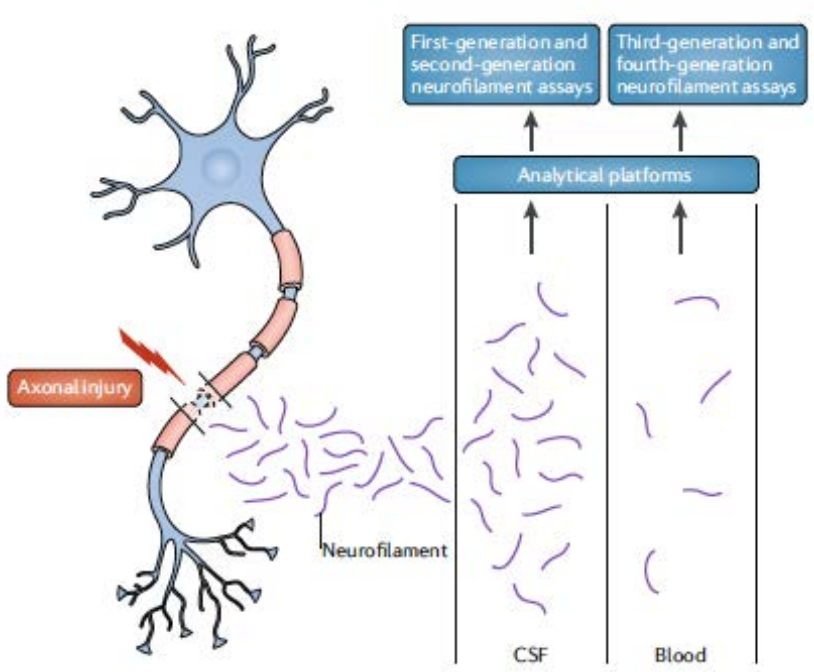
pTau181 in Open Label Extension



E McDade, Alz Res Therapy 2022

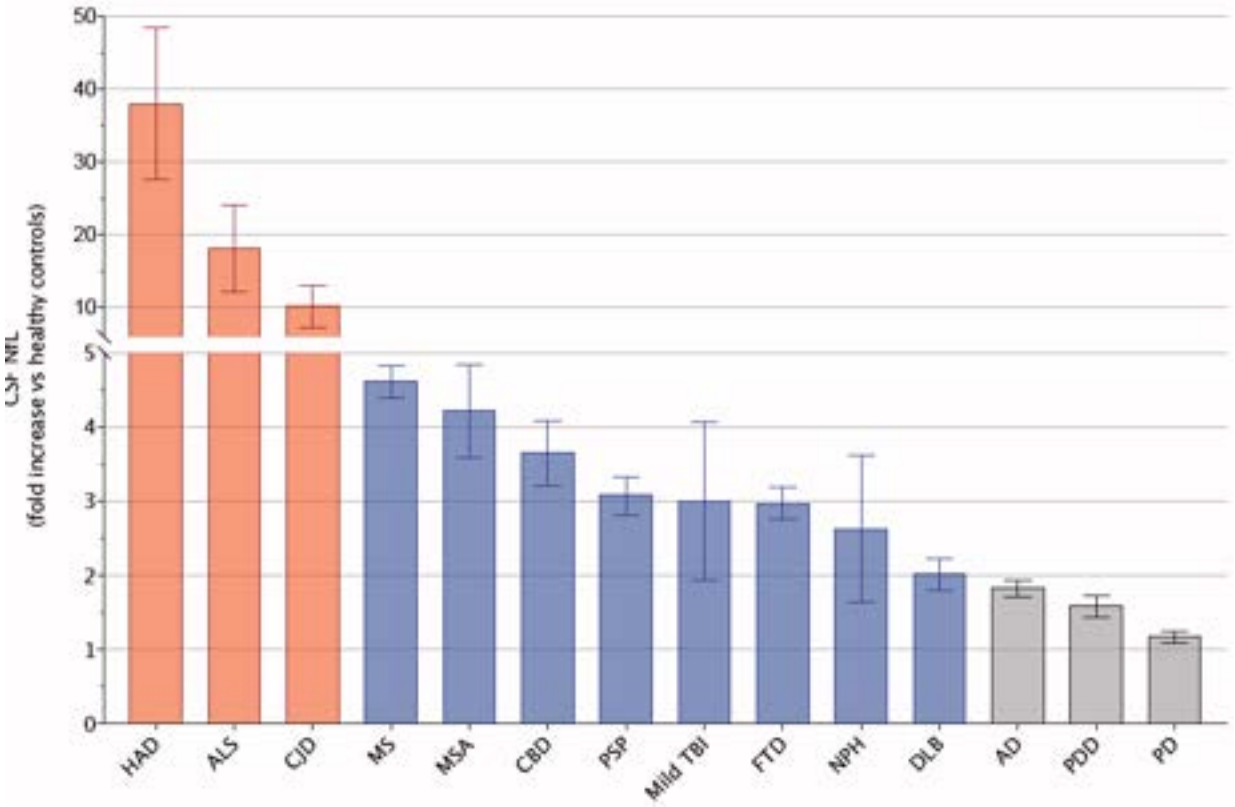
Neurofilament-Light Chain

- 70 kDa Class IV intermediate filament protein
- Highly abundant in neurons, esp. axons
- Elevated in many neurological diseases and injuries
- Emerging as a clinically useful biomarker in ADRDs, ALS, MS, TBI, stroke, delirium
- Good correlation between CSF and plasma/serum using ultrasensitive assays makes it especially interesting



Khalil et al., Nat Rev Neurol 2018; 14:577

CSF NfL Levels Across Diagnoses

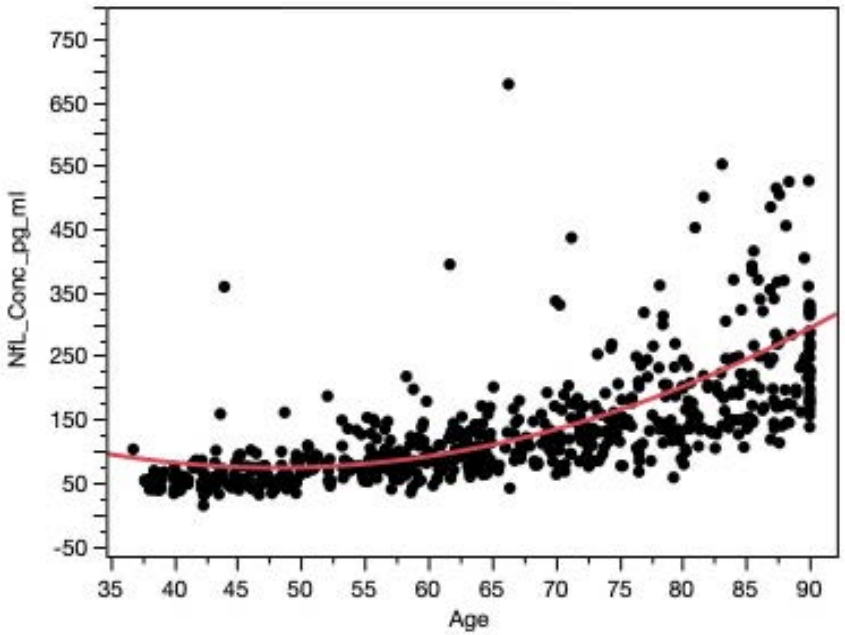


Gaetani et al., JNNP'19

Neurofilament-Light in Aging and Neurodegenerative Diseases

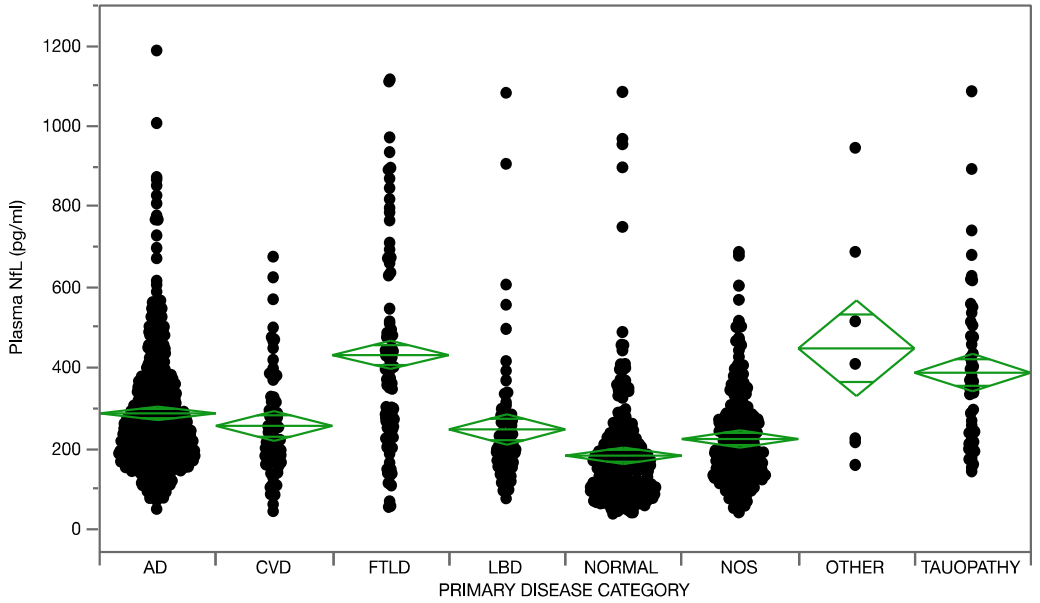
NfL

AABC-HCPA



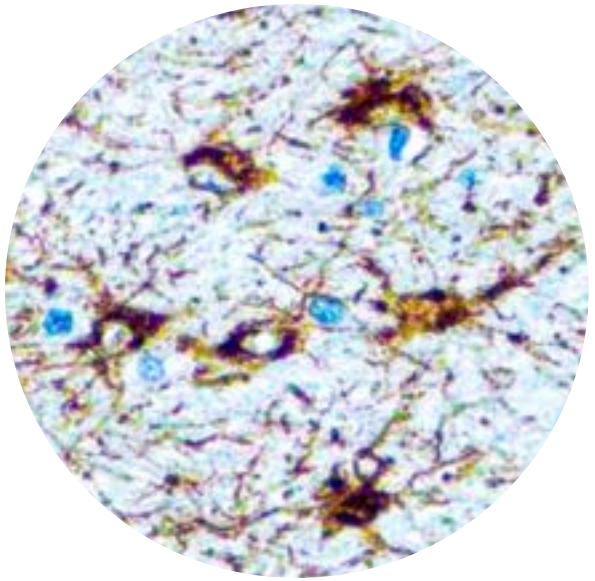
AAOC
AGING ADULT BRAIN CONNECTOME

MADRC-RC

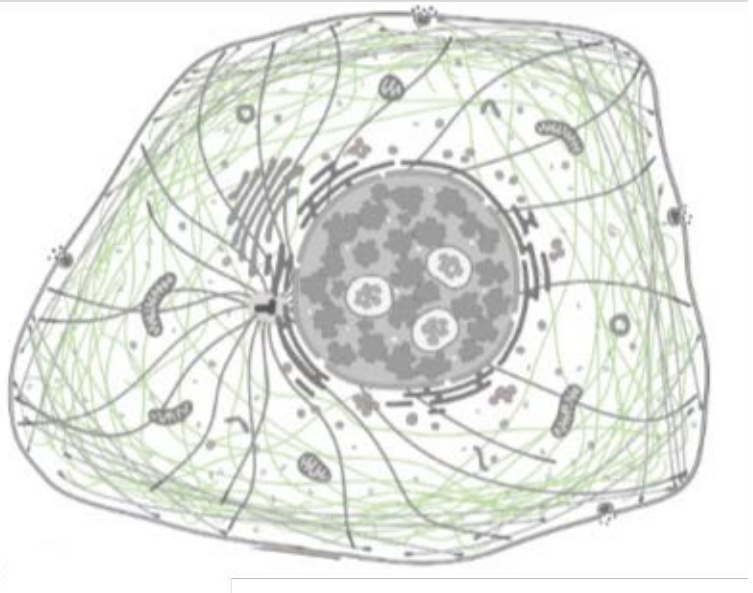


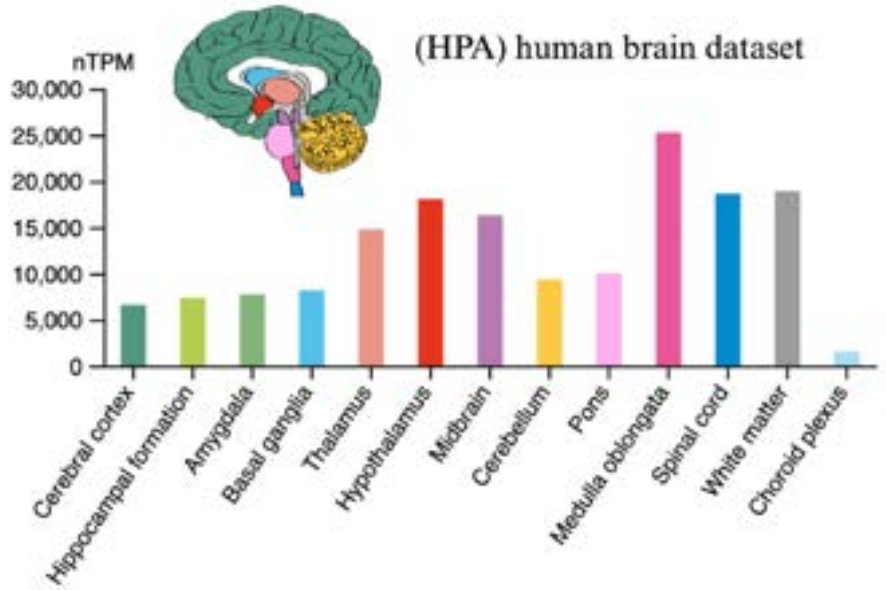
MASSACHUSETTS
Alzheimer's Disease
Research Center

Glial Fibrillary Acidic Protein



- Type III intermediate filament protein
- Highly abundant in astrocytes
- Also expressed in in kidney, testis, GI
- Maintains mechanical strength of astrocytes
- Many roles in neuron-astrocyte interaction and BBB
- Elevated in many neurological diseases and injuries
- Emerging as a clinically useful biomarker in AD
- Good correlation between CSF and plasma/serum using ultrasensitive assays makes it especially interesting



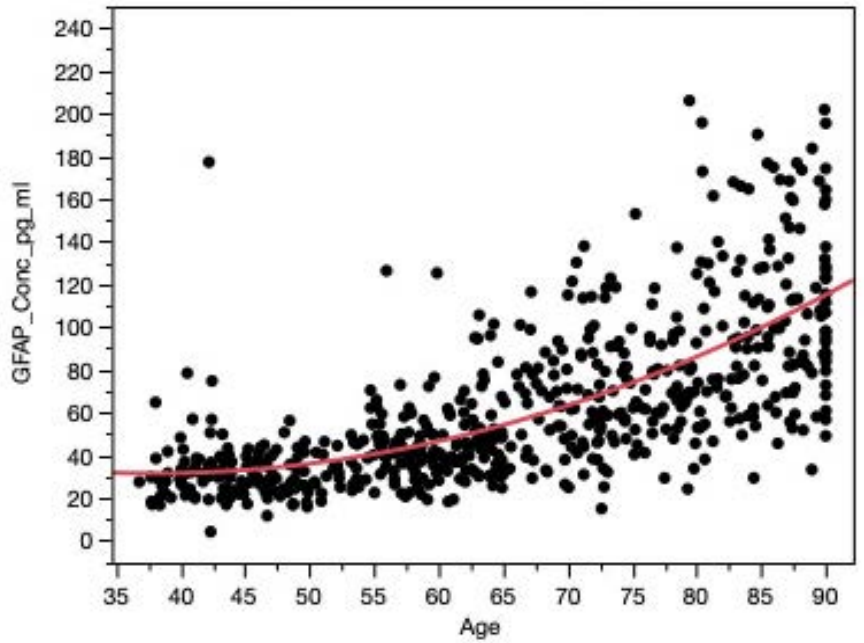


D Gogishvili et al, J Neurochem 2024

Glial Fibrillary Acidic Protein in Aging and Neurodegenerative Diseases

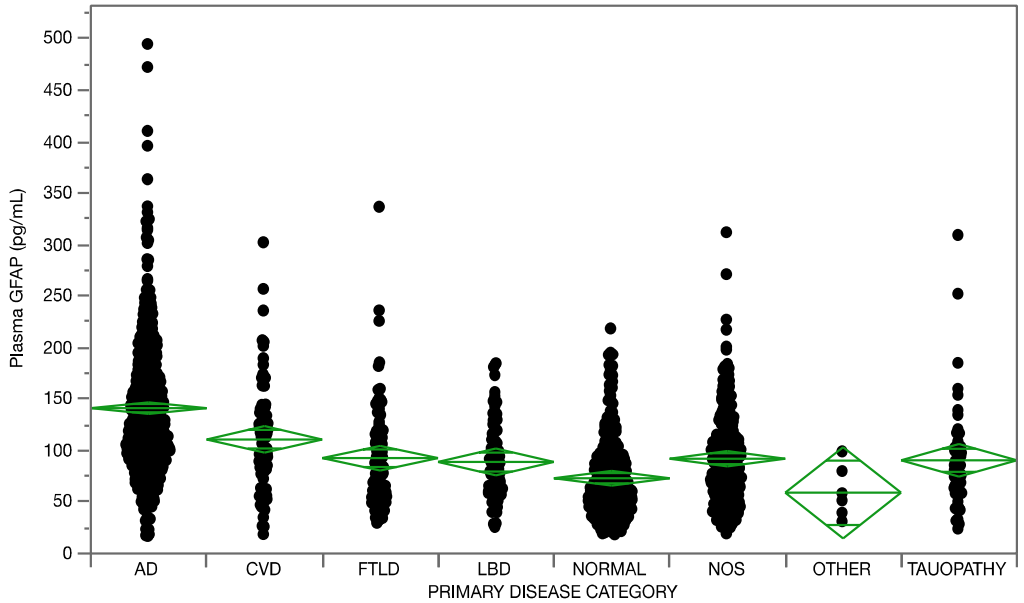
GFAP

AABC-HCPA



AAOC
AGING ADULT BRAIN CONNECTOME

MADRC-RC



MASSACHUSETTS
Alzheimer's Disease
Research Center

Postmortem associations between Alzheimer's disease (AD) pathology and plasma pTau217, GFAP, and NfL in AD and AD-related dementias

Table 1. Demographic, clinical, and histopathological information
Table includes normal controls and participants with postmortem examination and a blood sample collected within 6 years of death

1° Neuropathological category	AD	CAA	TDP-43	SYN	TAU	CVD	NC
n	85	3	20	29	37	13	67
Sex, female	34 (40%)	2 (67%)	8 (40%)	8 (28%)	15 (41%)	5 (39%)	48 (72%)
APOe4 (≥1 allele)	56 (66%)	0 (0%)	6 (30%)	9 (31%)	6 (16%)	3 (23%)	19 (28%)
Age at death (years)	82.7 (57-9)	84.8 (66-98)	71.8 (51-82)	78.7 (61-97)	71.7 (32-92)	88.2 (83-96)	N/A
Time last visit to death (years)	3.1 (0.0-6.0)	1.8 (0.8-3.0)	2.6 (0.2-5.7)	2.9 (0.6-6.0)	2.1 (0.4-6.0)	3.6 (1.2-4.9)	N/A
Global CDR at last visit	1 (0-3)	1 (0.5-1)	2 (0.5-3)	0.5 (0-3)	1 (0-3)	0.5 (0-1)	0 (0-0)
MOCA* at last visit	13 (0-29)	25 (21-29)	12 (0-22)	21 (3-29)	21 (0-29)	23 (14-29)	28 (22-30)
Number (frequency) of participants with histopathological lesions of the different AD and ADRD pathologies at autopsy							
AD pathology	85 (100%)	1 (33%)	2 (10%)	11 (38%)	1 (2.7%)	7 (54%)	n.d.
CAA pathology	39 (46%)	3 (100%)	3 (15%)	8 (28%)	3 (8.1%)	3 (23%)	n.d.
TDP pathology	6 (7.1%)	1 (33%)	20 (100%)	2 (6.9%)	2 (5.4%)	0	n.d.
SYN pathology	17 (20%)	0	0	29 (100%)	1 (2.7%)	1 (7.7%)	n.d.
TAU pathology	1 (1.2%)	0	2 (10%)	3 (10%)	37 (100%)	0	n.d.
CVD pathology	74 (87%)	3 (100%)	17 (85%)	27 (93%)	27 (73%)	12 (100%)	n.d.

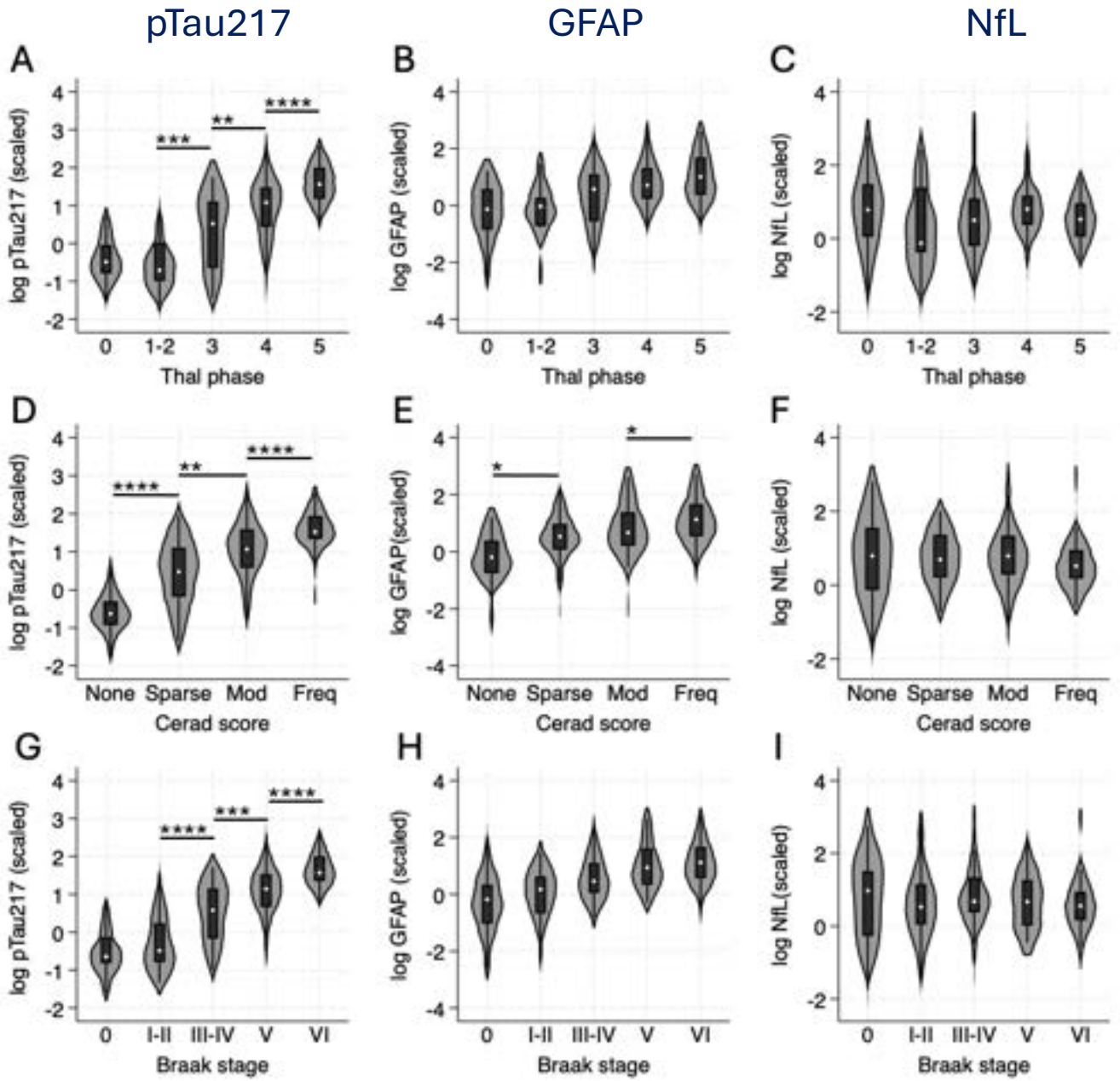
Data presented as median (range) or n (%). AD=Alzheimer's disease; CAA=Cerebral amyloid angiopathy; TDP=TAR DNA-binding protein 43 proteinopathy; SYN=Neuronal a-synuclein disease; TAU=Primary tauopathy; CVD=Cerebrovascular disease; NC=normal controls; CDR=Clinical Dementia Rating; MOCA=Montreal Cognitive Assessment; MMSE=Mini Mental State Examination; n.d.=not determined. *Combined MOCA and MMSE.[46]

Neurology

Kivisakk et al., in revision

MASSACHUSETTS Alzheimer's Disease Research Center

Associations with Thal, CERAD and Braak ratings



Neurology

Kivisakk et al., in revision

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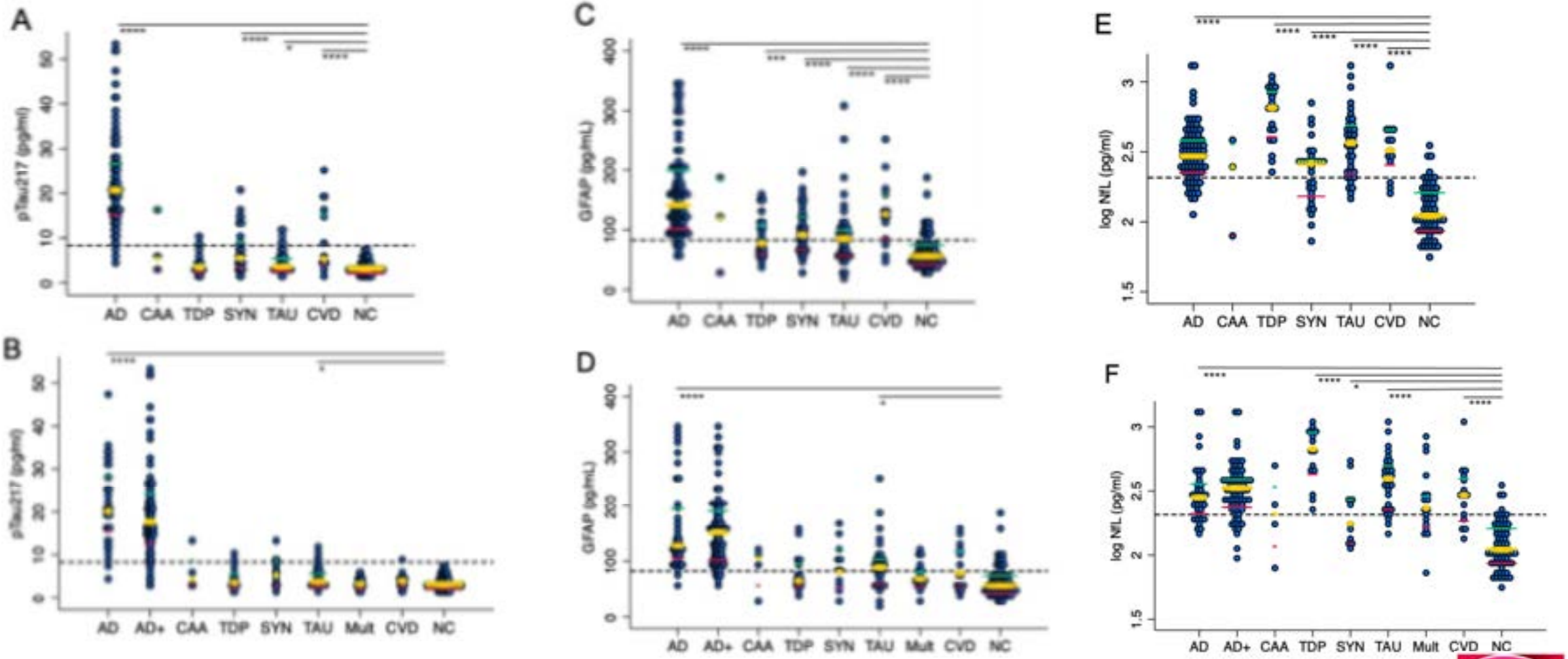
Plasma biomarker levels in relation to neuropathological category in the presence vs absence of AD co-pathology

pTau217 | GFAP | NfL

Primary NP Dx1

Sole NP Dx



Neurology

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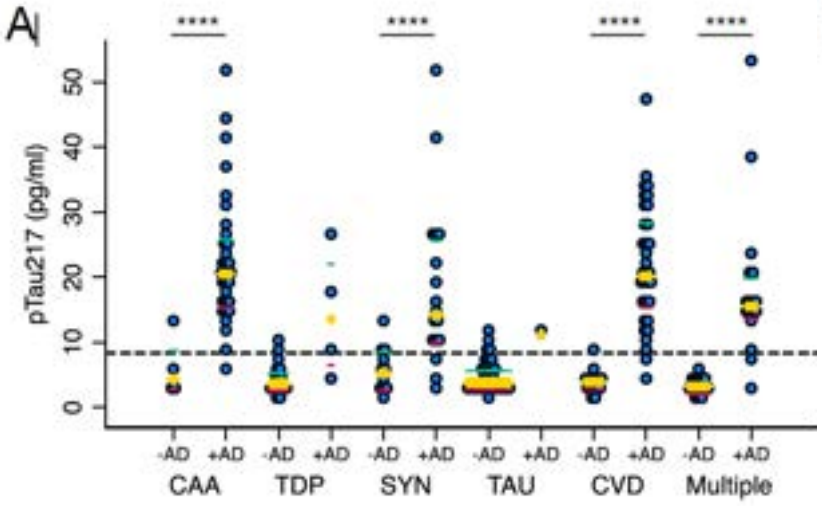
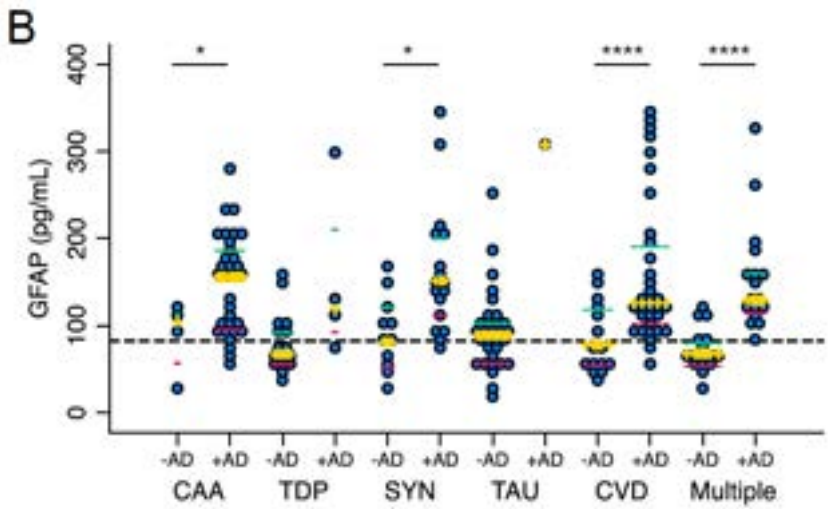
Effects of AD pathology on biomarker levels in participants with isolated or multiple non-AD pathologies irrespectively of primary neuropathological diagnosis or clinical syndromes

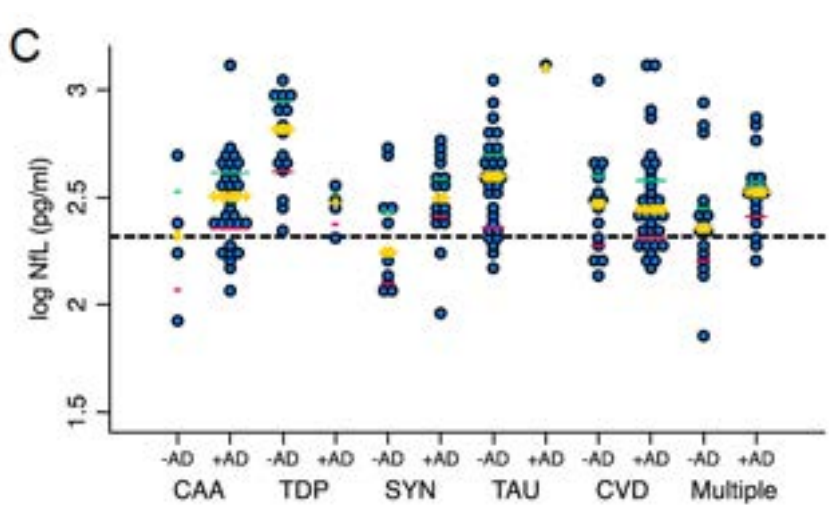
pTau217



GFAP



NfL



Neurology

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Postmortem associations between Alzheimer's disease (AD) pathology and plasma pTau217, GFAP, and NfL in AD and AD-related dementias

Key Findings

Biomarker	AD Specificity	Key Associations	Impact of Co-Pathologies
pTau217	High (AUC 0.97)	↑ with Thal, Braak, CERAD; predicts AD pathology ≥8 yrs prior to death	↑ in non-AD cases due to AD co-pathology
GFAP	Moderate (AUC 0.88)	↑ with tau > Aβ; less sensitive to severity	↑ in many non-AD cases even without AD pathology
NfL	Low (non-specific)	↑ in TDP, TAU, CVD > AD	Not significantly influenced by AD pathology

Conclusions:

- *pTau217 is a robust plasma biomarker of AD pathology, even in individuals with other primary diagnoses.*
- *A "positive" pTau217 test in non-AD dementia likely reflects AD co-pathology, not a false positive.*
- *GFAP and NfL are less specific, reflecting astrocytic and axonal injury across multiple pathologies.*

Kivisakk et al., in revision

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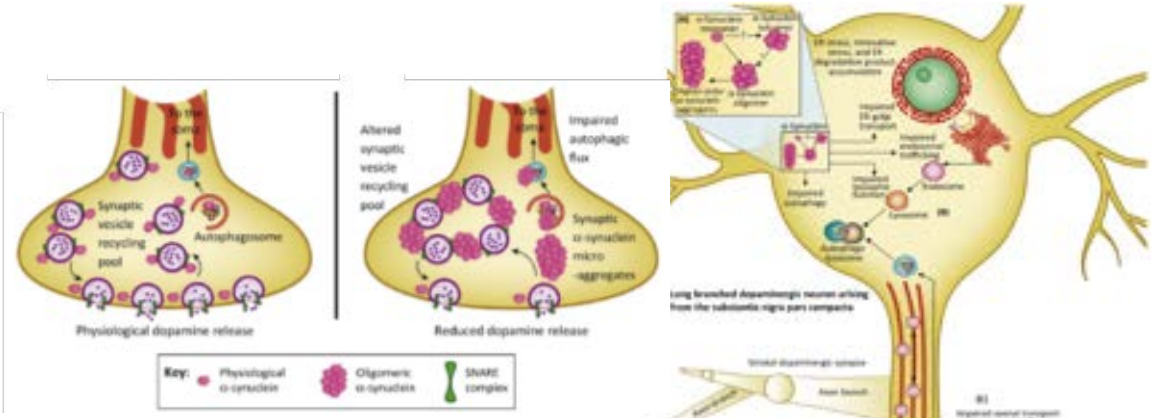
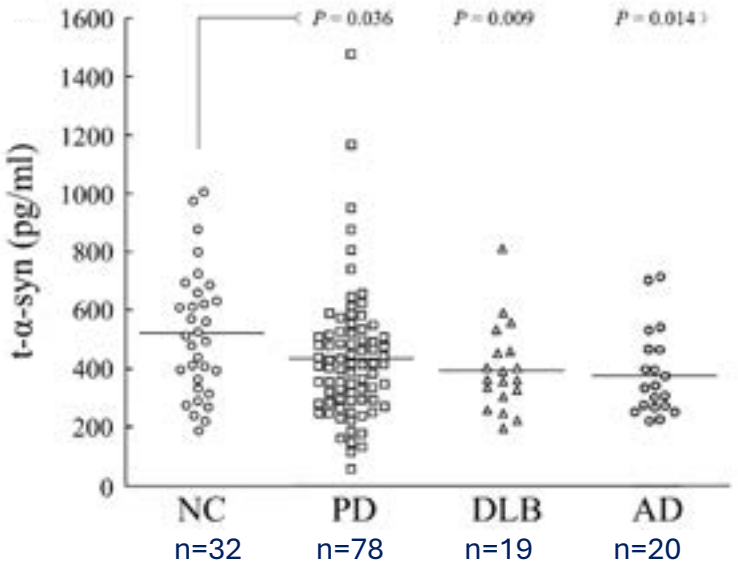
α-Synucleinopathies

- 140 aa protein encoded by SNCA
- Present in neurons, heart, muscle
- Interacts with phospholipids to help regulate neurotransmitter release
- Oligomerizes and aggregates into fibrils in Lewy bodies, neurites and other inclusions
- α-Synuclein biomarkers:
  - Total α-syn
  - Oligomeric α-syn
  - Phospho α-syn and other PTMs



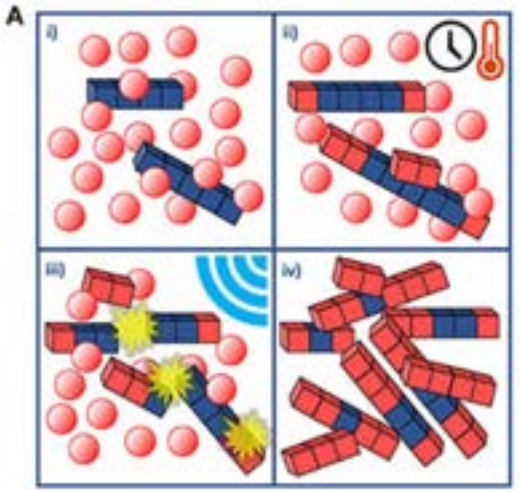
Hunn et al., TNS 2015; 38:178

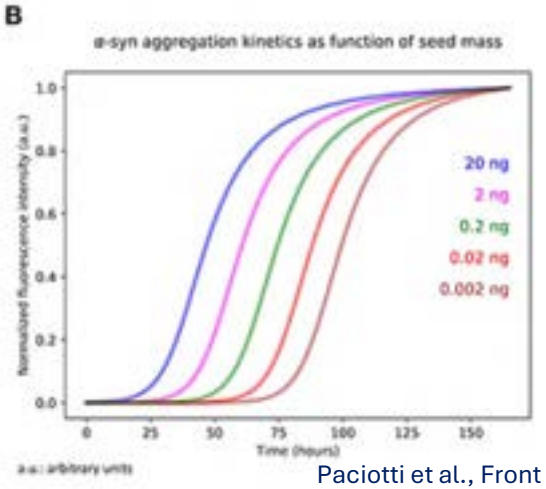
CSF Total α-Synuclein



Ultrasensitive Methods for α-Synucleinopathy

Protein Misfolding Cyclic Amplification (PMCA) and Real-Time Quaking-Induced Conversion





Paciotti et al., Front Neurol 9:415, 2018

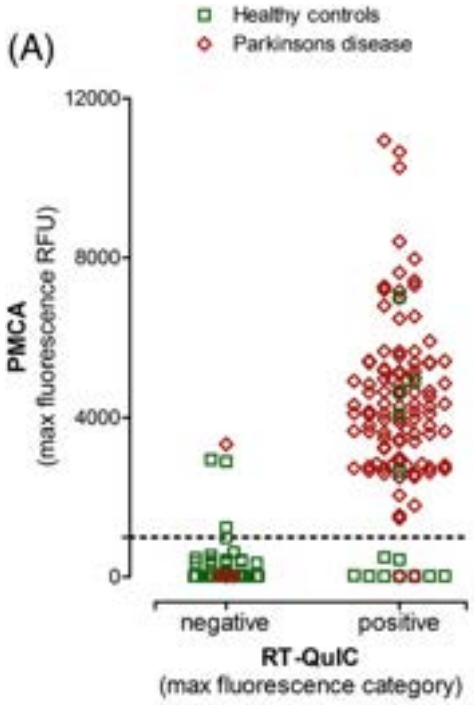
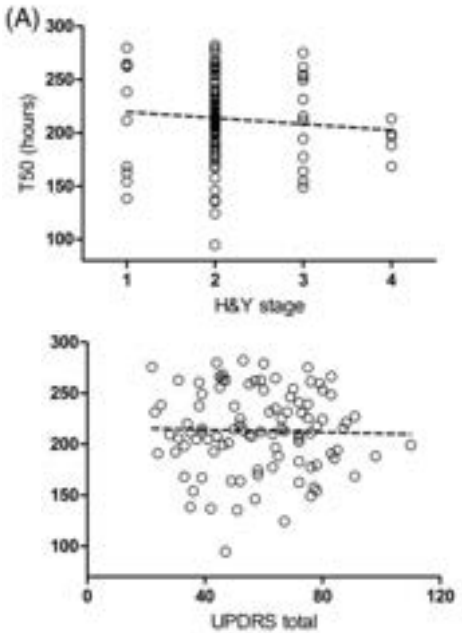


TABLE 2. Predictability of assays for PD diagnosis

	Only Assay Concordant Subjects Included	PMCA	RT-QuIC
Sensitivity	97.1% (92.9–99.1)	95.2% (90.6–98.0)	96.2% (91.4–98.7)
Specificity	92.5% (86.2–95.7)	89.9% (83.8–93.5)	82.3% (76.0–85.6)
PPV	95.2% (91.1–97.2)	92.6% (88.1–95.2)	87.8% (83.5–90.1)
NPV	95.4% (88.9–98.6)	93.4% (87.1–97.2)	94.2% (87.0–98.0)
AUC	0.9480	0.9256	0.8923

Sensitivity, specificity, PPV, NPV, and AUC of the ROC analysis. Values in parentheses indicate 95% confidence intervals. Of 105 PD and 79 HC subjects, the assay results were concordant in 102 PD and 67 HC subjects.



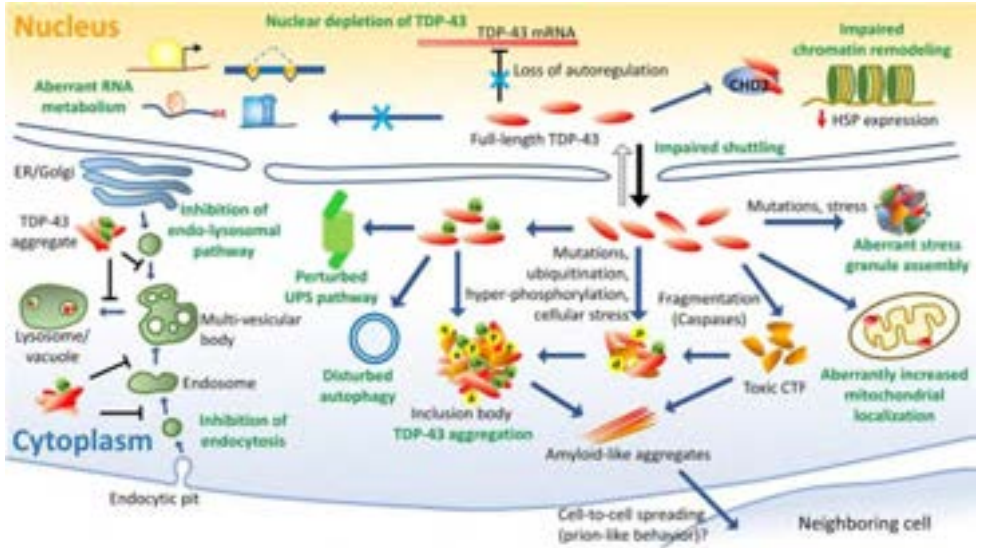
Kang et al., Mov Disord 34:536, 2019

Blood-based Biomarkers for α-Synucleinopathies

Biomarker	Sample Type	Cohort Size	Reported Performance	Key Strength	Reference
α-synuclein (total)	Plasma/Serum	Varies (50–200+)	Conflicting; not specific to PD	Widely studied but low specificity	Parnetti et al., 2019
Oligomeric α-synuclein	Plasma/Serum	Small to moderate (30–150)	Higher in PD/DLB; modest discrimination	Potentially specific to pathology	El-Agnaf et al., 2006 (Retracted)
pS129 α-synuclein	Plasma/Serum	Small (20–100)	Increased in synucleinopathies; early-stage detection	Pathologically relevant; early changes	Majbour et al., 2016
DJ-1	Plasma	Small (30–100)	Increased in PD vs controls; low specificity	Oxidative stress marker	Waragai et al., 2006
Exosomal α-synuclein	Plasma-derived exosomes	Small (20–80)	Potential early biomarker for PD	Enriched in PD-derived vesicles	Shi et al., 2014
Inflammatory cytokines (IL-6, TNF-α)	Plasma/Serum	Variable	Elevated in PD and DLB, but nonspecific	Reflects immune activation	Qin et al., 2016
ApoA1	Plasma	Small to moderate (50–200)	Lower in PD vs controls; candidate risk biomarker	Lipid metabolism; inverse risk association	Qiang et al., 2013
Clusterin (ApoJ)	Plasma	Moderate (100–250)	Increased in DLB; also seen in AD	Common in multiple dementias	Thambisetty et al., 2011

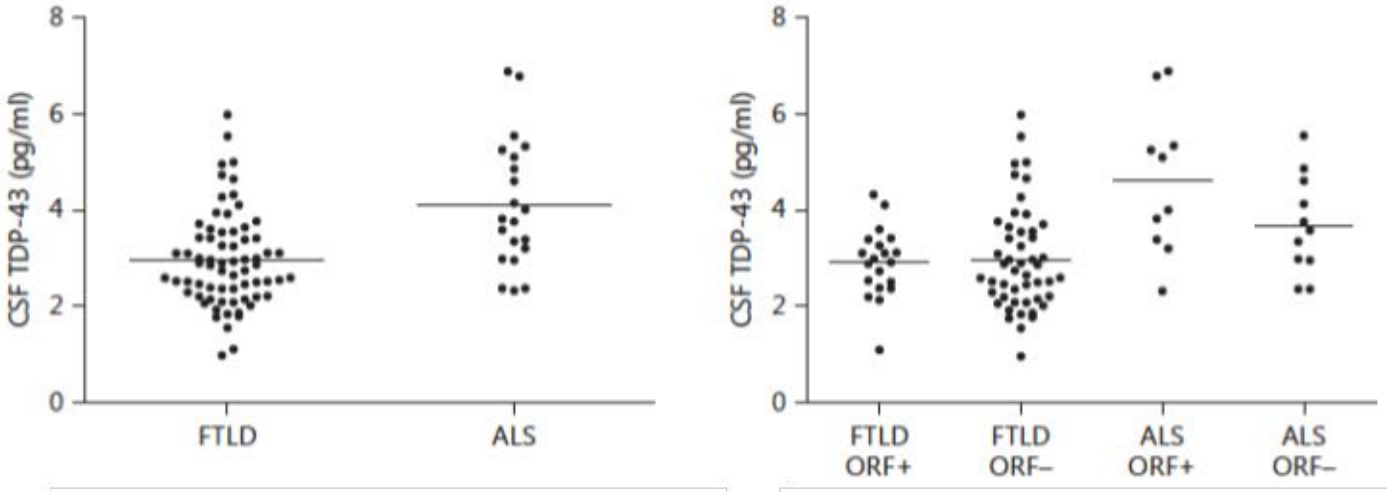
TDP-43

- Trans-active response (TAR) DNA binding protein-43 (43 kDa)
- Versatile RNA/DNA binding protein involved in RNA metabolism
- Highly expressed in brain but many other tissues as well
- Phosphorylated and ubiquitinated TDP-43 aggregates into extranuclear inclusions in most MND, some FTD and other neurodegenerative diseases (variable).



Prasad et al., Frontiers Mol Neurosci 2019; 12:25

CSF TDP-43 in FTLD / ALS /C9orf72



Juntilla et al., Dement Ger Cogn Disorders 2016; 6:142

Biomarkers for Autopsy-Confirmed TDP-43 Pathology (FTD-TDP, LATE, ALS)

Biomarker	Biofluid/ Modality	Disease	Cohort (n)	Key Findings	Reference (AMA)
Plasma GFAP, NfL, IL-6, IL-8, TNFR2 (composite)	Plasma	LATE, AD controls	ROSMAP (n > 300+ autopsy-confirmed)	Composite proteomic signature predicted LATE-NC (stage ≥2) independently of AD pathology	Guo T et al. JAMA Neurol. 2024;81(2):152-162.
CSF phosphorylated TDP-43 (pTDP-43)	CSF	ALS, FTD	Small series (n < 50) with some autopsy-confirmed	Elevated in ALS, but low sensitivity/specificity; poor reproducibility	Feneberg E et al. Brain. 2021;144(8):2383-2395.
[18F]AV-1451 (tau PET) (negative)	PET Imaging	LATE vs. AD	Autopsy-confirmed FTLD cohort (n = 84)	LATE-NC cases had low AV-1451 retention, helping distinguish from AD	Robinson JL et al. Brain. 2021;144(6):1970-1981.
Cortical thinning (MRI)	MRI	FTD-TDP vs. FTD-tau	Autopsy-confirmed FTLD cohort (n = 84)	MRI atrophy patterns differentiate FTLD-TDP vs. FTLD-tau	Whitwell JL et al. Brain. 2010;133(3):720-735.
Skin biopsy TDP-43 aggregates	Skin	ALS, FTD	Small n (<20), some autopsy correlation	Cytoplasmic pTDP-43 inclusions found in dermal fibroblasts; not yet validated broadly	Gonzalez-Rojas R et al. Acta Neuropathol. 2020;139(5):827-836.

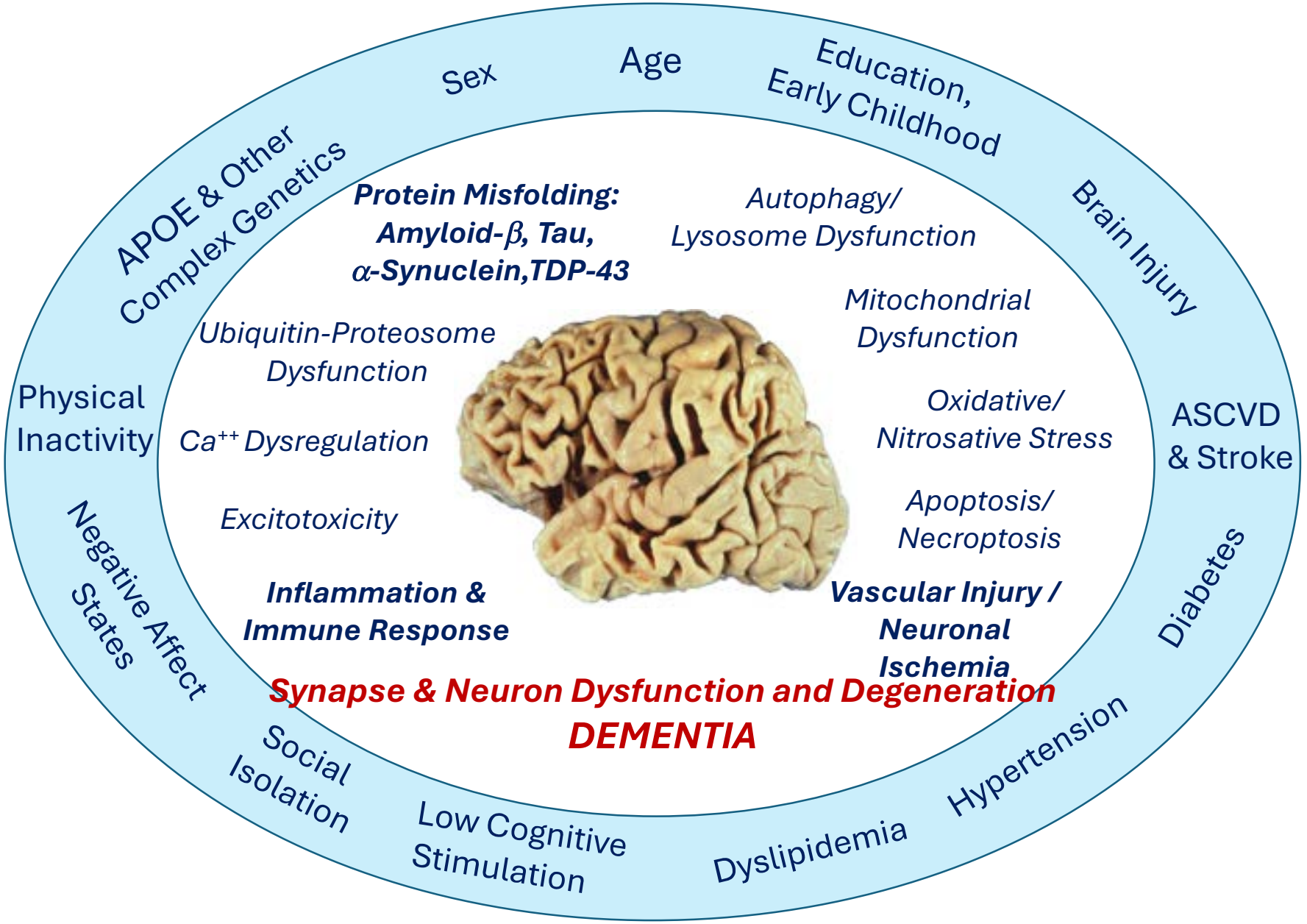
Blood-based Biomarkers for FTD diseases

Assay	Sample	Cohort Size	Sensitivity / Specificity / AUC	Key Strength	Reference
GFAP + Aβ42/40 + ApoE4	Plasma	497 decedents (ROSMAP)	AUC ~0.75 (LATE)	Multimarker panel; autopsy validated	Yu et al., Nat Commun. 2023
NfL	Plasma	Subset of ROSMAP	Modest elevation; nonspecific	Robust axonal injury marker	Yu et al., Nat Commun. 2023
Progranulin (GRN carriers)	Plasma	~100 FTD (GRN+ / GRN–)	High sensitivity/specificity for GRN mutation	Reliable genetic biomarker for GRN mutation	Various reviews
Plasma TDP-43 (total, pTDP-43)	Plasma	85 FTD-mutation carriers	Increased in GRN/C9orf72; inconsistent	First direct TDP-43 blood measure; experimental	Suarez-Calvet et al., JNNP 2014
EV TDP-43 + 3R/4R tau ratio	Plasma EVs	~1100 across 2 cohorts	AUC >0.85–0.99 (FTLD-TDP vs tau)	High diagnostic accuracy; validated	Nature Med 2024 (DESCRIBE study)

Blood-based Biomarkers for Other Tauopathies

Assay	Sample	Cohort Size	Sensitivity / Specificity / AUC	Key Strength	Reference
Plasma NfL	Plasma	PSP cohorts, size varies	Elevated in PSP; correlates with severity	Robust axonal injury marker	Wilke C et al. Front Neurol. 2019;10:659.
Plasma total tau + p-tau181 + Aβ	Plasma	APS cohort (incl. PSP, CBD, FTD-P)	AUC 0.932 for FTD-P vs APS	Multimarker differential diagnosis tool	Wang Y et al. Front Aging Neurosci. 2018;10:343.
Plasma p-tau217	Plasma	9 PSP/CBD in larger cohort	Low in PSP/CBD; not useful	Specific for AD, not PSP/CBD	Palmqvist S et al. JAMA Neurol. 2020;77(3):349–359.
Plasma EV 3R/4R tau ratio	Plasma EVs	~704 discovery + ~292 validation	Sens 93%, Spec 95% for PSP	High accuracy for 4R tauopathies	Chatterjee P et al. Nat Med. 2024;30(2):234–245.
Plasma EV TDP-43 + EV tau ratio	Plasma EVs	~996 total incl. PSP, FTD, ALS	AUC >0.9 for tau vs TDP vs PSP	Molecular differentiation of FTD subtypes	Chatterjee P et al. Nat Med. 2024;30(2):234–245.

Heterogeneous Risk Factors and Pathophysiological Drivers of Alzheimer's Disease & Related Dementias



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