Measurement and clinical utility of CSF proteins

Kaj Blennow, Gothenburg University, Sweden

Alzheimer's disease

Slowly progressive memory loss and dementia

Neuropathology:

plaques	β-amyloid
tangles	phosphorylated tau protein
neuronal and synaptic degeneration	

Very rare (< 0.1%) familial form - very common sporadic and age-related form

USA 2014

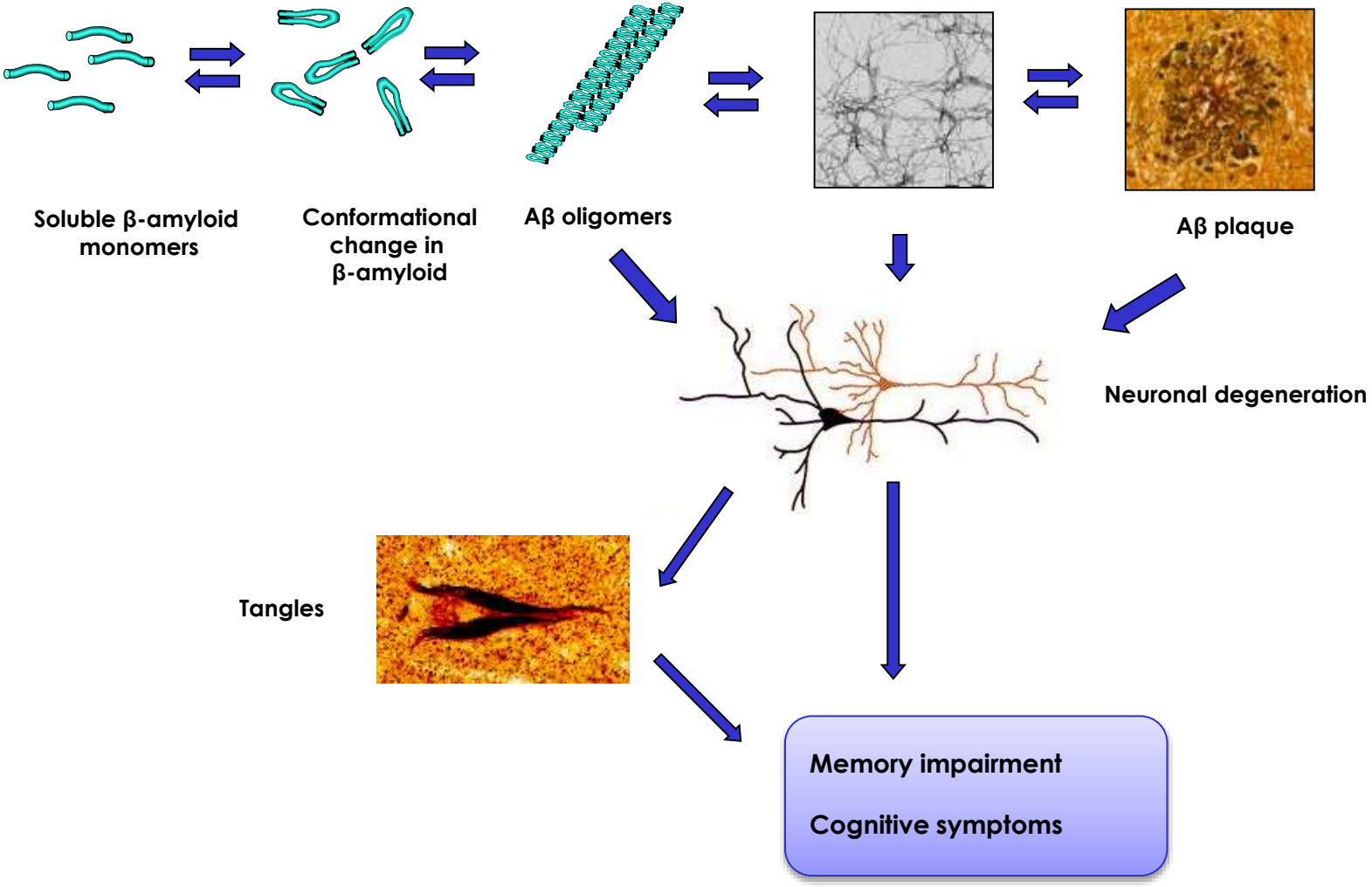
Around 5.200.000 patients with Alzheimer's

A new patient every minute

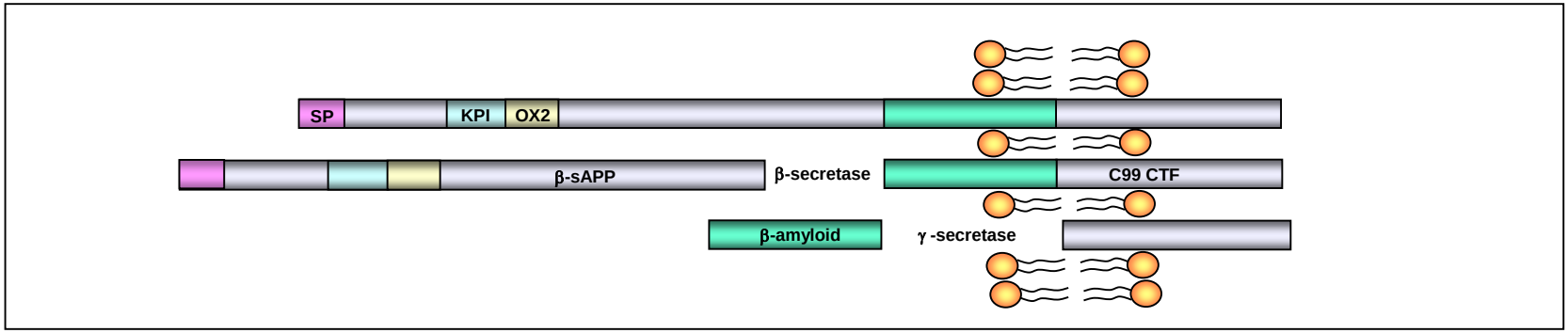
Around 200.000 patients < 65 years

Costs for society – around 214 billion USD per year
more than costs of cancer, heart disease and stroke together

Amyloid aggregation and deposition is believed to be key in Alzheimer's



Promising β-amyloid drugs for Alzheimer's disease are tested in trials



- Immunotherapy — Active β-amyloid vacination; Passive immunotherapy with anti-Aβ antibodies
- Reduce production — β-secretase (BACE) inhibitors and γ-secretase modulators

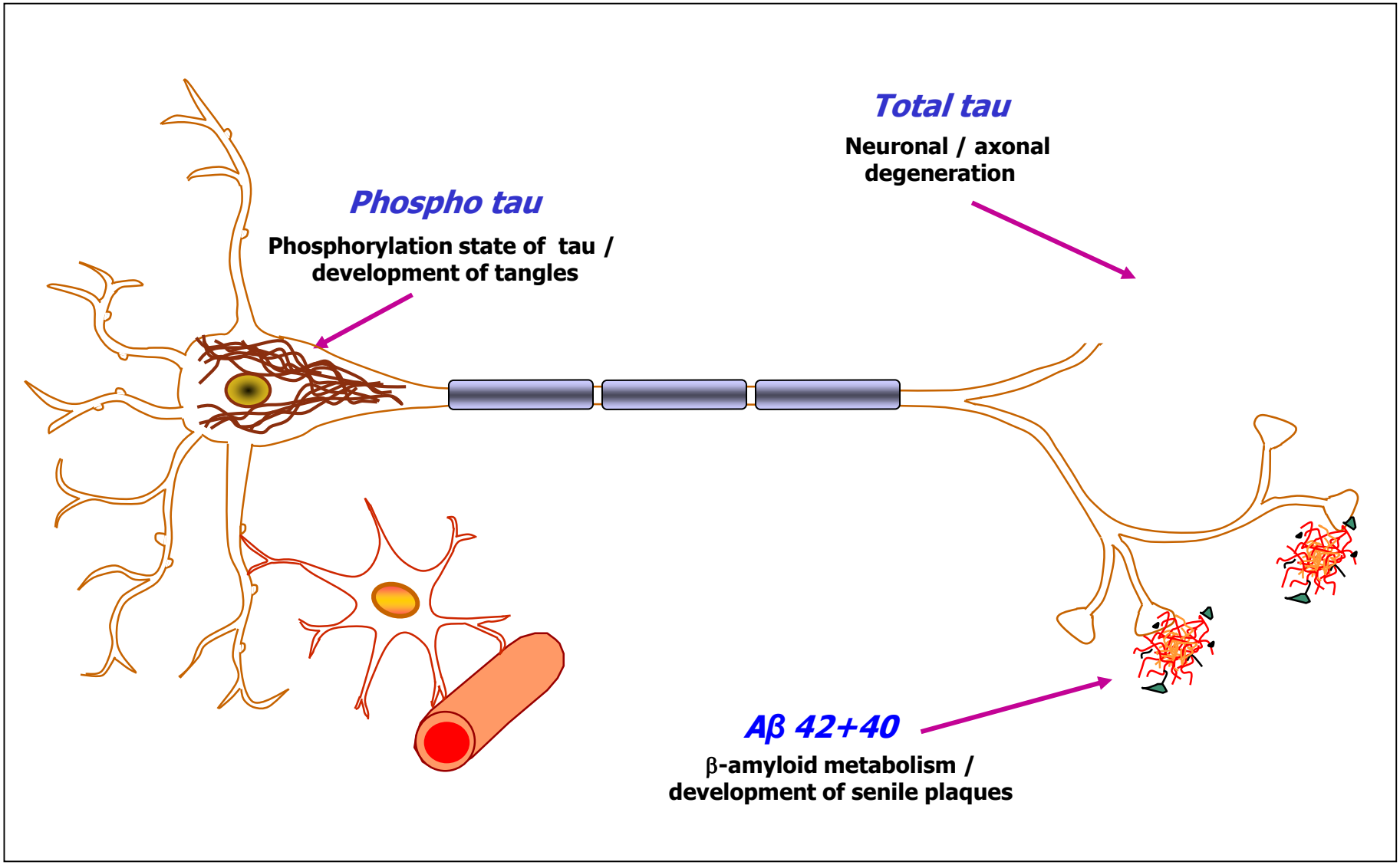
- Up to 20-30% of clinically diagnosed "Alzheimer" cases are mis-diagnosed
- Alzheimer's disease cannot be diagnosed clinically in the early MCI stage

Biomarkers are needed for:

- Diagnostics
- Thereagnostics
- Clinical research

- Select true AD cases for inclusion in clinical trials
- Identify target engagement and monitor effects on neurodegeneration
- Study disease pathogenesis directly in patients

The core CSF biomarkers for Alzheimer's disease



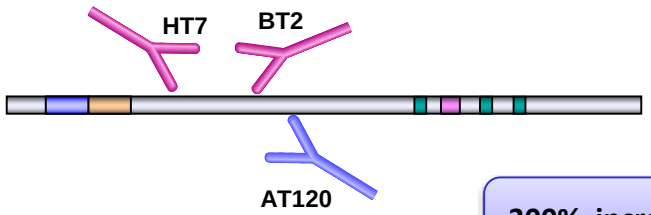
The three established ELISA methods for AD CSF biomarkers

tau Protein in Cerebrospinal Fluid

A Biochemical Marker for Axonal Degeneration in Alzheimer Disease?

K. BLENNOW,*[,1] A. WALLIN,[2] H. ÅGREN,[2]
C. SPENGER,[3] J. SIEGFRIED,[4] AND E. VANMECHELEN[5]

Mol Chem Neuropathol 1995



300% increase in AD

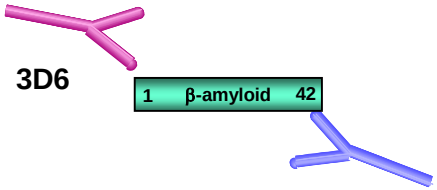
ORIGINAL CONTRIBUTION

Cerebrospinal Fluid β-Amyloid(1-42) in Alzheimer Disease

Differences Between Early- and Late-Onset Alzheimer Disease and Stability During the Course of Disease

Niels Andreasen, MD; Camilla Hesse; Pia Davidsson, PhD; Lennart Minthon, MD, PhD; Anders Wallin, MD, PhD; Bengt Winblad, MD, PhD; Hugo Vanderstichele, PhD; Eugeen Vanmechelen, PhD; Kaj Blennow, MD, PhD

Arch Neurol 1999

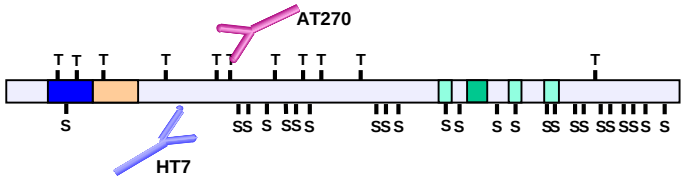


50% decrease in AD

ELSEVIER
Neuroscience Letters
Neuroscience Letters 289 (2000) 49–52
www.elsevier.com/locate/neulet

Quantification of tau phosphorylated at threonine 181 in human cerebrospinal fluid: a sandwich ELISA with a synthetic phosphopeptide for standardization

E. Vanmechelen[a,*], H. Vanderstichele[a], P. Davidsson[b], E. Van Kerschaver[a], B. Van Der Perre[a], M. Sjögren[c], N. Andreasen[d], K. Blennow[b,e]

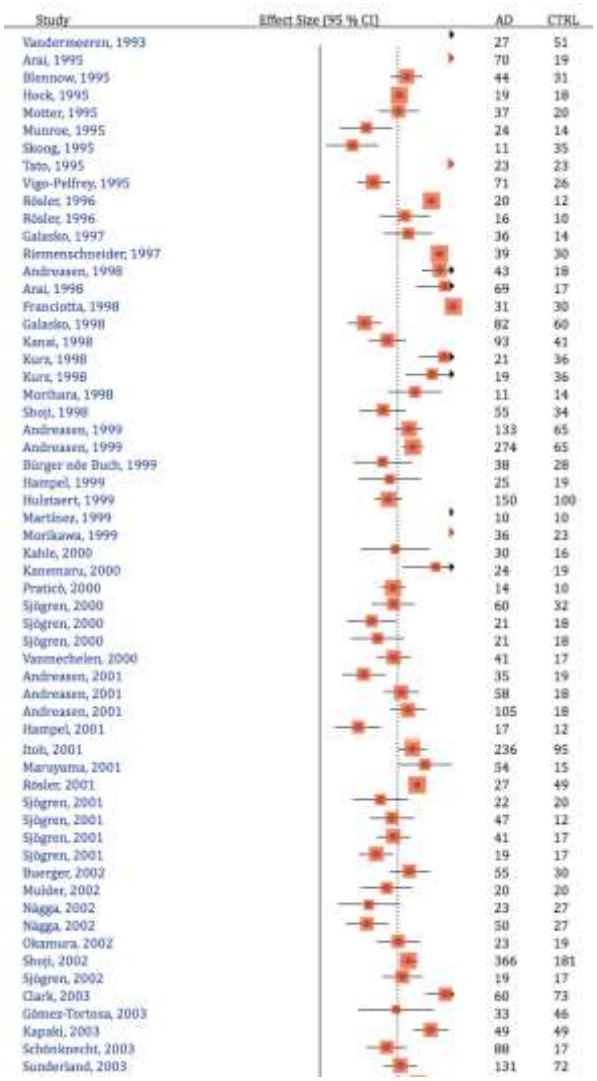


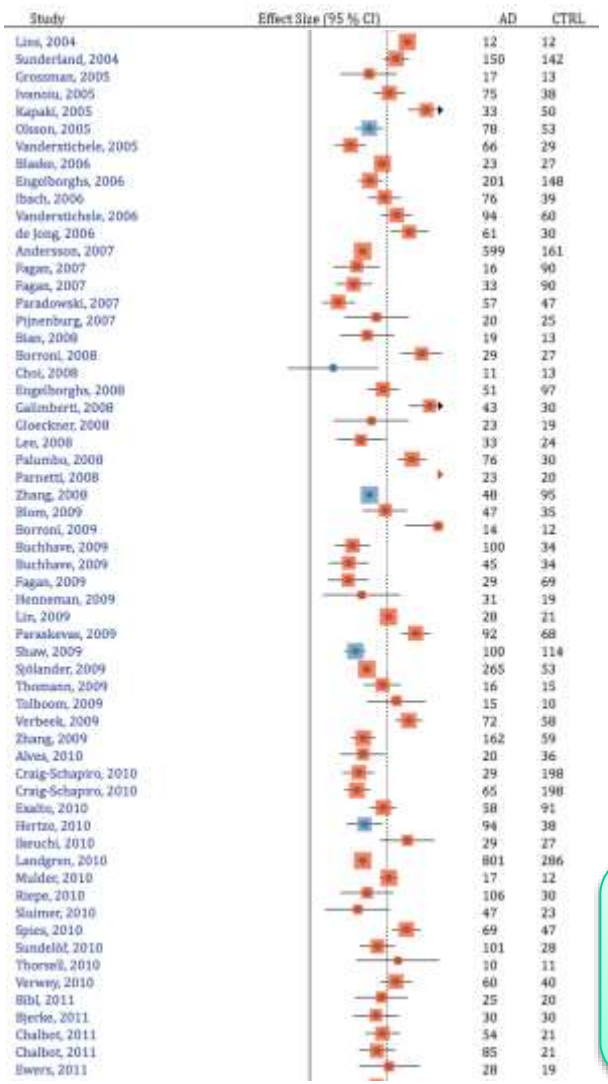
2-300% increase in AD

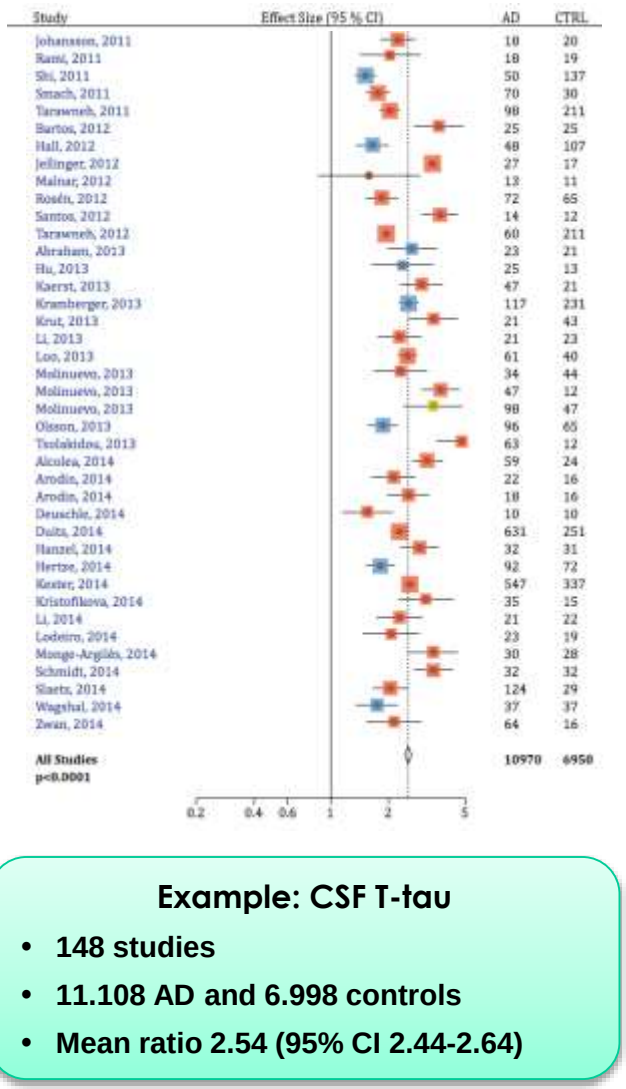
How well validated are the core AD CSF biomarkers clinically ?

ALZFORUM
NETWORKING FOR A CURE

http://www.alzforum.org/alzbiomarker







Example: CSF T-tau

- **148 studies**
- **11.108 AD and 6.998 controls**
- **Mean ratio 2.54 (95% CI 2.44-2.64)**

Olsson B, et al. Lancet Neurol 2016, in press

Can CSF biomarkers identify prodromal AD ?

Articles

Lancet Neurol 2006; 5: 228–34

Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: a follow-up study

Oskar Hansson, Henrik Zetterberg, Peder Buchhave, Elisabet Londos, Kaj Blennow, Lennart Minthon

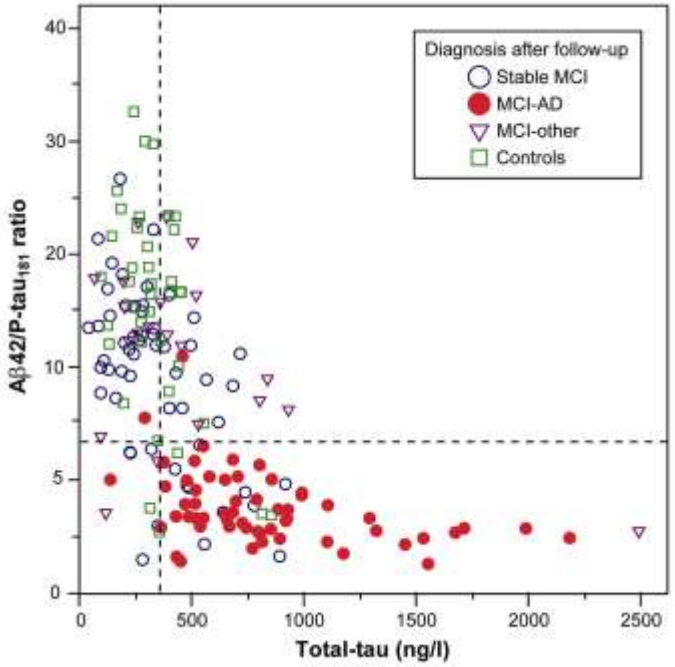
Follow-up study on MCI (>4 years)

CSF samples taken at baseline

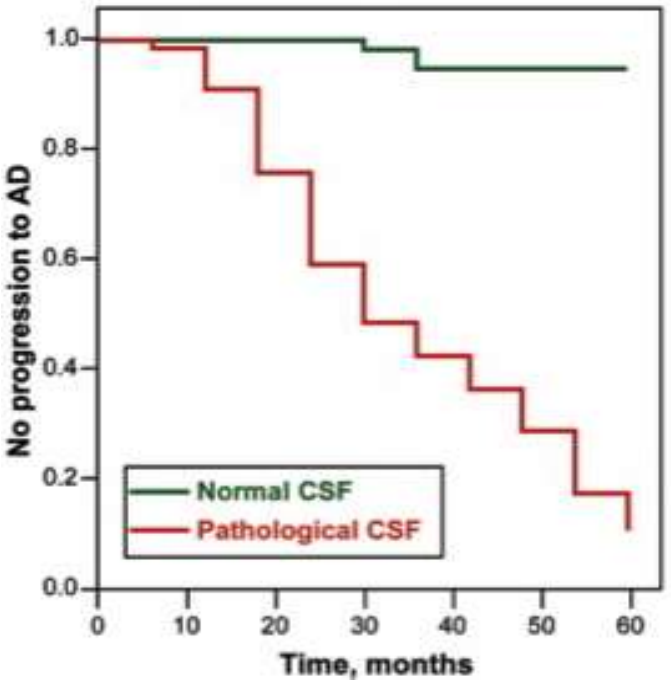
MCI n= 134
57 MCI → AD
56 MCI → MCI
21 MCI → other dem.

Controls n = 37

Cut-off: T-tau >350 pg/mL + Aβ42 / P-tau ratio < 6.5



Sensitivity MCI ⇒ AD 95 %
Specificity MCI ⇒ MCI + other 87 %



Hazard ratio : 25.5 (7.7 – 84.9)

Biomarker-based diagnostic research criteria for AD

Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria

Bruno Dubois, Howard H Feldman, Claudia Jacova, Harald Hampel, José Luis Molinuevo, Kaj Blennow, Steven T DeKosky, Serge Gauthier, Dennis Selkoe, Randall Bateman, Stefano Cappa, Sebastian Crutch, Sebastiaan Engelborghs, Giovanni B Frisoni, Nick C Fox, Douglas Galasko, Marie-Odile Habert, Gregory A Jicha, Agneta Nordberg, Florence Pasquier, Gil Rabinovici, Philippe Robert, Christopher Rowe, Stephen Salloway, Marie Sarazin, Stéphane Epelbaum, Leonardo C de Souza, Bruno Vellas, Pieter J Visser, Lon Schneider, Yaakov Stern, Philip Scheltens, Jeffrey L Cummings

In the past 8 years, both the International Working Group (IWG) and the US National Institute on Aging–Alzheimer's Association have contributed criteria for the diagnosis of Alzheimer's disease (AD) that better define clinical phenotypes and integrate biomarkers into the diagnostic process, covering the full staging of the disease. This Position Paper considers the strengths and limitations of the IWG research diagnostic criteria and proposes advances to improve the diagnostic framework. On the basis of these refinements, the diagnosis of AD can be simplified, requiring the presence of an appropriate clinical AD phenotype (typical or atypical) and a pathophysiological biomarker consistent with the presence of Alzheimer's pathology. We propose that downstream topographical biomarkers of the disease, such as volumetric MRI and fluorodeoxyglucose PET, might better serve in the measurement and monitoring of the course of disease. This paper also elaborates on the specific diagnostic criteria for atypical forms of AD, for mixed AD, and for the preclinical states of AD.

Lancet Neurol 2014; 13: 614–29

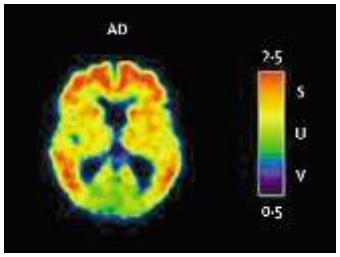
- **Impairment in episodic memory**

Plus one or more of

- **CSF** - **low Aβ42, high T-tau or P-tau**
- **PET** - **high cortical amyloid ligand uptake**

➔ **Need of studies on how the AD biomarkers complement each other and can be combined**

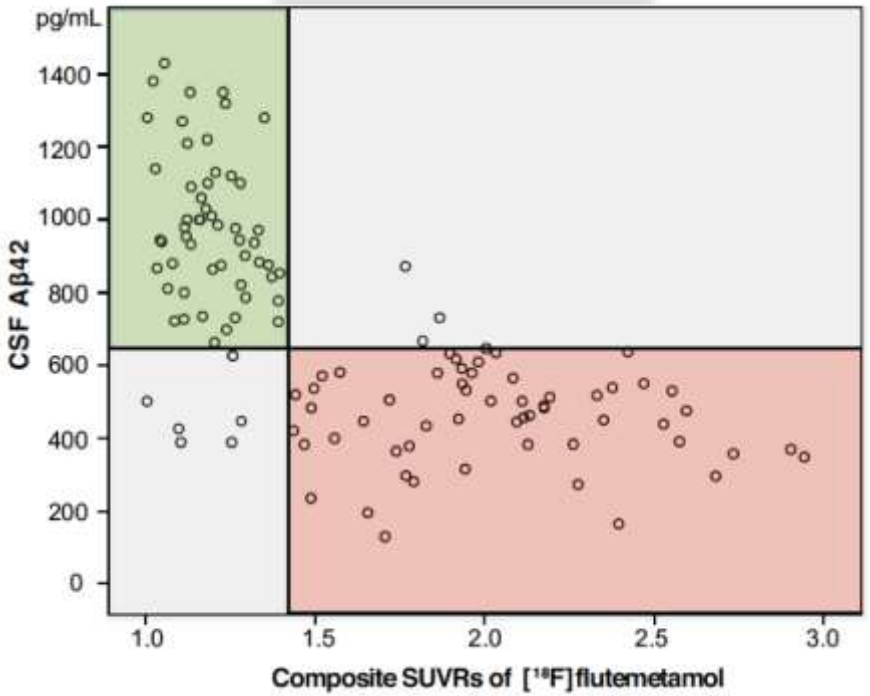
How do amyloid PET and CSF Aβ42 compare ?



Study design: 118 patients with cognitive complaint examined for both CSF biomarkers - as part of clinical routine – 2 years and amyloid ^{18}F-flutemetamol PET

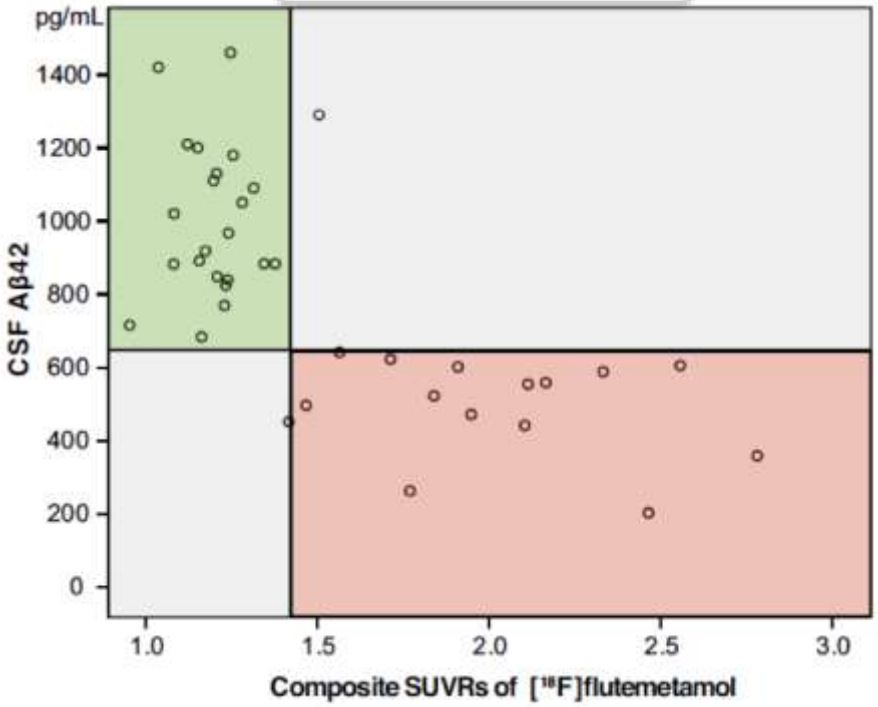
Cut-offs: CSF Aβ42 < 647 pg/mL
^{18}F-flutemetamol PET > 1.42

Original cohort n= 118



Positive PET+CSF or Negative PET+CSF 92 %

Validation cohort n= 38



Positive PET+CSF or Negative PET+CSF 97 %

Palmquist S, et al, JAMA Neurol 2014

Are amyloid PET and CSF Aβ42 really equivalent ?

Trends in Pharmacol Sci 2015;36:297-309

Review

CellPress

Amyloid biomarkers in Alzheimer's disease

Kaj Blennow[1,2], Niklas Mattsson[1,3,4], Michael Schöll[5,6], Oskar Hansson[7,8], and Henrik Zetterberg[1,9]

Brain Advance Access published March 2, 2016

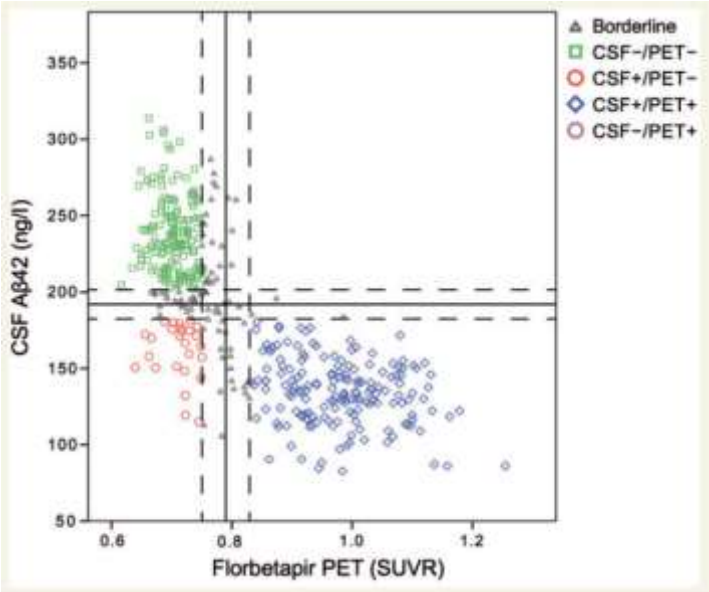
BRAIN

A JOURNAL OF NEUROLOGY

Cerebrospinal fluid analysis detects cerebral amyloid-β accumulation earlier than positron emission tomography

Sebastian Palmqvist[1,2] Niklas Mattsson[1,3] and Oskar Hansson[1,3] for the Alzheimer's Disease Neuroimaging Initiative*

- Meta-analysis of 10 papers on CSF Aβ42 vs. amyloid PET
- Total no. of cases (AD, MCI, control): 1064
- PET+CSF in agreement (both positive or negative): 88.0 %
- Cases that are PET neg but CSF positive: 8 %



➔ CSF Aβ42 and amyloid PET give similar but NOT identical diagnostic accuracy

➔ CSF-pos / PET-neg subjects show future amyloid accumulation but not yet evidence of neurodegeneration

➔ CSF Aβ42 is an earlier biomarker than amyloid PET

Large variation in Alzheimer CSF Aβ42 levels between laboratories

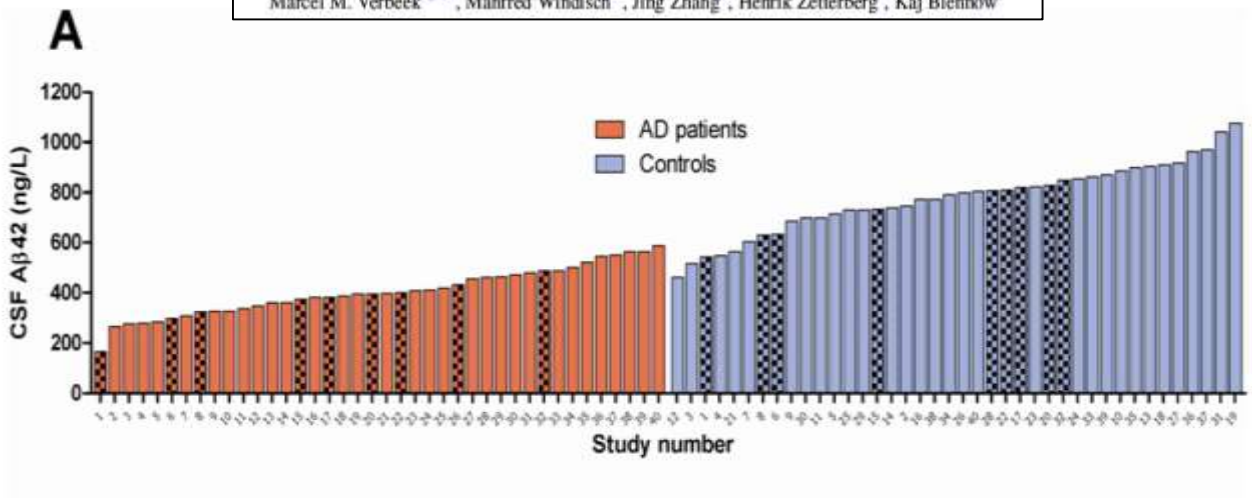
ELSEVIER

Alzheimer's & Dementia

Alzheimer's & Dementia 7 (2011) 386–395

The Alzheimer's Association external quality control program for cerebrospinal fluid biomarkers

Niklas Mattsson[a,*], Ulf Andreasson[a], Staffan Persson[a], Hiroyuki Arai[b], Sat Dev Batish[c], Sergio Bernardini[d], Luisella Bocchio-Chiavetto[e], Marinus A. Blankenstein[f], Maria C. Carrillo[g], Sonia Chalbot[h], Els Coart[i], Davide Chiasserini[j], Neal Cutler[k], Gunilla Dahlfors[l], Stefan Duller[m], Anne M. Fagan[n], Orestes Forlenza[o], Giovanni B. Frisoni[e], Douglas Galasko[p], Daniela Galimberti[q], Harald Hampel[r], Aase Handberg[s], Michael T. Heneka[t], Adrianna Z. Herskovits[u], Sanna-Kaisa Herukka[v], David M. Holtzman[n], Christian Humpel[w], Bradley T. Hyman[u], Khalid Iqbal[h], Mathias Jucker[x], Stephan A. Kaeser[x], Elmar Kaiser[y], Elisabeth Kapaki[z], Daniel Kidd[aa], Peter Klivenyi[bb], Cindy S. Knudsen[s], Markus P. Kummer[t], James Lui[cc], Albert Lladó[dd], Piotr Lewczuk[ee], Qiao-Xin Li[ff], Ralph Martins[cc], Colin Masters[ff], John McAuliffe[c], Marc Mercken[gg], Abhay Moghekar[hh], José Luis Molinuevo[ii], Thomas J. Montine[ii], William Nowatzke[k], Richard O'Brien[hh], Markus Otto[jj], George P. Paraskevas[z], Lucilla Parnetti[j], Ronald C. Petersen[kk], David Prvulovic[r], Herman P. M. de Reus[ll,mm], Robert A. Rissman[p], Elio Scarpini[q], Alessandro Stefani[nn], Hilkka Soininen[v], Johannes Schröder[y], Leslie M. Shaw[oo], Anders Skinningsrud[pp], Brith Skrogstad[pp], Annette Spreer[qq], Leda Talib[o], Charlotte Teunissen[f], John Q. Trojanowski[oo], Hayrettin Tumani[jj], Robert M. Umek[rr], Bianca Van Broeck[gg], Hugo Vanderstichele[i], Laszlo Vecsei[bb], Marcel M. Verbeek[ll,mm], Manfred Windisch[ss], Jing Zhang[tt], Henrik Zetterberg[a], Kaj Blennow[a]



➔Large CSF Aβ42 variability across laboratories

The Alzheimer's Association QC program for CSF biomarkers

alzheimer's association
the compassion to care, the leadership to conquer

Principle for the QC program:

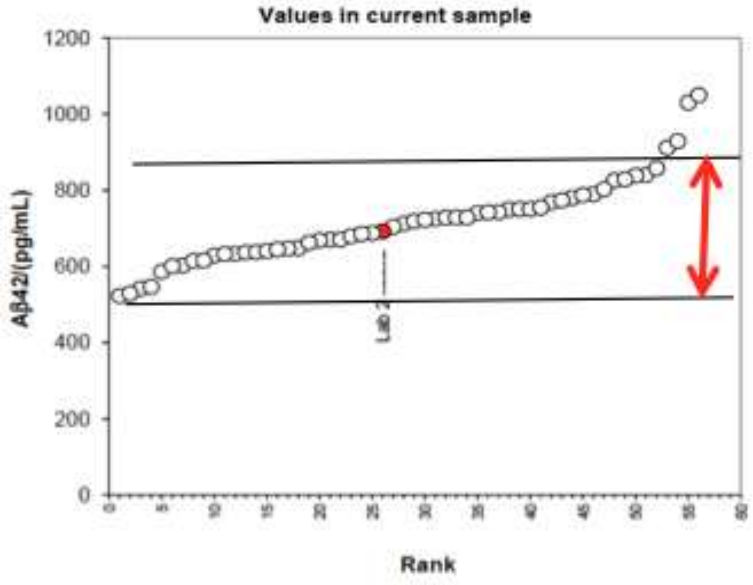
For each round, 3 QC samples (pooled CSF) are sent out

2 unique samples - for comparisons between labs
1 identical sample - for comparisons over time

Frequency: 3 times per year

> 90 labs

	Gothenburg (Lab 2)		All 56 labs in this round
Round:	2013:12A	Mean:	717 pg/mL
Result:	693 pg/mL	SD:	110 pg/mL
Method:	INNOTEST	CV:	15,3%



➔ Variability between labs and between ELISA batches

- need of standardization efforts:

pre-analytics
analytical procedures
assay manufacturing

The IFCC Work Group for CSF proteins

Reference Measurement Procedure (RMP)

- **High precision**
  - Mass spectrometry-based technique
  - Certified calibrator (amino acid analysis)
  - Tested in Round Robin studies
- **Intended use**
  - Set level in the Certified Reference Material

Golden standard method
for absolute quantification

Certified Reference Material (CRM)

- **Large aliquoted CSF pool**
  - Exact level set using RMPs
  - Commutability between assays tested
  - Tested for long-term stability etc.
- **Intended use**
  - Distribution to kit vendors and large labs
    - Harmonize CSF levels between assay formats
    - Assure stability between production lots

Golden standard CSF
with exact levels

Reference method for CSF Aβ42 - Validated "Golden standard" method

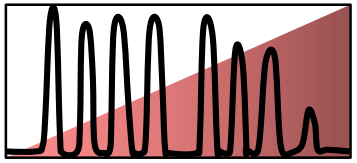
- Antibody-free Single Reation Monitoring (SRM) Triple Quad mass spec method for CSF Aβ isoforms

CSF +
internal Aβ standards

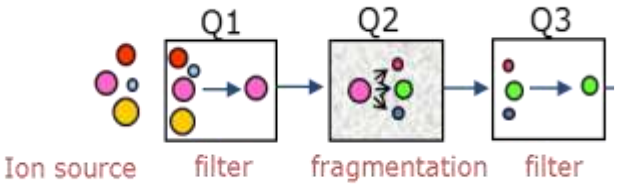
Guanidine HCl
→ denaturation

SPE antibody-free
purification

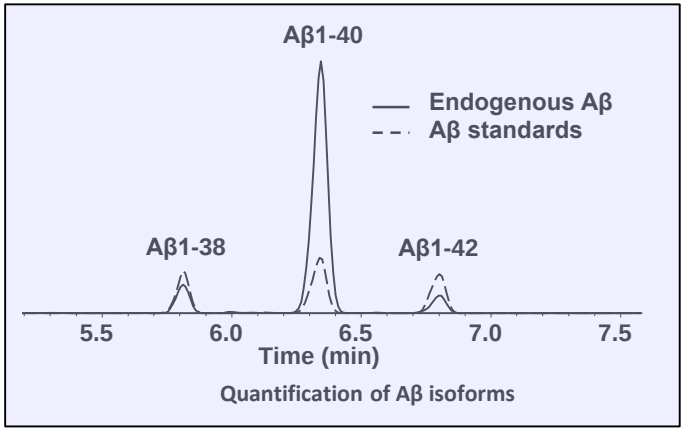
Elute + dry
+ redissolve in
ACN and NH_4OH



Separation of Aβ by HPLC



Vantage Triple Quad mass spectrometry



- Isotope labelled Aβ calibrator added to the CSF sample (and thus processed identically)
- No antibodies involved

➔ absolute quantification without interference (matrix effects)

ELSEVIER

Alzheimer's & Dementia 12 (2016) 55-59

Alzheimer's & Dementia

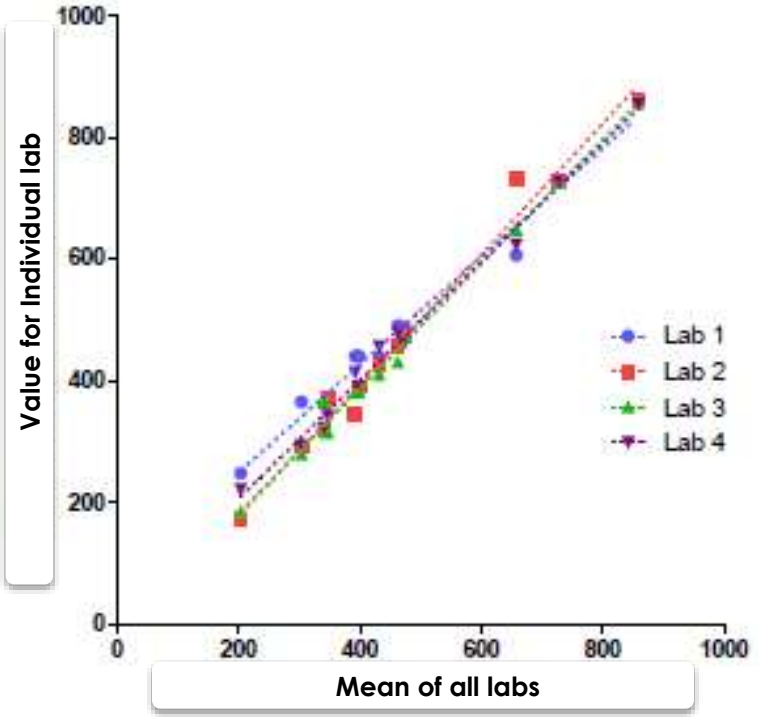
Featured Article

Round robin test on quantification of amyloid-β 1–42 in cerebrospinal fluid by mass spectrometry

Josef Pannee[a,*], Johan Gobom[a], Leslie M. Shaw[b], Magdalena Korecka[b], Erin E. Chambers[c], Mary Lame[c], Rand Jenkins[d], William Mylott[d], Maria C. Carrillo[e], Ingrid Zegers[f], Henrik Zetterberg[a,g], Kaj Blennow[a], Erik Portelius[a]

- **Four laboratories with SRM methods for CSF Aβ42:**
  University of Gothenburg
  University of Pennsylvania
  PPD, USA
  Waters, USA
- **12 CSF samples analyzed**
- **One CSF served as a Candidate Reference Material**

➔ SRM mass spec suitable as a Reference Measurement Procedure (RMP) for CSF Aβ42



Mass spectrometry Reference measurement procedure (RMP) for CSF Aβ42

Clinical Chemistry 60:7
987–994 (2014)

Proteomics and Protein Markers

Mass Spectrometry–Based Candidate Reference Measurement Procedure for Quantification of Amyloid-β in Cerebrospinal Fluid

Andreas Leinenbach,[1†] Josef Pannee,[2†] Thomas Dülffer,[1] Andreas Huber,[1] Tobias Bittner,[1] Ulf Andreasson,[2] Johan Gobom,[2] Henrik Zetterberg,[2,3] Uwe Kobold,[1] Erik Portelius,[2] and Kaj Blennow[2*] on behalf of the IFCC Scientific Division Working Group on CSF proteins

Journal of Alzheimer's Disease 41 (2014) 441–451
DOI 10.3233/JAD-132489
IOS Press

441

Qualification of a Surrogate Matrix-Based Absolute Quantification Method for Amyloid-β_{42} in Human Cerebrospinal Fluid Using 2D UPLC-Tandem Mass Spectrometry

Magdalena Korecka[a], Teresa Waligorska[a], Michal Figurski[a], Jon B. Toledo[a,d], Steven E. Arnold[b,c], Murray Grossman[c], John Q. Trojanowski[a,d] and Leslie M. Shaw[a,d,*]

Joint Committee for Traceability in Laboratory Medicine (JCTLM) approvals

Bureau International des Poids et Mesures

Database of higher-order reference materials, measurement methods/procedures and services

JCTLM

JCTLM Database
Laboratory medicine and in vitro diagnostics

> You are here : JCTLM-DB > Reference measurement methods/procedures > List

Result of the search: list of reference measurement methods/procedures

JCTLM Database
- Search Form
- List of reference materials no longer listed in the JCTLM Database
- List of reference measurement methods no longer listed in the JCTLM database
- Contact us
- Survey Form

JCTLM Newsletters
- Issue 2 - March 2015
- Issue 1 - April 2014

JCTLM
- Preamble
- Joint Committee for Traceability in Laboratory Medicine (JCTLM)
- Leaflet

Your search criteria: Reference measurement methods/procedures; Analyte: amyloid ; Analyte category: - ; Matrix category: -

Save as PDF file | Modify your selection

Results of the search

Isotope dilution mass spectrometry methods for amyloid beta 1-42 in other

▸ 2D-UPLC-tandem mass spectrometric method for analysis of amyloid beta 1-42 in human CSF

Applicable matrix(es)	frozen human cerebrospinal fluid (CSF)
Full description of technique(s)	Liquid chromatography tandem mass spectrometry, solid phase extraction
Quantity	Mass concentration
Applicable range	100 pg/mL to 3000 pg/mL
Expected uncertainty (level of confidence 95%)	14.3 pg/mL to 358.2 pg/mL
Reference(s)	Quantification of a surrogate matrix-based absolute quantification method for Amyloid β_{42} in human cerebrospinal fluid using 2D UPLC-Tandem Mass Spectrometry, Korecka M et al., Journal of Alzheimer's Disease (JAD), 2014, 41(2), 441-451
Comparability assessment study(ies)	Clinical comparison with immunoassay as cited in: Korecka M et al., JAD, 2014, 41(2), 441-451 Round robin test on quantification of amyloid-β-1-42 in cerebrospinal fluid by mass spectrometry, Pannee J et al., Alzheimer's and Dementia, 2016, 12(1), 55-59
Comment(s)	The reference measurement method, C12RMP1, for quantification of Aβ42 in cerebrospinal fluid was developed and validated by the Biomarker Research Laboratory of Perelman School of Medicine, University of Pennsylvania
JCTLM DB identification number	C12RMP1

▸ Mass spectrometry-based candidate reference measurement procedure for quantification of Aβ42 in cerebrospinal fluid

Applicable matrix(es)	human cerebrospinal fluid
Full description of technique(s)	Isotope dilution mass spectrometry
Quantity	Mass concentration
Applicable range	150 pg/ml to 4000 pg/ml
Expected uncertainty (level of confidence 95%)	15.7 %
Reference(s)	Mass spectrometry-based candidate reference measurement procedure for quantification of Aβ42 in cerebrospinal fluid, A. Leinenbach et al. on behalf of the IFCC Scientific Division Working Group on CSF proteins (WG-CSF) Clin. Chem., 2014, 60(7), 987-994
Comparability assessment study(ies)	See reference cited above for comparability assessment study
Comment(s)	The reference measurement procedure, C11 RMP8, for quantification of Aβ42 in cerebrospinal fluid was developed and validated by Roche Diagnostics GmbH in collaboration with the University of Gothenburg
JCTLM DB identification number	C11RMP8

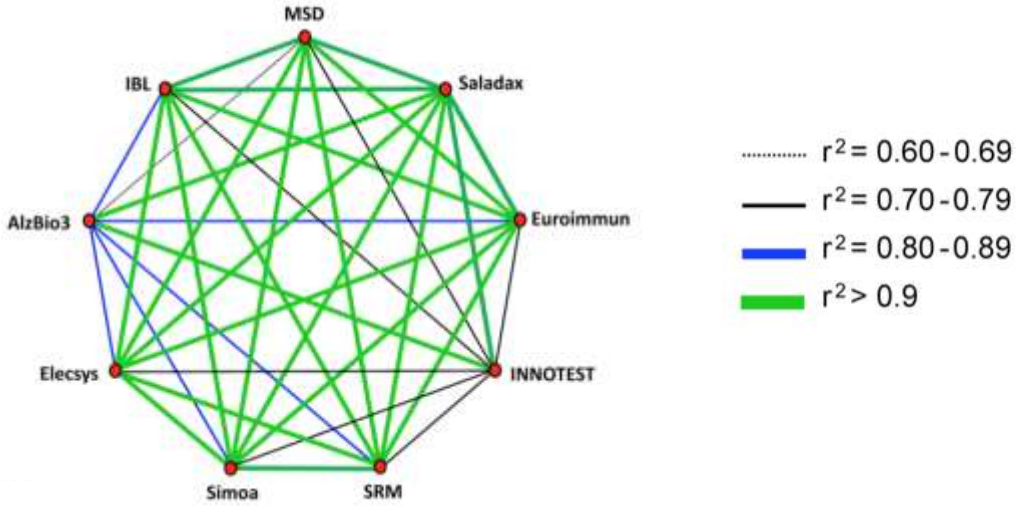
➔ **Certified methods for harmonization of results between assays and laboratories**

No.	Symbols	Non individual samples	Spiked Aβ42 concentration, ng/L
		Individual CSF samples	0
1		CSF pool low Aβ42	0
2		CSF pool high Aβ42	0
3		aCSF	1000
4		PBS	1000
5		CSF pool low Aβ42	2000
6		CSF pool low Aβ42	1000
7		CSF pool low Aβ42	500
8		CSF pool low Aβ42	250
9		CSF pool low Aβ42+0.05% Tween	0
10		CSF pool high Aβ42+0.05% Tween	0
11		aCSF + 0.05% Tween	1000
12		PBS + 0.05% Tween	1000
13		CSF pool low Aβ42+0.05% Tween	2000
			1000
14		CSF pool low Aβ42+0.05% Tween	
15		CSF pool low Aβ42+0.05% Tween	500
16		CSF pool low Aβ42+0.05% Tween	250

DE GRUYTER Clin Chem Lab Med 2015; aop

Maria Bjerke, Ulf Andreasson, Julia Kuhlmann, Erik Portelius, Josef Pannee, Piotr Lewczuk, Robert M. Umek, Eugeen Vanmechelen, Hugo Vanderstichele, Erik Stoops, Jennifer Lewis, Manu Vandijck, Vesna Kostanjevecki, Andreas Jeromin, Salvatore J. Salamone, Oliver Schmidt, Anja Matzen, Kairat Madin, Udo Eichenlaub, Tobias Bittner, Leslie M. Shaw, Ingrid Zegers, Henrik Zetterberg and Kaj Blennow*

Assessing the commutability of reference material formats for the harmonization of amyloid beta measurements



- **Native CSF pools commutable for almost all method combinations**
- **CSF pool with spiked Aβ42 was only commutable at low levels**

➔ **Three different levels of native CSF pools will be used for three CRMs**

The final destination: CSF biomarker assays on fully automated clinical analyzers

- Fully automated - minimize variations due to differences in laboratory procedures
  - reduced between-run, between-batch and between-lab variations

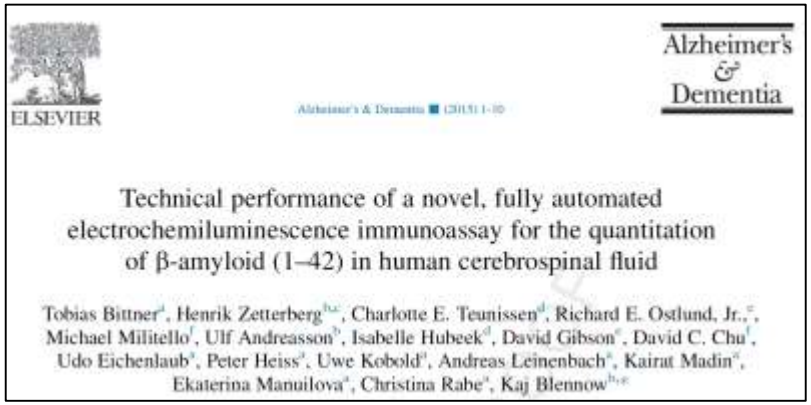
➔ Will allow uniform cut-off levels

- Single sample analysis ➔ fast results (< 30 min) to the clinician

Roche Diagnostics – Cobas

Fujirebio - Lumipulse

New fully automated techniques in the Alzheimer's Association QC program for CSF biomarkers



ELSEVIER

Alzheimer's & Dementia

Technical performance of a novel, fully automated electrochemiluminescence immunoassay for the quantitation of β-amyloid (1–42) in human cerebrospinal fluid

Tobias Bittner[a], Henrik Zetterberg[b,c], Charlotte E. Teunissen[d], Richard E. Ostlund, Jr.[e], Michael Militello[f], Ulf Andreasson[b], Isabelle Hubeek[d], David Gibson[e], David C. Chu[f], Udo Eichenlaub[a], Peter Heiss[a], Uwe Kobold[a], Andreas Leinenbach[a], Kairat Madin[a], Ekaterina Manuilova[a], Christina Rabe[a], Kaj Blennow[b,c]

Roche Diagnostics – Cobas Elecsys

Between laboratory CV (percent)

Round	INNOTEST® β-AMYLOID (1-42) (CE-IVD) Fujirebio	AlzBio3 (RUO) Fujirebio	MULTI-SPOT® Human Aβ42 V-PLEX MSD	β-amyloid (1-42) EuroImmune ADx	Elecsys® β-Amyloid(1–42) Roche Diagnostics
2014-14A	18	16	50	ND	2,9
2014-14B	21	19	43	ND	4,4
2014-15A	15	7,1	12	ND	4,6
2014-15B	17	14	12	ND	3,4
2104-16A	27	40	13	57	3
2014-16B	17	30	11	19	2,5
2015-17A	19	17	21	6,5	1,9
2015-17B	14	15	20	8,2	3,2
2015-18A	13	25	10	22	7,2
2015-18B	13	13	9,4	16	4,7
2015-19A	13	40	10	13	3
2015-19B	13	15	13	13	1,5
MEAN	**16,7**	**20,9**	**18,7**	**19,3**	**3,5**

The CSF biomarkers Aβ42 and T-tau on the fully automated Lumipulse instruments

Lumipulse G1200

Lumipulse G600 II
(benchtop model)

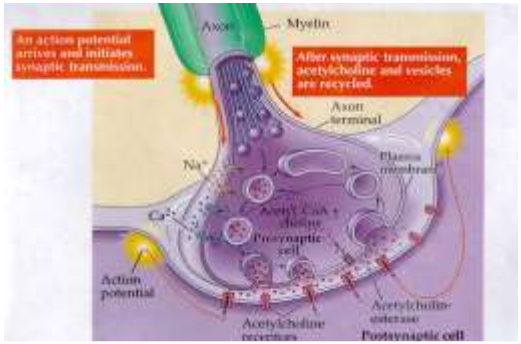
Analytical performance (in-house data)

CSF Aβ42 ➔ CVs of 2-5% within-run, between instrument and between-day

CSF T-tau ➔ CVs of 1-3% within-run, between instrument and between-day

The Lumipulse assays are not yet in the QC program

Can we develop new Alzheimer CSF biomarkers ?

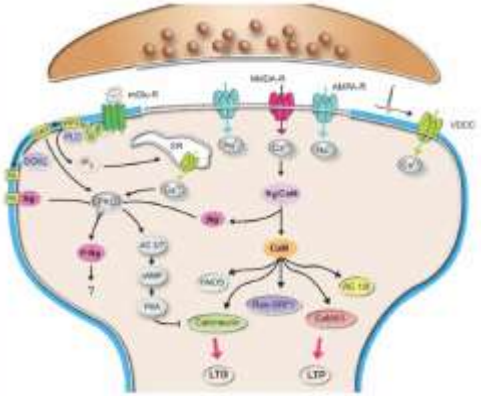


Synaptic proteins in CSF:

- May predict rate of memory loss and cognitive dysfunction
- May give information on disease pathogenesis
- May serve as surrogate biomarkers in clinical trials

The dendritic protein neurogranin:

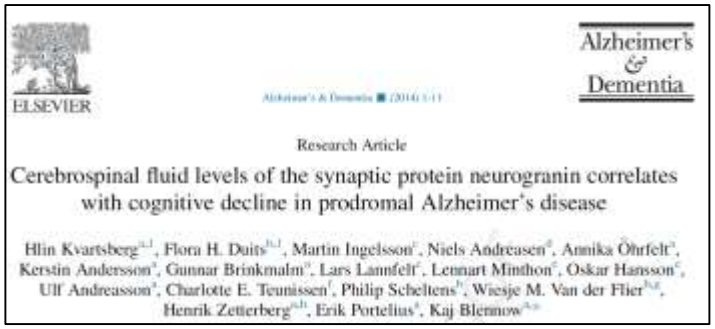
- Abundant in cortex, hippocampus, amygdala
- Concentrated in dendritic spines
- Important for memory consolidation and LTP induction



Neurogranin: small (78 aa) soluble protein

IQ motif
(CaM binding sequence)

MDCCTENACSKPDDDILDIPLDDPGANAAAAKIQASFRGHMARKKIKSGERGRKGPGPGGPGGAGVARGGAGGGPSGD



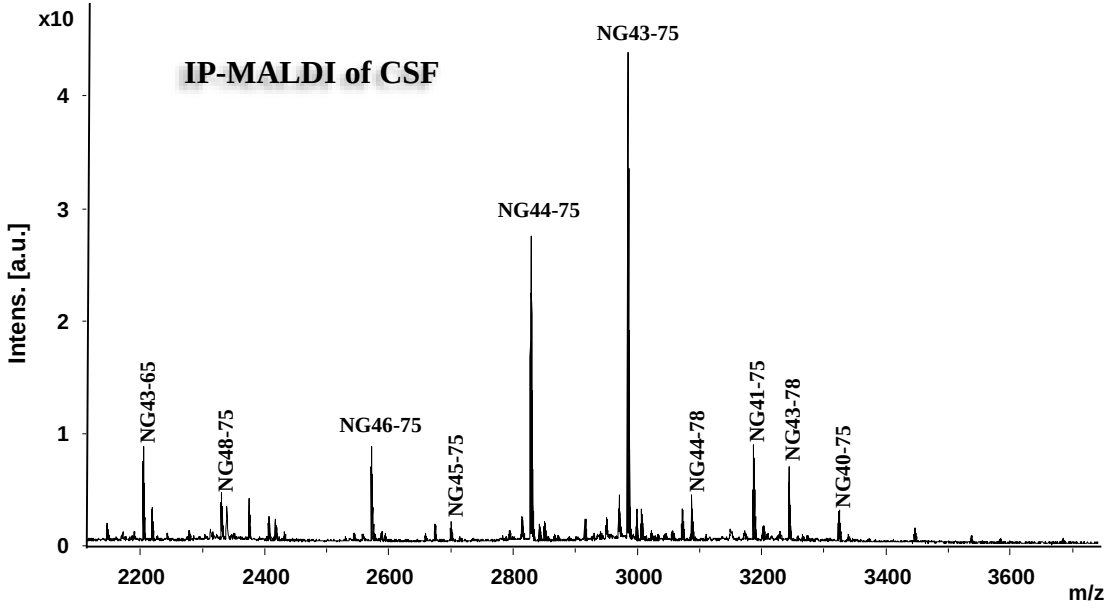
ELSEVIER

Alzheimer's & Dementia

Research Article

Cerebrospinal fluid levels of the synaptic protein neurogranin correlates with cognitive decline in prodromal Alzheimer's disease

Hlin Kvartsberg[a,1], Flora H. Duits[b,1], Martin Ingelsson[c], Niels Andreasen[d], Annika Öhrfelt[a], Kerstin Andersson[a], Gunnar Brinkmalm[a], Lars Lannfelt[c], Lennart Minthon[e], Oskar Hansson[e], Ulf Andreasson[a], Charlotte E. Teunissen[f], Philip Scheltens[b], Wiesje M. Van der Flier[b,g], Henrik Zetterberg[a,h], Erik Portelius[a], Kaj Blennow[a,*]



➔ **Neurogranin is cleaved to C-terminal peptides before release to CSF**

MDCCTENACSKPDDDILDIPLDDPGANAAAAKIQASFRGHMARKKIKSGERGRKGPGPGGPGGAGVARGGAGGGPSGD

RKKIKSGERGRKGPGPGGPGGAGVARGGAGGGPSGD

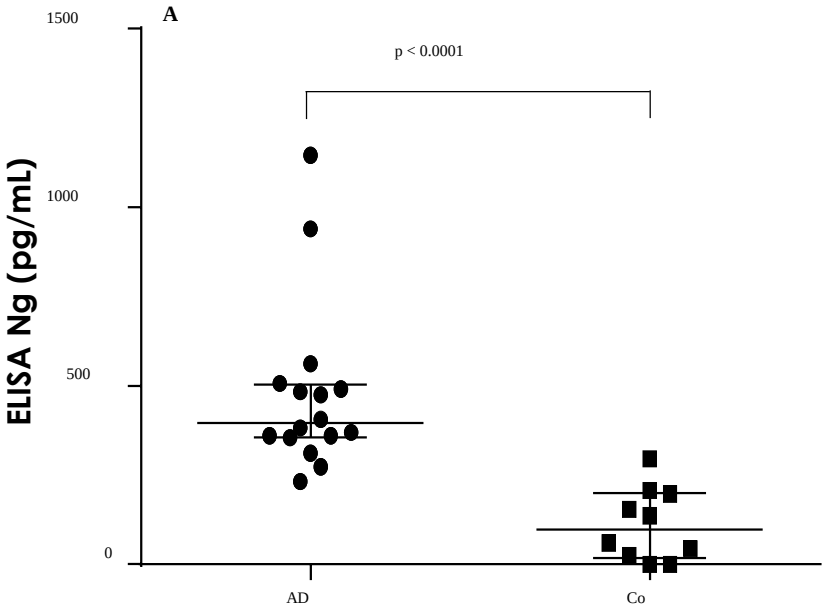
Novel monoclonals

Epitope	
NG2	52-63
NG3	54-65
NG7	54-65

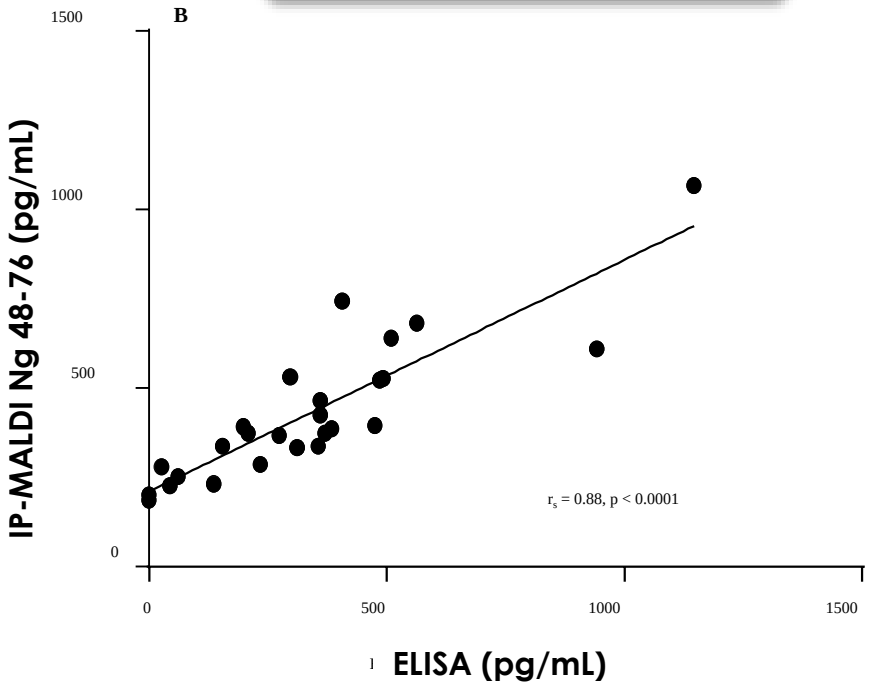
Epitope	
NG13	65-75
NG22	65-75

CSF Neurogranin as a biomarker for Alzheimer's disease

Pilot cohort: 16 AD and 10 Controls



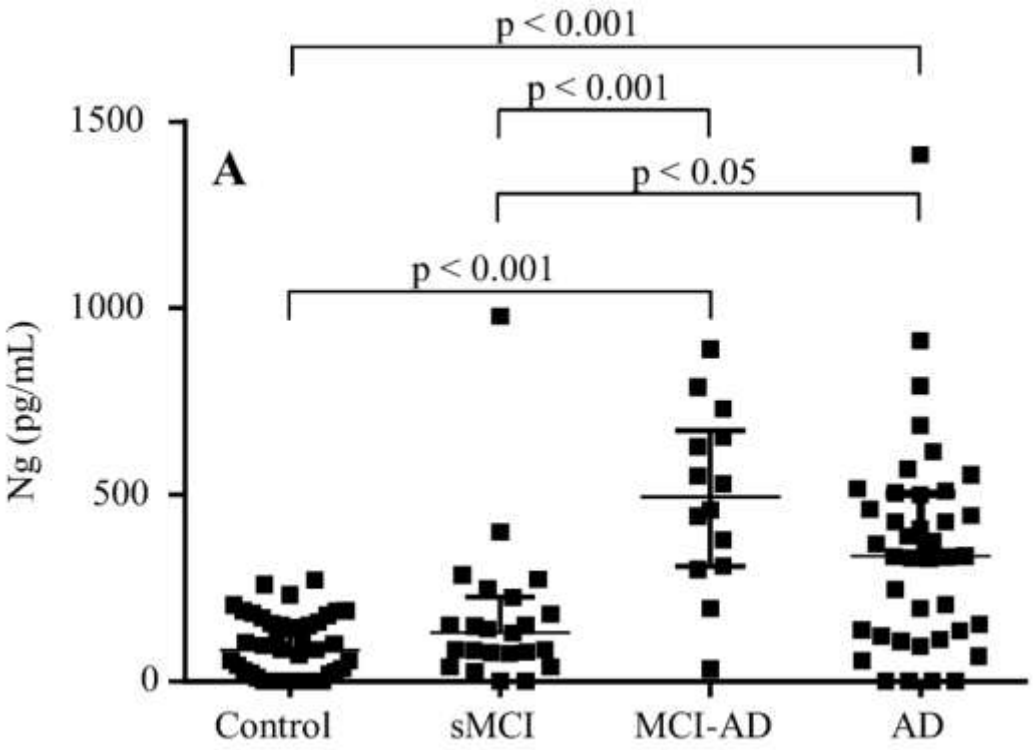
ELISA vs. mass spec data



- ➔ CSF Neurogranin show a marked increase in AD
- ➔ ELISA values correlate with MS values (Ng 48-76)

CSF Neurogranin as a biomarker for prodromal AD

Amsterdam cohort: 40 AD
37 MCI (14 progressive)
40 Controls



➔ CSF Neurogranin is increased in prodromal AD

CSF Neurogranin to predict rate of progression in ADNI cases with MCI

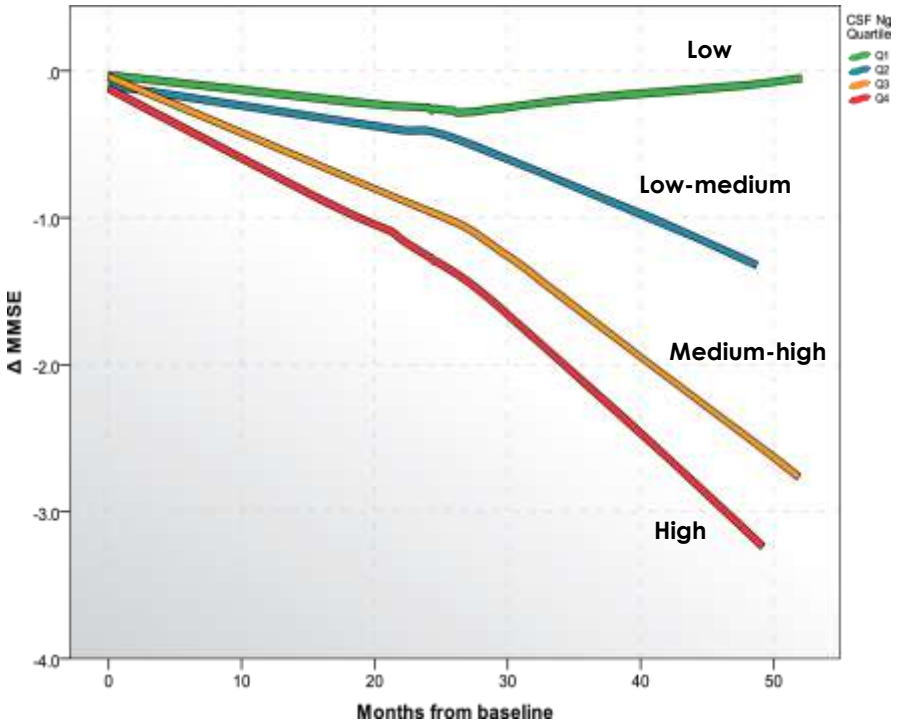
193 MCI cases -

CSF neurogranin levels stratified in quartiles

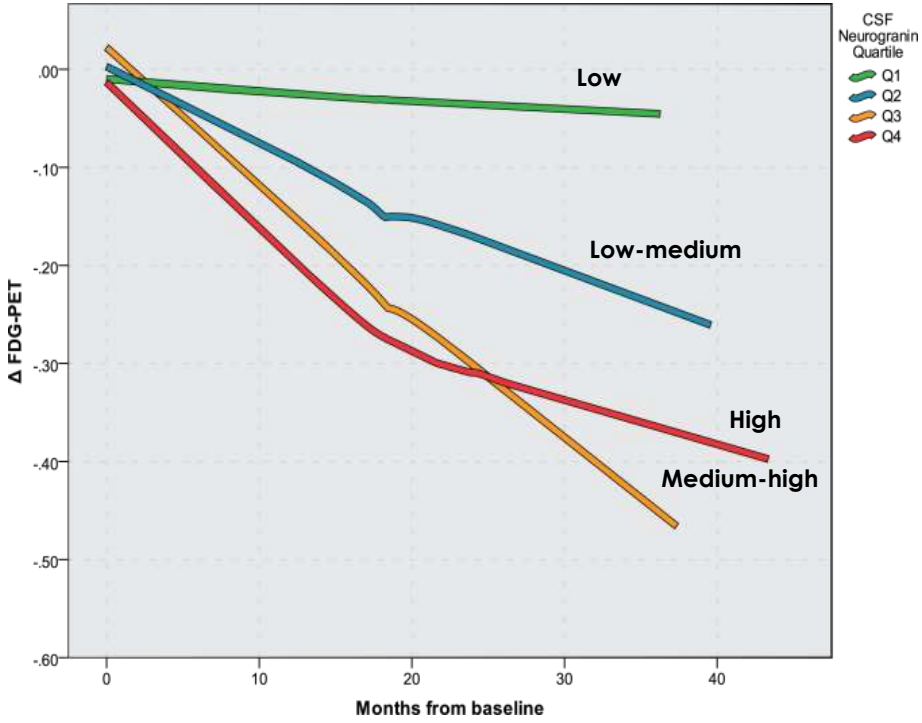
Change in MMSE score during follow-up

Change in FDG-PET SUVR during follow-up

CSF neurogranin vs. change in MMSE during follow-up



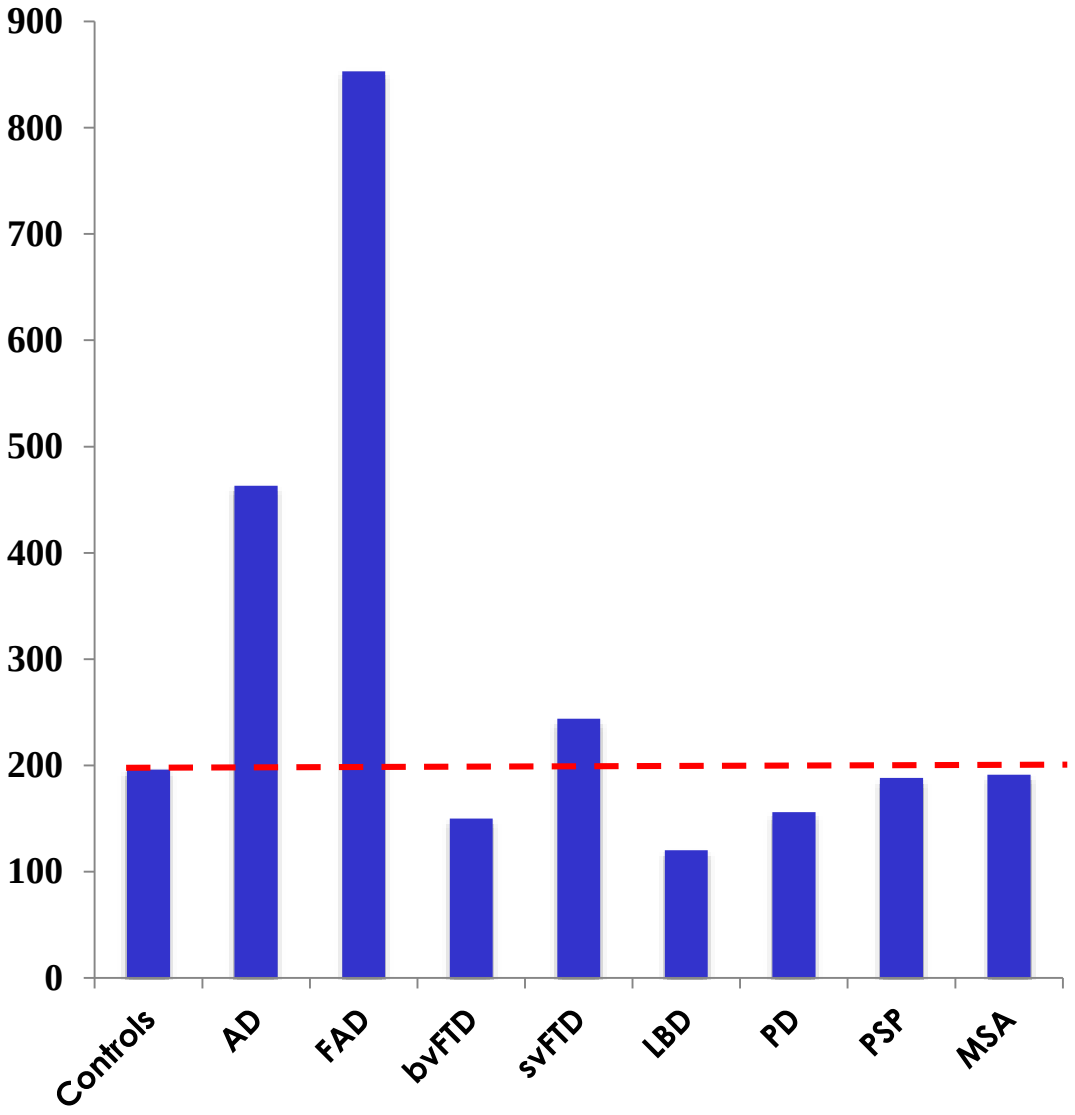
CSF neurogranin vs. decline in FDG-PET during follow-up



➔ CSF neurogranin predicts future rate of synaptic loss and cognitive decline

Is CSF Neurogranin specific for Alzheimer's ?

Diagnostic groups:	
Controls	n= 19
Alzheimer s disease	n= 100
Familial AD	n= 3
Behavioral variant FTD	n= 20
Semantic variant FTD	n= 21
Lewy body dementia	n= 13
Parkinson's disease	n= 31
Progr. supranucl. palsy	n= 46
Multiple system atrophy	n= 29



Wellington H, et al. Neurology 2015, in press

Thanks for listening !