Standardization efforts for Alzheimer CSF biomarkers, and Plasma neurofilament light (NFL) as a biomarker for AD

Kaj Blennow, Professor

Academic Chair in Neurochemistry, University of Gothenburg
The Söderberg Professorship, Royal Swedish Academy of Sciences

The AD core CSF biomarkers reflect key pathogenic events and are highly clinically validated


Articles

CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis

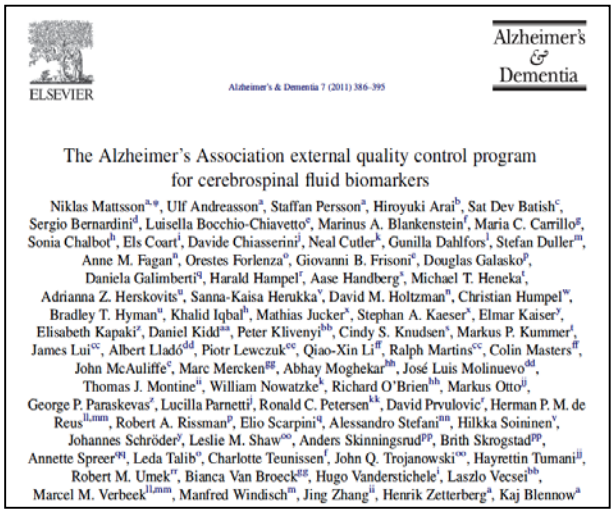
Bob Olsson, Ronald Lautner, Ulf Andreasson, Annika Öhrfelt, Erik Portelius, Maria Bjerke, Mikko Hölttä, Christoffer Rosén, Caroline Olsson, Gabrielle Strobel, Elizabeth Wu, Kelly Dakin, Max Petzold, Kaj Blennow, Henrik Zetterberg

ALZFORUM
NETWORKING FOR A CURE

AlzBiomarker database - Version 2.0 April 26, 2017

CSF T-tau	CSF Aβ42	CSF P-tau
➔Intensity of neurodegeneration	➔ Brain amyloid deposition	➔ Phosphorylation state of tau and tau pathology
•188 studies • 20.600 AD patients and controls • Effect size 2.48	• 168 studies • 19.600 AD patients and controls • Effect size 0.56	• 116 studies • 14.300 AD patients and controls • Effect size 1.88

Background for starting the Alzheimer's Association CSF program



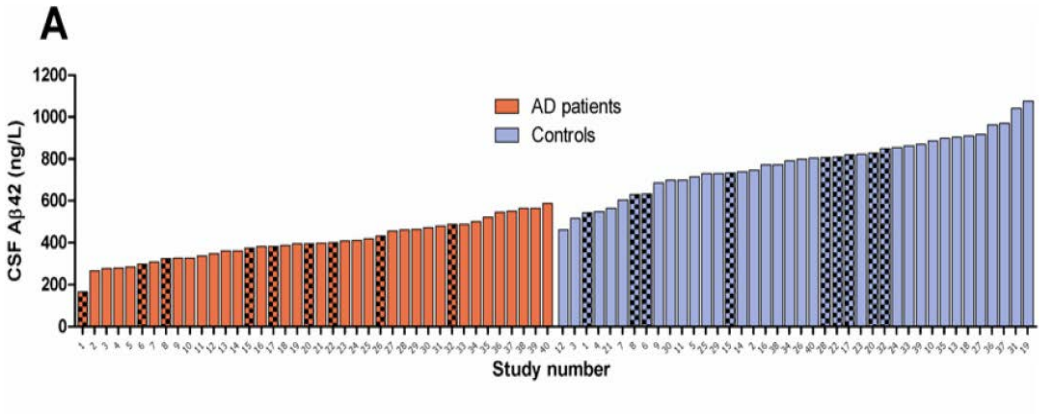
ELSEVIER

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

Alzheimer's & Dementia

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[n], 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[dd], 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[m], Jing Zhang[ii], Henrik Zetterberg[a], Kaj Blennow[a]



➔ **Large variability for CSF Aβ42 across laboratories**

Variability due to:

Pre-analytical factors	**e.g. type of test tube, CSF transfer, freeze-thaw effects,**
Analytical factors	**e.g. analytical procedures, technician training, run acceptance**
Assay manufacturing	**e.g. reagent purity, plate coating variability, calibrator stability, lot-to-lot consistency (batch bridging procedure)**

The Alzheimer's Association QC program for CSF biomarkers

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

- **Ongoing project since 2009**
- **Led by Gothenburg University, funded by the Alzheimer's Association (private sponsor)**

Principle for the QC program:

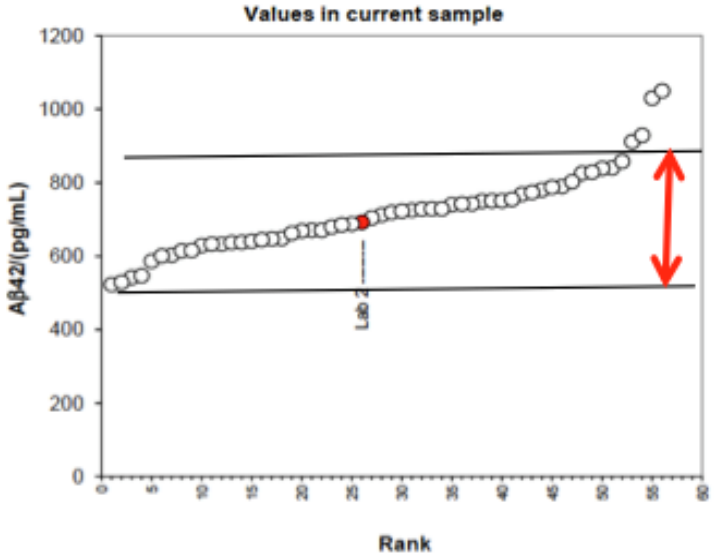
For each round, 3 QC samples (pooled CSF) are sent out

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%



➔ **Need of standardization efforts**

IFCC Work Group for CSF proteins (IFCC WG-CSF)
and
Global Biomarker Standardization Consortium (GBSC)

Reference Measurement Procedure (RMP)

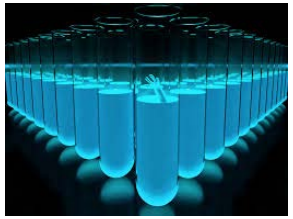
- **High precision**
  - Mass spectrometry-based technique
  - Certified calibrator (amino acid analysis)
  - Tested in Round Robin studies
- **Intended use**
  - Assign value on Certified Reference Material

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

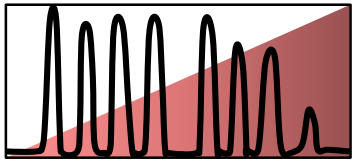
- **Antibody-free Single Reation Monitoring (SRM) Triple Quad mass spec method for CSF Aβ isoforms**

CSF +
internal Aβ standards

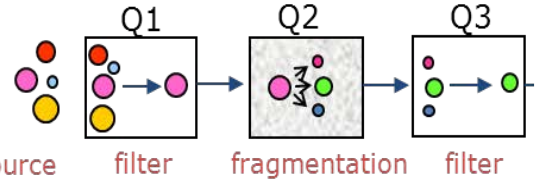
Guanidine HCl
→ denaturation

SPE antibody-free
purification

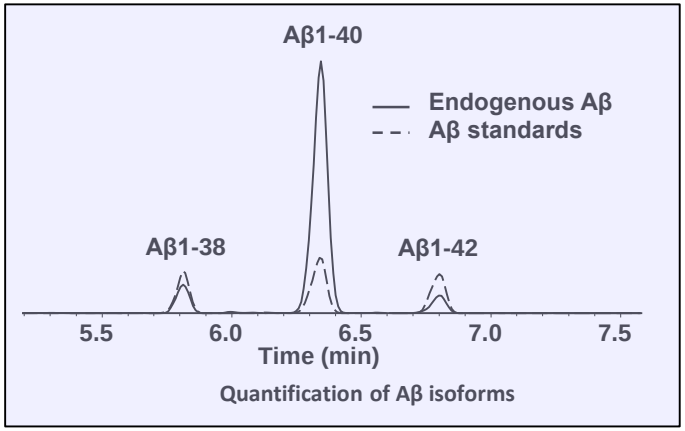
Elute + dry
+ redissolve in
ACN and NH_4OH



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)**

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

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Laboratory medicine and *in vitro* diagnostics

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JCTLM Newsletters
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- Issue 1 - April 2014

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- *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 matrice(s)	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 355.2 pg/mL
Reference(s)	Qualification 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 matrice(s)	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 RMP9, 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	C11RMP9

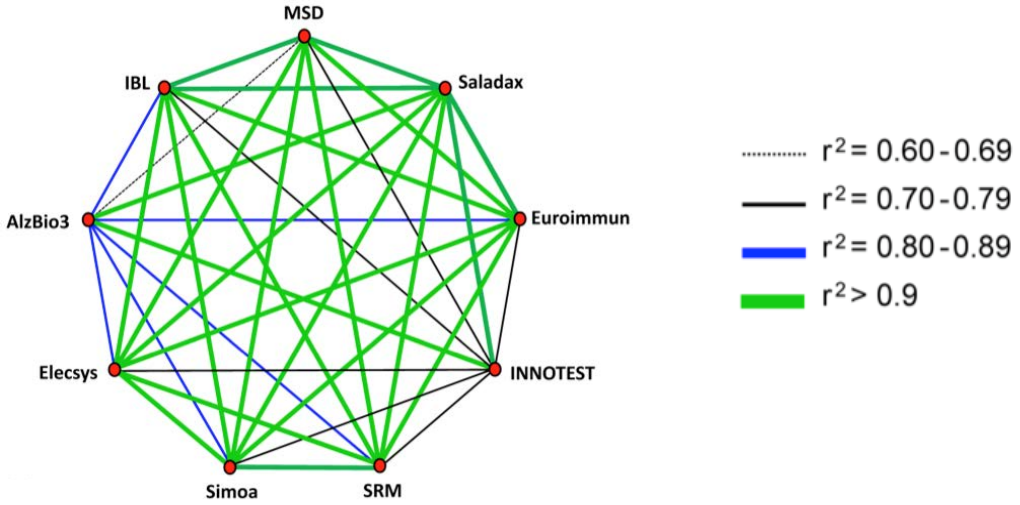
➔ **Certified methods for harmonization of results between assays and laboratories**

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**

Certified Reference Materials for CSF Aβ42

The certification of Amyloid β_{1-42} in CSF in ERM®-DA480/IFCC, ERM®-DA481/IFCC and ERM®-DA482/IFCC

Julia Kuhlmann[1], Sébastien Boulo[1], Ulf Andreasson[2], Maria Bjerke[2], Josef Pannee[2], Jean Charoud-Got[1], Guy Auclair[1], Stéphane Mazoua[1], Stefanie Trapmann[1], Heinz Schimmel[1], Hendrik Emons[1], Doris Florian[1], Milena Quaglia[3], Erik Portelius[2], Magdalena Korecka[4], Leslie M. Shaw[4], Mary Lame[5], Erin Chambers[5], Hugo Vanderstichele[6], Erik Stoops[6], Andreas Leinenbach[7], Tobias Bittner[7], Rand G. Jenkins[8], Vesna Kostanjavecki[9], Piotr Lewczuk[10], Henrik Zetterberg[2], Ingrid Zegers[1], Kaj Blennow[2]

Amyloid β_{1-42} peptide in human CSF[1)]	Mass concentration	
	Certified value [2)] [μg/L]	Uncertainty [3)] [μg/L]
ERM-DA480/IFCC	0.45	0.07
ERM-DA481/IFCC	0.72	0.11
ERM-DA482/IFCC	1.22	0.18

[1)] As obtained by solid phase extraction and subsequent quantification by liquid chromatography with mass spectrometry detection, according to the reference methods (Leinenbach *et al.* Clin. Chem. 60 (2014) 987-94; Korecka *et al.* J. Alzheimers Dis. 41 (2014) 441-451) [5,6].

[2)] Certified values are values that fulfil the highest standards of accuracy and represent the unweighted mean value of the means of 5 accepted sets of data, each set being obtained in a different laboratory. The certified value and its uncertainty are traceable to the International System of Units (SI).

[3)] The uncertainty is the expanded uncertainty of the certified value with a coverage factor $k = 2$ corresponding to a level of confidence of about 95 % estimated in accordance with ISO/IEC Guide 98-3, Guide to the Expression of Uncertainty in Measurement (GUM:1995), ISO, 2008 [4].

➔ **The CRMs (+dilutions) can be run as a standard curve, to calibrate the master calibrator for an immunoassay**

➔ **Harmonize CSF Aβ42 readouts between assay formats (different immunoassays)**

➔ **Candidate RMP for CSF Aβ40 submitted to JCTLM**
➔ **One of the CRMs will be used also for CSF Aβ40**

➔ **Work in ongoing for a CSF tau mass spec RMP and a CRM for tau**

CSF biomarker assays on fully automated clinical analyzers

- Fully automated – no variations due to differences in laboratory procedures
  - precise: low between-run, between-batch and between-lab variations

➔ Give promise of uniform cut-off levels

- Single sample analysis ➔ analyses can be done directly – better service / fast results to the clinician
  ➔ no need to await enough samples (n= 35 or 70) to fill an ELISA plate

- Assays available or under development on several platforms:

Cobas Elecsys	- Roche
Lumipulse	- Fujirebio
RA Analyzer	- Euroimmune

ELSEVIER

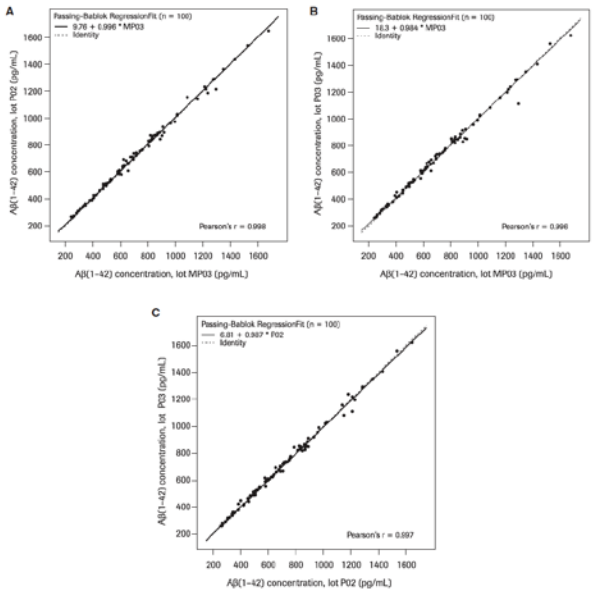
Alzheimer's & Dementia 12 (2016) 517-526

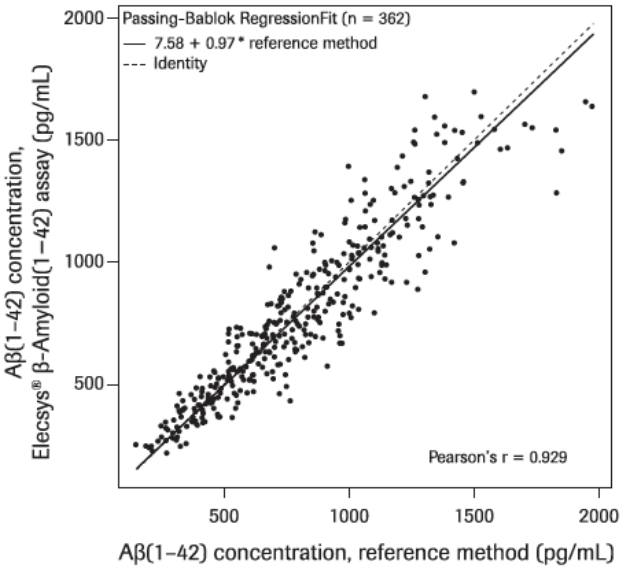
Alzheimer's & Dementia

Featured Article

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,*]





- ➔ LLOQ 11 pg/mL, linear range 200–1700 pg/mL
- ➔ High lot-to-lot comparability (r= 0.0.995)
- ➔ High precision (repeatability CVs of 1.0%–1.6%)

➔ standardized to the mass spectrometry RMP for CSF Aβ42 (r= 0.93)

➔ CSF assays on fully automated analyzers show a marked improvement in performance

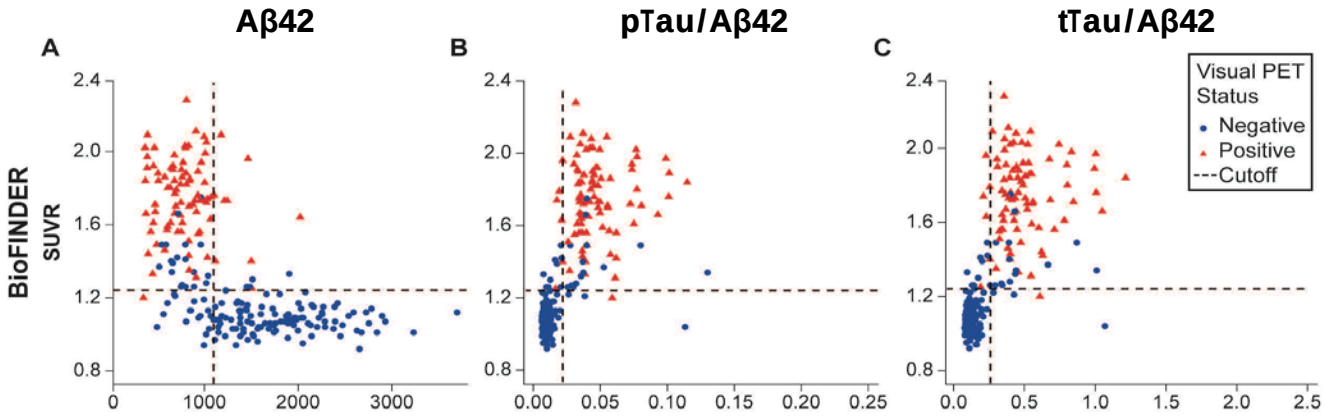
CSF biomarkers of Alzheimer's disease concord with amyloid-β PET and predict clinical progression: A study of fully-automated immunoassays in BioFINDER and ADNI cohorts

Oskar Hansson MD[a,b,*,†], John Seibyl MD[c], Erik Stomrud MD[a,b], Henrik Zetterberg MD[d,e,f,g], John Q. Trojanowski PhD[h], Tobias Bittner PhD[it], Valeria Lifke PhD[j], Veronika Corradini MSc[k], Udo Eichenlaub PhD[j], Richard Batrla MD[k], Katharina Buck PhD[j], Katharina Zink MSc[j], Christina Rabe PhD[it], Kaj Blennow MD[d,e,*,†], Leslie M Shaw PhD[h,*,†], for the Swedish BioFINDER study group[§] and the Alzheimer's Disease Neuroimaging Initiative[||]

Study design:

Elecsys assays for Aβ1-42, tTau and Ptau

BioFINDER (n= 277) and ADNI (n= 646)



Performance of CSF biomarkers vs. visual amyloid PET

Cohort	CSF biomarker	Cutoff	OPA, %
BioFINDER	Aβ(1–42)	1100 pg/mL	79·8 (74·6–84·4)
	pTau/Aβ(1–42)	0·022	89·9 (85·7–93·2)
	tTau/Aβ(1–42)	0·26	89·9 (85·7–93·2)
ADNI	Aβ(1–42)	880 pg/mL	84·4 (81·3–87·1)
	pTau/Aβ(1–42)	0·028	90·3 (87·7–92·4)
	tTau/Aβ(1–42)	0·33	89·2 (86·5–91·5)

Inter-rater PET agreement **OPA = 90%**
Visual vs. SUVR PET agreement **OPA = 90-91%**

➔ **CSF pTau/Aβ42 and tTau/Aβ42 show very high concordance with amyloid PET**

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

Cobas Elecsys

Lumipulse

	Between laboratory CV (percent)			
	INNOTEST® Fujirebio ELISA	EuroImmune / ADx ELISA	AlzBio3 Fujirebio Luminex	Meso-Scale ECL V-PLEX
Round 14-25 (2014-2018)	β-AMYLOID (1-42)	β-amyloid (1-42)	β-amyloid (1-42)	Human Aβ42
MEAN	16,0	15,2	21,6	17,2
Round 14-25 (2014-2018)	Total tau	Total tau	Total tau	
MEAN	16,0	14,1	15,5	
Round 14-25 (2014-2018)	Phospho tau	Phospho tau		
MEAN	12,3	33,7		

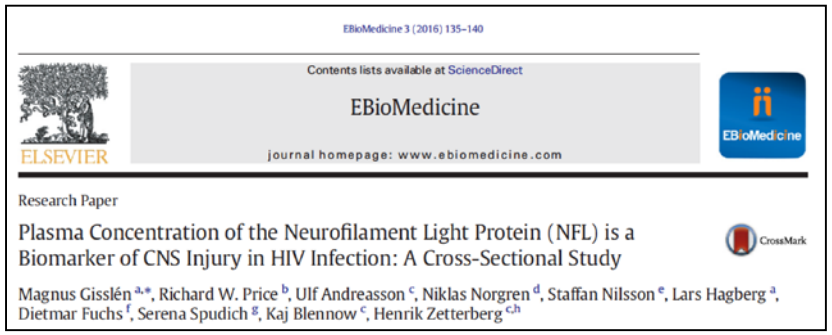
➔ CSF assays on fully automated analyzers show a marked improvement in performance

Development of the Simoa assay for NFL in blood

Vinnova (University – Small Enterprise) project in 2013:

Aim to develop a Simoa assay for NFL in blood, for use as a biomarker for traumatic brain injury (TBI):

- **the same Mabs as in the Uman diagnostics ELISA**
- **purified bovine NFL as calibratior**



EBioMedicine 3 (2016) 135–140

Contents lists available at ScienceDirect

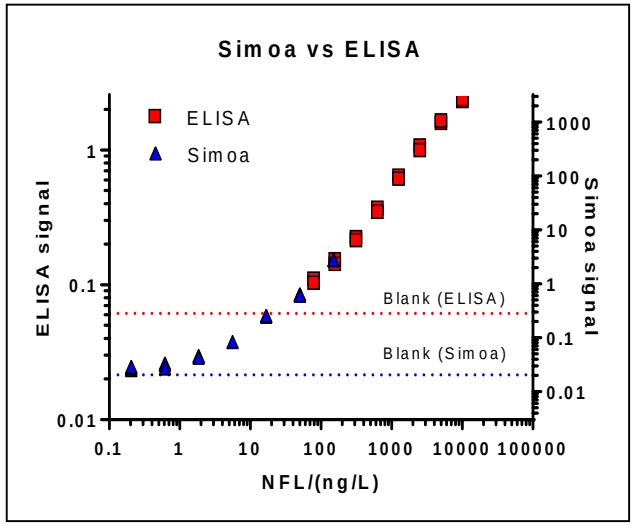
EBioMedicine

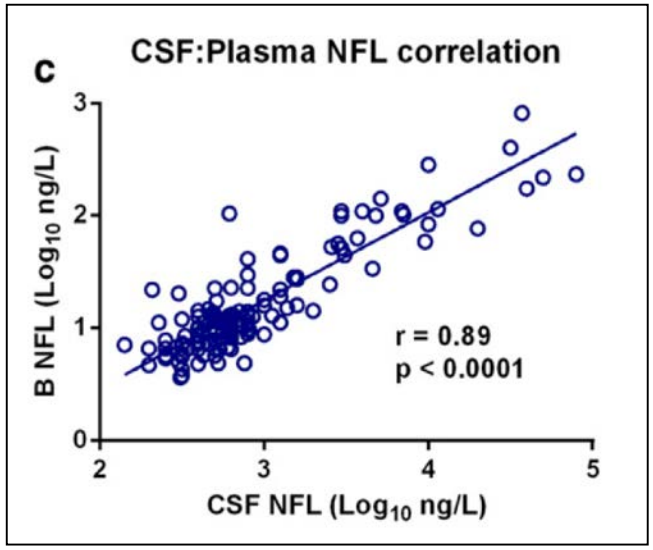
journal homepage: www.ebiomedicine.com

Research Paper

Plasma Concentration of the Neurofilament Light Protein (NFL) is a Biomarker of CNS Injury in HIV Infection: A Cross-Sectional Study

Magnus Gisslén [a,*], Richard W. Price [b], Ulf Andreasson [c], Niklas Norgren [d], Staffan Nilsson [e], Lars Hagberg [a], Dietmar Fuchs [f], Serena Spudich [g], Kaj Blennow [c], Henrik Zetterberg [c,h]





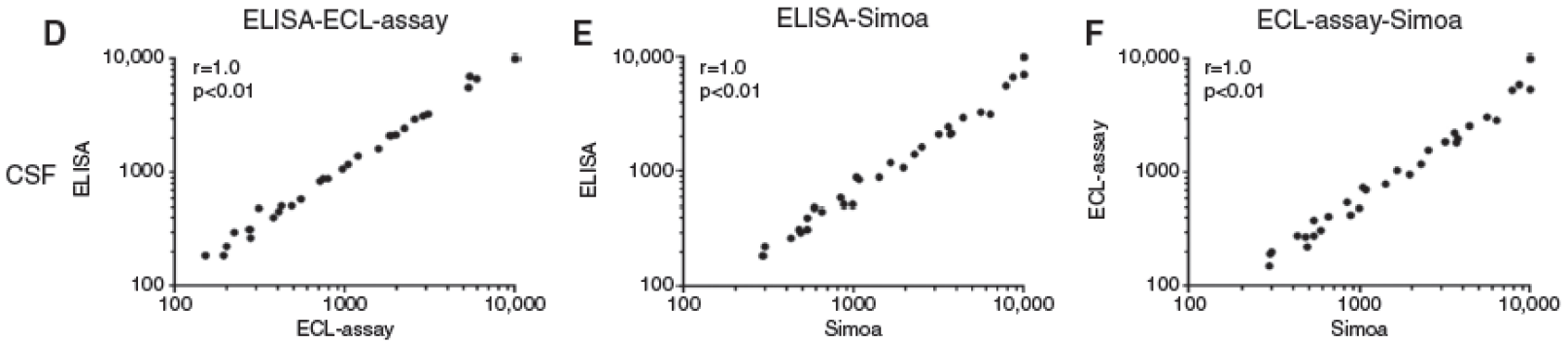
- **LLOQ = 0.3 pg/mL (70 pg/mL for ELISA**

- **Very high correlation between plasma and CSF**

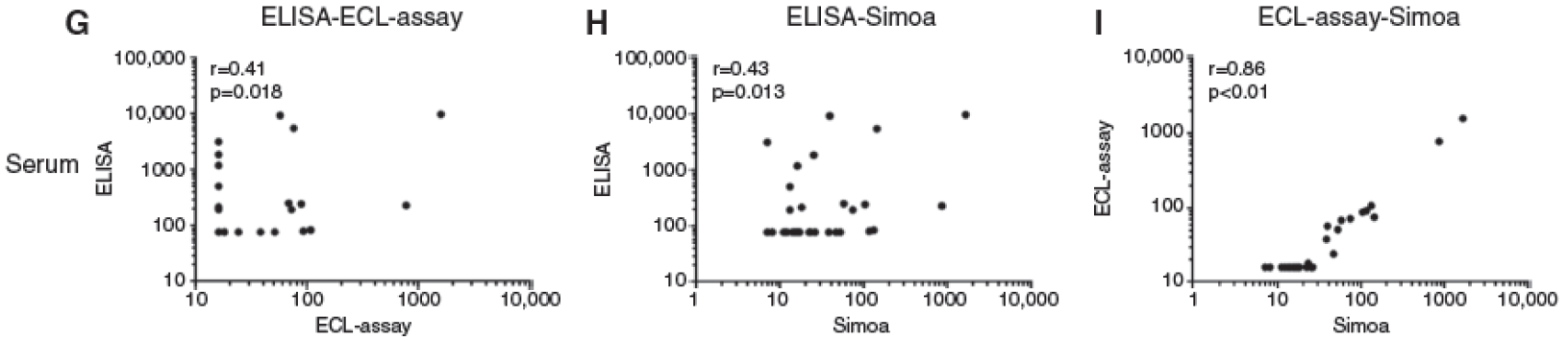
DE GRUYTER Clin Chem Lab Med 2016; aop

Jens Kuhle*, Christian Barro, Ulf Andreasson, Tobias Derfuss, Raija Lindberg, Åsa Sandelius, Victor Liman, Niklas Norgren, Kaj Blennow[a] and Henrik Zetterberg[a]

Comparison of three analytical platforms for quantification of the neurofilament light chain in blood samples: ELISA, electrochemiluminescence immunoassay and Simoa



➔ **All three assays correlate tightly for CSF samples**



➔ **Poor correlations in serum - the ECL and ELISA assay lack analytical sensitivity**

SCIENTIFIC REPORTS

OPEN

Serum neurofilament light protein predicts clinical outcome in traumatic brain injury

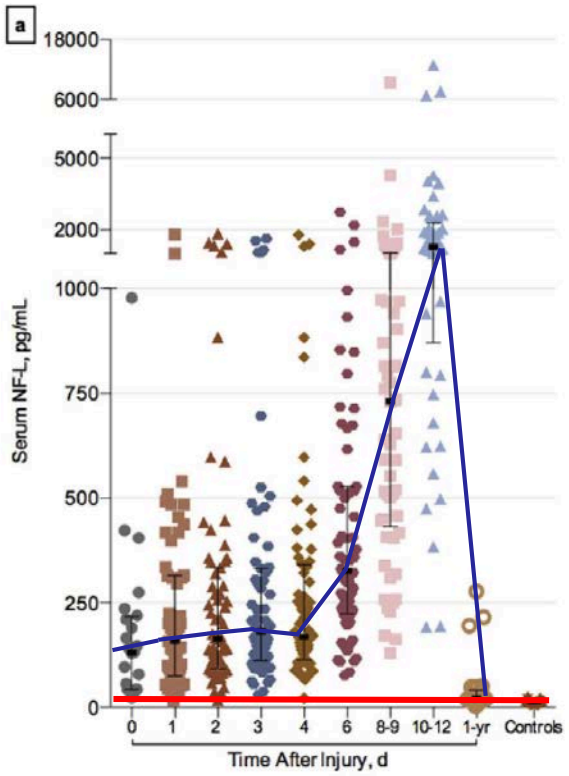
Received: 01 July 2016
Accepted: 17 October 2016
Published: 07 November 2016

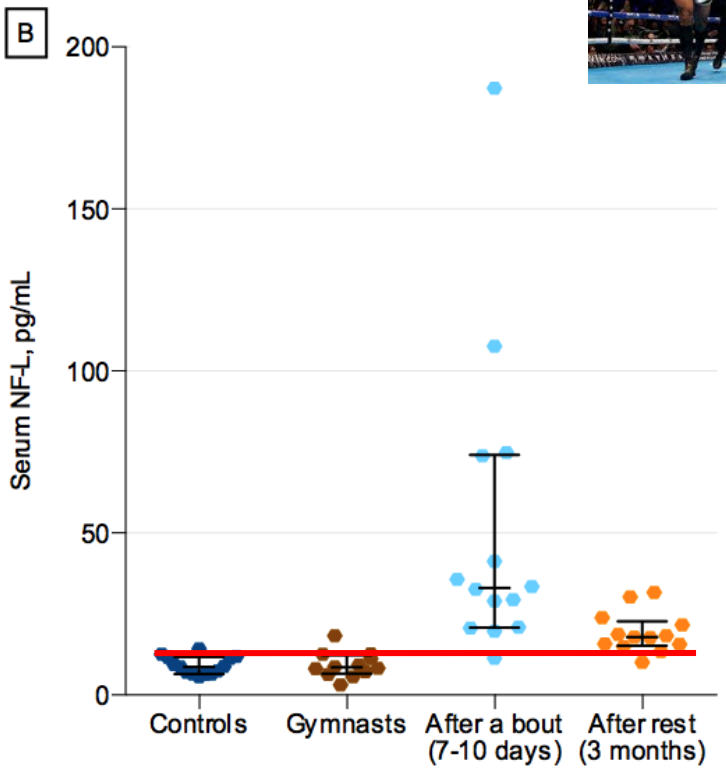
Pashtun Shahim[1], Magnus Gren[1], Victor Liman[1], Ulf Andreasson[1], Niklas Norgren[2], Yelverton Tegner[3], Niklas Mattsson[4], Niels Andreasen[5], Martin Öst[6], Henrik Zetterberg[1,7], Bengt Nellgård[6] & Kaj Blennow[1]

Serum neurofilament light as a biomarker for mild traumatic brain injury in contact sports

Neurology® 2017;88:1-7

Pashtun Shahim, MD, PhD
Henrik Zetterberg, MD, PhD
Yelverton Tegner, MD, PhD
Kaj Blennow, MD, PhD





Very marked increase in serum-NFL (400 – 4400 % of controls)

Predicts 1-year clinical outcome

Increased serum NFL after bout

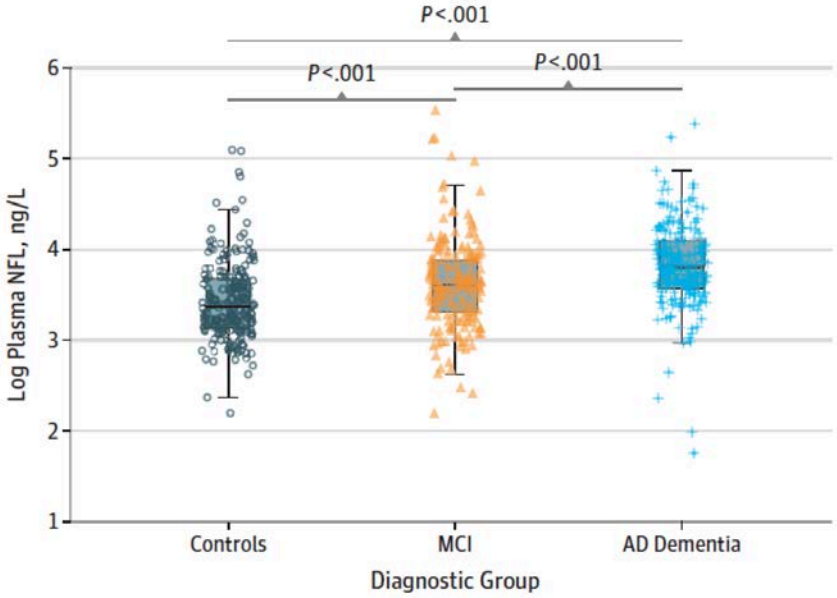
Higher level with more severe head impact

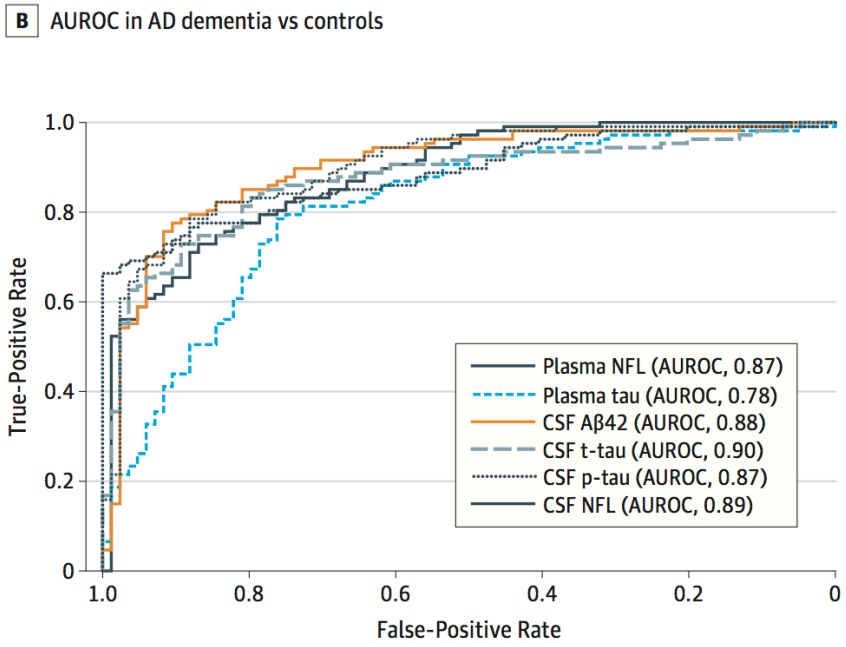
JAMA Neurology | Original Investigation

Association of Plasma Neurofilament Light With Neurodegeneration in Patients With Alzheimer Disease

Niklas Mattsson, MD, PhD; Ulf Andreasson, PhD; Henrik Zetterberg, MD, PhD; Kaj Blennow, MD, PhD; for the Alzheimer's Disease Neuroimaging Initiative

ADNI cohort: 180 AD dementia, 197 MCI, 193 controls





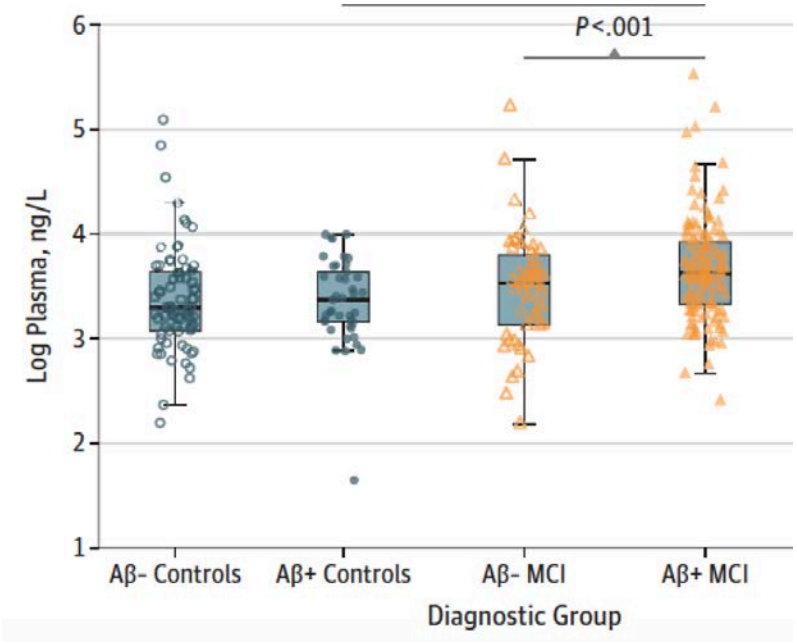
➔Plasma NFL is increased in AD and MCI

➔High AUC values for AD dementia, similar to CSF Aβ42, T-tau and P-tau

Plasma NFL and amyloid load

ADNI cohort

193 controls, 197 MCI



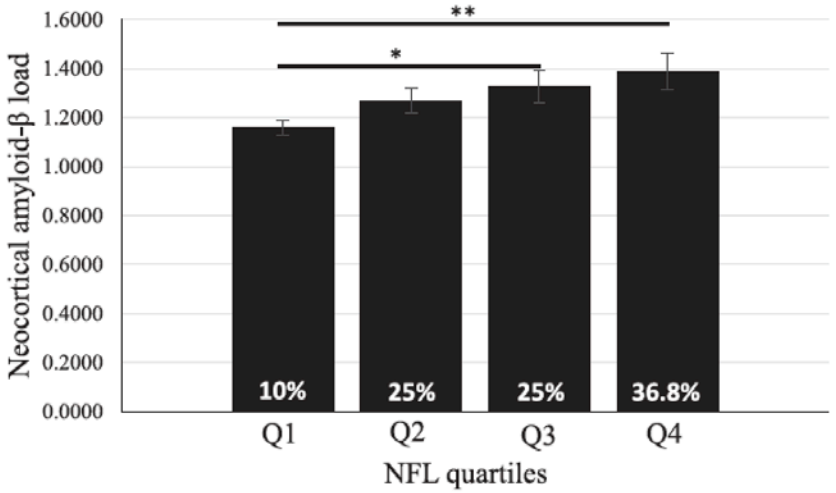
Slightly higher plasma NFL associated with amyloid load in MCI but not in controls

Mattsson N et al. JAMA Neurol 2017

Kerr Anglican Retirement Village Initiative in Ageing Health (KARVIAH) cohort

100 cognitively normal elderly

Within APOE ε4 non-carriers (n=65)



Q1 < 23 Q2 23-34 Q3 34-45 Q4 >45 pg/mL

➔ **No difference in plasma NFL between amyloid positive and negative normal elderly**

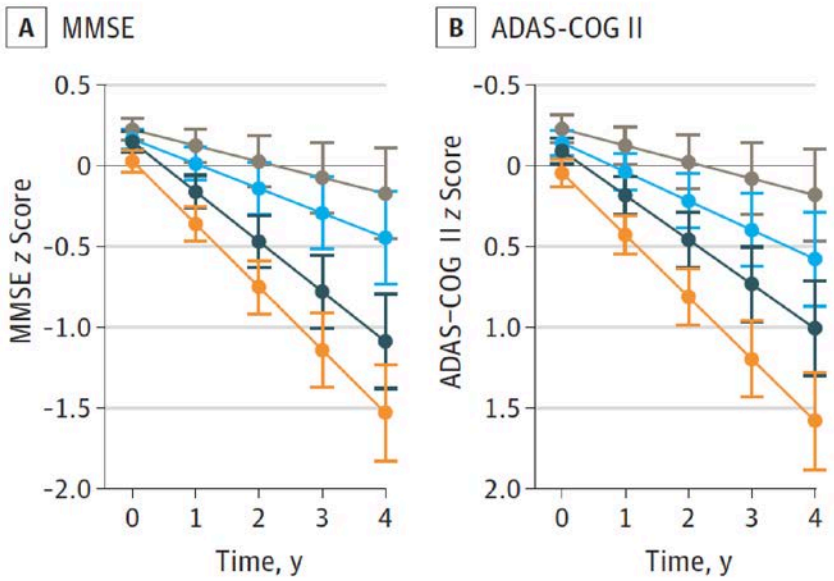
➔ **Higher amyloid load in highest plasma NFL quartiles**

Chatterjee P et al. J Alzheimer Dis 2018, in press

Plasma NFL and cognition

ADNI cohort

180 AD dementia, 197 MCI, 193 controls



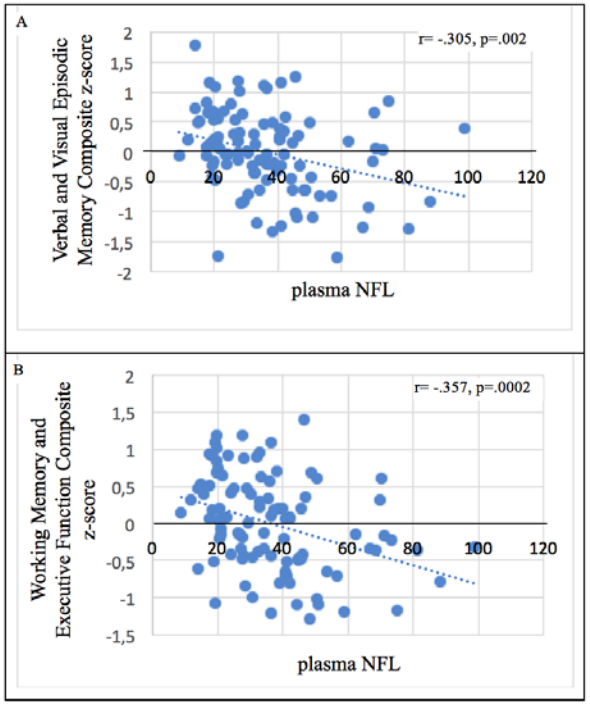
High plasma NFL

associated with baseline MMSE and ADAS-COG
And predicts future rate of cognitive decline,

Mattsson N et al. JAMA Neurol 2017

Kerr Anglican Retirement Village Initiative in Ageing Health (KARVIAH) cohort

100 cognitively normal elderly



High plasma NFL associated with worse cognition (episodic memory and executive function)

Chatterjee P et al. J Alzheimer Dis 2018, in press

Serum neurofilament light in familial Alzheimer disease

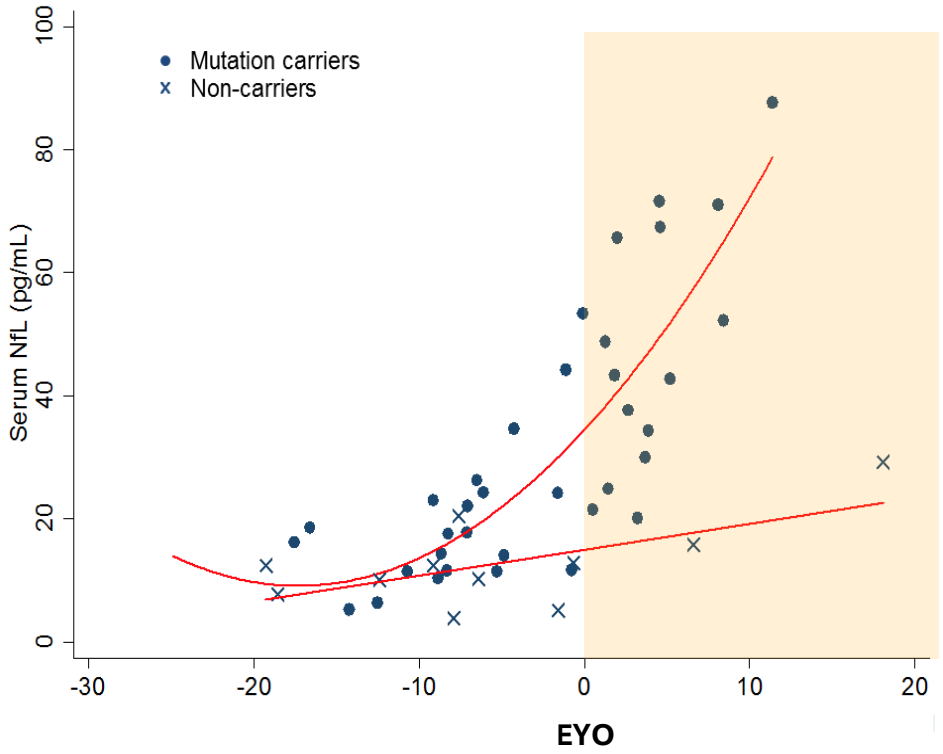
A marker of early neurodegeneration

OPEN

Weston, PSJ, et al. Neurology® 2017;89:2167-2175

Study design:

- **18 symptomatic FAD (*APP* or *PSEN*)**
- **19 pre-symptomatic carriers**
- **11 non-mutation carriers**



➔Plasma NFL show promise as a future screening test for neurodegeneration

N.B. Plasma NFL is not AD specific - increase found in several neurodegenerative disorders

Plasma NFL in other neurodegenerative disorders

Blood-based NfL

A biomarker for differential diagnosis of parkinsonian disorder

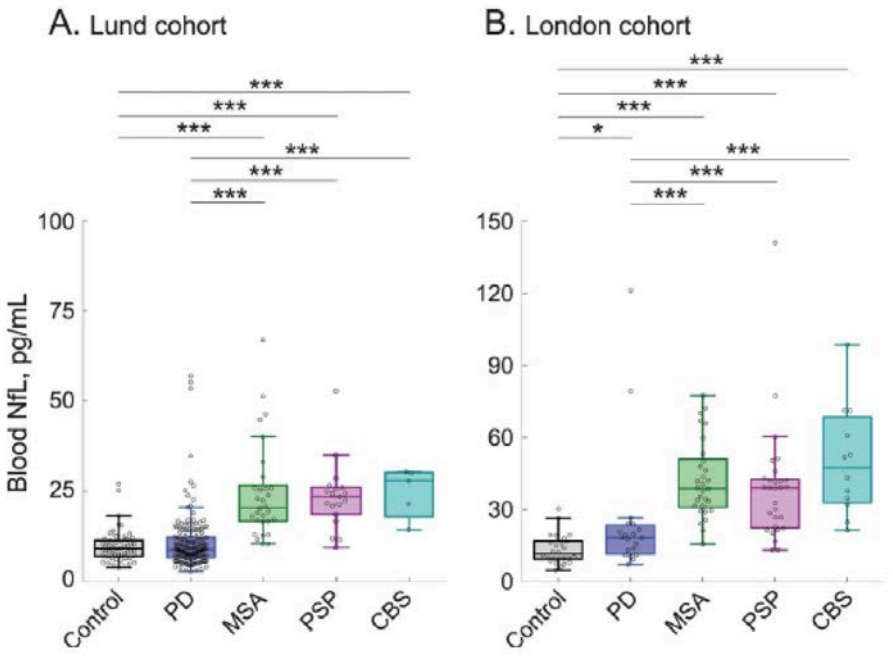
OPEN

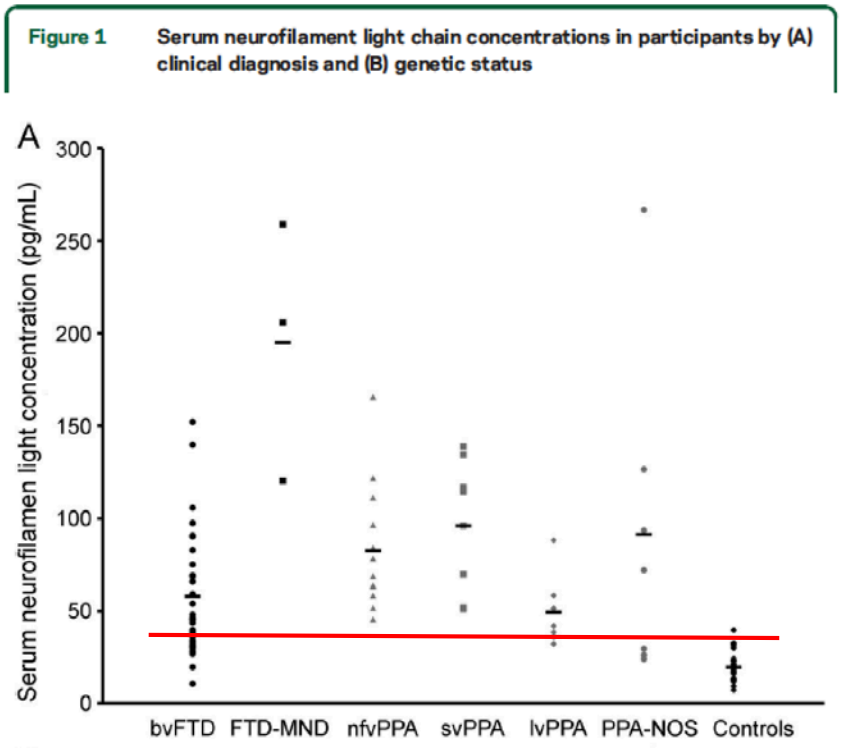
Mattsson N et al, 2017

Serum neurofilament light chain protein is a measure of disease intensity in frontotemporal dementia

OPEN

Rohrer JD et al, 2016





➔ **NFL in blood is a sensitive but disease-unspecific biomarker for neurodegeneration**

Plasma NFL to monitor treatment effects on neurodegeneration

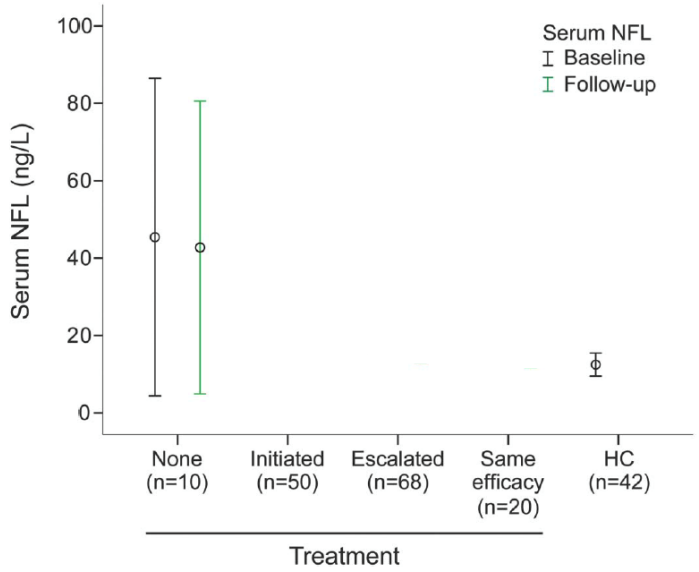
Monitoring disease activity in multiple sclerosis using serum neurofilament light protein

OPEN

Lenka Novakova *Neurology*® 2017;89:1-8

- **148 MS patients – followed with/without treatmen during 12 monts**
- **Less effective DMTs (e.g. interferon-β) more effective DMTs (e.g. fingolimod, natalizumab, or rituximab)**

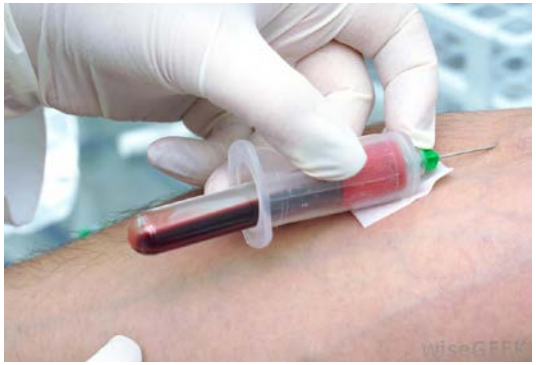
Figure 1 Serum NFL concentrations in patients with MS at baseline and follow-up and in HCs



➔Reduction in serum NFL with DMTs and with more effective DMTs

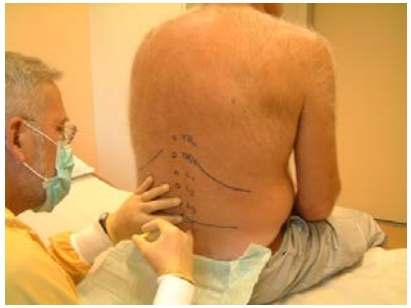
➔ Serum NFL may be useful to monitor downstream drug effects on intensity of neurodegeneration

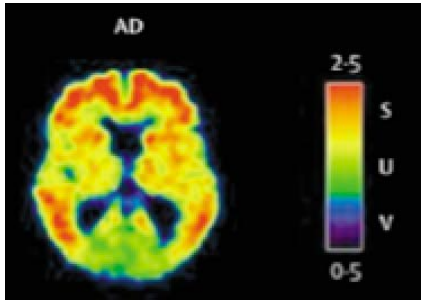
Blood biomarkers for AD

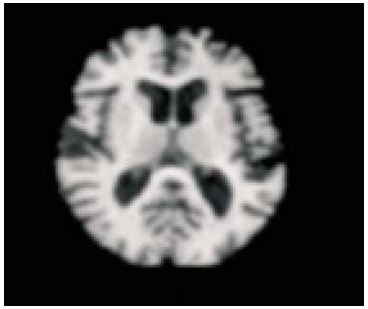


- Plasma NFL may be useful to screen for neurodegeneration in the first assessment of patients with cognitive symptoms
- May guide clinical management:
  - normal ➔ no further examination
  - increased ➔ admission to specialist clinic

- At the specialist clinic – detailed diagnostic evaluation using 2nd grade biomarkers







- Blood NFL may also be valuable in clinical trials
  - to identify and monitor drug effects on neurodegeneration