

Overview

Useful For

Assessing neuronal damage related to various neurodegenerative diseases

Method Name

Digital Immunoassay

NY State Available

Yes

Specimen

Specimen Type

Plasma EDTA

Specimen Required

Collection Container/Tube: Lavender top (EDTA)

Submission Container/Tube: Plastic screw-top vial

Specimen Volume: 1.5 mL

Collection Information: Centrifuge and aliquot plasma into a plastic vial. Do not submit specimen in original tube.

Specimen Stability Information: Frozen (preferred) 16 months/Refrigerated 7 days

Forms

If not ordering electronically, complete, print, and send a [Neurology Specialty Testing Client Test Request](#) (T732) with the specimen.

Specimen Minimum Volume

0.75 mL

Reject Due To

Gross hemolysis	Reject
Gross lipemia	OK
Gross icterus	OK

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Plasma EDTA	Frozen (preferred)		

	Refrigerated	7 days	
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Clinical & Interpretive

Clinical Information

Neurofilaments (NF) are exclusively located in the neuronal cytoskeleton and are released to the interstitial fluid upon axonal injury or neurodegeneration. NF concentrations in cerebrospinal fluid (CSF) and blood have been shown to correlate with the extent of axonal damage or neurodegeneration in various neurodegenerative diseases. Of the family of NF proteins, neurofilament light chain (NfL) has gained the most interest as a candidate marker of neurodegeneration. During axonal damage, NfL is released into the CSF, and eventually into the blood where concentrations are 40-fold lower than in the CSF. Concentrations of NfL in plasma have been shown to be approximately 5% to 10% lower than those measured in serum.

Circulating NfL concentrations increase with age with reported increases of approximately 2% to 3% per year in both males and females. While the specific cause of this increase has not been elucidated, it is believed to be related to the aging process as well as to the development of subclinical ischemic events. NfL concentrations in blood (plasma or serum) reflect the extent of axonal damage, making them a generic marker of disease activity. Increases in NfL concentrations have been reported in individuals with traumatic brain injury, amyotrophic lateral sclerosis, multiple sclerosis, frontotemporal dementia, Alzheimer disease, and other neurodegenerative diseases.

Reference Values

- <2.5 years: < or =12.8 pg/mL
- 2.5 to 4 years: < or =11.8 pg/mL
- 5 to 9 years: < or =10.4 pg/mL
- 10 to 14 years: < or =8.8 pg/mL
- 15 to 19 years: < or =9.2 pg/mL
- 20 to 24 years: < or =10.4 pg/mL
- 25 to 29 years: < or =11.9 pg/mL
- 30 to 34 years: < or =13.5 pg/mL
- 35 to 39 years: < or =15.3 pg/mL
- 40 to 44 years: < or =17.3 pg/mL
- 45 to 49 years: < or =19.7 pg/mL
- 50 to 54 years: < or =22.4 pg/mL
- 55 to 59 years: < or =25.4 pg/mL
- 60 to 64 years: < or =28.8 pg/mL
- 65 to 69 years: < or =32.7 pg/mL
- 70 to 74 years: < or =37.1 pg/mL
- 75 to 79 years: < or =42.1 pg/mL
- 80 to 84 years: < or = 47.8 pg/mL
- > or =85 years: < or =54.3 pg/mL

Interpretation

Blood neurofilament light chain (NfL) is a non-specific marker of neuro-axonal injury showing promising associations with outcomes in several neurological conditions. In neurodegenerative diseases, NfL may also serve as a prognostic

marker of decline and an efficacy biomarker of experimental therapies. In a meta-analysis of Alzheimer disease (AD), frontotemporal dementia, and amyotrophic lateral sclerosis (ALS), plasma NfL levels were elevated in patients compared to controls with utility in differentiating neurodegenerative conditions from non-neurodegenerative mimics. However, due to a lack of specificity to a particular neurodegenerative disease, its role as a diagnostic marker is limited.

In multiple sclerosis (MS), NfL is elevated in the blood of newly diagnosed patients and concentrations correlate with disease severity and prognosis. However, measured circulating NfL in MS patients often overlaps with concentrations found in healthy individuals, potentially limiting its utility. Early measures of blood NfL in newly diagnosed MS patients can predict brain atrophy and lesion load on magnetic resonance imaging. The use of blood NfL in serial disease monitoring and treatment response has been evaluated in various prospective clinical trials. Reductions in NfL concentrations after different treatments tend to follow the hierarchy of treatment efficacy, with greatest reductions observed with the most intensive treatments. A study that included over 1000 MS patients receiving various treatments, reported the largest reductions in plasma NfL concentrations following alemtuzumab treatment (54% reduction), and the smallest reduction with teriflunomide treatment (7%).

Pediatric-onset multiple sclerosis prevalence and incidence rates are increasing globally. Between 3 and 10% of patients with MS present under 16 years of age. Guidelines for pediatric MS recommend that treatment can be started early in the disease course. Circulating NfL is a useful biomarker for monitoring disease activity and treatment response in pediatric MS. It is most likely helpful to predict disease severity and to guide treatment decisions in patients with pediatric MS. Elevated blood NfL levels were significantly associated with higher numbers of cerebral and spinal MRI lesions at baseline. High concentrations of blood NfL (>100 pg/mL) are predictive of disease events within four months.

In AD, blood NfL concentrations have been shown to correlate with cortical thinning and cognitive decline in both sporadic and familial AD. While there are elevations of NfL in patients with AD, at this point the clinical value of blood NfL is not fully understood, especially in light of the availability of other more sensitive and specific biomarkers for AD.

Circulating NfL has been evaluated both in the context of mild traumatic brain injury (mTBI) diagnosis (acute setting) and prognosis (outcome prediction). In the acute setting, the utility of NfL in identifying mTBI within 24 hours of an injury has been controversial, likely due to the different timepoints used in studies for evaluating NfL concentrations after the injury (ranging from 1, 4, 6, 12, and 24 hours post-injury). A recent 2022 review describes the findings of six different publications looking at the role of NfL in acute mTBI. Three out of four studies involving athletes reported data supporting the efficacy of NfL in identifying mTBI within 24 hours of an injury. However, studies using either military cadets or emergency department patients presenting with possible mTBI as subjects did not show evidence supporting NfL use in the acute setting. As a prognostic marker, data has been inconclusive as to whether NfL is able to predict recovery time, post-concussion syndrome, or potential return to sport after mTBI.

In ALS, NfL concentrations have been suggested to be able to discriminate ALS from ALS-mimics. NfL levels at symptom onset may be prognostic of disease progression rate and may be used to stratify patients into groups with a similar prognosis in clinical trials. Blood NfL concentrations remain relatively stable throughout the disease. The US Food and Drug Administration has approved Qalsody (tofersen) to treat patients with ALS associated with a mutation in the superoxide dismutase 1 (SOD1) gene. The approval was based on a reduction in plasma neurofilament light at the end treatment compared to the placebo arm. Therefore, NfL might be a useful biomarker of assess effectiveness of some ALS therapies.

Parkinson disease (PD) patients with elevated NfL concentrations have been reported to have worse cognitive decline,

brain cortical atrophy, and motor scores. Blood NfL concentrations in atypical forms of Parkinson disease are higher than in PD and may be used to help differentiate PD from atypical parkinsonian disorders.

In frontotemporal dementia (FTD), blood NfL was able to discriminate patients with the behavioral form of FTD from patients with primary psychiatric disorders. It has been suggested that blood NfL could be used to support the diagnosis of the behavioral form of FTD, monitor disease progression, and prognosis of FTD.

A study that evaluated blood NfL concentrations in 13 neurodegenerative disorders, Down syndrome, depression, and cognitive normal controls showed that plasma NfL concentrations were elevated in all cortical neurodegenerative disorders, ALS, and atypical parkinsonian disorders. Plasma NfL was clinically useful in differentiating atypical parkinsonian disorders from PD, in identifying dementia in Down syndrome, distinguishing neurodegenerative disorders from depression in older adults, and potentially identifying frontotemporal dementia in patients with cognitive impairment. Individuals with ALS, FTD, and Down syndrome with AD presented with the highest concentrations of plasma NfL.

### Cautions

Increases in neurofilament light chain (NfL) are not disease specific. Results should only be used in conjunction with other clinical information when evaluating patients with neurodegeneration.

Higher concentrations of NfL may be found in persons with history of stroke, atrial fibrillation, myocardial infarction, chronic kidney disease, pregnancy, and diabetes.

Lower concentrations of NfL may be found in individuals with a BMI of 30 or more.

All immunometric assays can, on rare occasions, be subject to a hooking effect at extremely high analyte concentrations (false-low results), heterophilic antibody interference (false-high results), or autoantibody interference (unpredictable effects). If the laboratory result does not fit the clinical picture, these possibilities should be considered.

### Clinical Reference

1. Barro C, Chitnis T, Weiner HL. Blood neurofilament light: a critical review of its application to neurologic disease. *Ann Clin Transl Neurol*. 2020;7(12):2508-2523
2. Ashton NJ, Janelidze S, Al Khleifat A, et al. A multicentre validation study of the diagnostic value of plasma neurofilament light. *Nat Commun*. 2021;12(1):3400
3. Khalil M, Teunissen CE, Otto M, et al. Neurofilaments as biomarkers in neurological disorders. *Nat Rev Neurol*. 2018;14(10):577-589
4. Farragher CD, Ku Y, Powers JE. The potential role of neurofilament light in mild traumatic brain injury diagnosis: a systematic review. *Cureus*. 2022;14(11):e31301. doi:10.7759/cureus.31301. PMID: 36514599; PMCID: PMC9733779.5. Disanto G, Barro C, Benkert P, et al. Serum neurofilament light: A biomarker of neuronal damage in multiple sclerosis. *Ann Neurol*. 2017;81(6):857-870
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7. Verde F, Steinacker P, Weishaupt JH, et al. Neurofilament light chain in serum for the diagnosis of amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry*. 2019;90(2):157-164
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9. Khalil M, Pirpamer L, Hofer E, et al. Serum neurofilament light levels in normal aging and their association with morphologic brain changes. Nat Commun. 2020;11(1):812

10. Bornhorst JA, Figdore D, Campbell MR, et al. Plasma neurofilament light chain (NfL) reference interval determination in an age-stratified cognitively unimpaired cohort. Clin Chim Acta. 2022;535:153-156. doi:10.1016/j.cca.2022.08.017

Performance

Method Description

Neurofilament light chain (NfL) is measured on the Quanterix Simoa HD-X analyzer using the Simoa NF-Light advantage kit. The assay uses two NfL specific monoclonal antibodies. Sample, paramagnetic capture beads coated with anti-NfL antibody, and a biotinylated detector antibody are combined. Anti-NfL antibody coated paramagnetic capture beads and labeled biotinylated detector antibody will bind to NfL molecules present in the sample. Following a washing step, a conjugate of streptavidin-beta-galactosidase (SBG) is mixed with the capture beads. The captured NfL becomes enzymatically labeled when the SBG binds to the biotinylated detector antibodies. A second wash is performed, and the capture beads are resuspended in a resorufin beta-D-galactopyranoside (RGP) substrate solution.

This suspension is transferred to the Simoa Disc. Individual paramagnetic capture beads settle into 216,000 femtoliter-sized microwells designed to hold no more than one bead per well. The beads are sealed into the microwells while excess beads are washed away with a synthetic fluorinated polymer sealing oil. If NfL is present in the sample and subsequently captured and labeled, the beta-galactosidase hydrolyzes the RGP substrate and produces a fluorescent signal. This signal is detected and counted by the Simoa optical system. The concentration of NfL is interpolated from a standard curve.(Unpublished Mayo method)

PDF Report

No

Day(s) Performed

Monday, Wednesday, Friday

Report Available

1 to 7 days

Specimen Retention Time

12 months

Performing Laboratory Location

Rochester

Fees & Codes

Fees

- Authorized users can sign in to [Test Prices](#) for detailed fee information.

- Clients without access to Test Prices can contact [Customer Service](#) 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact [Customer Service](#).

Test Classification

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. It has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information

0361U

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
NFLC	Neurofilament Light Chain, P	101281-4

Result ID	Test Result Name	Result LOINC® Value
616854	Neurofilament Light Chain, P	101281-4