

Stato dell'arte in tema di demenza

L'evoluzione della diagnostica neurochimica della m. di Alzheimer dal liquor al sangue

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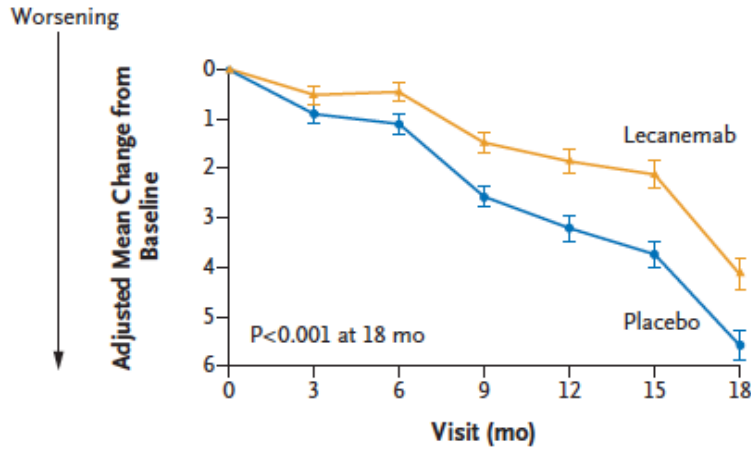
Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Università degli Studi di Milano

Indice

1. Esempio di farmaco anti-amiloide: lecanemab
2. Neuropatologia della m. di Alzheimer
3. Biomarcatori liquorali
4. Biomarcatori plasmatici
 - A-beta
 - P-tau
 - (GFAP)
5. Possibile ruolo dei biomarcatori plasmatici nel prossimo futuro

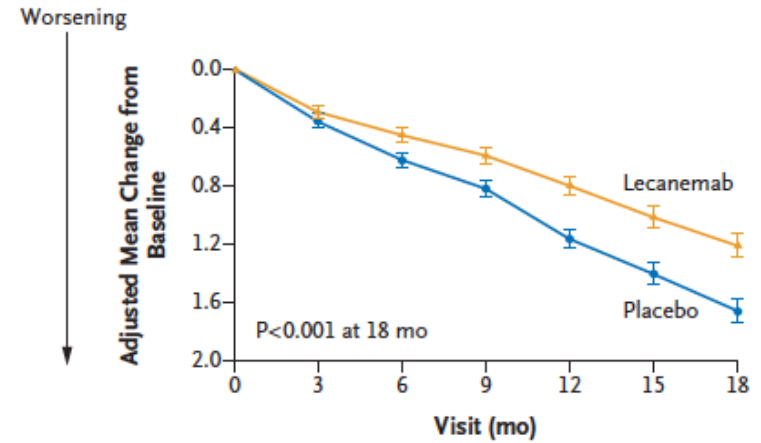
Un farmaco anti-amiloide: lecanemab

C ADAS-Cog14 Score



No. of Participants

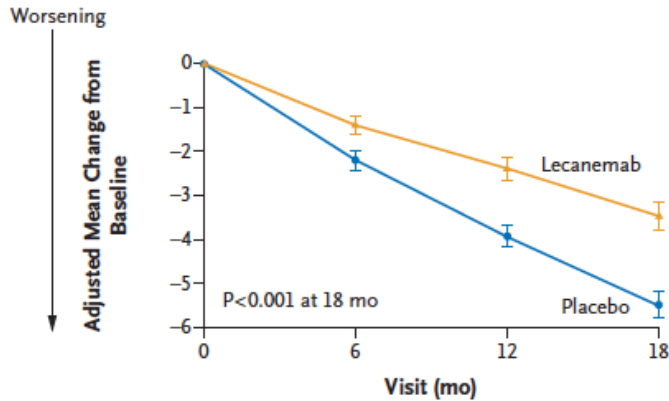
Lecanemab	854	819	793	771	753	730	703
Placebo	872	844	823	807	770	762	738



No. of Participants

Lecanemab	859	824	798	779	765	738	714
Placebo	875	849	828	813	779	767	757

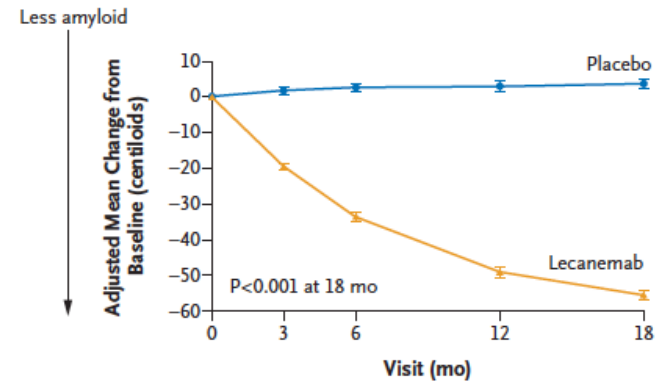
E ADCS-MCI-ADL Score



No. of Participants

Lecanemab	783	756	716	676
Placebo	796	783	739	707

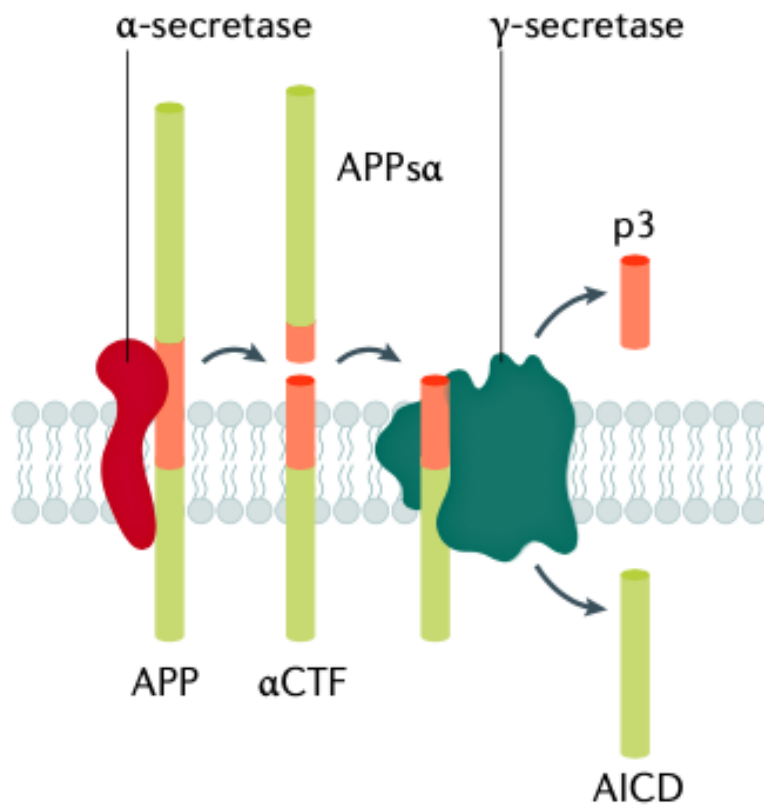
B Amyloid Burden on PET



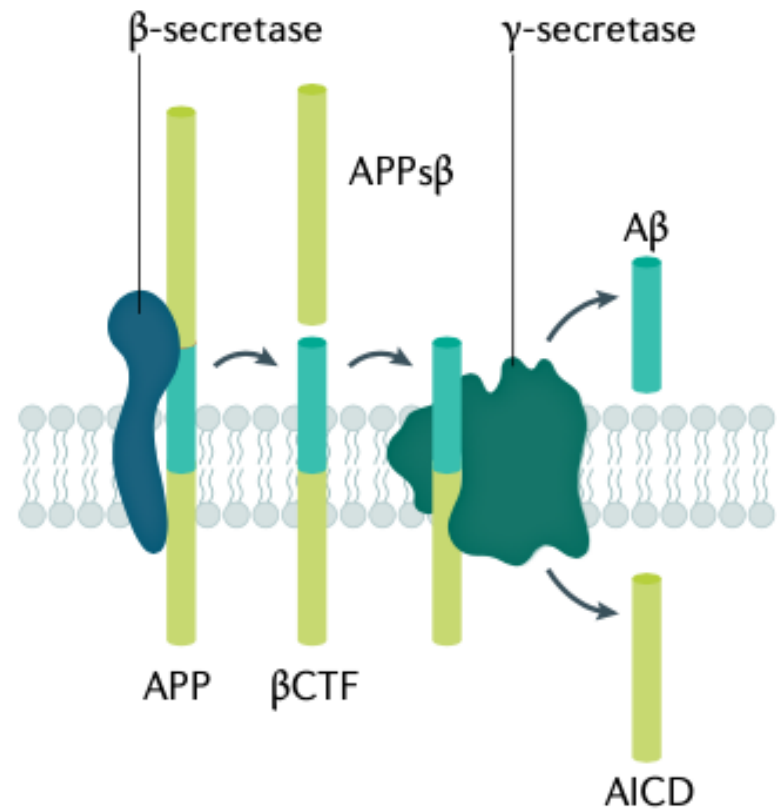
No. of Participants

Lecanemab	354	296	275	276	210
Placebo	344	303	286	259	205

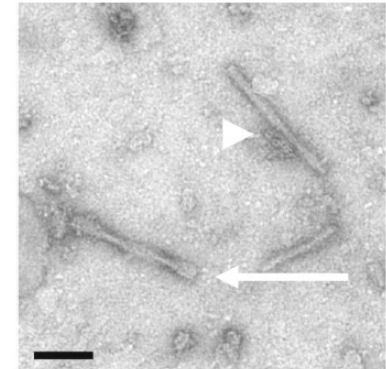
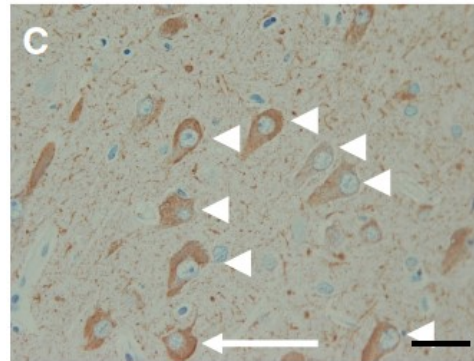
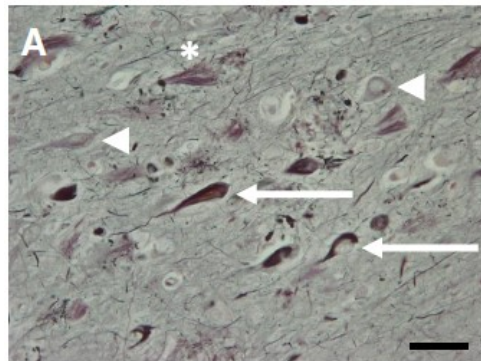
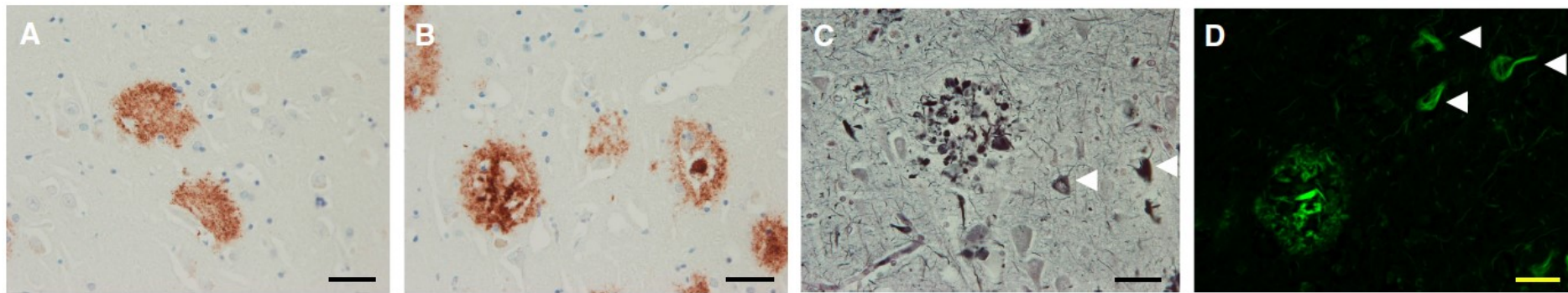
a α -secretase first pathway



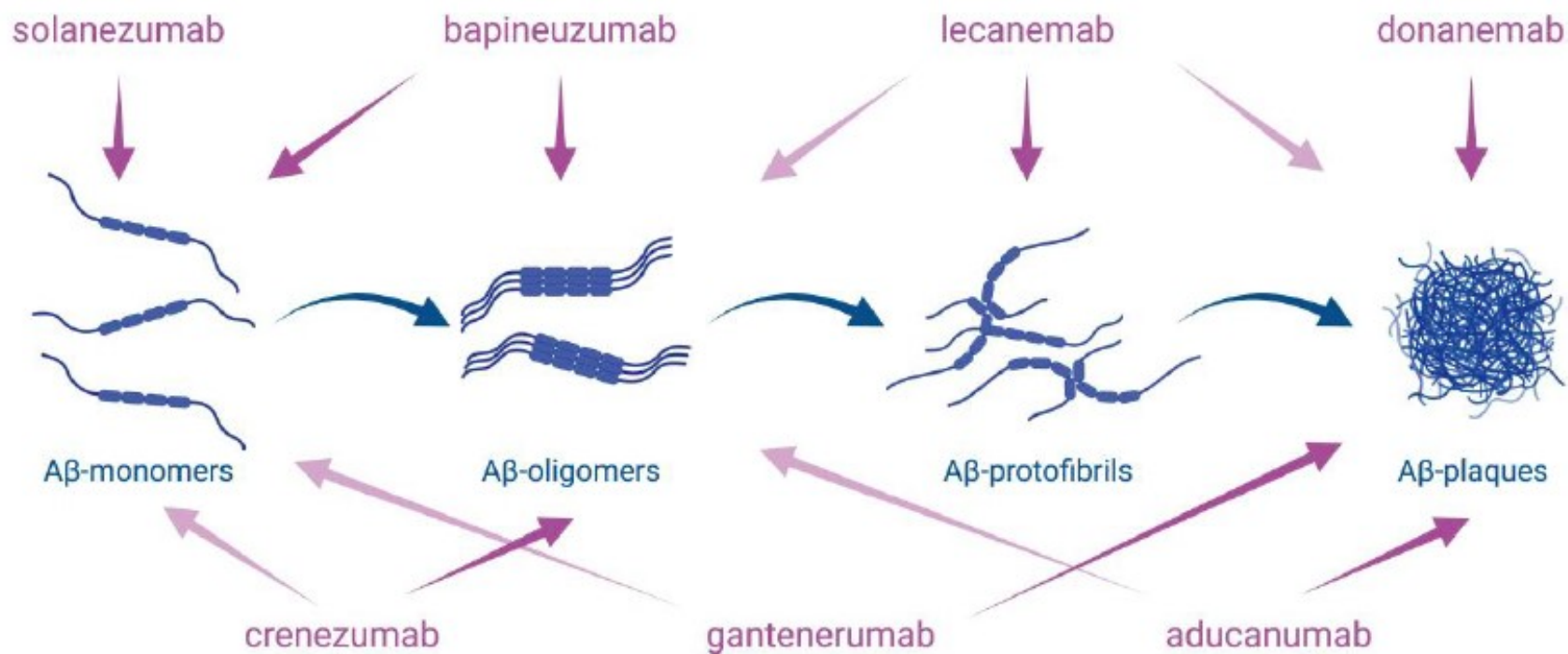
b β -secretase first pathway



Alterazioni neuropatologiche fondamentali

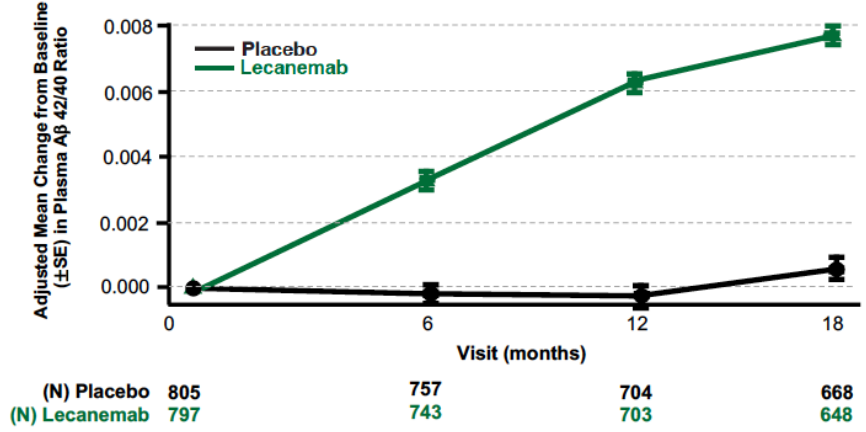


Dove agiscono i farmaci anti-amiloide

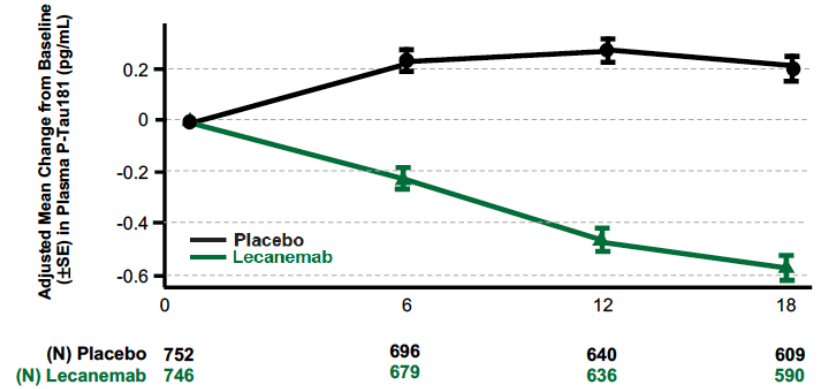


Biomarcatori nello studio di lecanemab

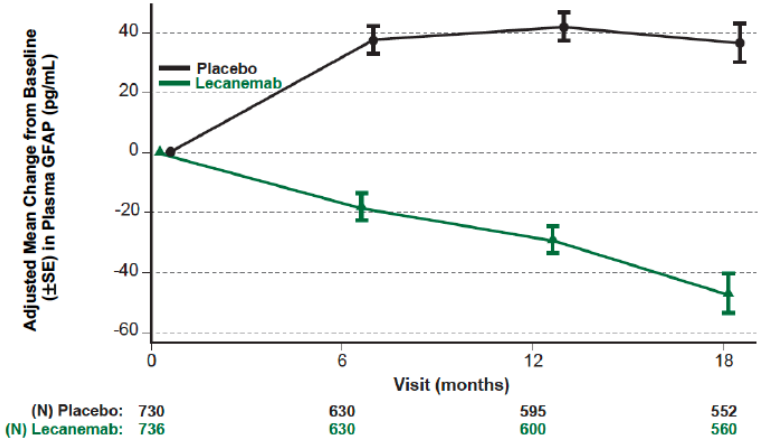
G. Plasma Aβ42/40 Ratio



H. Plasma P-Tau181



I. Plasma GFAP



Ma perché c'è bisogno dei biomarcatori?

TABLE 2. Sensitivity and Specificity of the Clinical Diagnosis of AD Relative to Stratified Clinical Confidence Levels and Minimum Threshold Levels for Histopathologic Severity

Neuropathologic AD Definition	Clinically Probable AD, n = 526	Clinically Probable or Possible AD, n = 648
CERAD NP Freq	n = 327	n = 373
Braak Stage V or VI n = 427	Sensitivity 76.6% Specificity 59.5%	Sensitivity 87.3% Specificity 44.3%
CERAD NP Mod or Freq	n = 366	n = 418
Braak Stage V or VI n = 486	Sensitivity = 75.3% Specificity = 63.0%	Sensitivity = 85.9% Specificity = 47.0%
CERAD NP Freq	n = 370	n = 421
Braak Stage III–VI n = 490	Sensitivity = 75.5% Specificity = 63.6%	Sensitivity = 85.9% Specificity = 47.1%
CERAD NP Mod or Freq	n = 438	n = 511
Braak Stage III–VI n = 618	Sensitivity = 70.9% Specificity = 70.8%	Sensitivity = 82.7% Specificity = 54.5%

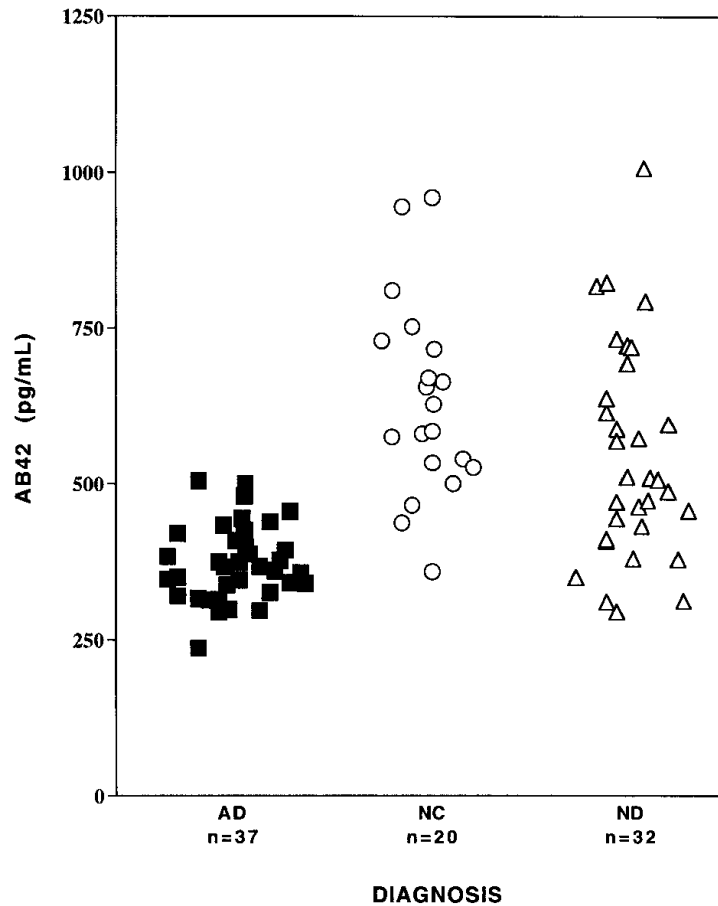
TABLE 5. Primary Neuropathologic Findings in the 271 Subjects Clinically Diagnosed as Not Being Either Probable or Possible AD

Primary Neuropathological Diagnosis*	No. Cases
Histopathologically defined AD	107†
Frontotemporal lobar degeneration	60‡
Lewy body disease, with or without AD	31§
Creutzfeldt-Jakob disease and other prion encephalopathies	23
Progressive supranuclear palsy	18
Tangle-only dementia or argyrophilic grain disease	9
Corticobasal degeneration	8
Pick's disease	6
Cerebrovascular disease	6
Hippocampal sclerosis, with or without AD‡	2
Amyotrophic lateral sclerosis	2
Miscellaneous (1 case each of neuronal intermediate filament disease, "leukodystrophy" and cerebellar atrophy)	3

TABLE 4. Primary Neuropathologic Diagnosis for the 88 Subjects Clinically Diagnosed as Probable AD But Not Meeting a Defined Minimum Threshold Level of Histopathologic Severity

Primary Neuropathologic Findings	No. Cases
Primary neuropathologic diagnosis of AD despite low level of AD histopathology	17
Tangle-only dementia or argyrophilic grain disease	15
Frontotemporal lobar degeneration*	15
Cerebrovascular disease	10
Lewy body disease, with or without AD†	9
Hippocampal sclerosis, with or without AD‡	9
Progressive supranuclear palsy	3
Corticobasal degeneration	2
Neuroaxonal dystrophy/Hallervorden-Spatz-like condition	2
Miscellaneous (1 case each of amyloid angiopathy, "small vessel disease," "TDP-43 proteinopathy," limbic encephalitis, Rosenthal fiber encephalopathy, "clinical dementia, no neuropathological substrate")	6

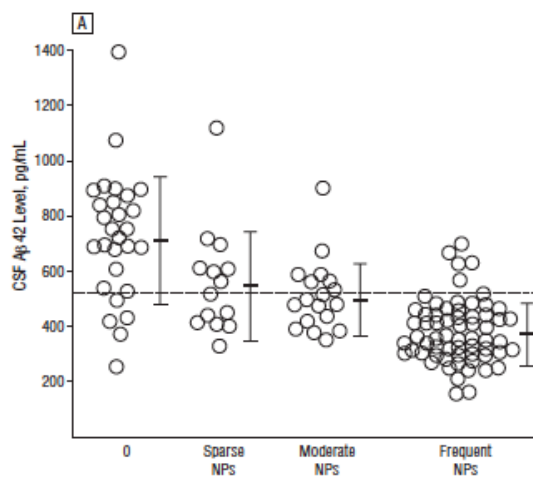
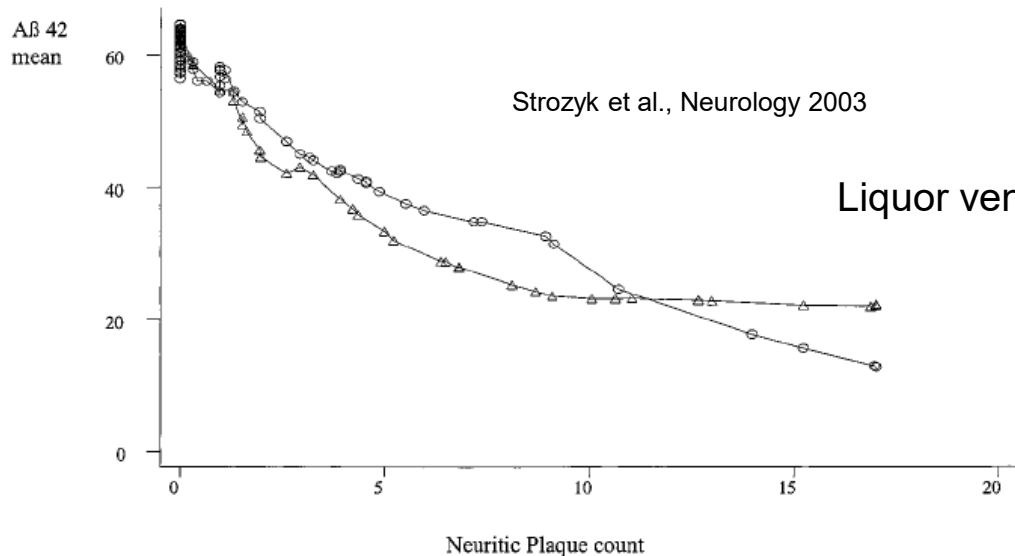
A β 42 è ridotta nel liquor



Reduction of β -Amyloid Peptide₄₂ in the Cerebrospinal Fluid of Patients with Alzheimer's Disease

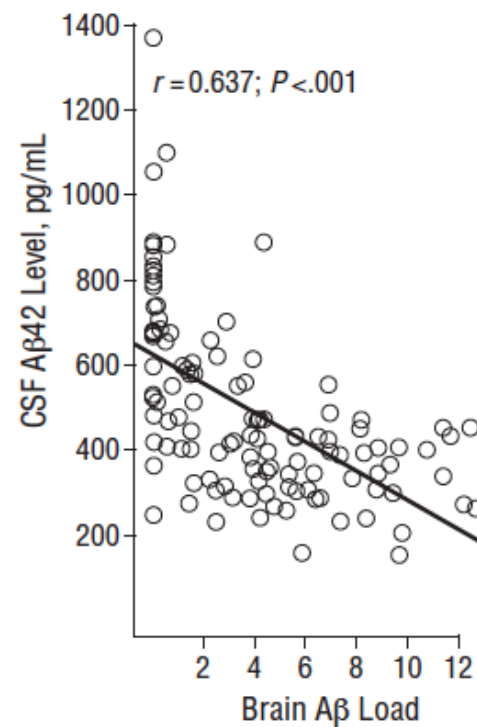
R. Motter, MPH,* C. Vigo-Pelfrey, PhD,* D. Kholodenko, MS,* R. Barbour, BS,* K. Johnson-Wood, BA,*
D. Galasko, MD,† L. Chang, MD,‡ B. Miller, MD,‡ C. Clark, MD,§ R. Green, MD,¶
D. Olson, MD,‡ P. Southwick, PhD,† R. Wolfert, PhD,* B. Munroe, PhD,†
I. Lieberburg, MD, PhD,* P. Seubert, PhD,* and D. Schenk, PhD*

Bassa A β 42: razionale fisiopatologico

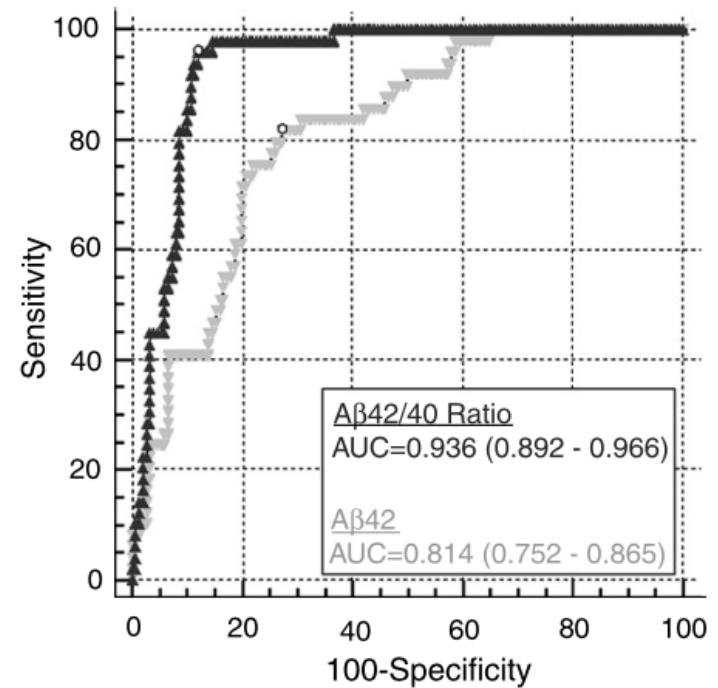
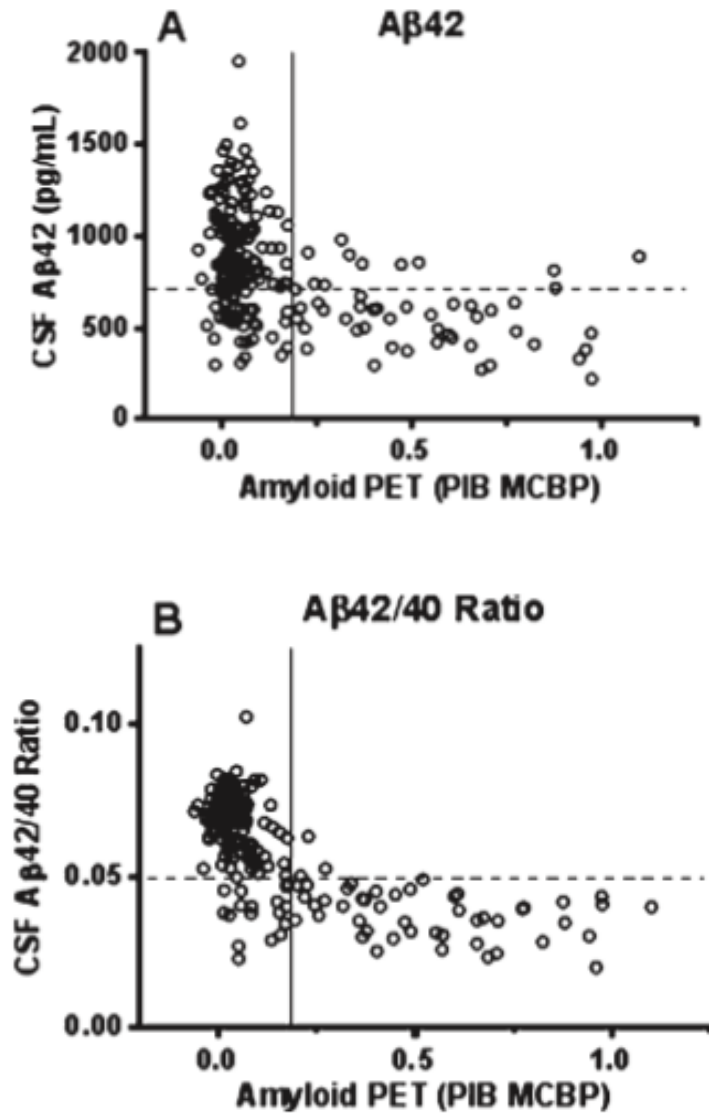


Liquor lombare da viventi

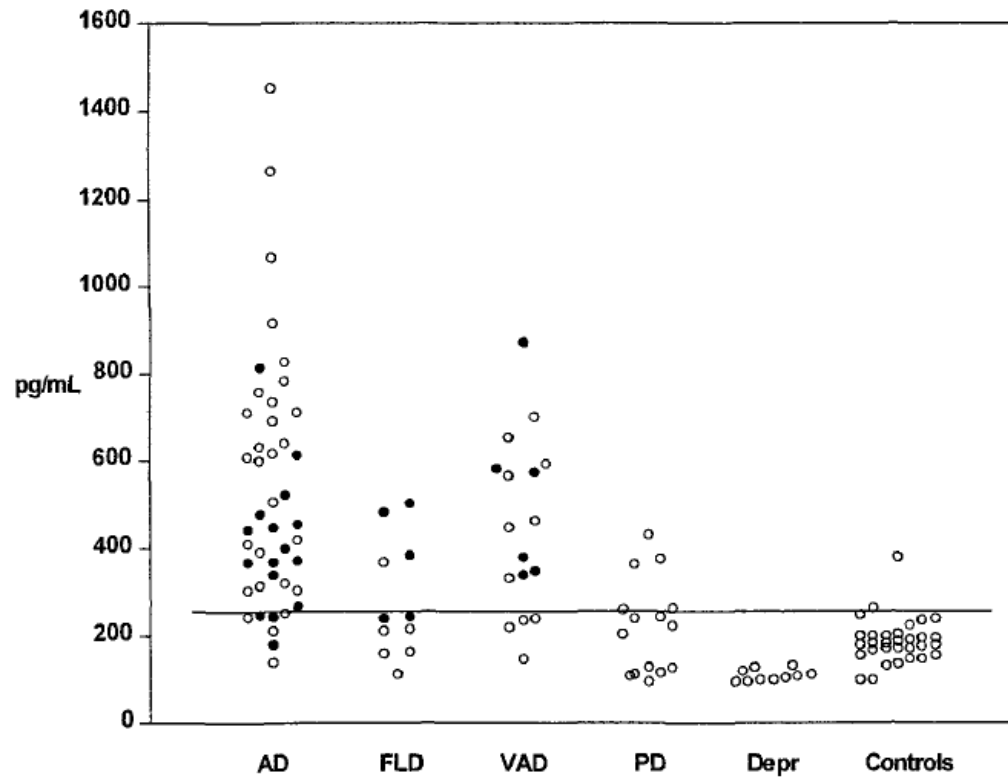
Tapiola et al., Arch Neurol 2009



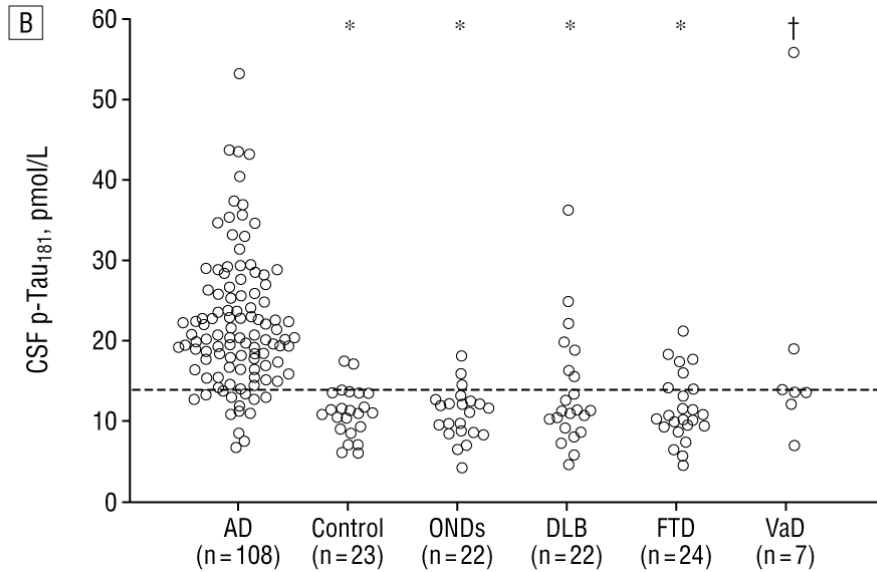
Rapporto con $A\beta$ PET e superiorità della ratio 42/40



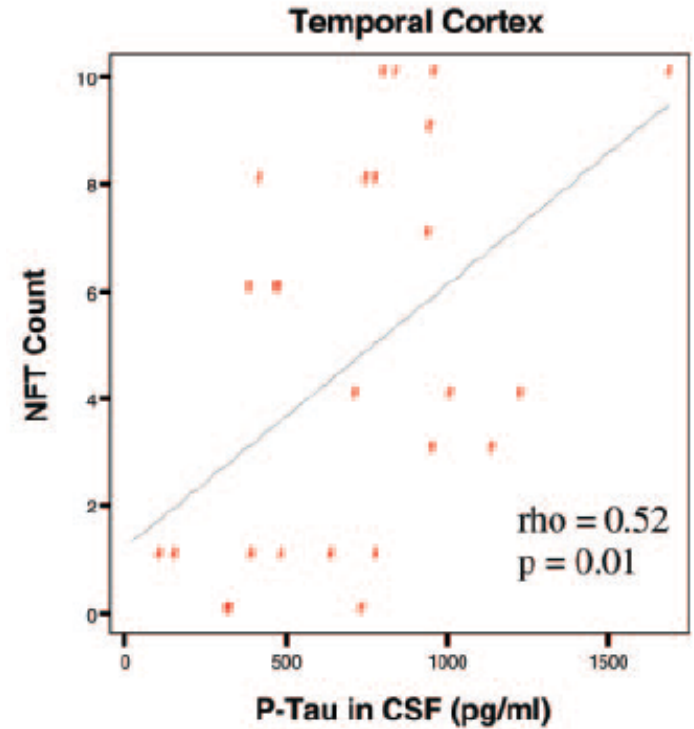
Tau totale



Tau fosforilata

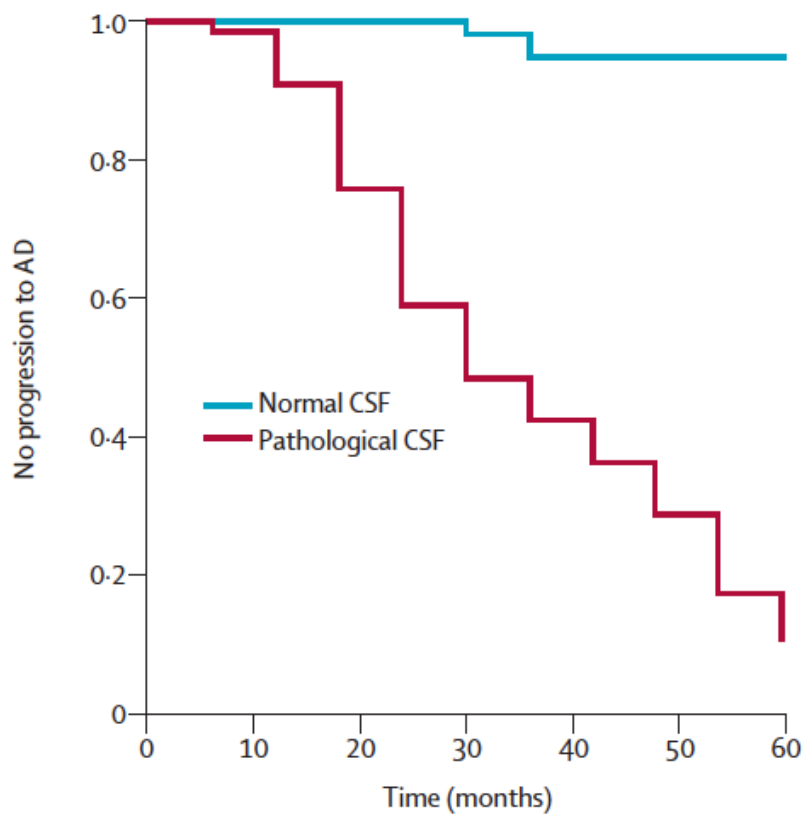


Hampel et al., Arch Gen Psychiatry 2004



Buerger et al., Brain 2006

Valore prognostico dei biomarcatori liquorali



Numbers at risk		0	10	20	30	40	50	60
Total	134	131	111	87	74	55	31	
Normal CSF	67	66	62	56	47	40	28	
Pathological CSF	67	65	49	31	27	15	3	

Ruolo crescente dei biomarcatori: Research Framework NIA-AA (2018)

2018 National Institute on Aging—Alzheimer’s Association (NIA-AA) Research Framework
NIA-AA Research Framework: Toward a biological definition of Alzheimer’s disease

Clifford R. Jack, Jr.,^{a,*}, David A. Bennett^b, Kaj Blennow^c, Maria C. Carrillo^d, Billy Dunn^e,
 Samantha Budd Haeberlein^f, David M. Holtzman^g, William Jagust^h, Frank Jessenⁱ,
 Jason Karlawish^j, Enchi Liu^k, Jose Luis Molinuevo^l, Thomas Montine^m, Creighton Phelpsⁿ,
 Katherine P. Rankin^o, Christopher C. Rowe^p, Philip Scheltens^q, Eric Siemers^r,
 Heather M. Snyder^d, Reisa Sperling^s
Contributors[†]: Cerise Elliott, Eliezer Masliah, Laurie Ryan, and Nina Silverberg

AT(N) biomarker grouping

-
- A:** Aggregated A β or associated pathologic state
 CSF A β_{42} , or A β_{42} /A β_{40} ratio
 Amyloid PET
- T:** Aggregated tau (neurofibrillary tangles) or associated pathologic state
 CSF phosphorylated tau
 Tau PET
- (N):** Neurodegeneration or neuronal injury
 Anatomic MRI
 FDG PET
 CSF total tau
-

		Cognitive stage		
		Cognitively Unimpaired	Mild Cognitive Impairment	Dementia
Biomarker Profile	A ⁻ T ⁻ (N) ⁻	normal AD biomarkers, cognitively unimpaired	normal AD biomarkers with MCI	normal AD biomarkers with dementia
	A ⁺ T ⁻ (N) ⁻	Preclinical Alzheimer’s pathologic change	Alzheimer’s pathologic change with MCI	Alzheimer’s pathologic change with dementia
	A ⁺ T ⁺ (N) ⁻	Preclinical Alzheimer’s disease	Alzheimer’s disease with MCI(Prodromal AD)	Alzheimer’s disease with dementia
	A ⁺ T ⁺ (N) ⁺			
	A ⁺ T ⁻ (N) ⁺	Alzheimer’s and concomitant suspected non Alzheimer’s pathologic change, cognitively unimpaired	Alzheimer’s and concomitant suspected non Alzheimer’s pathologic change with MCI	Alzheimer’s and concomitant suspected non Alzheimer’s pathologic change with dementia
	A ⁻ T ⁺ (N) ⁻	non-Alzheimer’s pathologic change, cognitively unimpaired	non-Alzheimer’s pathologic change with MCI	non-Alzheimer’s pathologic change with dementia
	A ⁻ T ⁻ (N) ⁺			
A ⁻ T ⁺ (N) ⁺				

Parziale marcia indietro? (IWG 2021)

Clinical diagnosis of Alzheimer's disease: recommendations of the International Working Group

Bruno Dubois*, Nicolas Villain*, Giovanni B Frisoni, Gil D Rabinovici, Marwan Sabbagh, Stefano Cappa, Alexandre Bejanin, Stéphanie Bombois, Stéphane Epelbaum, Marc Teichmann, Marie-Odile Habert, Agneta Nordberg, Kaj Blennow, Douglas Galasko, Yaakov Stern, Christopher C Rowe, Stephen Salloway, Lon S Schneider, Jeffrey L Cummings, Howard H Feldman

"We recommend that Alzheimer's disease diagnosis be restricted to people who have positive biomarkers together with specific Alzheimer's disease phenotypes, whereas biomarker-positive cognitively unimpaired individuals should be considered only at-risk for progression to Alzheimer's disease"

Panel 4: Proposed stratification of risk of asymptomatic people according to biomarker results

People with absolute risk

Carriers of autosomal dominant mutations (*APP*, *PSEN1*, *PSEN2*, or trisomy 21)¹⁰⁶

People with high risk

Cognitively unimpaired individuals with:

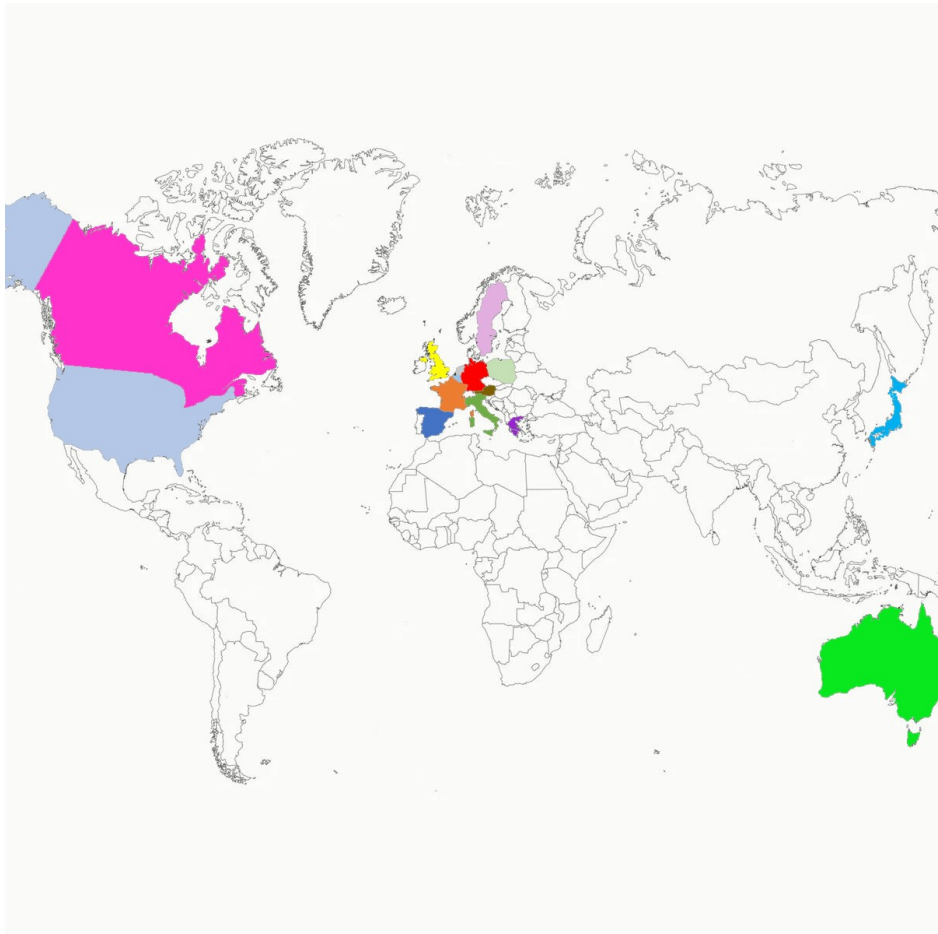
- CSF or PET that is amyloid-positive and tau positive²⁴⁻²⁶
- PET that is tau positive outside the limbic cortex (Braak stage 5 or higher)¹⁰⁷
- *APOE* ε4 homozygosity¹⁰⁸

People with undefined risk*

Cognitively unimpaired individuals with an incomplete biomarker pattern:

- Amyloid positive; tau negative or unknown³³
- Amyloid negative; tau positive⁵¹

Proposta di consenso internazionale su refertazione CSF

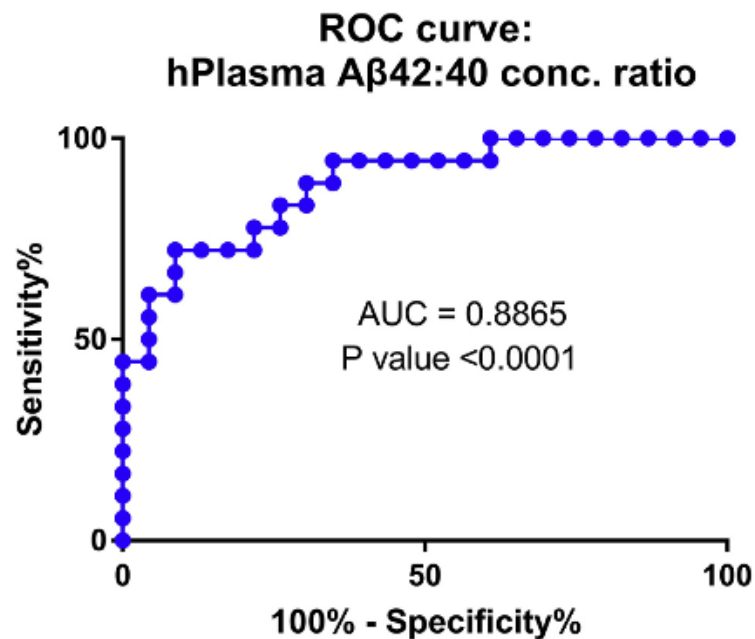
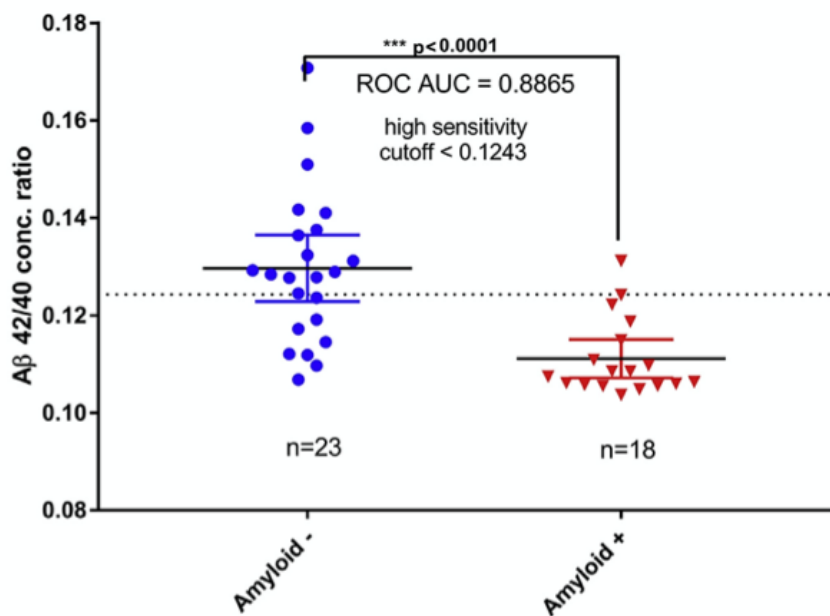


amyloid	t-tau	p-tau(181)	Consensus comments
N	N	N	Biochemical profile not consistent with Alzheimer's disease.
P	P	P	Biochemical profile consistent with Alzheimer's disease.
P	N	N	Biochemical profile consistent with an amyloidopathy.
N	P	N	Biochemical profile not consistent with Alzheimer's disease; may be consistent with other neurodegenerative disease and/or neuronal damage. (If t-tau is close to/above upper limit of detection with a high t-tau/p-tau[181] ratio, the profile may indicate Creutzfeldt-Jakob disease)
P	P	N	Atypical biochemical profile; may be consistent with Alzheimer's disease.
P	N	P	Atypical biochemical profile; consistent with Alzheimer's disease.
N	P	P	Atypical biochemical profile; not consistent with Alzheimer's disease.
N	N	P	Atypical biochemical profile; not consistent with Alzheimer's disease.

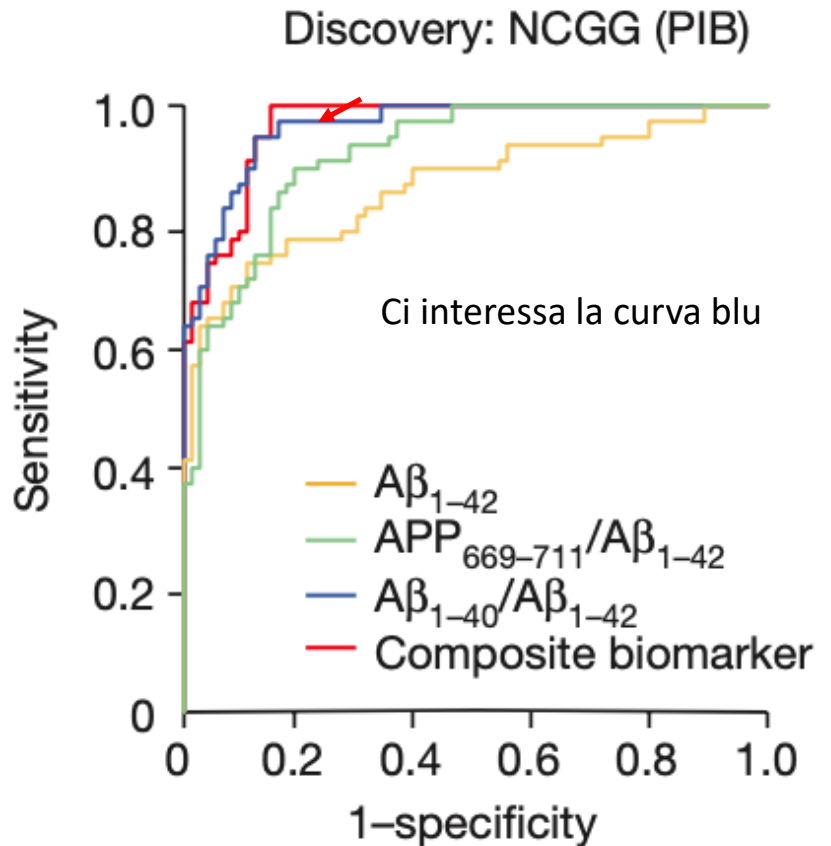
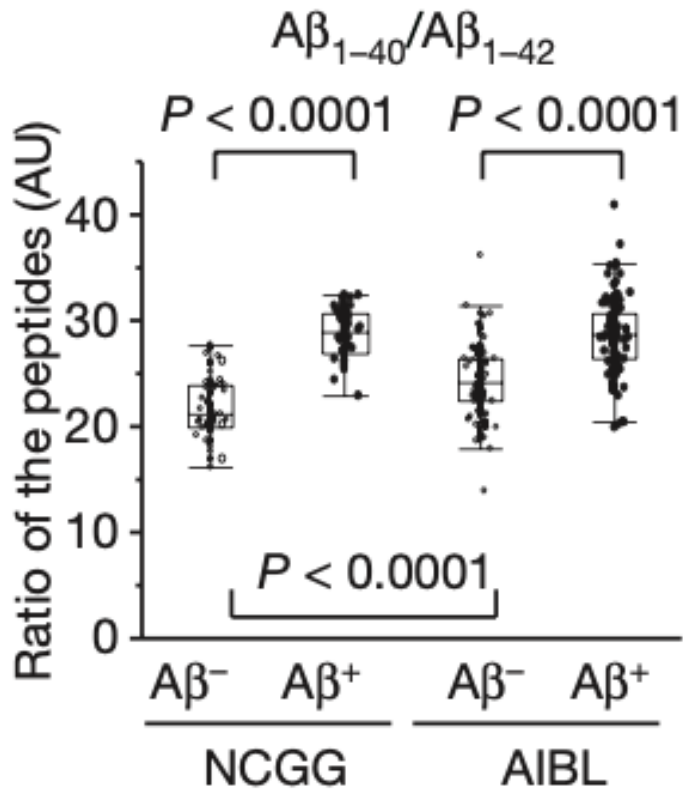
Note to be added to all comments: This biochemical profile must be interpreted in its clinical context and in conjunction with a physician.

Abbreviations: N, normal; P, pathological; p-tau(181), tau phosphorylated at threonine 181; t-tau, total tau.

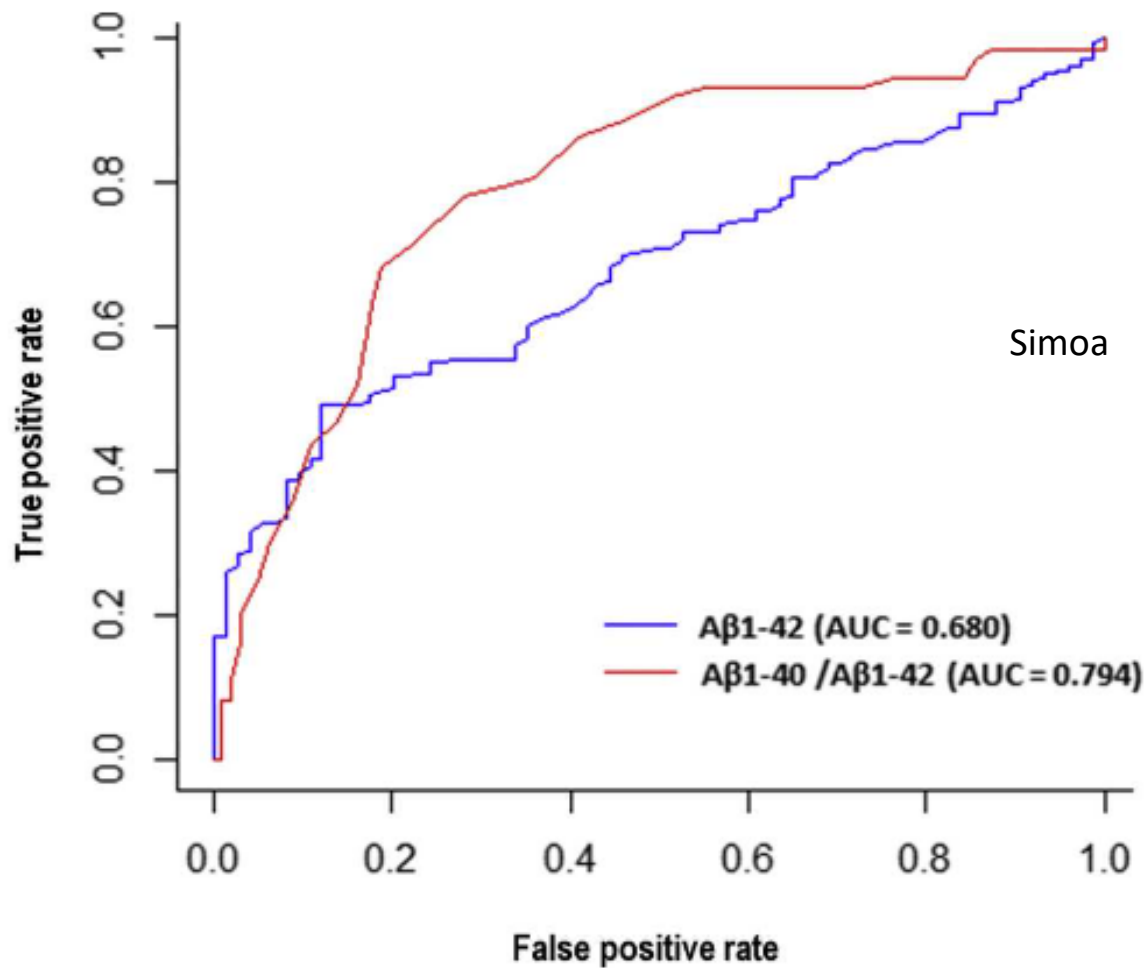
Biomarcatori NEL PLASMA: A β misurata con SILK



A-beta plasmatica con IP-MS

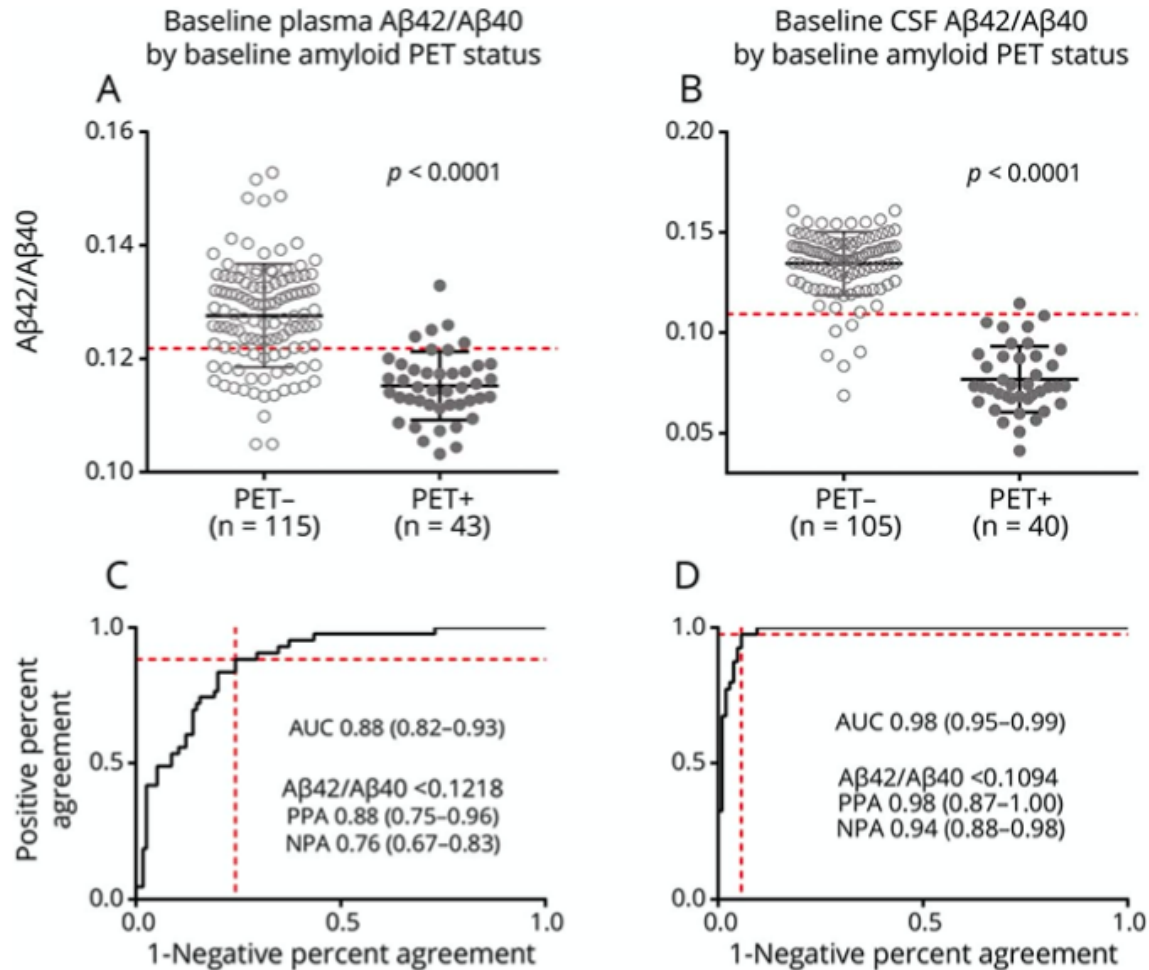


Superiorità della ratio 42/40

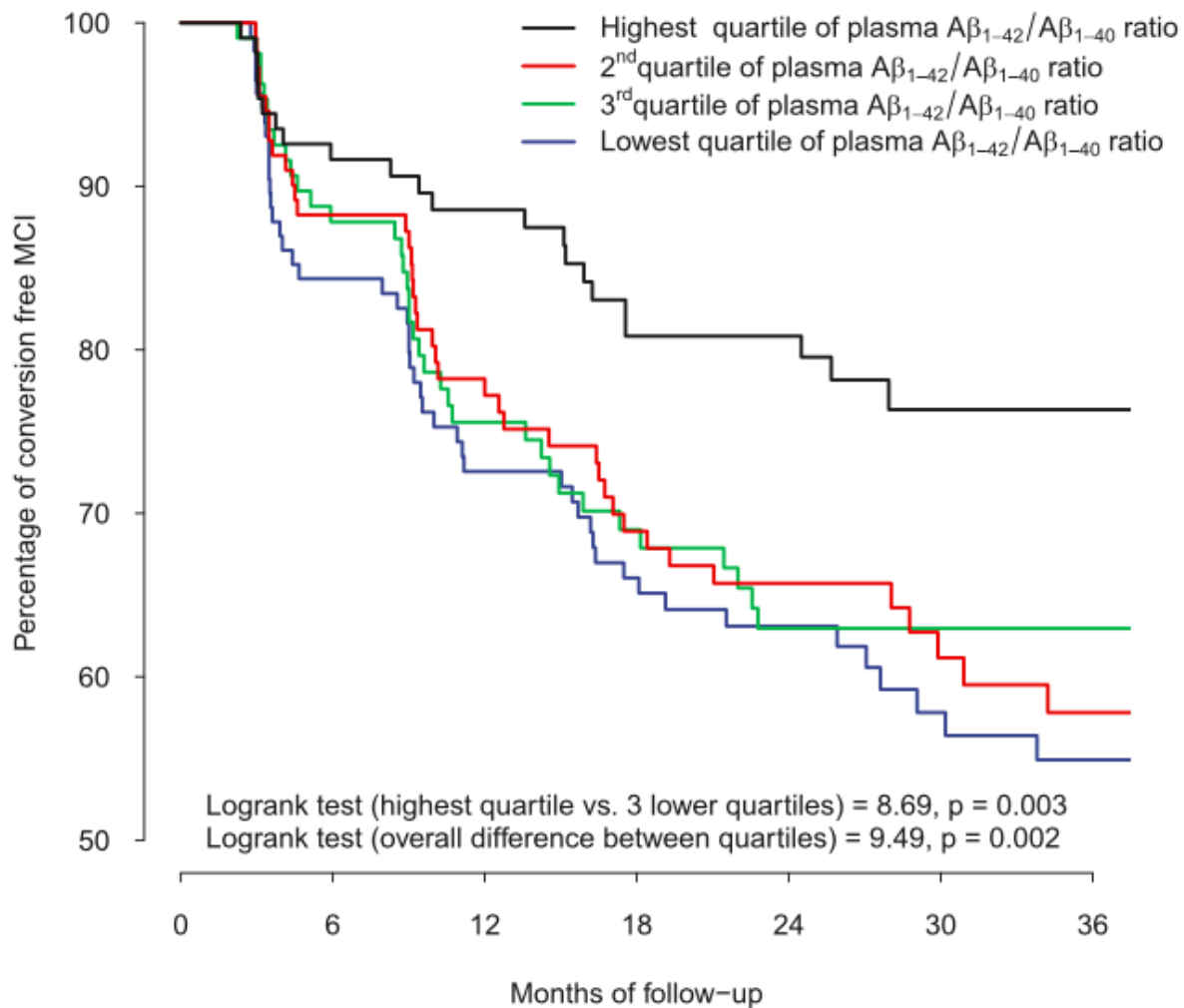


Differenza liquor vs plasma

Capacità della ratio su plasma/liquor di discriminare amy-PET +/-: liquor un po' meglio di plasma

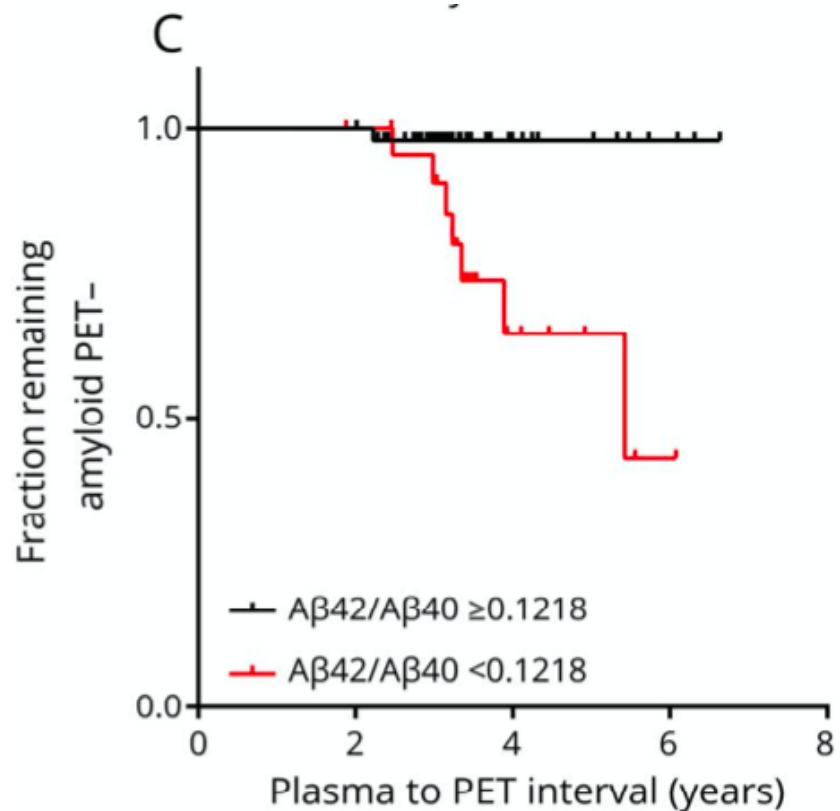


Conversione da MCI a demenza

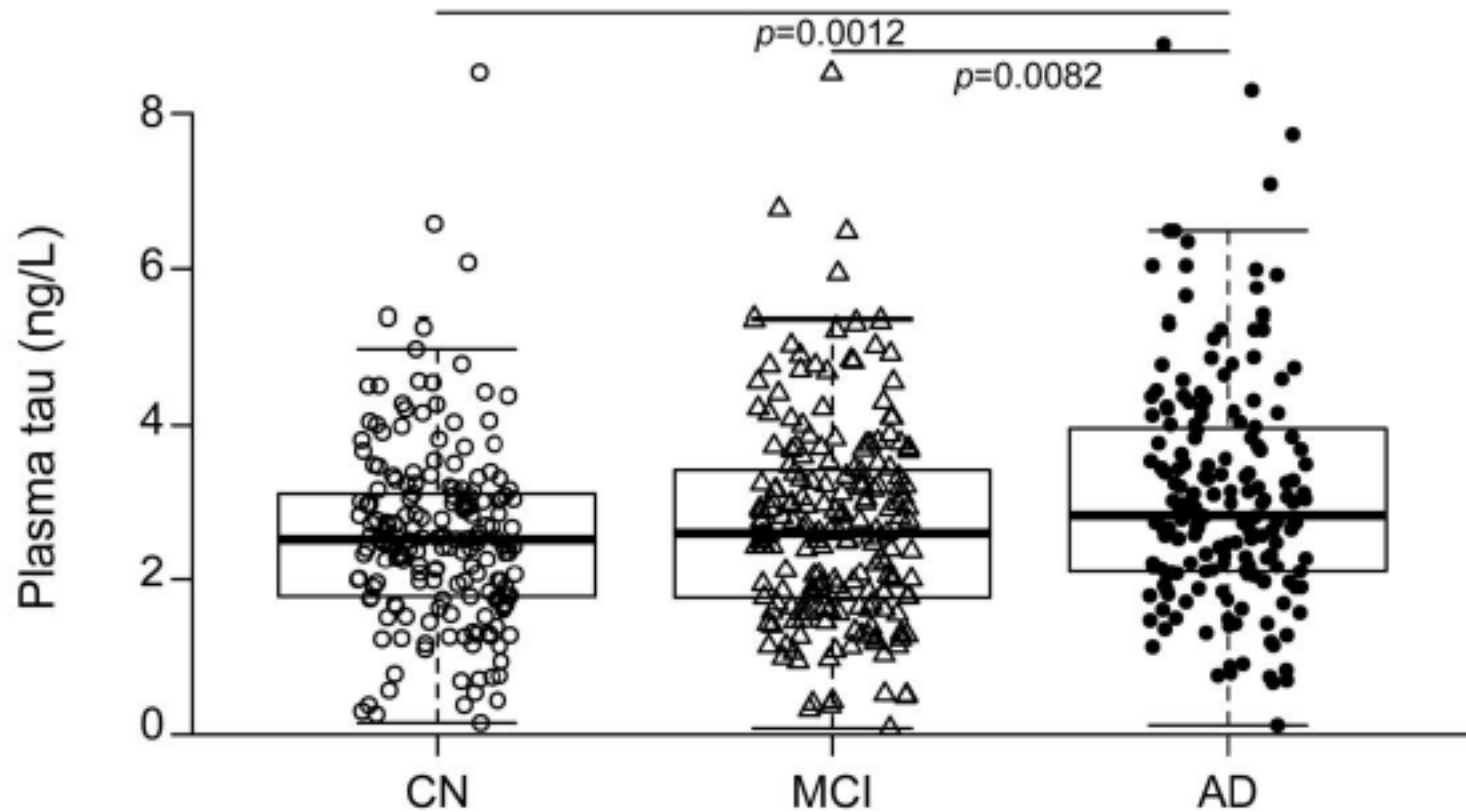


Predizione di futura conversione della amy-PET

Se io ho la amy-PET negativa ma una ratio 42/40 plasmatica patologica, probabilmente la mia amy-PET diventerà positiva



Tau totale su plasma



Brain-derived tau

<https://doi.org/10.1093/brain/awac407>

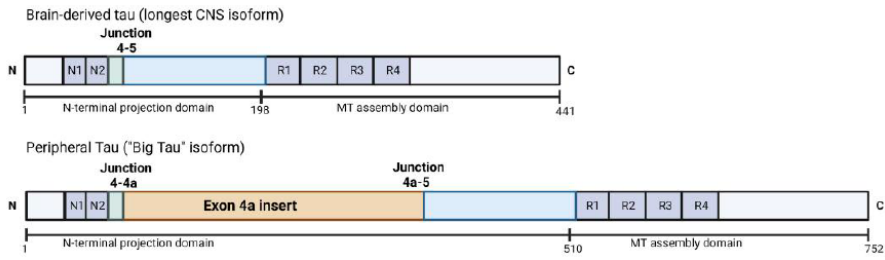
BRAIN 2023; 146; 1152-1165 | 1152

BRAIN
ORIGINAL ARTICLE

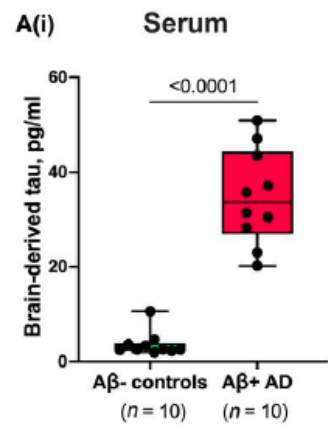


Brain-derived tau: a novel blood-based biomarker for Alzheimer's disease-type neurodegeneration

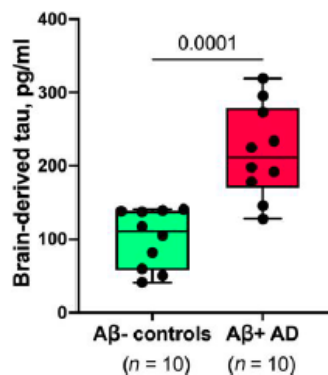
Fernando Gonzalez-Ortiz,¹ Michael Turton,² Przemyslaw R. Kac,¹ Denis Smirnov,³ Enrico Premi,⁴ Roberta Ghidoni,⁵ Luisa Benussi,⁵ Valentina Cantoni,⁴ Claudia Saraceno,⁵ Jasmine Rivolta,⁴ Nicholas J. Ashton,^{1,6,7,8} Barbara Borroni,⁴ Douglas Galasko,³ Peter Harrison,² Henrik Zetterberg,^{1,9,10,11,12} Kaj Blennow^{1,9} and Thomas K. Karikari^{1,13}



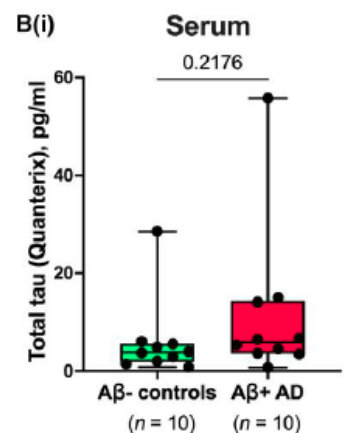
BRAIN-DERIVED TAU



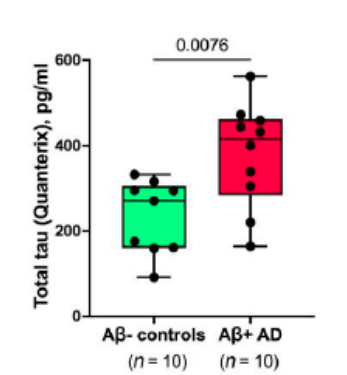
A(ii) CSF



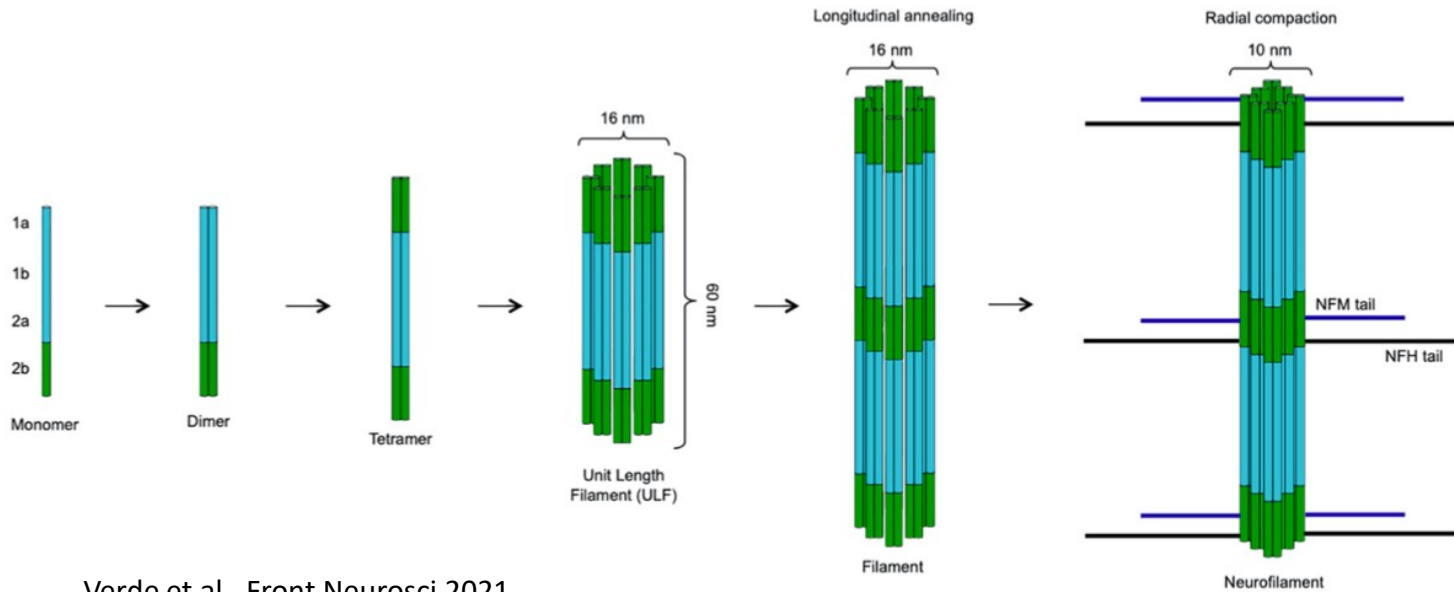
TOTAL TAU (QUANTERIX)



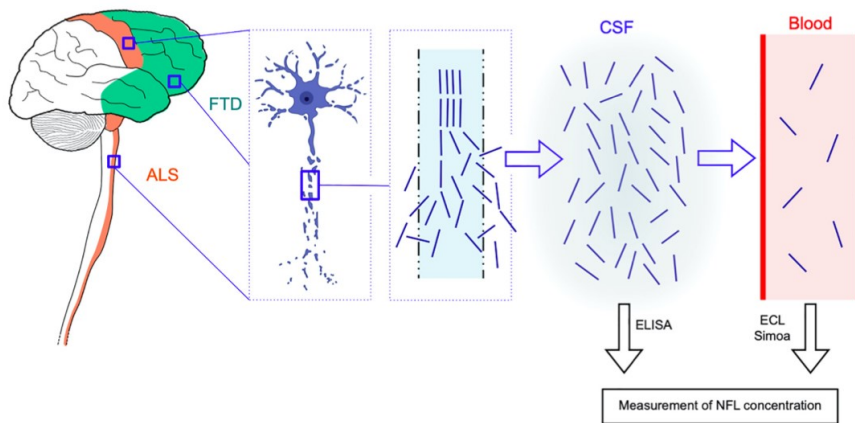
B(ii) CSF



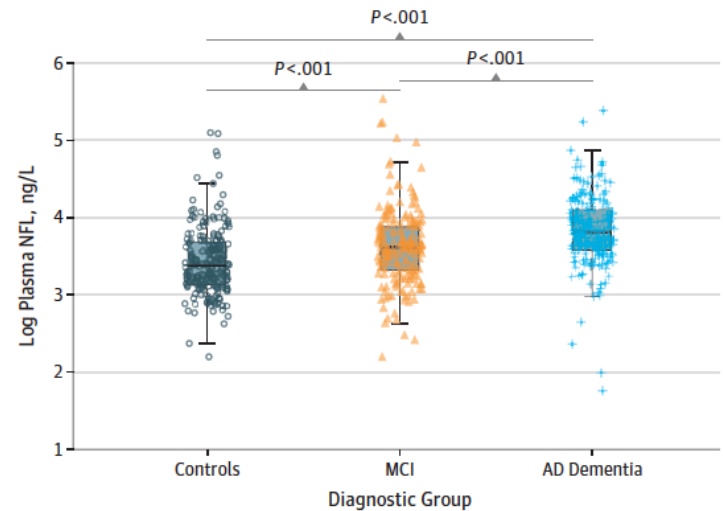
Neurofilamenti (NFL)



Verde et al., Front Neurosci 2021

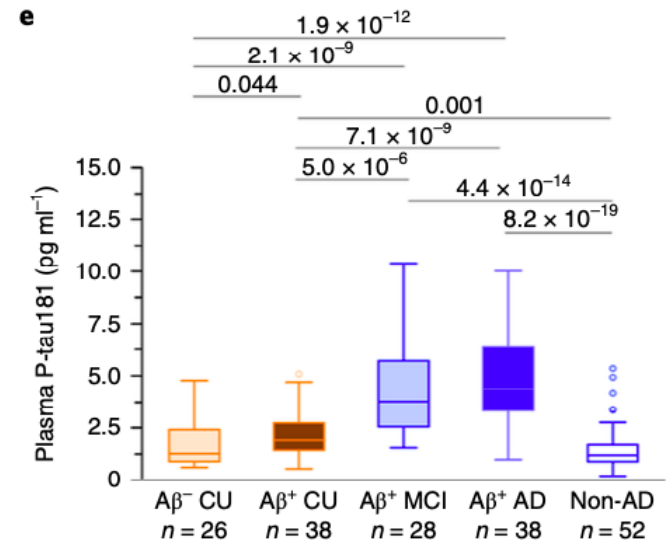
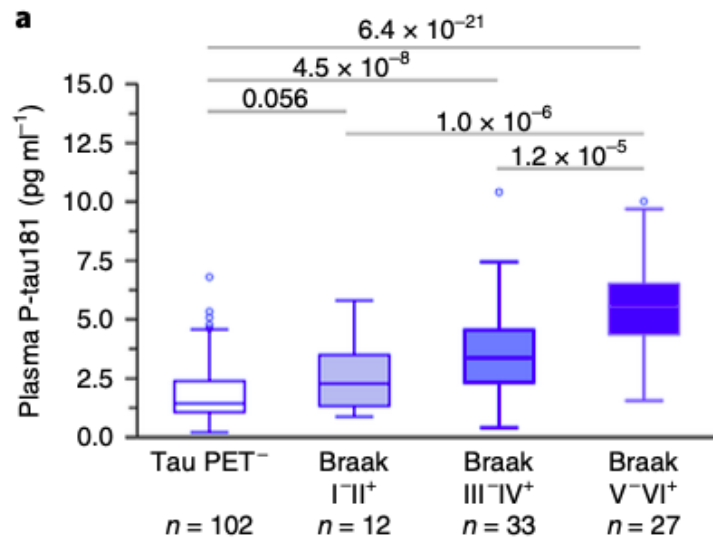


A Plasma NFL by diagnosis

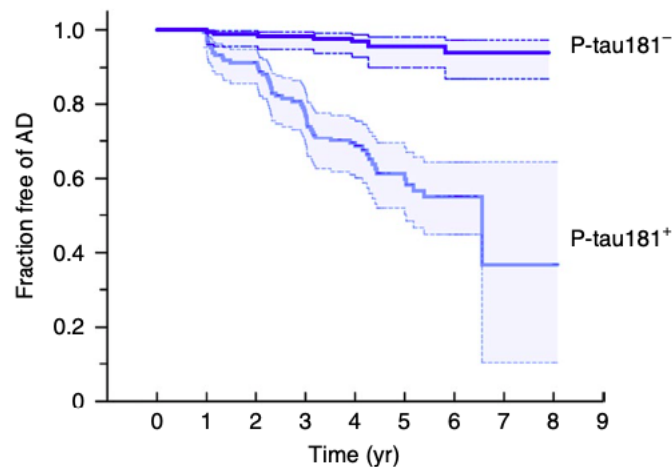


Mattsson et al., JAMA Neurol 2017

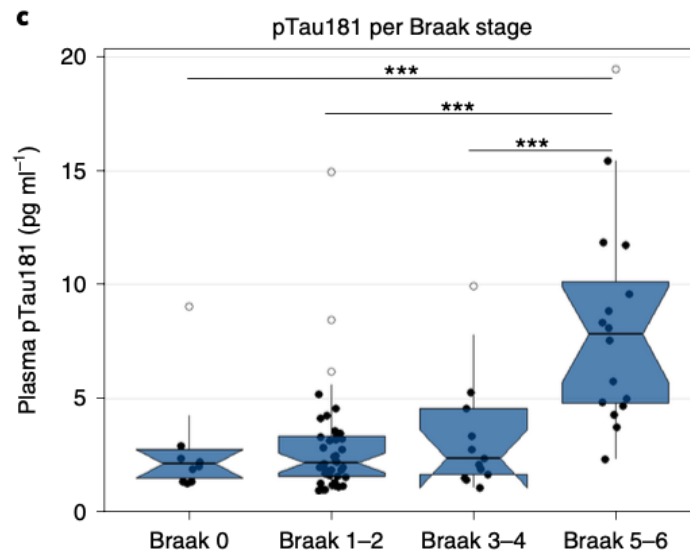
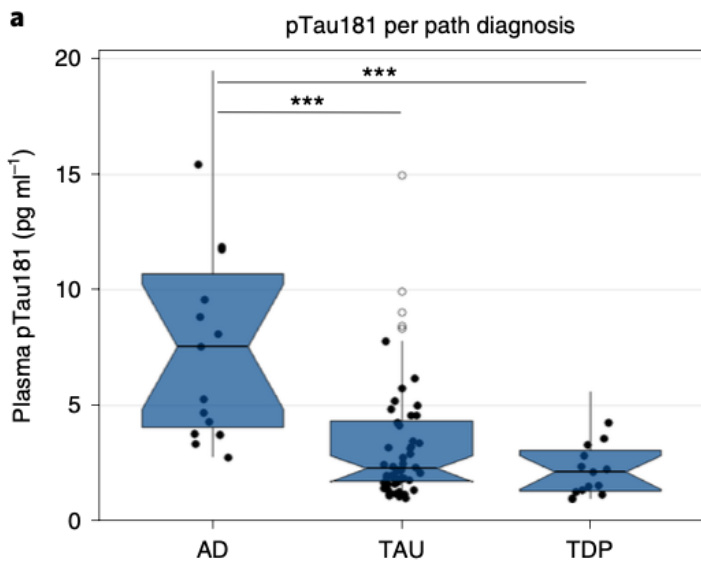
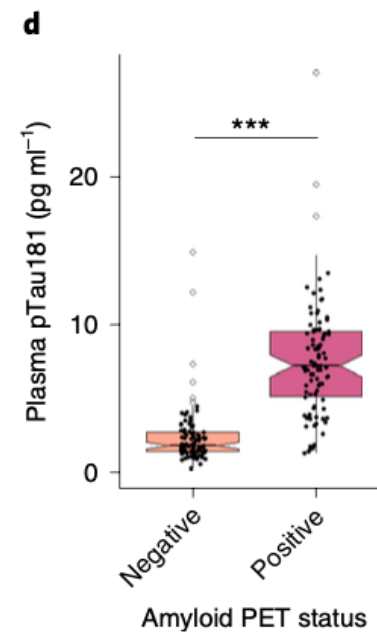
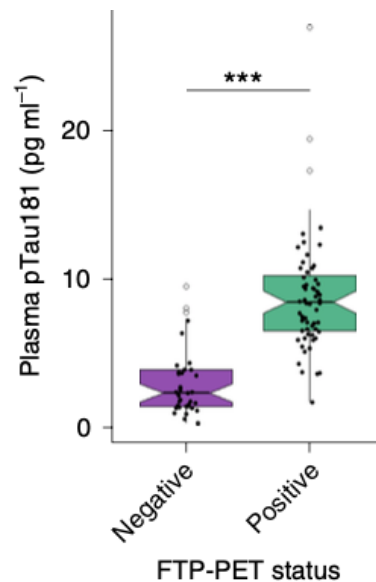
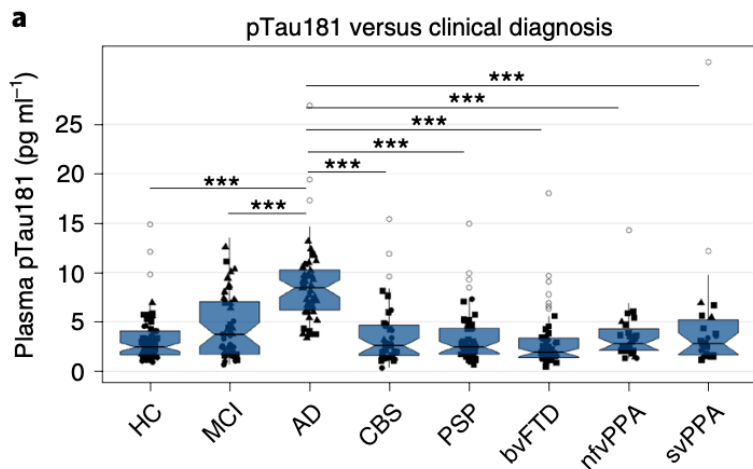
P-tau181 plasmatica: i lavori della primavera 2020 (I)



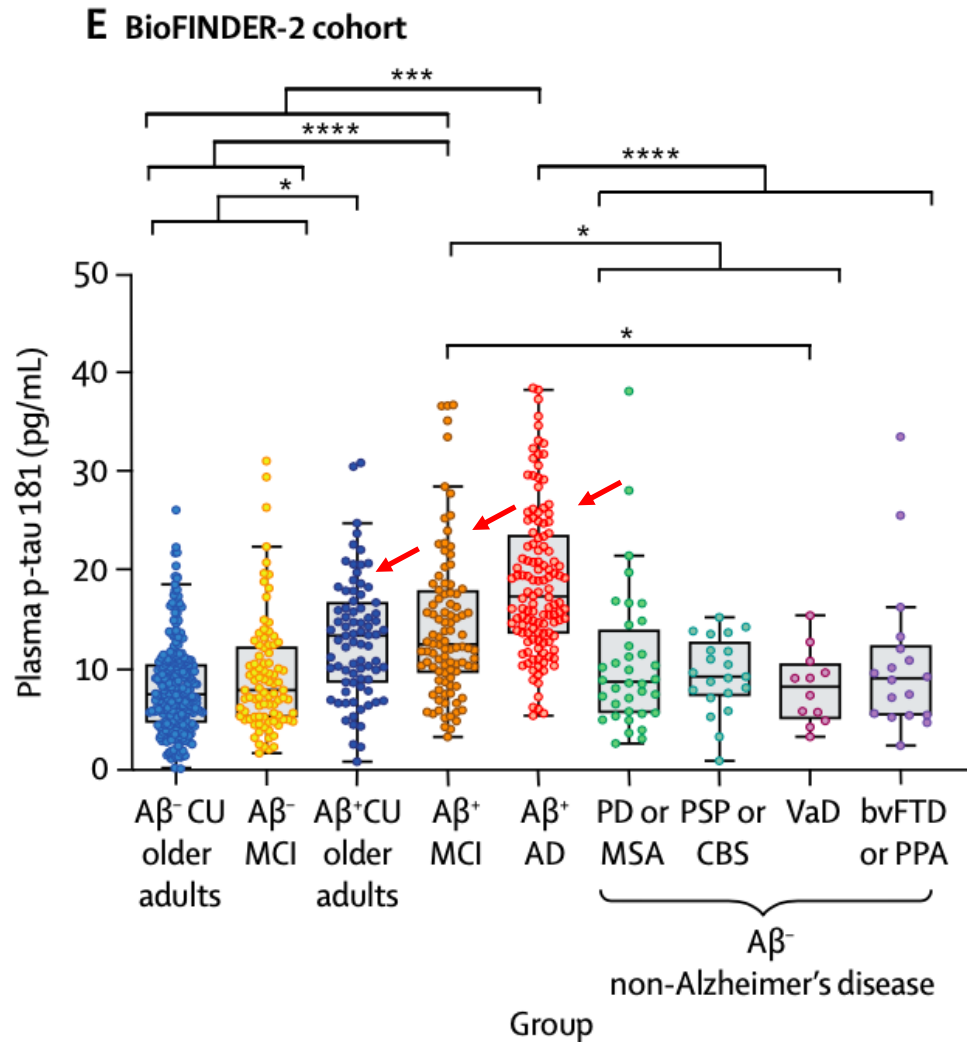
Conversione verso AD dementia (versus stabilità ma anche versus non-AD dementia)



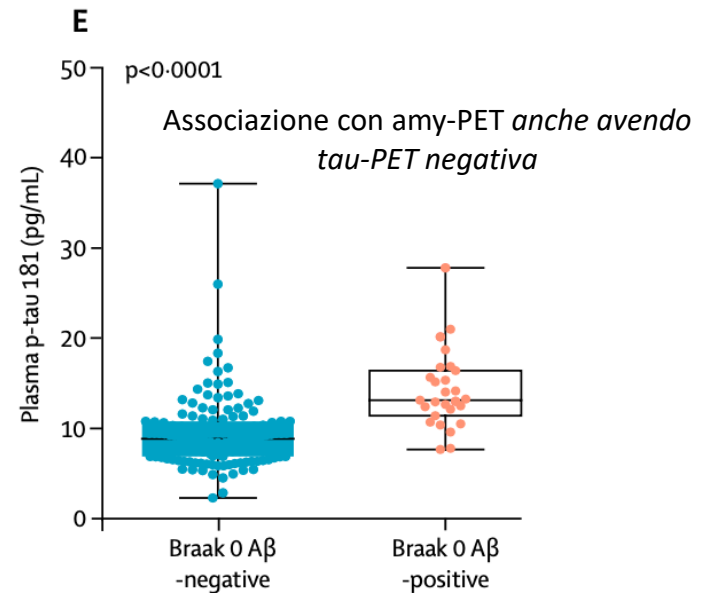
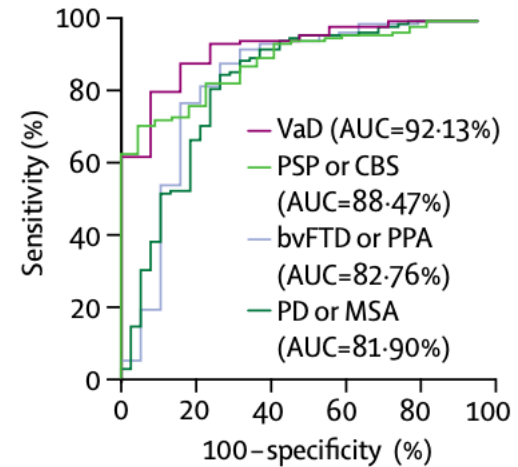
P-tau181 plasmatica: i lavori della primavera 2020 (II)



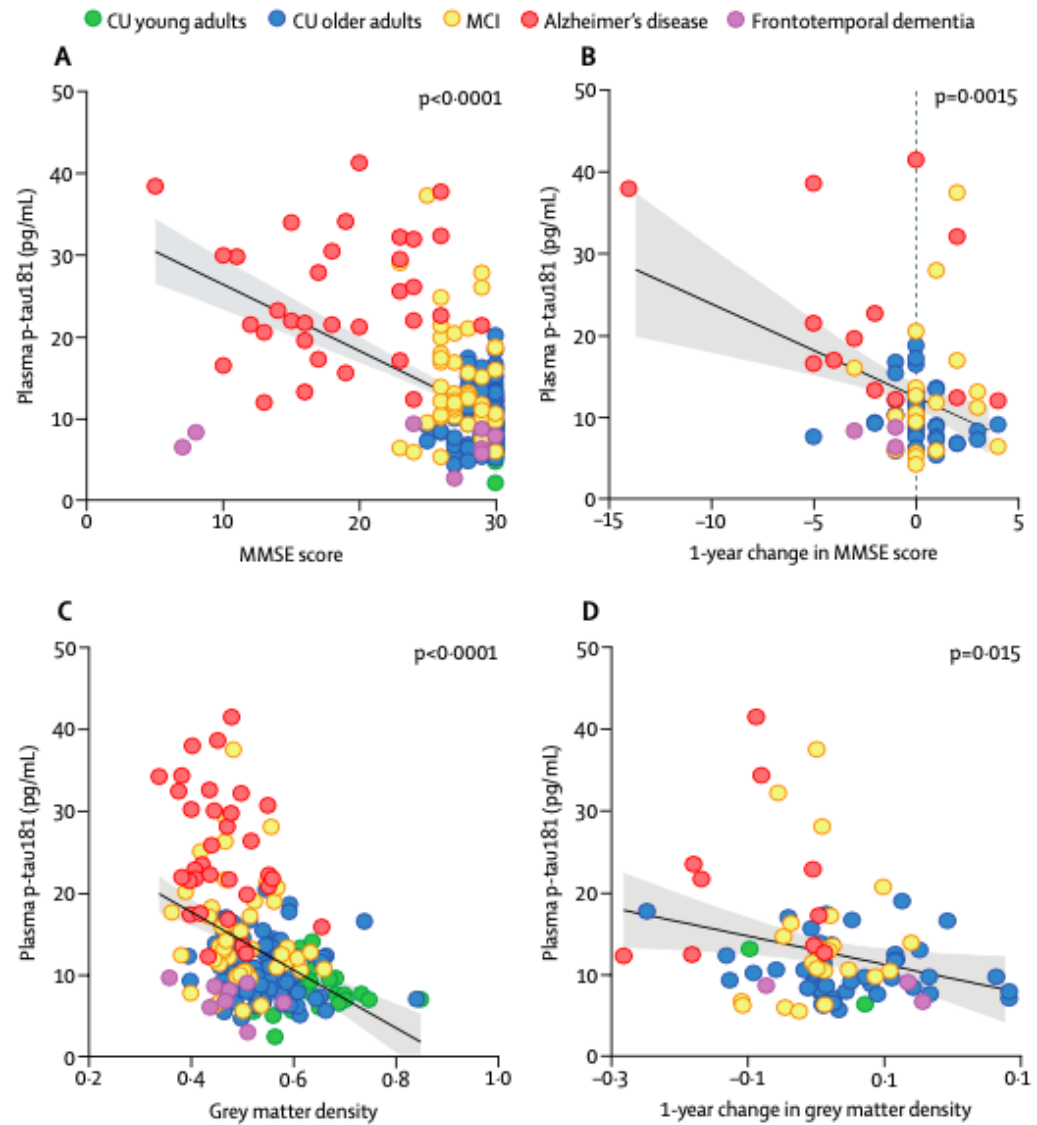
P-tau181 nel siero con Simoa



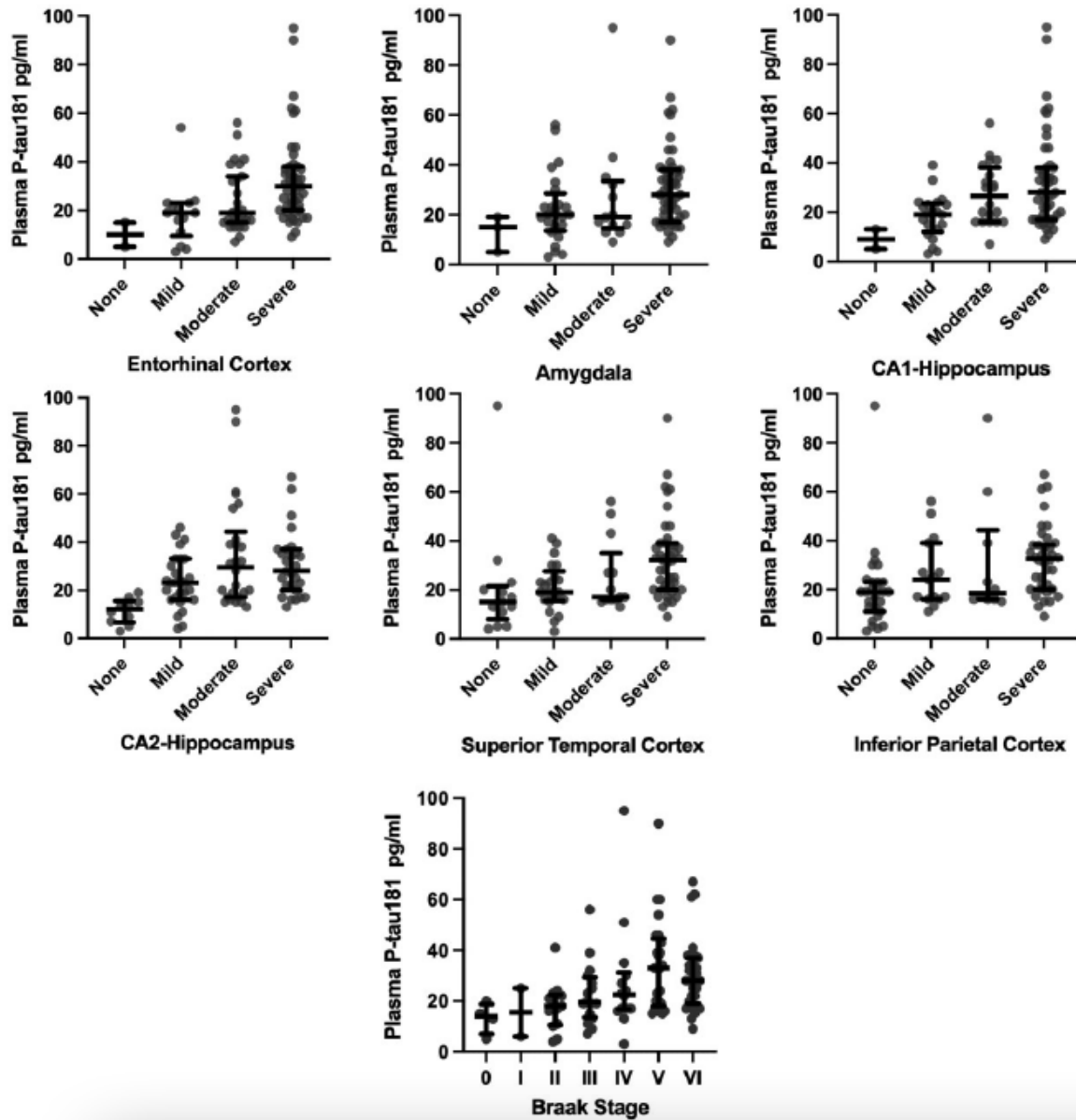
Discriminazione da altre demenze



Associazione con atrofia e cognitivà anche longitudinali



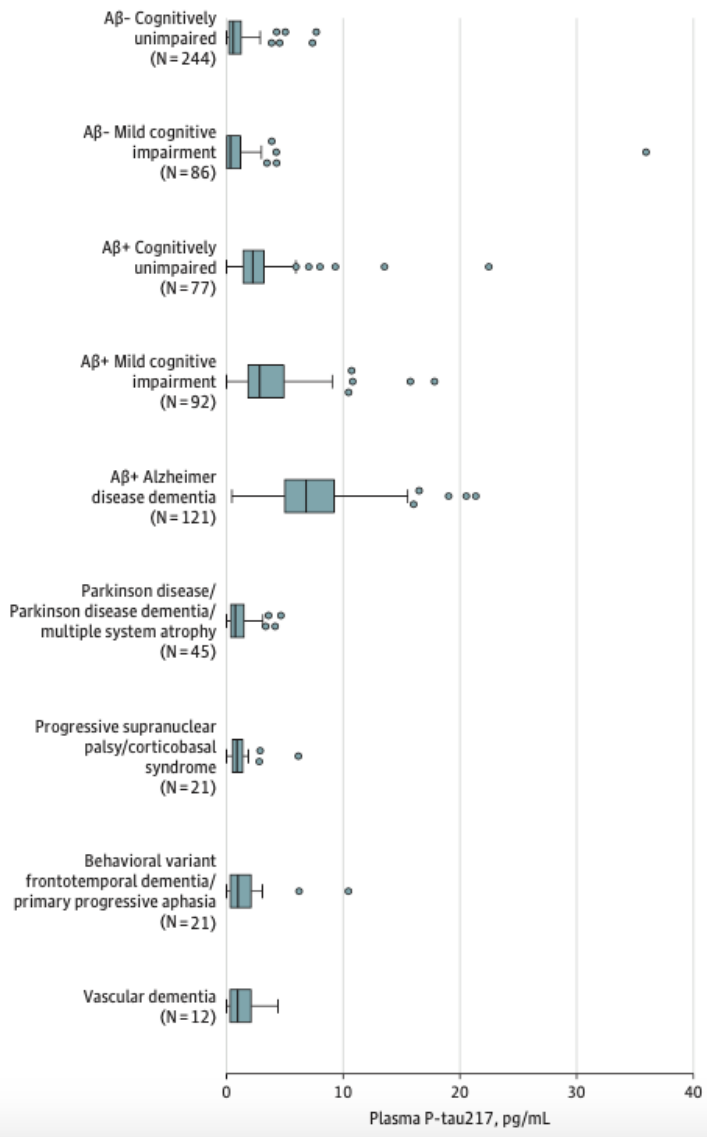
Associazione plasma P-tau181 con neuropatologia



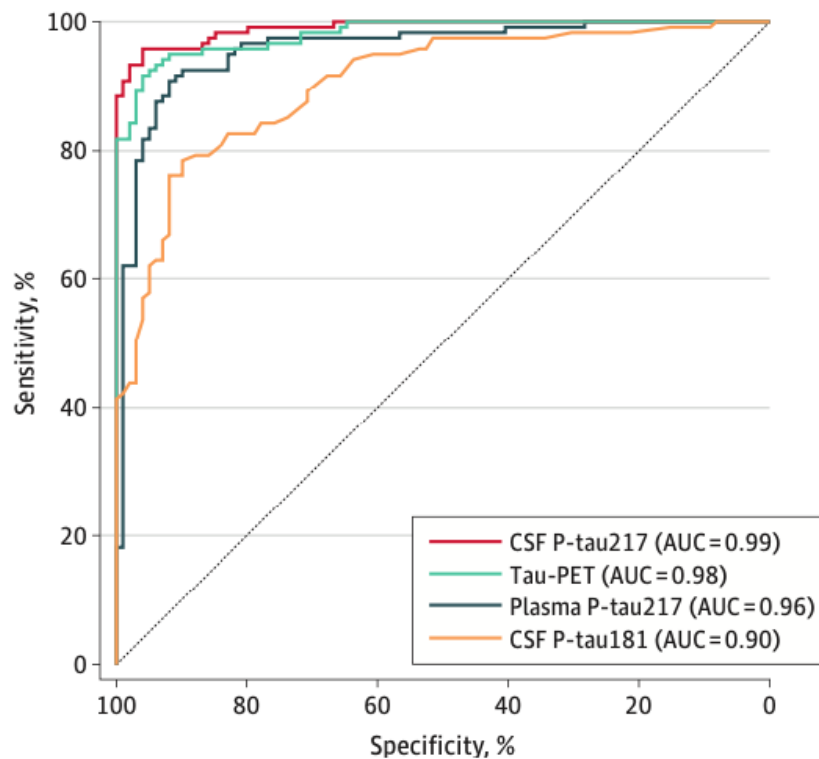
Morrison et al., Brain 2022

Seconda P-tau species: P-tau217 (plasma)

A Levels of P-tau217 in plasma across diagnostic groups

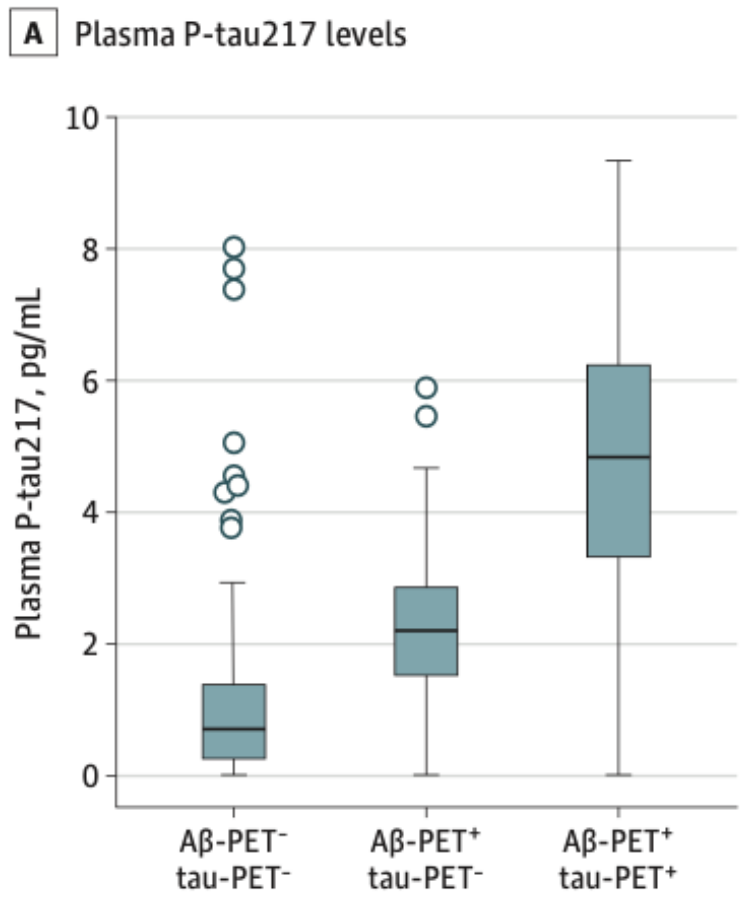


C AD dementia vs other neurodegenerative diseases: comparison of plasma P-tau217 vs CSF and tau-PET biomarkers



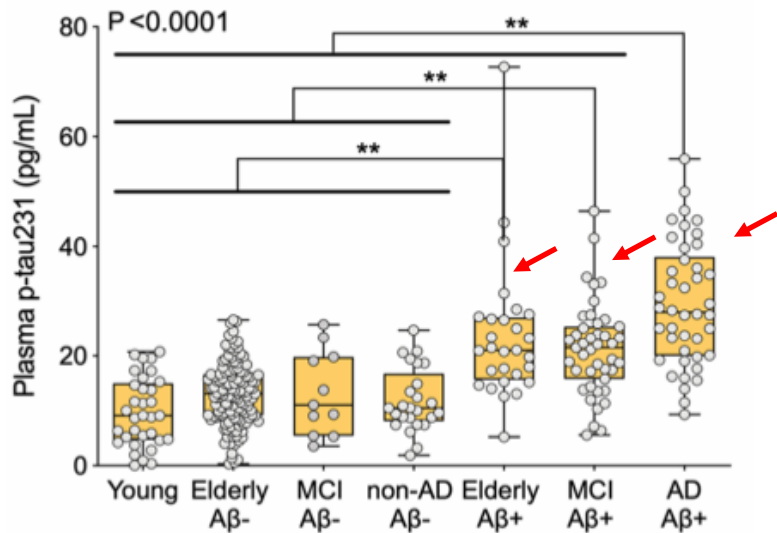
Plasma P217 addirittura meglio di CSF P181

P-tau217: marcatore più «precoce» in confronto alla tau-PET

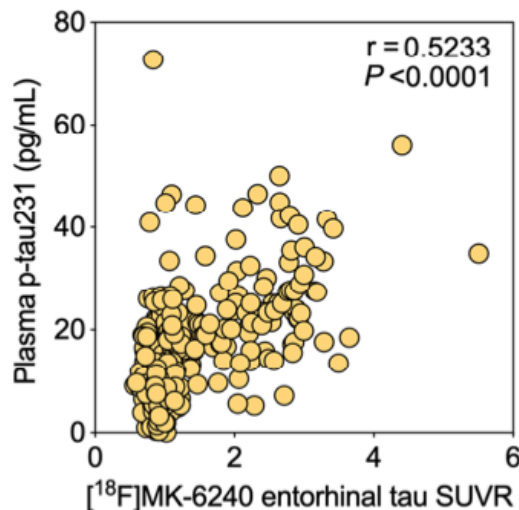


Terza P-tau species: P-tau231 (plasma)

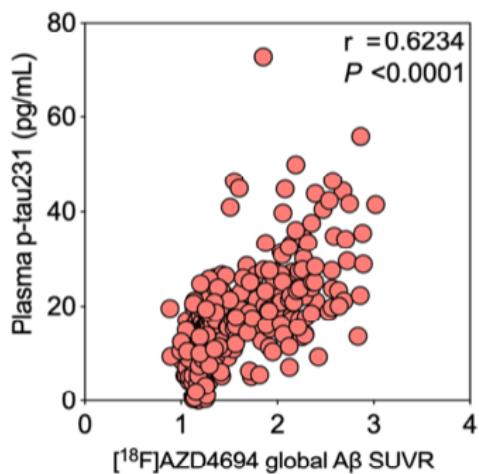
c TRIAD cohort



Correlazione con tau-PET

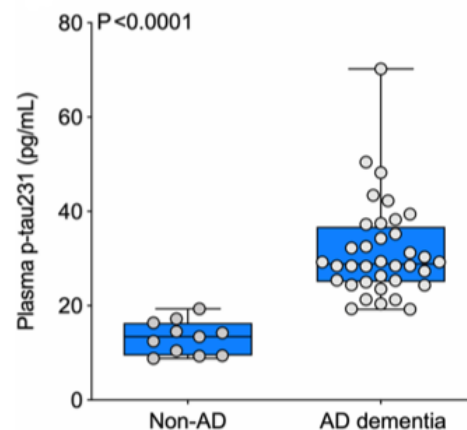


Correlazione con amy-PET

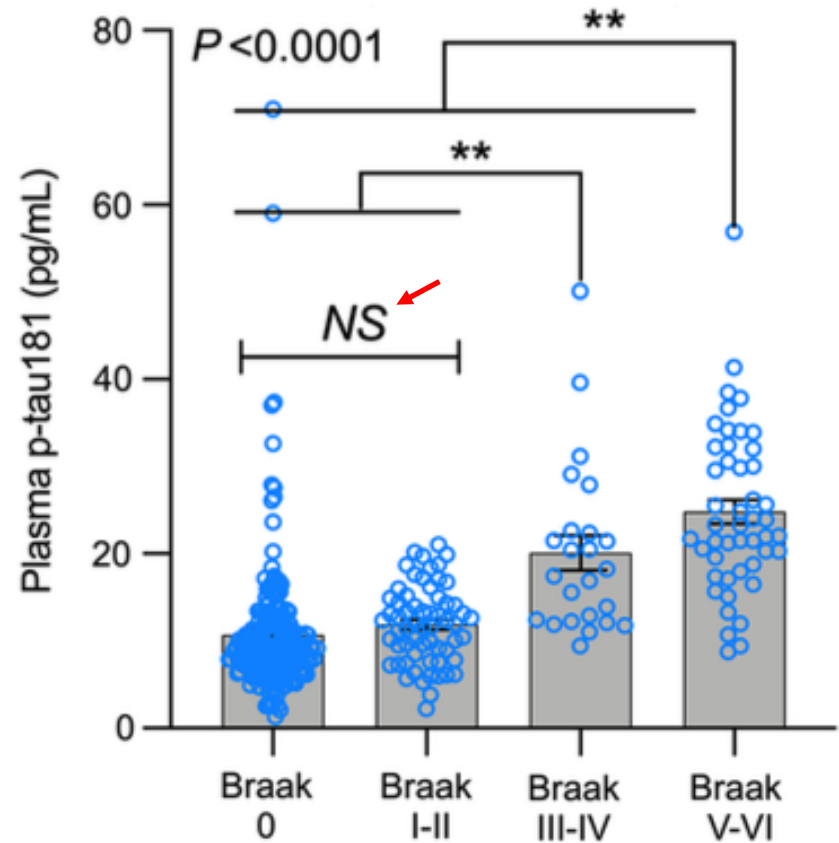
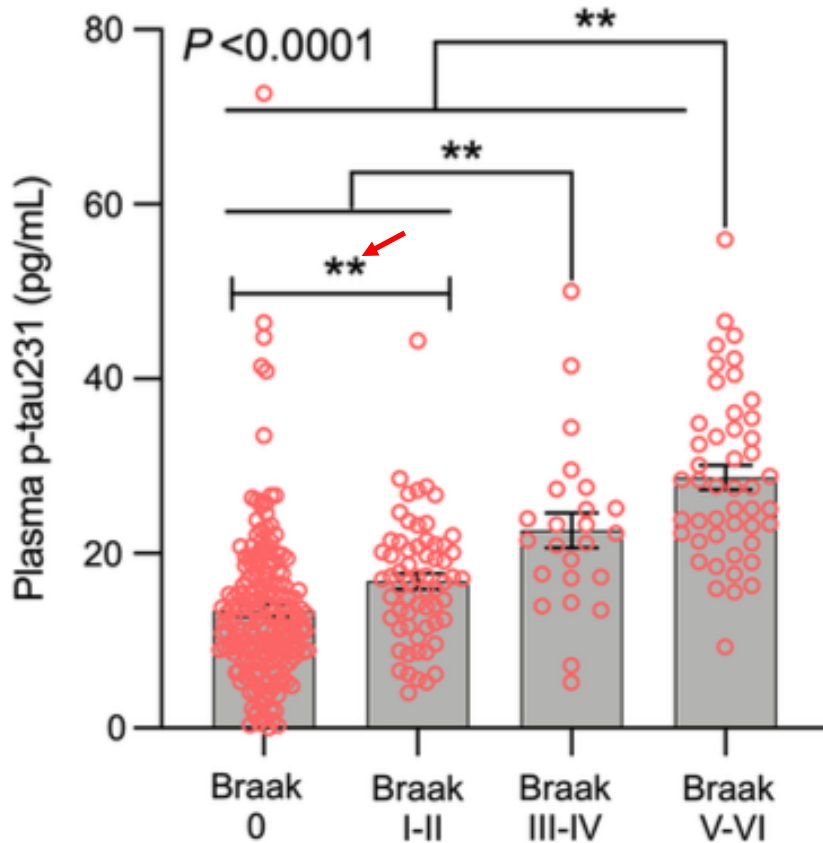


Eccellente discriminazione in coorte neuropatologica

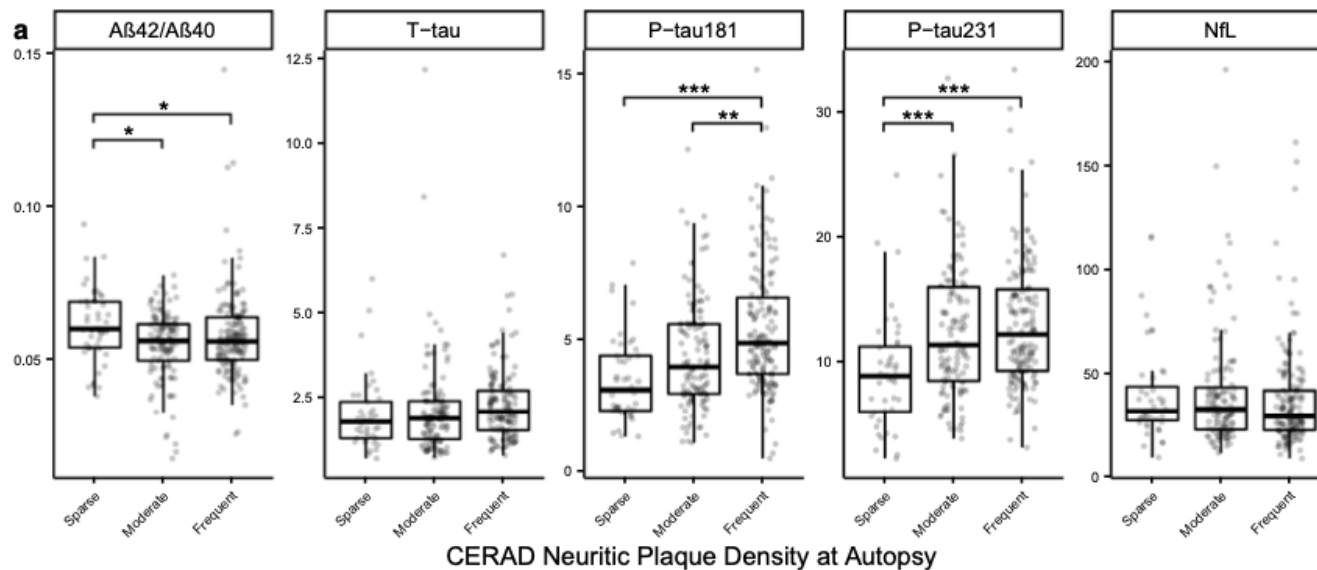
g Neuropathology cohort



P-tau231: superiorità in fase neuropatologica precoce?



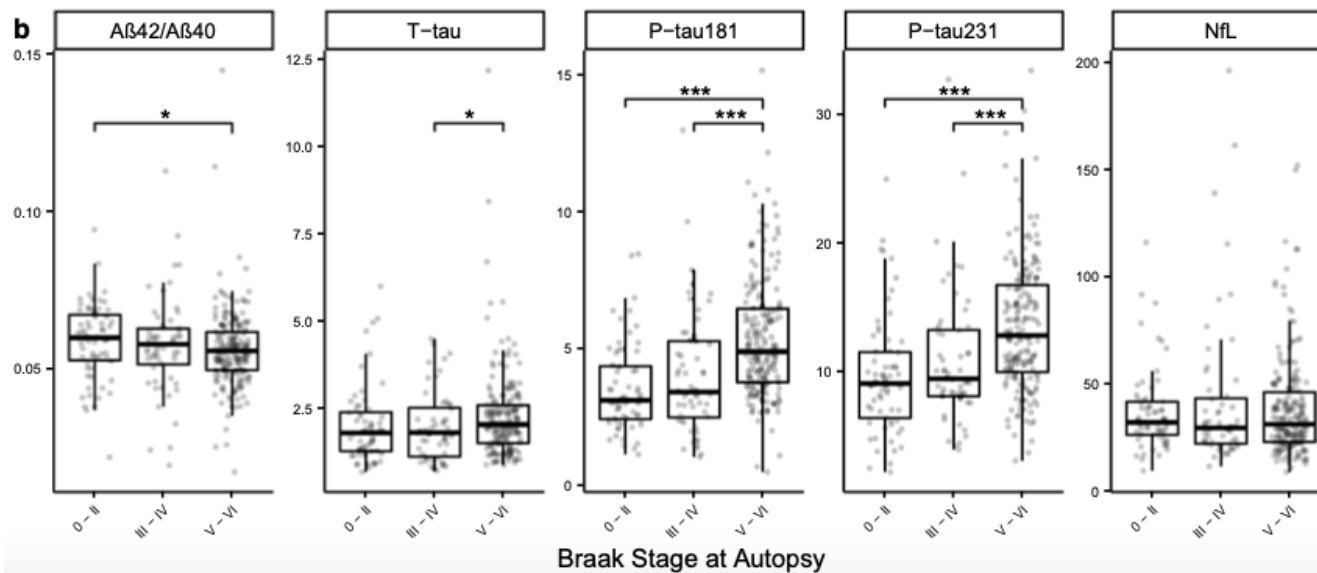
Tutti i biomarcatori plasmatici vs neuropatologia



NfL: non ci siamo

T-tau: non bene

A-beta (ratio): così così

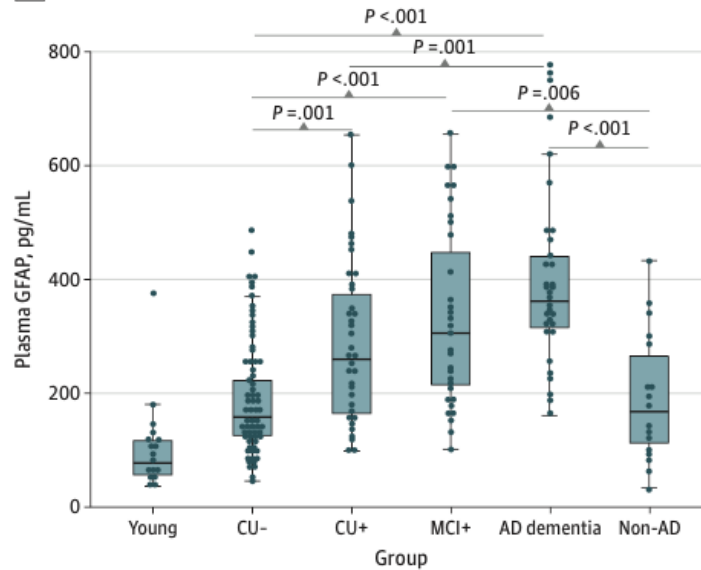


P-tau181: bene

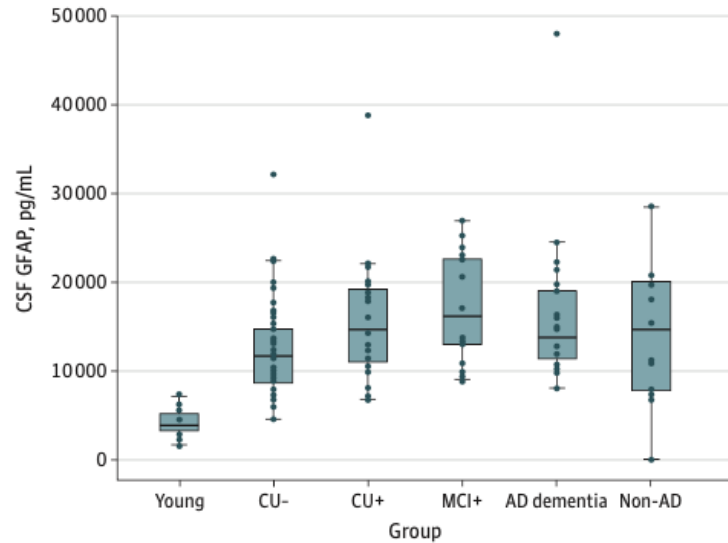
P-tau231: bene

Glial fibrillary acidic protein (GFAP)

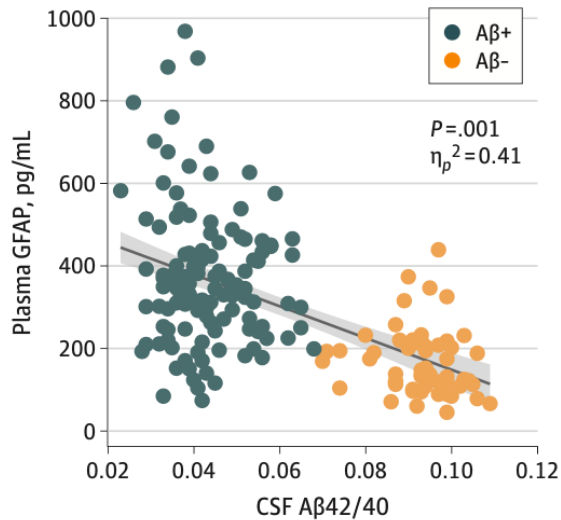
A Plasma GFAP levels in the TRIAD cohort



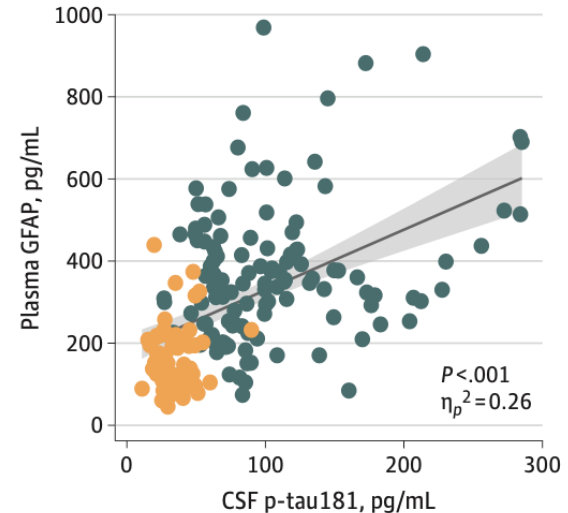
B CSF GFAP levels in the TRIAD cohort



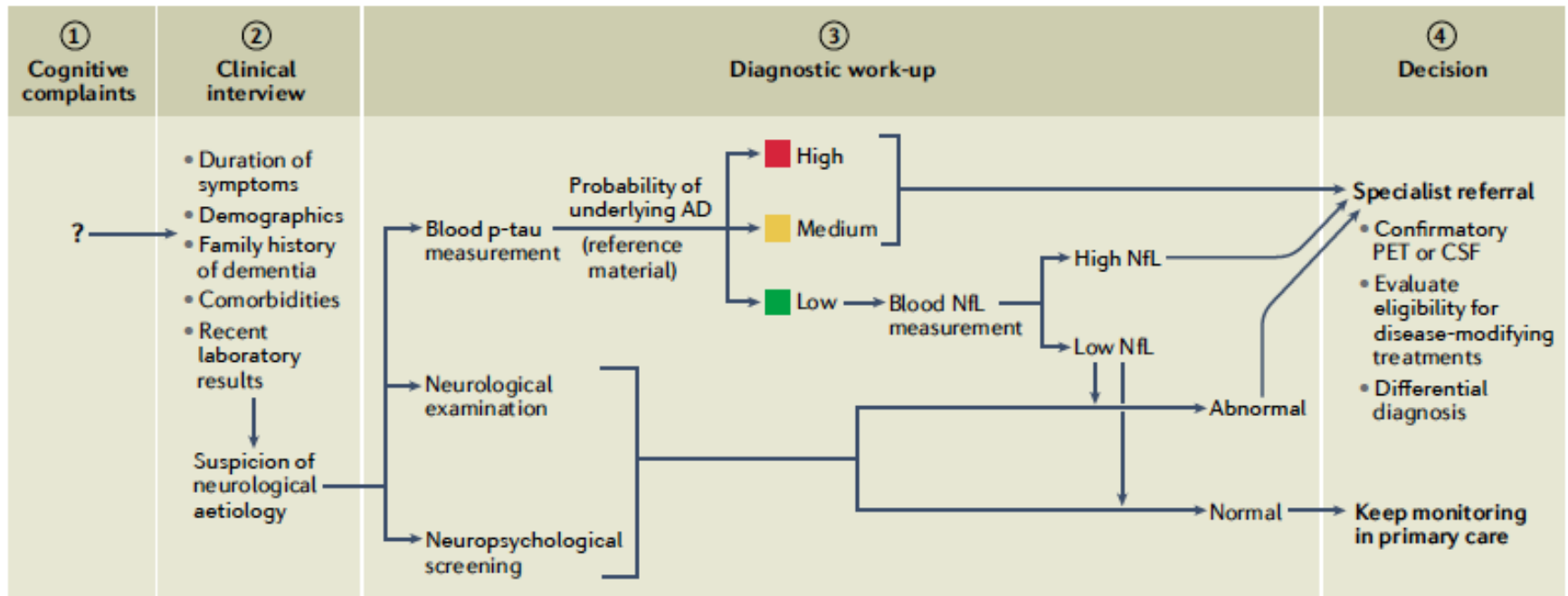
G Plasma GFAP levels in the Paris cohort



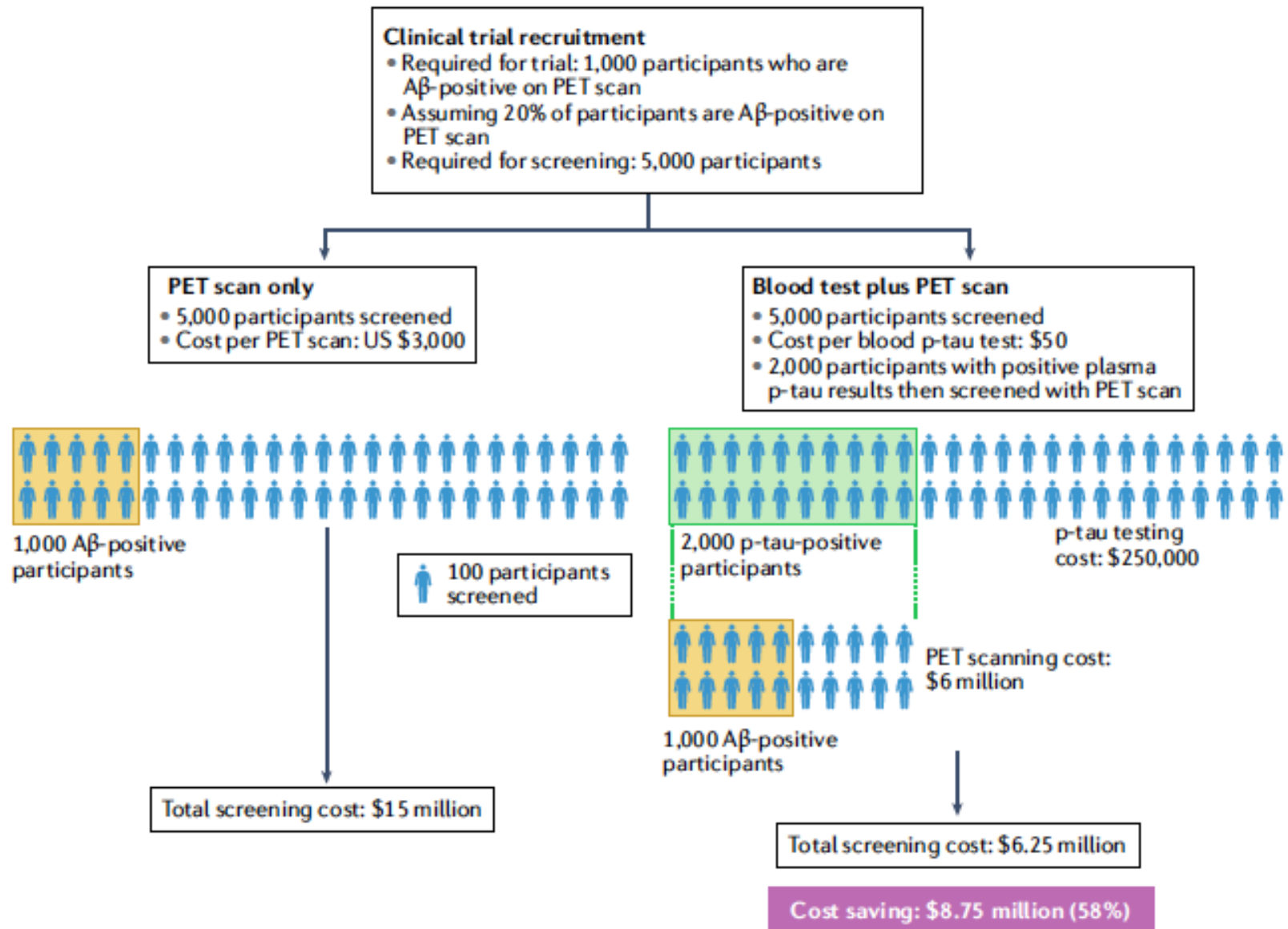
E Plasma GFAP and CSF p-tau181 in the Paris cohort



Ruolo nel prossimo futuro nella clinica?



Ruolo nella ricerca?



Conclusioni

1. I biomarcatori liquorali riflettono la neuropatologia della malattia di Alzheimer
2. Ruolo crescente nei criteri diagnostici
3. Evoluzione tecnologica → biomarcatori plasmatici
4. Il biomarcatore plasmatico più promettente è P-tau
5. GFAP: paradossalmente meglio su plasma che su liquor
6. NFL: aspecifico marcatore di neurodegenerazione
7. Possibile ruolo dei biomarcatori nel prossimo futuro