Pioneering Pathways: Evolving Use of Neurofilaments in Neurodegenerative Disease

Neurofilaments (NFL) are structural proteins, released into interstitial fluid (CSF and blood) following **axonal damage or neuronal degeneration**[1,2]

NFL levels may be particularly elevated in some individuals with neurodegenerative diseases such as ALS and SMA[3,4]

NFL in SMA

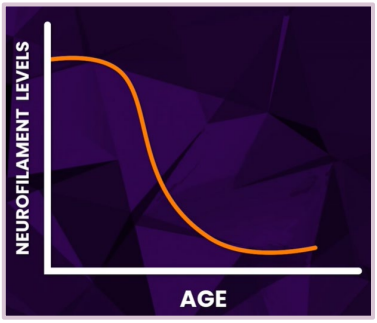


Figure is for illustrative purposes only

In infants and younger children with SMA, NFL levels have been shown to be:[4]

- **Elevated**, reflecting neuroaxonal damage that is central to the disease
- **Prognostic for disease severity** and responsive to treatment

NFL levels in adolescents and adults with SMA may be similar to those without SMA[1]

NFL levels may be **prognostic** for **disease severity** and **response to treatment**[1,5]

NFL levels are higher in people with:[1]

- A more severe disease phenotype (infantile-onset vs later-onset SMA)
- Two vs more than three SMN2 copies

Potential utility of NFL levels in SMA[a,4,6]

Risk/susceptibility marker

NFL could potentially be used for monitoring of genetically at-risk individuals

Prognostic marker

NFL levels could help monitor disease course and inform treatment decision-making

Pharmacodynamic marker

NFL levels may have utility for monitoring response to treatment in younger people with SMA who have two *SMN2* copies

Considerations for use of NFL:

- Use is well-studied in young children with two *SMN2* copies, but not in adolescents and adults with SMA
- Sample collection from infants remains challenging (e.g. due to blood volume requirements)

ALS, amyotrophic lateral sclerosis; CSF; cerebrospinal fluid; SMA, spinal muscular atrophy.
[a] More research is needed to better understand potential utility of NFL levels in SMA; currently NFL levels are most well-established for use in clinical research/population level rather than for use on the patient level.

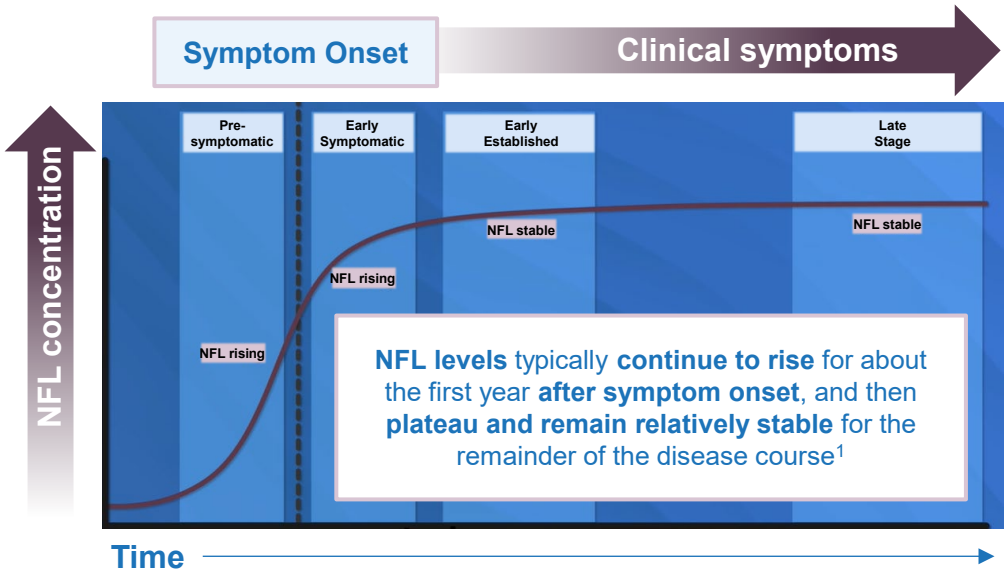
1. Yuan A, et al. *Cold Spring Harb Perspect Biol*. 2017;9(4):a018309; 2. Verde F, et al. *Front Neurosci.* 2021;15:679199; 3. Witzel S, et al. *Ann Neurol.* 2024;96(6):1040-1057; 4. Bayoumy S, et al. *Clin Chem Lab Med*. 2024;62(7):1252-1265; 5. Giorgia Q, et al. *Front Neurol*. 2023;14:1226969; 6. Glascock J, et al. *J Neuromuscul Dis*. 2023;10:937-954.

Biogen-265496
Date of preparation: June 2025

Pioneering Pathways: Evolving Use of Neurofilaments in Neurodegenerative Disease

NFL in ALS

NFL levels are thought to **begin rising before clinical symptoms are observable** (in the first 12–18 months prior to clinical manifestation)[1]



NFL levels typically **continue to rise** for about the first year **after symptom onset**, and then **plateau and remain relatively stable** for the remainder of the disease course[1]

NFL levels can vary by genotypes, with **higher NFL levels** associated with **faster disease progression and shorter survival**[1]

Lower NFL levels → **Slower progression**

Higher NFL levels → **Faster progression**

Use of NFL in ALS clinical trials[2–4]

Risk/susceptibility marker
For predicting phenoconversion to clinically manifest disease in at-risk mutation carriers

Prognostic marker
As a marker of disease progression and survival, and to control for the heterogeneity of disease progression

Pharmacodynamic marker
For monitoring response to treatment

Clinical trial only
Safety marker
Indication of potential neurotoxity

NFL level use in clinical settings is limited by:

- Being a nonspecific marker of axonal injury
- Results from different platforms cannot be compared due to the lack of established reference values used reliably across the field

ALS, amyotrophic lateral sclerosis; NFL, neurofilaments

1. Benatar M, et al., *Brain*. 2023; 146(7):2711–2716; 2. van den Berg LH, et al. *Neurology*. 2019;92(14):e1610-e1623; 3. Benatar M, et al. *Ann Neurol*. 2024;95(2):211-216; 4. Yuan A, Nixon RA. *Front Neurosci*. 2021;15:689938.

Biogen-265496
Date of preparation: June 2025