# I neurofilamenti nelle patologie neurodegenerative

Hot topics- Giornata dello Specializzando

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Discussant
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Milano, 11 giugno 2019

# Definizione di biomarcatori

**Diagnostico**

**Prognostico**

**Predittivo**: identificare individui che hanno maggiore probabilità di rispondere favorevolmente/non favorevolmente a un intervento

**Farmaco-dinamico**

"**Monitoring**": misurato serialmente per valutare lo stato di una malattia

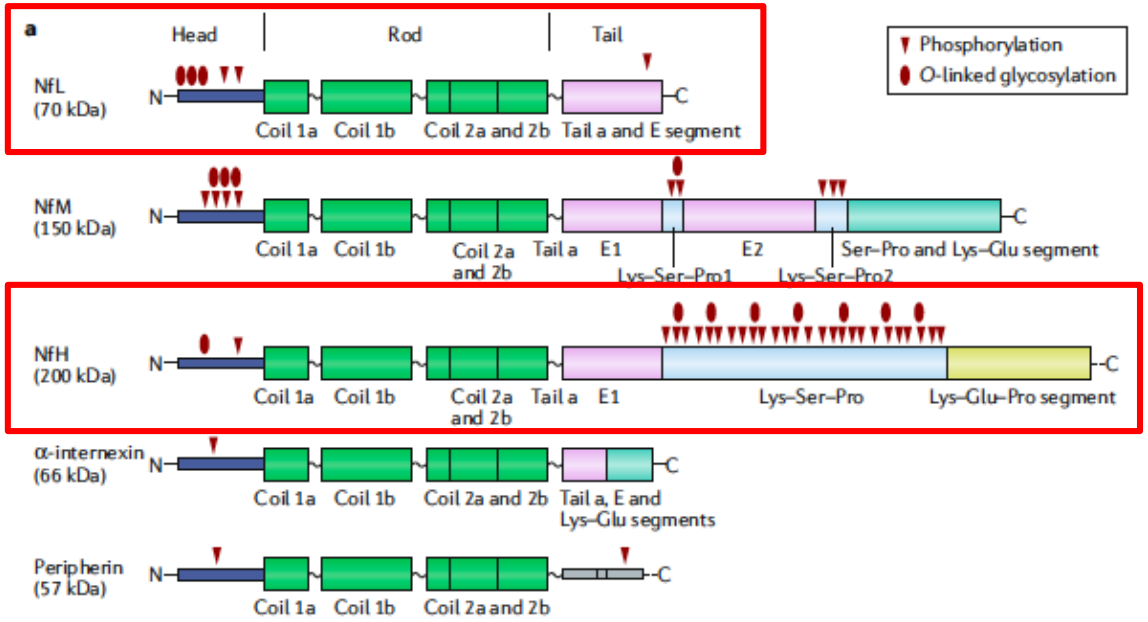
"**Safety**"

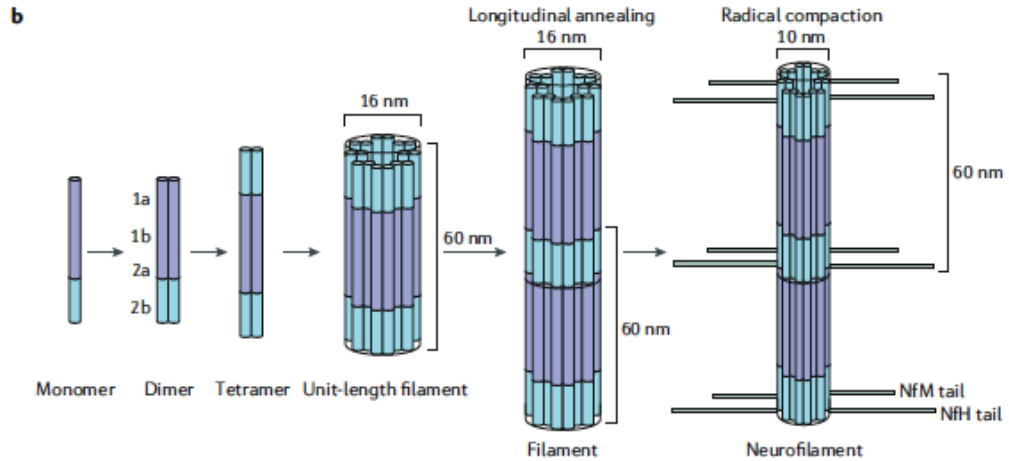
"**Susceptibility/Risk**": indicare il potenziale di sviluppare una malattia in un individuo che al momento non ne ha evidenza clinica


Biomarcatori "ideali" in Neurologia

**diagnostico in una fase iniziale e possibilmente pre-sintomatica in modo che la terapia possa avere un maggior effetto**

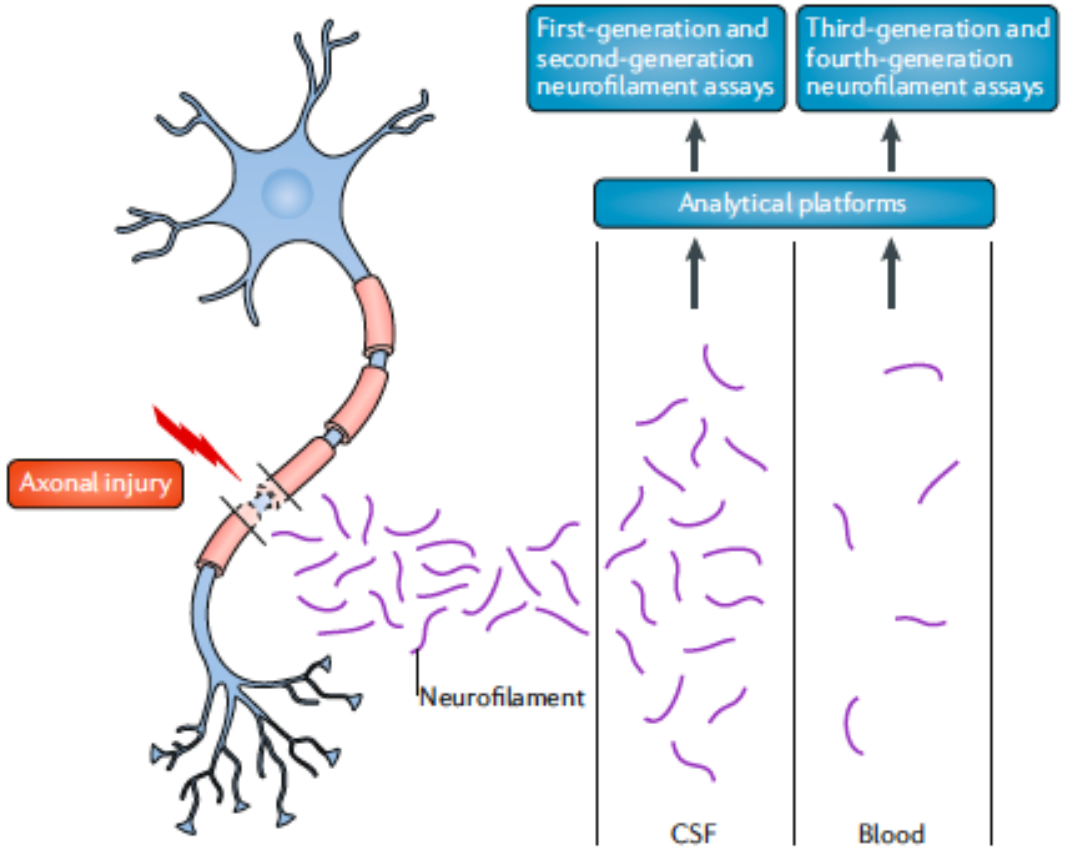
# Neurofilamenti – cosa sono




Khalil et al., Nature Reviews, 2018

# Tecniche di analisi dei neurofilamenti




Khalil et al., Nature Reviews, 2018

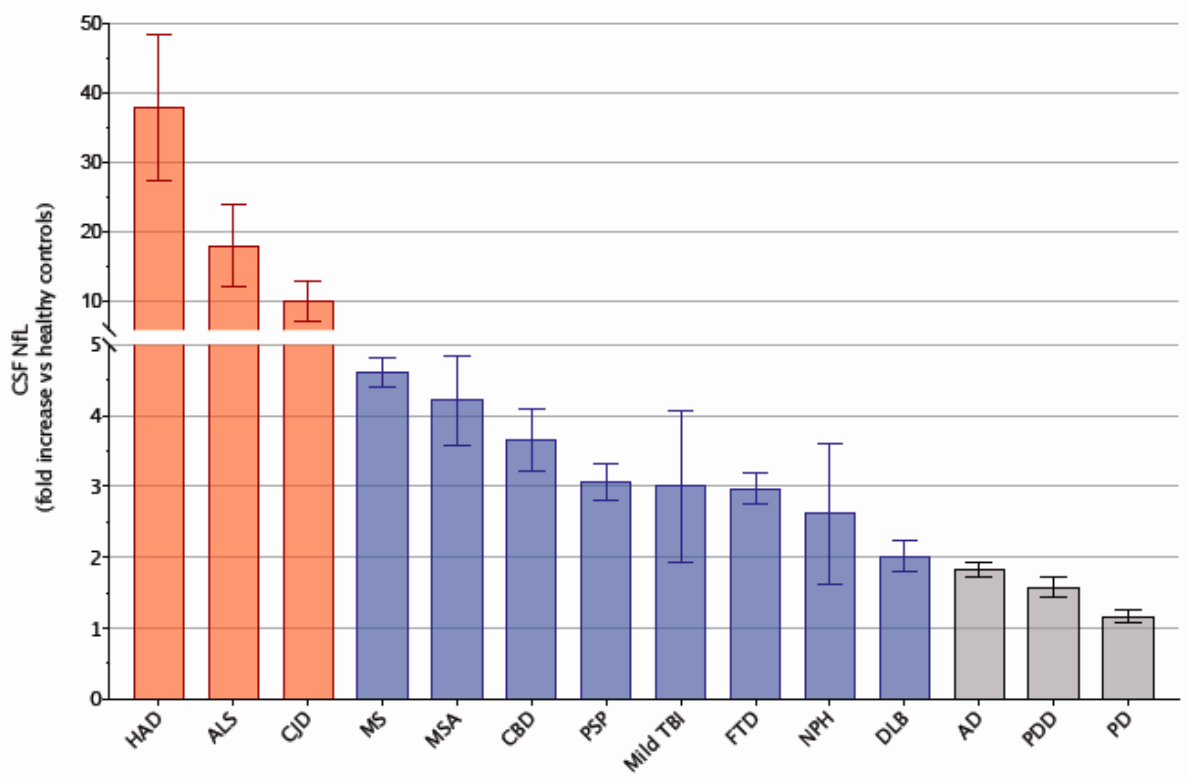
**I generazione**: metodi semi-quantititativi (WB, dot blot)

**II generazione**: sandwich ELISA → quantificazione con possibile valore prognostico e diagnostico. Buona precisione in lab esperti, ma alta variabilità inter-laboratoristica.

**III generazione**: ECL ELISA → aumento della sensibilità, possibile misurazione su siero

**IV generazione**: SiMoA → aumento esponenziale della sensibilità, miglior correlazione CSF/siero, dosi minime di campione, metodo altamente automatizzato

# Neurofilamenti nelle patologie neurodegenerative




Gaetani et al., JNNP, 2019

1) Malattie del Motoneurone

2) Demenza (AD, FTD, CJD)

3) Disordini del movimento (PD, APD, HD)

# Neurofilamenti: marcatori diagnostici nella SLA

## Neurofilaments as Biomarkers for Amyotrophic Lateral Sclerosis: A Systematic Review and Meta-Analysis

PLOS ONE

October 12, 2016

Zhouwei Xu[1]*, Robert David Henderson[2], Michael David[3], Pamela Ann McCombe[1]

**Table 1. Summary of the meta-analyses.**

| | ALS v HC/non CNS disease | | | ALS v mimic disease | | | ALS v CNS disease | | |
|---|---|---|---|---|---|---|---|---|---|
| | No of studies | Total no of subjects (patients/ controls) | P value of meta-analysis | No of studies | Total no of subjects (patients/ control) | P value of meta-analysis | No of studies | Total no of subjects (patients/ controls) | P value of meta-analysis |
| NFH in CSF | 4 studies (5 cohorts) | 443/267 | P<0.0001 | 2 studies | 251/100 | P = 0.013 | 6 studies (11 cohorts) | 468/329 | P = 0.075 |
| NFH in blood | 2 studies | 117/78 | P = 0.057 | | | | | | |
| NFL in CSF | 6 studies(7 cohorts) | 463/214 | P<0.0001 | 2 studies | 250/99 | P<0.0001 | 5 studies | 398/405 | P = 0.001 |
| NFL in blood | 3 studies(5 cohorts) | 202/277 | P<0.0001 | | | | | | |

doi:10.1371/journal.pone.0164625.t001

# Neurofilamenti: marcatori diagnostici nella SLA

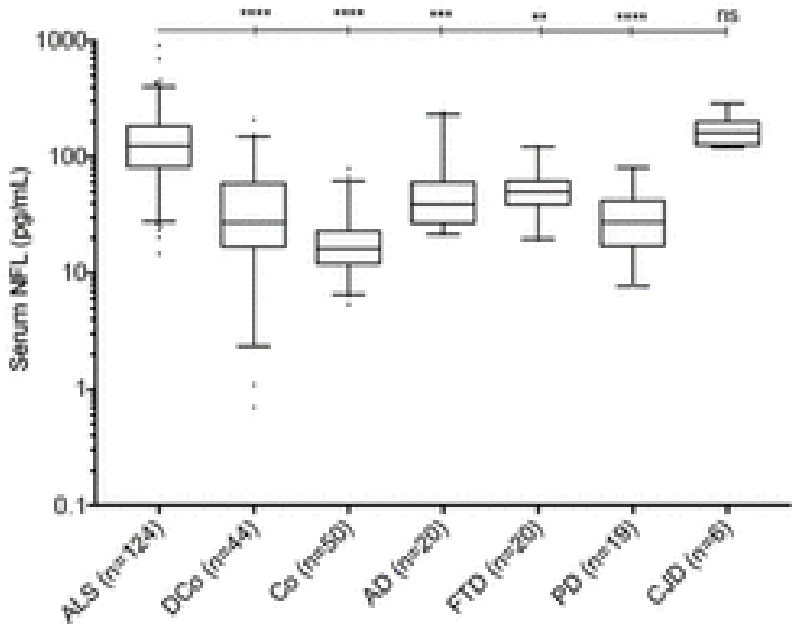
RESEARCH PAPER

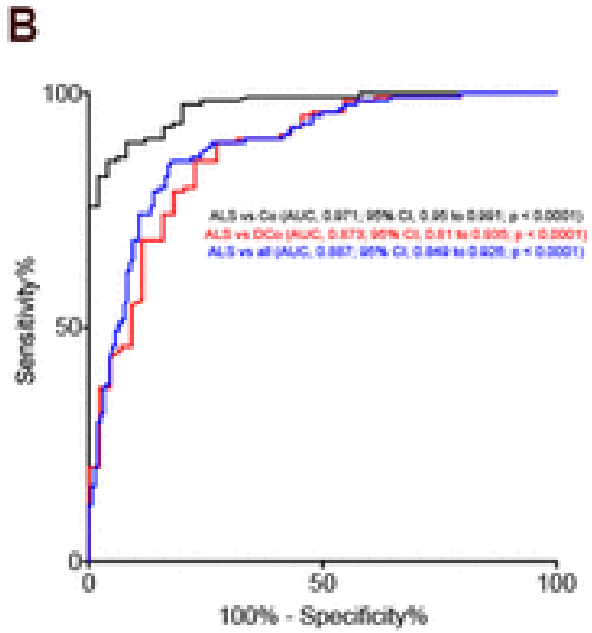
## Neurofilament light chain in serum for the diagnosis of amyotrophic lateral sclerosis

Federico Verde,[1,2] Petra Steinacker,[1] Jochen H Weishaupt,[1] Jan Kassubek,[1] Patrick Oeckl,[1] Steffen Halbgebauer,[1] Hayrettin Tumani,[1] Christine A F von Arnim,[1] Johannes Dorst,[1] Emily Feneberg,[1,3] Benjamin Mayer,[4] Hans-Peter Müller,[1] Martin Gorges,[1] Angela Rosenbohm,[1] Alexander E Volk,[5] Vincenzo Silani,[2] Albert C Ludolph,[1] Markus Otto[1]

CUT-OFF 62 pg/mL per discriminare da altre patologie neurodegenerative (FTD, AD, PD)

Sensibilità 85% Specificità 81.8%

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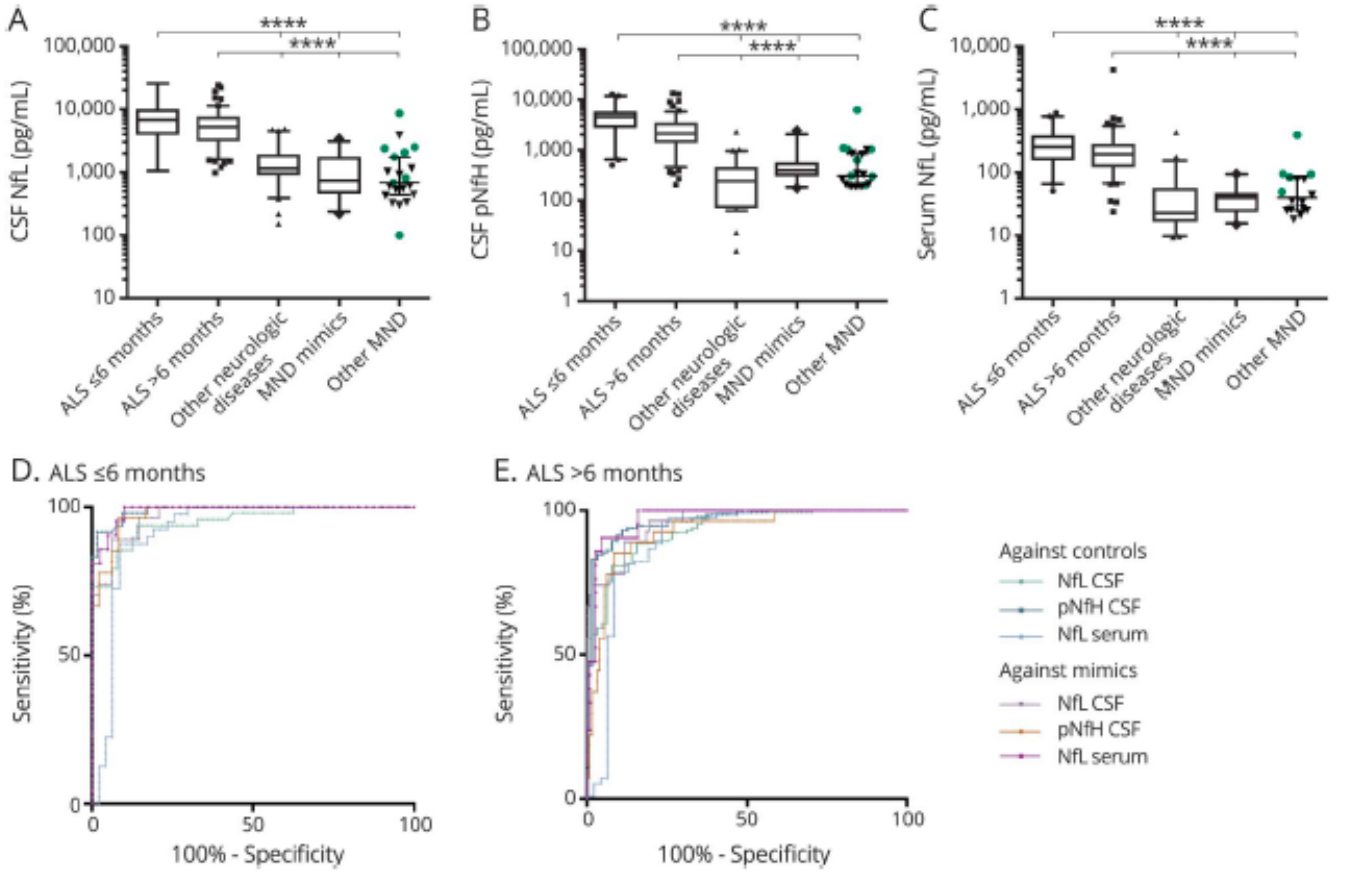
# Neurofilamenti & SLA: marcatori precoci?

**Figure 1** Early and later symptomatic phase neurofilament (Nf) profile




CSF Nf light chain (NfL) (A), phosphorylated heavy chain (pNfH) (B), and serum NfL (C) concentrations are increased in patients with early and later symptomatic phase amyotrophic lateral sclerosis (ALS). Boxplots show median concentrations, 25% and 75% percentile, and 5% and 95% whiskers. Individual symbols represent outliers. Green symbols mark primary lateral sclerosis cases. Receiver operating characteristic curves are shown to distinguish early (D) and later (E) ALS from other neurologic diseases and motor neuron disease (MND) mimics. $^{**}p < 0.01$, $^{***}p < 0.001$, $^{****}p < 0.0001$.

ARTICLE CLASS OF EVIDENCE

## Multicenter evaluation of neurofilaments in early symptom onset amyotrophic lateral sclerosis

- misurazione di NfL su siero e CSF, NfH su CSF *
- 53 SLA stadio iniziale (entro 6 mesi esordio), 135 SLA dopo 6 mesi dall'esordio
- altre MND: Kennedy, SMA

**Classification of evidence**
This study provides Class II evidence that CSF and serum Nf concentrations discriminate ALS with early symptom onset from other neurologic diseases.

*Feneberg, Neurology, 2018*

# Neurofilamenti & malattie del II MN

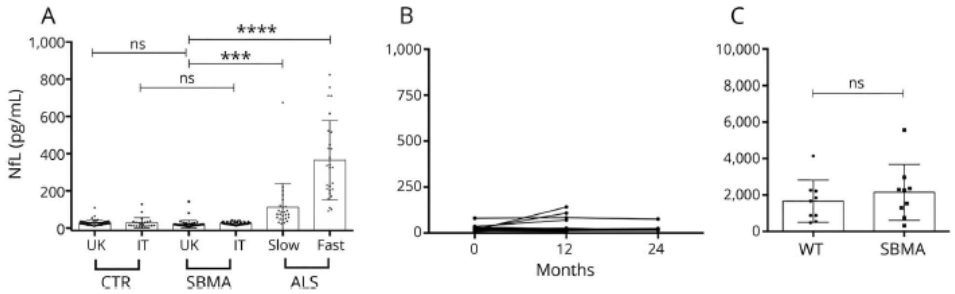
ARTICLE OPEN ACCESS

## Muscle and not neuronal biomarkers correlate with severity in spinal and bulbar muscular atrophy

*

Vittoria Lombardi, PhD, Giorgia Querin, MD,* Oliver J. Ziff, MD, MRCP,* Luca Zampedri,* Ilaria Martinelli, MD, Carolin Heller, Martha Foiani, Cinzia Bertolin, PhD, Ching-Hua Lu, MD, PhD, Bilal Malik, PhD, Kezia Allen, Carlo Rinaldi, MD, PhD, Henrik Zetterberg, PhD, Amanda Heslegrave, PhD, Linda Greensmith, PhD, Michael Hanna, FRCP, Gianni Soraru, MD, PhD,‡ Andrea Malaspina, MD, PhD, FRCP,‡ and Pietro Fratta, MD, PhD‡

**Figure 1** Neurofilament light chain (NfL) levels are unchanged in spinal and bulbar muscular atrophy (SBMA)




(A) NfL concentrations (pg/mL) from the UK cohort (plasma, UK control [CTR], UK SBMA, slow amyotrophic lateral sclerosis [ALS], and fast ALS) and the Italian cohort (IT CTR and IT SBMA). Assays were conducted together, but statistical analysis (analysis of variance, Bonferroni multiple comparison correction) is represented only between samples from the same cohort. (B) NfL concentrations in the longitudinal study in the UK cohort. Twelve-month (n = 28) and 24-month (n = 8) timepoints represent 12 ± 2 and 24 ± 2 months. (C) NfL levels from AR100 (SBMA) and littermate control (WT) mice are shown (Mann-Whitney test). Columns indicate mean, error bars indicate SD; ***$p < 0.001$; ****$p < 0.0001$; ns $p > 0.05$.

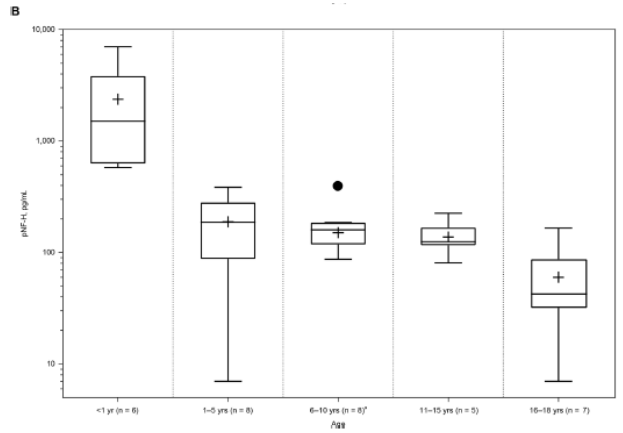
NFL su siero non statisticamente significativo fra HC e SBMA

RESEARCH ARTICLE

## Neurofilament as a potential biomarker for spinal muscular atrophy

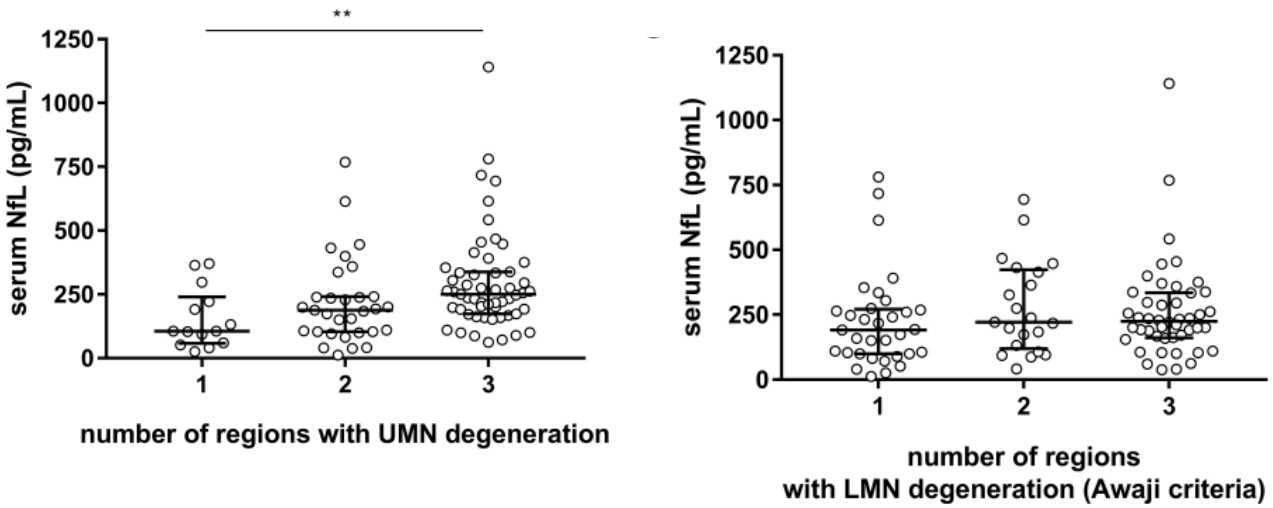
Basil T. Darras[1], Thomas O. Crawford[2,3], Richard S. Finkel[4], Eugenio Mercuri[5], Darryl C. De Vivo[6], Maryam Oskoui[7], Eduardo F. Tizzano[8], Monique M. Ryan[9], Francesco Muntoni[10,11], Guolin Zhao[12], John Staropoli[12,*], Alexander McCampbell[12], Marco Petrillo[12], Christopher Stebbins[12], Stephanie Fradette[12], Wildon Farwell[12] & Charlotte J. Sumner[2,13]

pNFH su siero 7030 pg/mL: 90% sensibile nel discriminare bambini SMA da non-SMA



# Neurofilamenti & malattie del I MN

**Serum Neurofilament Light Chain Levels as a Marker of UMN Degeneration in Patients with Amyotrophic Lateral Sclerosis**

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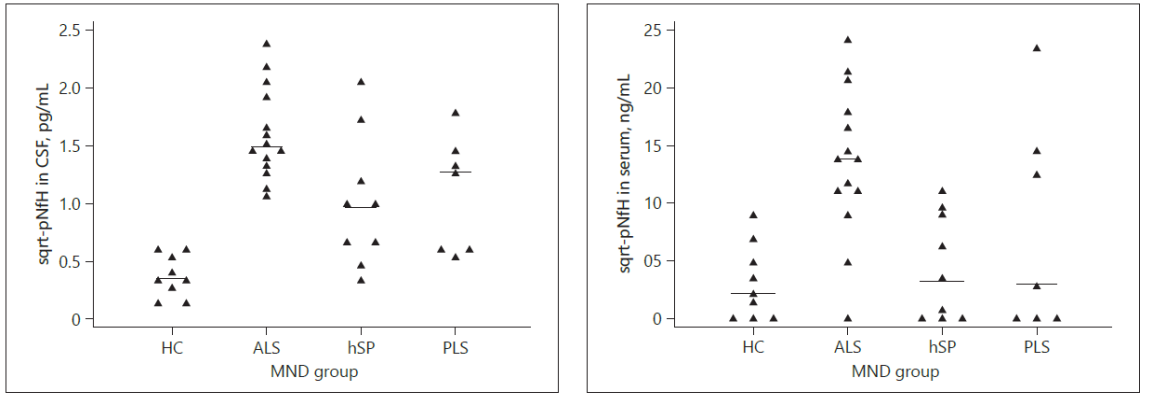
*Gille et al., J of Neurol, 2018*

**Cerebrospinal Fluid Neurofilaments May Discriminate Upper Motor Neuron Syndromes: A Pilot Study**

Elisabetta Zucchi Roberta Bedin Antonio Fasano Nicola Fini
Annalisa Gessani Marco Vinceti Jessica Mandrioli




- hSP, PLS, ALS a visita neurologica per segni di I MN
- CSF e siero NfH misurati al baseline
- ROC (ALS vs MND) CSF NfH: 0.79 (0.61-0.96)
  Siero NfH: 0.81 (0.63-0.97)

# Neurofilamenti & SLA: oltre il fenotipo

JAMA Neurology | Original Investigation

## Diagnostic and Prognostic Biomarkers in Amyotrophic Lateral Sclerosis Neurofilament Light Chain Levels in Definite Subtypes of Disease

Alessandra Gaiani, MD; Ilaria Martinelli, MD; Luca Bello, MD, PhD; Giorgia Querin, MD; Marco Puthenparampil, MD; Susanna Ruggero, MS; Elisabetta Toffanin, MS; Annachiara Cagnin, MD; Chiara Briani, MD; Elena Pegoraro, MD, PhD; Gianni Sorarù, MD, PhD

Analisi di regressione Cox hazard model:
relazione inversa fra [log]NFL e sopravvivenza
HR 2.45 (CI: 1.66-3.61)

Figure 1. Median Log-Transformed Neurofilament Light Chain (log[NFL]) Concentrations in the Study Groups

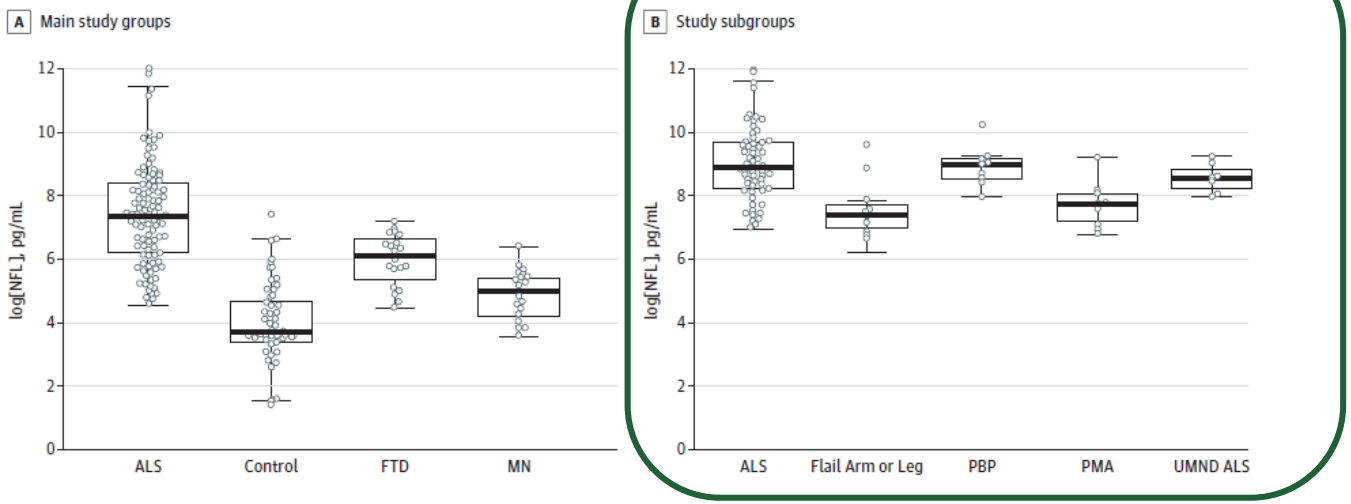
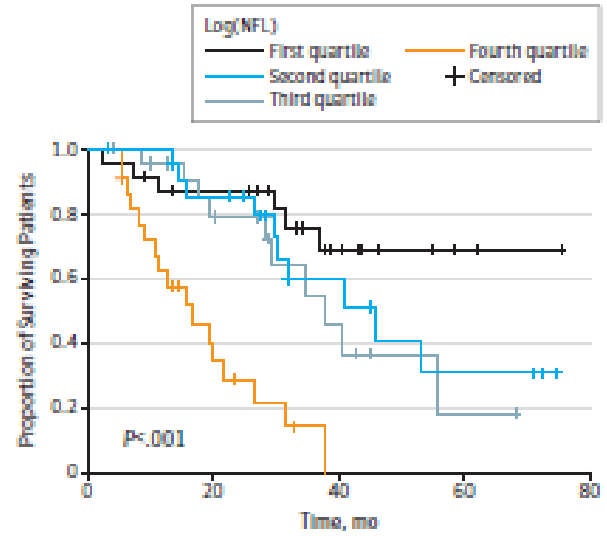


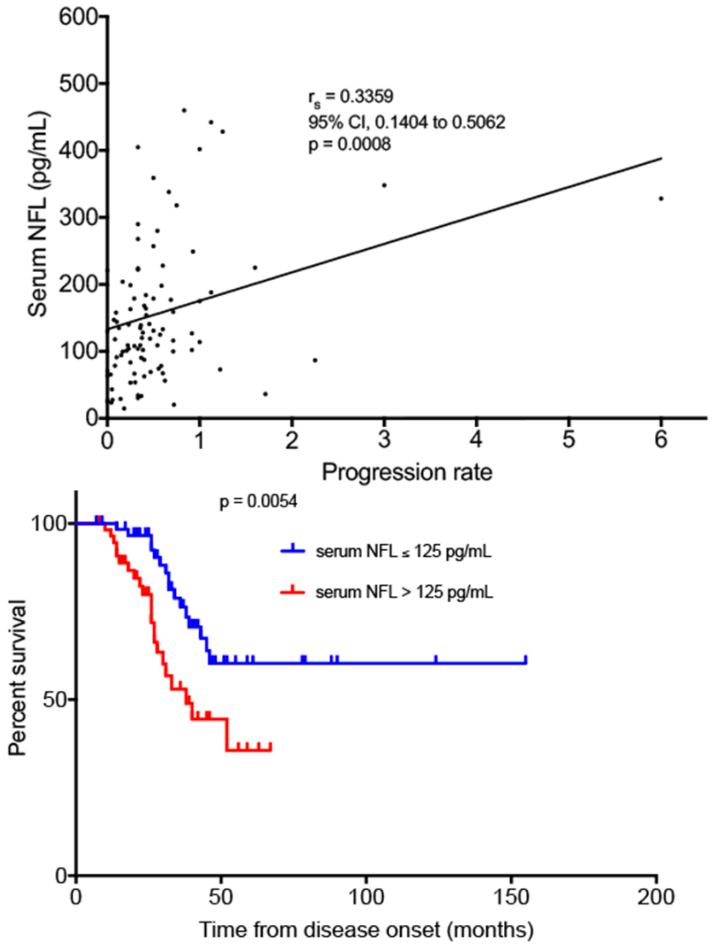

Figure 2. Kaplan-Meier Plots of the Proportion of Surviving Patients Relative to Time From Baseline Grouped by Log-Transformed Neurofilament Light Chain (Log[NFL]) Concentrations




| No. of patients | | | | | |
|---|---|---|---|---|---|
| First quartile | 24 | 19 | 9 | 3 | 0 |
| Second quartile | 21 | 16 | 7 | 3 | 0 |
| Third quartile | 22 | 15 | 8 | 1 | 0 |
| Fourth quartile | 22 | 7 | 0 | 0 | 0 |

# Biomarkers di prognosi: perchè?

1. Eterogeneità della malattia che preclude un giudizio prognostico, utile per le scelte terapeutiche e il counselling del paziente
2. Pianificazione e organizzazione dei servizi
3. Stratificazione e corretta allocazione dei pazienti nei trials clinici



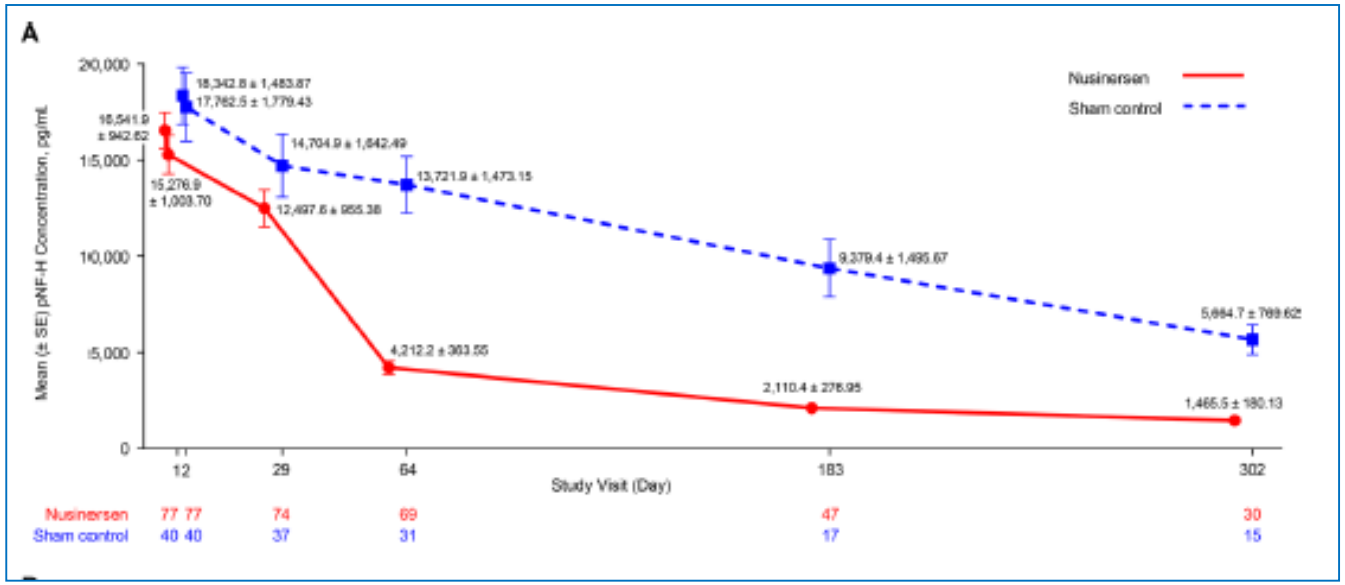

*Verde et al., JNNP 2018*

# pNFH: Biomarcatori farmacodinamici

RESEARCH ARTICLE

## Neurofilament as a potential biomarker for spinal muscular atrophy

Basil T. Darras[1], Thomas O. Crawford[2,3], Richard S. Finkel[4], Eugenio Mercuri[5], Darryl C. De Vivo[6], Maryam Oskoui[7], Eduardo F. Tizzano[8], Monique M. Ryan[9], Francesco Muntoni[10,11], Guolin Zhao[12], John Staropoli[12,*], Alexander McCampbell[12], Marco Petrillo[12], Christopher Stebbins[12], Stephanie Fradette[12], Wildon Farwell[12] & Charlotte J. Sumner[2,13]

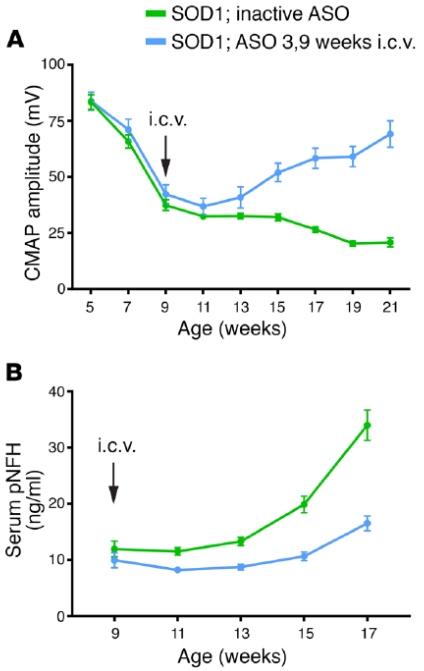



RESEARCH ARTICLE

The Journal of Clinical Investigation

## Antisense oligonucleotides extend survival and reverse decrement in muscle response in ALS models

Alex McCampbell,[1] Tracy Cole,[2] Amy J. Wegener,[3] Giulio S. Tomassy,[1] Amy Setnicka,[3] Brandon J. Farley,[1] Kathleen M. Schoch,[3] Mariah L. Hoye,[3] Mark Shabsovich,[3] Linhong Sun,[1] Yi Luo,[1] Mingdi Zhang,[1] Nicole Comfort,[1] Bin Wang,[1] Jessica Amacker,[1] Sai Thankamony,[1] David W. Salzman,[1] Merit Cudkowicz,[4] Danielle L. Graham,[1] C. F Eric E. Swayze,[2] and Timothy M. Miller[3]

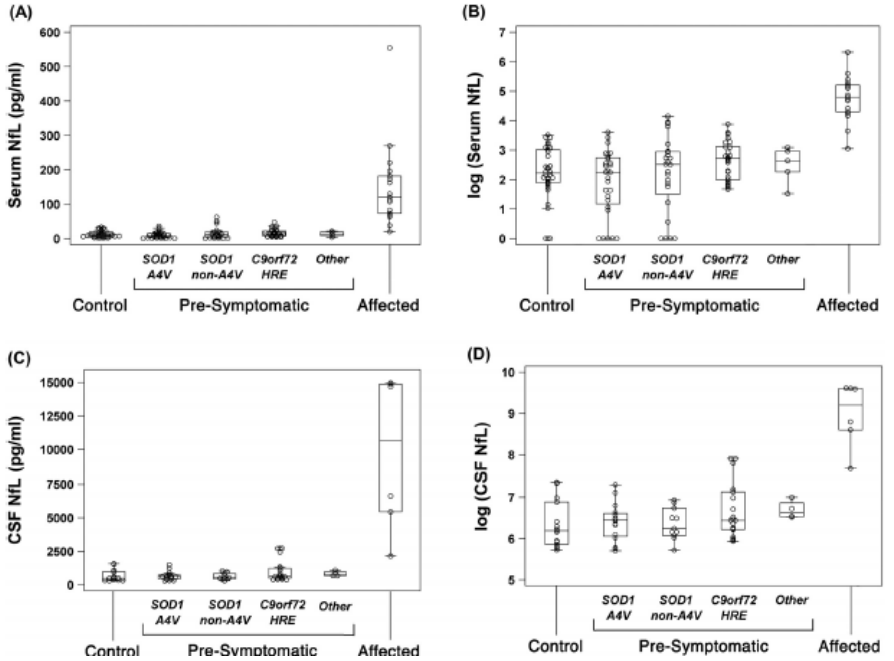


# NFL: Biomarcatori di fenoconversione (suscettibilità)

*

## Neurofilament Light: A Candidate Biomarker of Presymptomatic Amyotrophic Lateral Sclerosis and Phenoconversion

Michael Benatar, MD, PhD.[1]* Joanne Wuu, ScM.[1]* Peter M. Andersen, MD, PhD.[2]



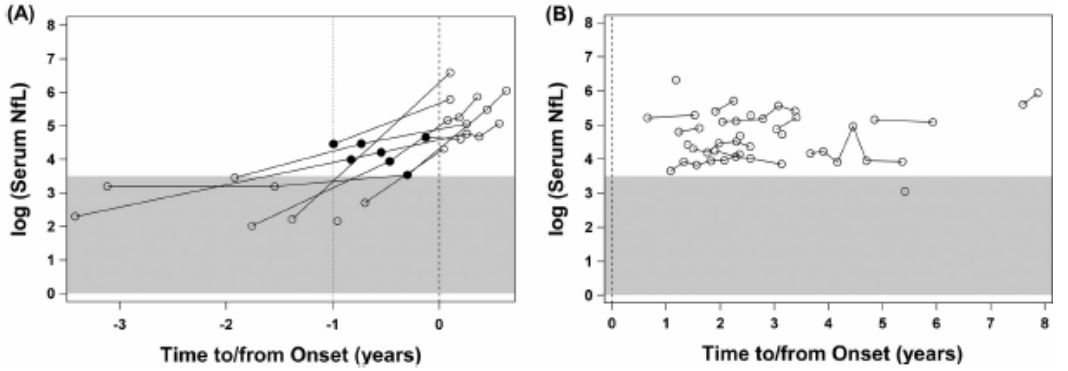
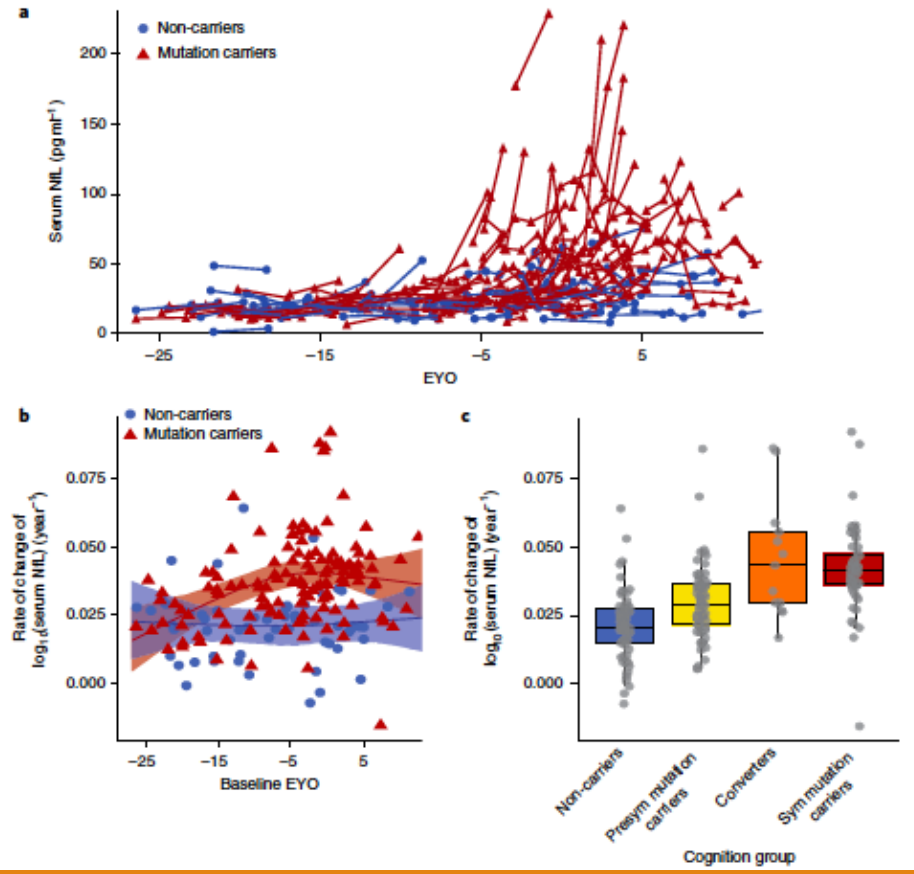




FIGURE 3: Longitudinal changes in serum NfL concentration, natural log-transformed: (A) phenoconverters; and (B) ALS patients The x-axis shows years to or since the onset of symptoms or signs, which is marked by the vertical dashed line at year = 0. The gray area covers the range of serum NfL values observed in the control group. The closed circles mark the elevated levels of NfL (ie, above the highest value observed in controls) that were measured in serum collected before the onset of symptoms or signs ALS = amyotrophic lateral sclerosis; NfL = neurofilament light.

- studio prospettico su portatori di mutazione patogeniche per SLA seguiti longitudinalmente
- 34 HC, 84 individui a rischio, 10 “converters”, 11 pazienti senza mutazione fra quelle note
- aumento di NFL su siero nei fenoconvertitori 11.6 mesi prima, con progressione dell’aumento fino a 6 mesi dopo l’esordio

# NFL: Biomarcatori di fenoconversione (suscettibilità)

Preische, Nat Medicine, 2019




**Serum neurofilament dynamics predicts neurodegeneration and clinical progression in presymptomatic Alzheimer's disease** *

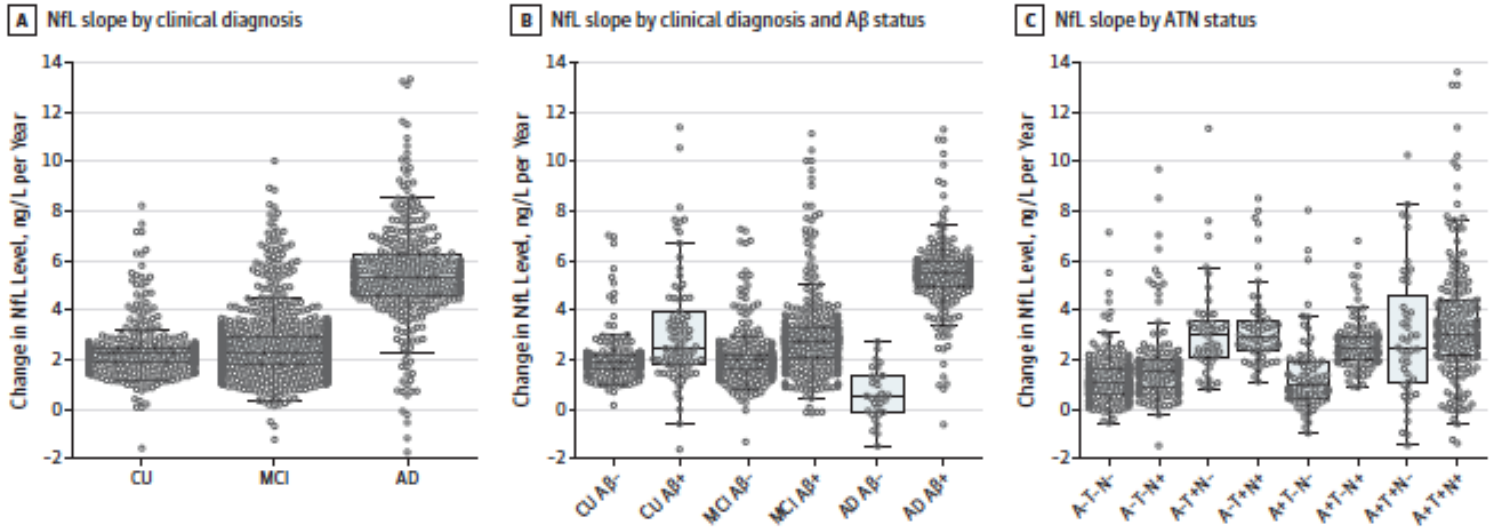
- misurazioni di NFL su siero e CSF mediante SiMoA nella coorte DIAN (Dominantly Inherited Alzheimer Network)
- controlli sono I familiari non portatori di mutazione
- NfL su siero aumenta significativamente 16 anni prima dell'EYO
- il livello sierico di NFL raggiunge picco in corrispondenza della conversione, poi si appiattisce o addirittura diminuisce

# NF & M. di Alzheimer

JAMA Neurology | Original Investigation

## Association Between Longitudinal Plasma Neurofilament Light and Neurodegeneration in Patients With Alzheimer Disease

Niklas Mattsson, MD, PhD; Nicholas C. Cullen, BSc; Ulf Andreasson, PhD; Henrik Zetterberg, MD, PhD; Kaj Blennow, MD, PhD




**CONCLUSIONS AND RELEVANCE** The findings suggest that plasma NfL can be used as a noninvasive biomarker associated with neurodegeneration in patients with AD and may be useful to monitor effects in trials of disease-modifying drugs.

JAMA Neurology | Original Investigation

## Association of Cerebrospinal Fluid Neurofilament Light Protein With Risk of Mild Cognitive Impairment Among Individuals Without Cognitive Impairment

Silke Kern, MD, PhD; Jeremy A. Syrjanen, MS; Kaj Blennow, MD, PhD; Henrik Zetterberg, MD, PhD; Ingmar Skoog, MD, PhD; Margda Waern, MD, PhD; Clinton E. Hagen, MS; Argonde C. van Harten, MD, PhD; David S. Knopman, MD; Clifford R. Jack Jr, MD; Ronald C. Petersen, MD, PhD; Michelle M. Mielke, PhD

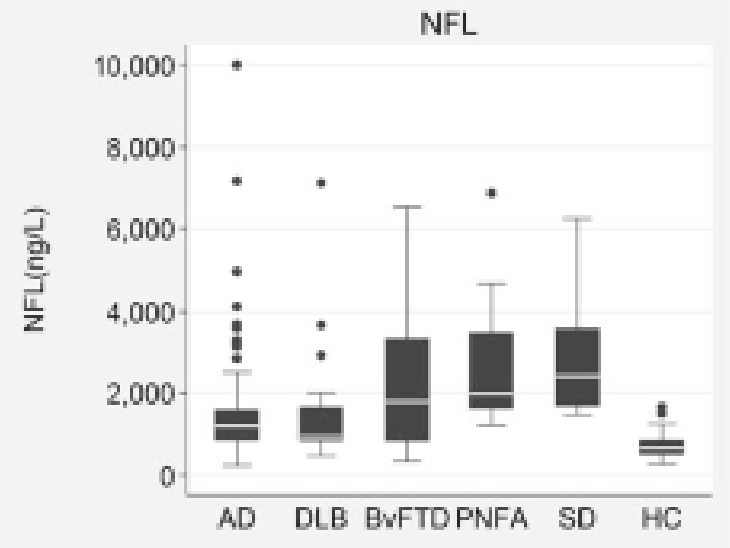
Table 4. Combination of CSF Neurofilament Light Protein and T-tau for Risk of Mild Cognitive Impairment

| | Model 1 (n = 632)[a] | | | Model 2 |
|---|---|---|---|---|
| Quartiles of Log CSF | Events | HR (95% CI) | *P* Value | Events |
| Neither T-tau nor NfL in the top quartile | 94 | 1 [Reference] | NA | 94 |
| T-tau in the top quartile | | 1.28 (0.68-2.41) | .44 | |
| NfL in the top quartile | | 2.24 (1.31-3.83) | .003 | |
| NfL and T-tau in the top quartile | | 2.29 (1.28-4.09) | .01 | |

# DDx nelle demenze

RESEARCH Open Access

Cerebrospinal fluid in the differential diagnosis of Alzheimer's disease: clinical utility of an extended panel of biomarkers in a specialist cognitive clinic




*Paterson et al., 2018*

CrossMark

**Table 5** AUC (and 95% CI) and specificity (at a fixed sensitivity of 85%) of the 'top 5' biomarkers, comparing AD with other neurodegenerative disorders and controls

| Diagnostic groups | Biomarker | AUC (95% CI) | Specificity (%)* |
|---|---|---|---|
| AD vs PNFA[a] | NFL (ng/L) | 0.84 (0.76–0.93) | 50% |
| | T-tau/Aβ1–42 ratio | 0.67 (0.54–0.80) | 24% |
| | Aβ1–42 (pg/mL) | 0.65 (0.50–0.80) | 35% |
| | All the above | 0.60 (0.16–0.76) | 42% |
| AD vs SD[b] | AβX-42/X-40 ratio | 0.92 (0.86–0.97) | 100% |
| | T-tau/Aβ1–42 ratio | 0.91 (0.86–0.96) | 86% |
| | Aβ1–42 (pg/mL) | 0.91 (0.84–0.98) | 86% |
| | NFL (ng/L) | 0.87 (0.78–0.96) | 67% |
| | P-tau (pg/L) | 0.85 (0.75–0.94) | 29% |

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

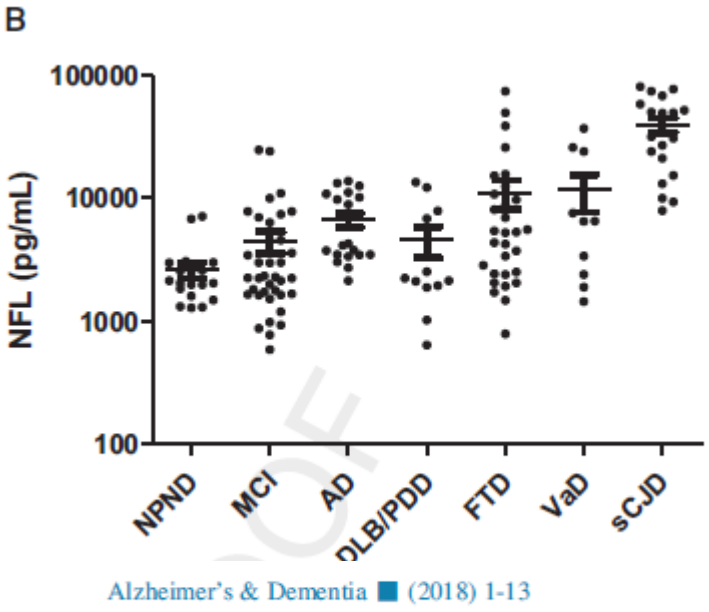
*Rohrer et al., 2016*

*

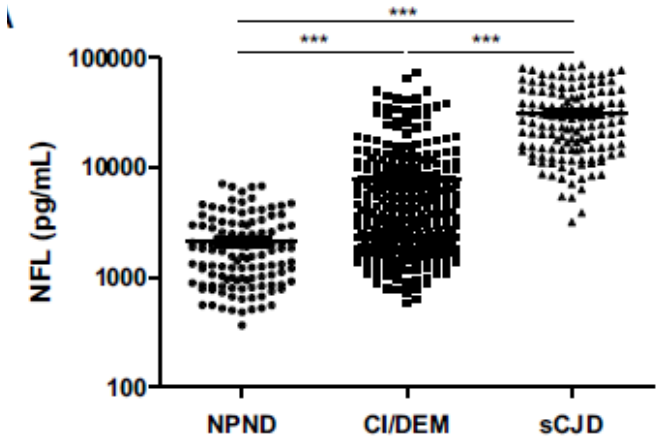
**Conclusions:** Increased serum NfL concentrations are seen in FTD but show wide variability within each clinical and genetic group. Higher concentrations may reflect the intensity of the disease in FTD and are associated with more rapid atrophy of the frontal lobes. **Neurology® 2016;87:1329-1336**

# Neurofilamenti e CJD

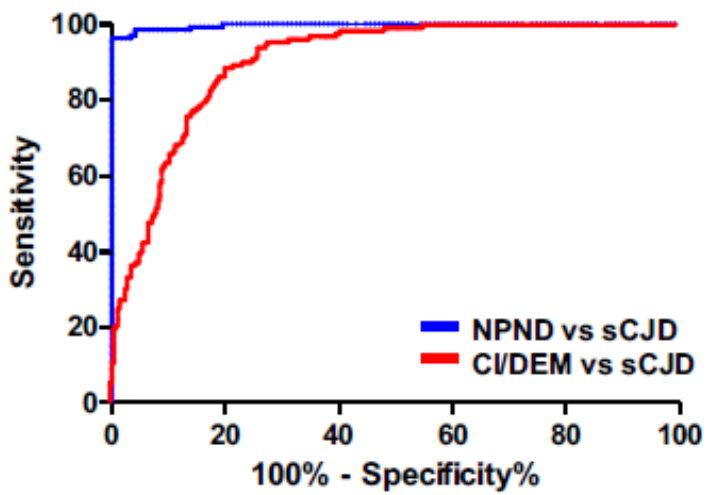
Cerebrospinal fluid neurofilament light levels in neurodegenerative dementia: Evaluation of diagnostic accuracy in the differential diagnosis of prion diseases




Alzheimer's & Dementia ■ (2018) 1-13




*Zerr et al., 2018*




| | NPND vs sCJD | CI/DEM vs sCJD |
|---|---|---|
| AUC (Area ± SE) | 0.9966 ± 0.0020 | 0.9008 ± 0.0143 |
| 95% CI | 0.9925 to 1 | 0.8726 to 0.9289 |
| p value | < 0.0001 | < 0.0001 |
| Cut-off (pg/mL) | > 7000 | > 10500 |
| Specificity (%) | 95 | 80 |
| Sensitivity (%) | 100 | 86 |

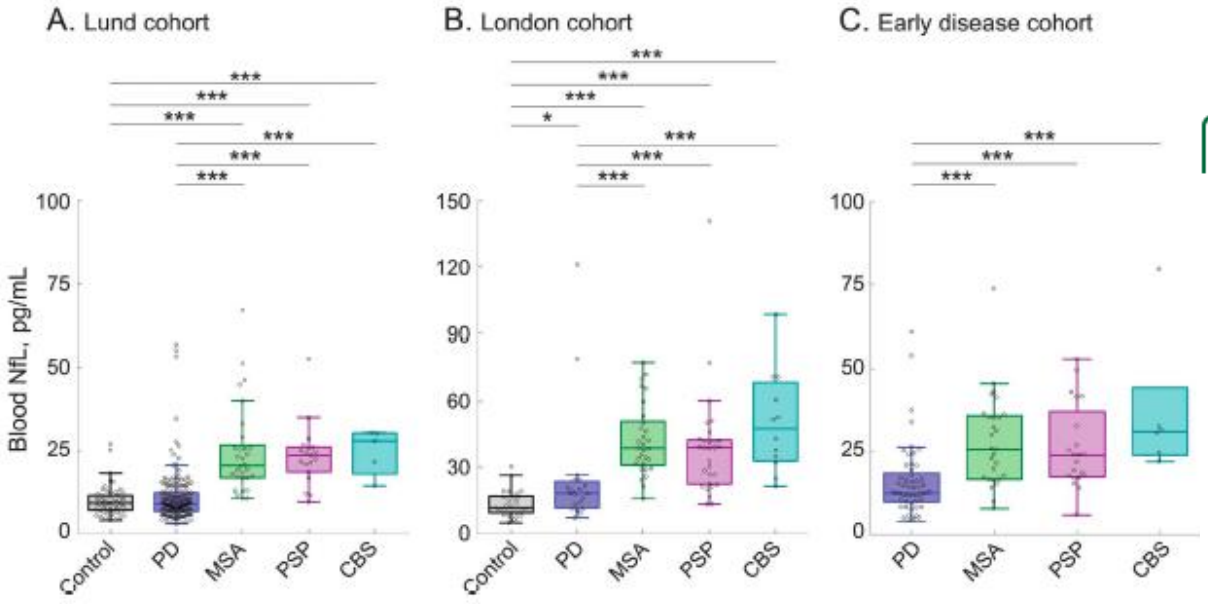
# Parkinson e parkinsonismi atipici

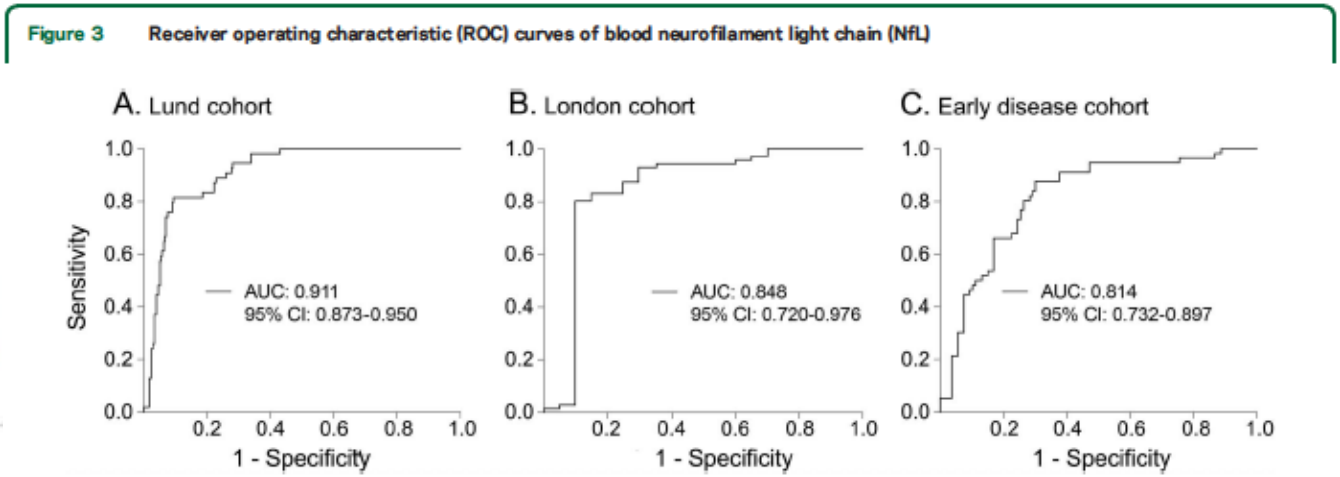
## Blood-based NfL

### A biomarker for differential diagnosis of parkinsonian disorder

*Hansson, Neurology, 2017*

*

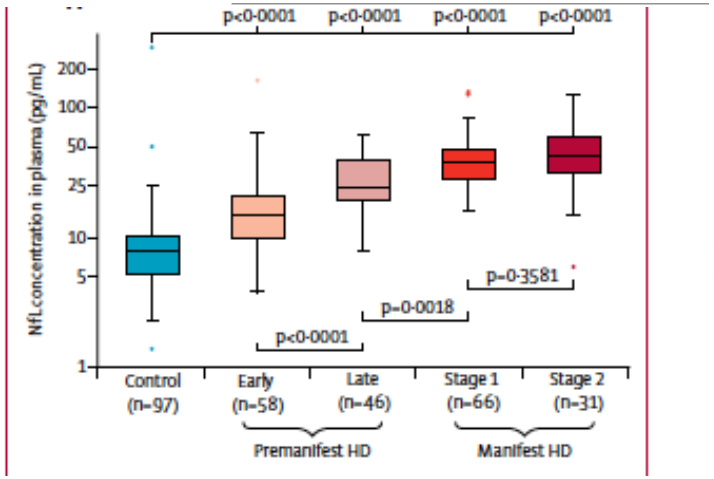


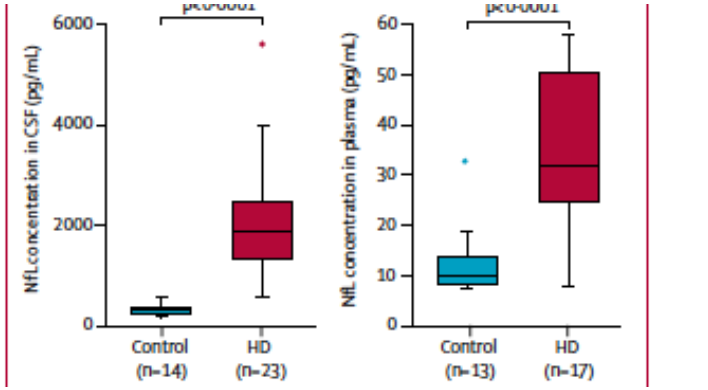



# Neurofilamenti: marcatori prognostici nei parkinsonismi

| | | | |
|---|---|---|---|
| PD | NFL CSF | correla con differenza media nel Dementia Rating Score | Olsson, Neurology, 2018 |
| | | correla con rischio di conversione in PDD | Backstrom, JAMA, 2015 |
| PSP | NFL plasma | correla con deterioramento sintomi motori<br>sintomi cognitivi<br>atrofia peduncoli cerebellari superiori | Rojas, Ann Clin Trans Neurol, 2016 |
| | NFL CSF | correla con deterioramento sintomi motori (PSPRS)<br>sintomi cognitivi (SEADL) | Rojas, Neurology, 2019 |

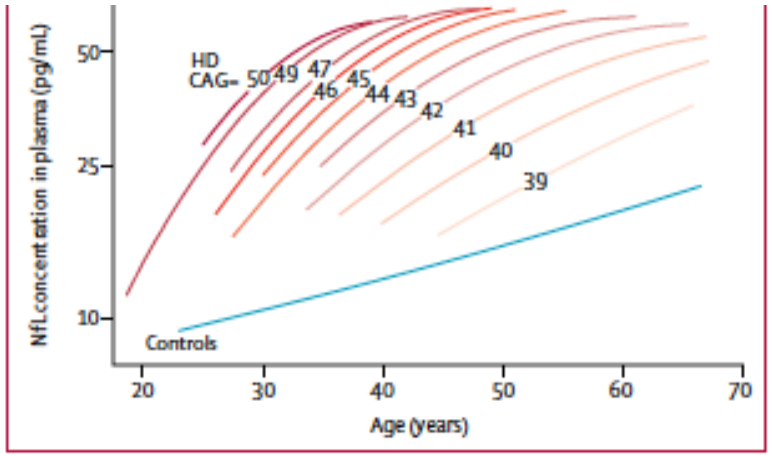
# Corea di Huntington



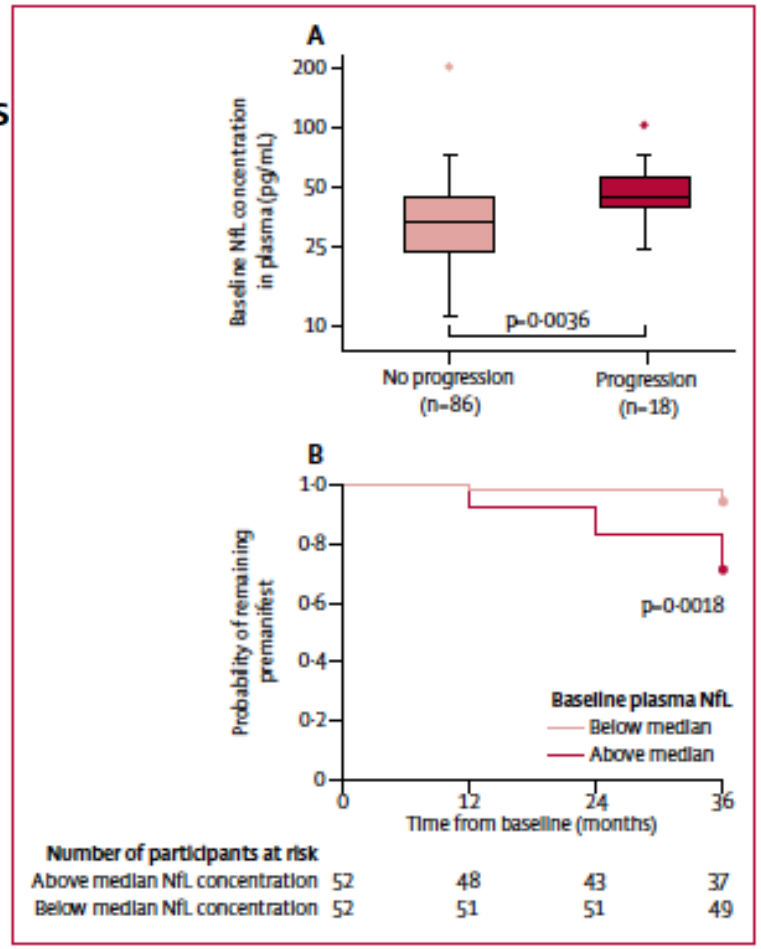




**Neurofilament light protein in blood as a potential biomarker of neurodegeneration in Huntington's diseas a retrospective cohort analysis**

*Lauren M Byrne, Filipe B Rodrigues, Kaj Blennow, Alexandra Durr, Blair R Leavitt, Raymund A C Roos, Rachael I Scahill, Sarah J Tabrizi, Henrik Zetterberg, Douglas Langbehn, Edward J Wild*




*Byrne, 2017*



| PROS | CONS |
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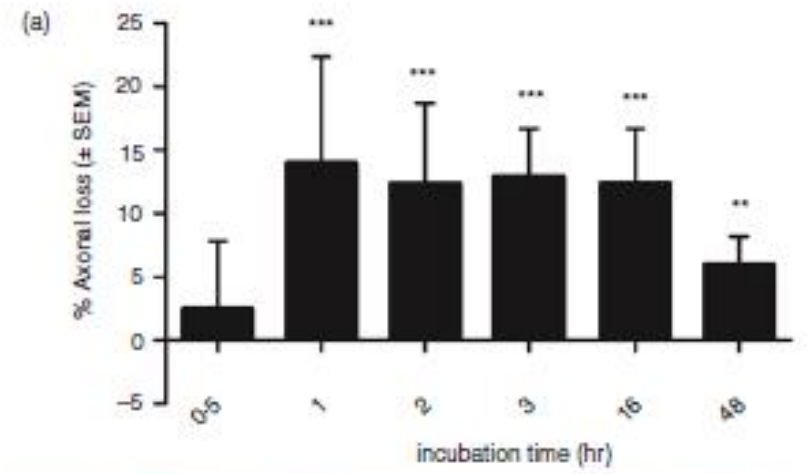
| I. Markers di neurodegenerazione malattia-indipendenti | I. Biomarcatori non specifici per patologia: ruolo nella patogenesi o epifenomeno? |
| II. Buona capacità di distinguere tra HC e demenze/MND, e tra FTD-MND e altre forme di demenza | II. Minor attendibilità nella diagnosi differenziale tra patologie degenerative del SNC |
| III. Buona correlazione con andamento malattie e sopravvivenza: indicatori prognostici | III. Quale neurofilamento usare? Quale matrice (CSF vs serum)? Quale cut off? Quale metodo? |
| IV. Biomarkers predittivi? | IV. Probabilmente anche se potenzialità terapeutiche limitate nelle malattie neurodegenerative (e.g. Topo Sod1/HAD) |
| V. Biomarcatori di suscettibilità (fenoconversione in C9orf72) | V. Dati ancora limitati |
| VI. Biomarcatori farmacodinamici? | |

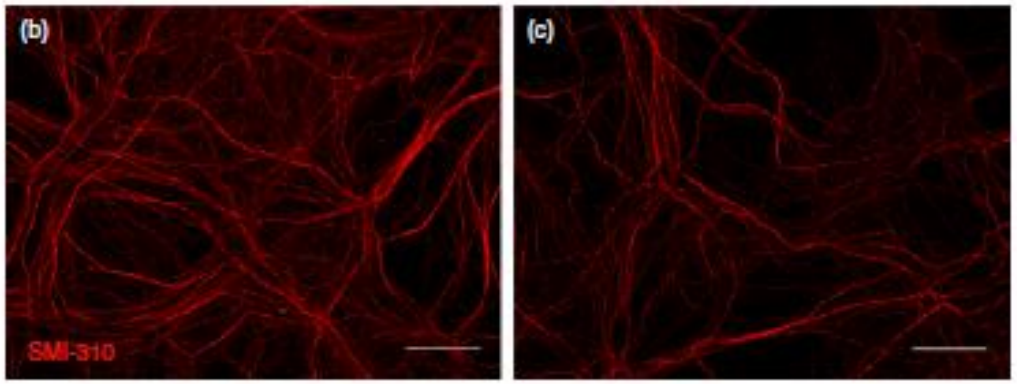
# Patogenetici o epifenomeno?

Immunology
The Journal of cells, molecules, systems and technologies
British Society for immunology
IMMUNOLOGY ORIGINAL ARTICLE

## Neurofilament light as an immune target for pathogenic antibodies

cord co-cultures where axonal loss was induced. Taken together, our results reveal that as well as acting as reliable biomarkers of neuronal damage, antibodies to NF-L exacerbate neurological disease, suggesting that antibodies to NF-L generated during disease may also be pathogenic and play a role in the progression of neurodegeneration.



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# Quale metodo?

**CSF neurofilament proteins as diagnostic and prognostic biomarkers for amyotrophic lateral sclerosis**

Daniela Rossi[1] · Paolo Volanti[2] · Liliana Brambilla[1] · Tiziana Colletti[3] · Rossella Spataro[3] · Vincenzo La Bella[3]

Single-batch ELISA kits from two different commercial sources were used for the NF-L assays (i.e., MyBioSource, San Diego, USA and UmanDiagnostics AB, Umeå, Sweden).

For pNF-H determinations, we used a single-batch ELISA kit from BioVendor Research and Diagnostic Product, Czech Republic.

190 ALS patients, 130 controls

| Variable | ALS ($n = 190$) | CTL-1 ($n = 82$) | CTL-2 (48) | $p$ |
|---|---|---|---|---|
| NF-L (ng/ml) | | | | |
| MyoBioSource kit | 2.14 (1.35–3.30) | 2.04 (1.25–3.39) | 3.09 (1.12–4.59) | 0.12* |
| UmanDiagnostics kit | 4.70 (1.18–7.98) | 0.61 (0.31–2.67) | 5.20 (0.57–8.32) | < 0.05* |
| pNF-H (ng(ml) | 1.70 (0.76–3.17) | 0.03 (0.00–0.32) | 0.82 (0.00–3.47) | < 0.05* |

For the NF-L assay, two ELISA kits from different commercial sources were compared. Data are expressed as median with interquartile ranges

*Rossi et al., J of Neurol 2019*

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# Grazie per l'attenzione