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RESEARCH ARTICLE

Clinical use and reporting of neurofilament quantification in neurological disorders: A global overview

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Abstract

INTRODUCTION: Neurofilament light chain (NfL) quantification aids in diagnosing and predicting neurological disorders, but clinical and laboratory practices vary across centers. Differences in result interpretation and reporting further challenge test commutability. This study aimed to review the global analytical and post-analytical

methods used for NfL measurement in routine clinical practice across different contexts.

METHODS: We established an international working group (WG) and distributed a survey to its members to gather information on context of use (COU), (pre) analytical methods, cutoff usage, as well as the interpretation and reporting of NfL measurements.

RESULTS: Among the centers, 63% measured NfL in cerebrospinal fluid (CSF), 87% in blood, and 53% in both. COU was widespread, with 50% defining pathological cutoffs based on publications and 42% considering age. Reporting was primarily done through numeric results (95%).

DISCUSSION: Harmonizing cutoffs, reporting, and interpretation across various clinical contexts will facilitate the incorporation of this biomarker into routine clinical practice.

KEYWORDS
biomarkers, blood, cerebrospinal fluid, clinical report, consensus approach, harmonization, neurofilaments

Highlights

- Unique international overview of current analytical and post-analytical methods for neurofilament light chain (NfL) measurement in routine clinical practice.
- Tailored sheets for each neurological application.
- Strategies to harmonize cutoffs, reporting, and interpretation of NfL's measurement.

1 | BACKGROUND

Neurofilaments (Nf) are a type of intermediate filament found exclusively in neurons. They differ from other intermediate filaments due to their complex structure and subunit composition. There are three identifiable subunits of Nf, which can be differentiated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS PAGE) based on their molecular weight: NfH (heavy chain, 200 kDa), NfM (medium chain, 160 kDa), and NfL (light chain, 68 kDa).[1] Nf subunits contribute to the radial growth of axons during neuronal development, as well as to the maintenance of their structure and diameter, which are essential for the transmission of nerve impulses. They also play a role in organizing and anchoring various axonal components to the microtubule network.[2,3] Due to their abundance in axons and their release into the blood and cerebrospinal fluid (CSF) following neuronal damage, the measurement of Nf in these biological fluids as biomarkers of axonal injury, axonal loss, and neuronal death holds significant promise for both diagnosis and prognosis of neurological disorders.[4,5] Among the Nf isoforms, NfL has emerged as one of the key biomarkers of neurodegeneration, not specific to any single condition but indirectly reflecting the pathogenesis of numerous neurological diseases.[6–9]

From an analytical standpoint, numerous methods have been developed over the past few years, enabling laboratories to implement the best method to be suited to their practice for measuring this biomarker. These advancements now enable detection and monitoring NfL not only in CSF but also in blood. Various studies have been published in recent years showing the correlation of some of the available methods.[10–13] Additionally, it is known that NfL levels in biological fluids are influenced by factors such as body mass index (BMI), age and renal function.[14–18] Therefore, given the increasing importance of NfL for the diagnosis and prognosis of many neurological diseases, it is essential to harmonize the practices implemented among laboratories involved in this measurement, from the pre-analytical,[19] analytical, and post-analytical perspectives. The normal/pathogenic thresholds (cutoffs) for NfL measurement still need to be standardized, or even defined, depending on the methods used,[20] clinical contexts, and physiological factors influencing concentrations, such as age, BMI, and renal function.[18–22]

We previously published a study conducted under the auspices of the AAIC (Alzheimer's Association), providing a comprehensive overview and consensual harmonization of the clinical reporting made by clinical biology laboratories following the measurement of CSF biomarkers for the diagnosis of Alzheimer's disease (AD).[23] In the

present work, we aim to provide a comprehensive review of the current state of analytical and post-analytical methods used for measuring NfL worldwide in clinical routine in a variety of clinical contexts (context of use [COU]), including AD, multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), frontotemporal dementia (FTD), psychiatric syndromes (PS), Creutzfeldt–Jakob disease (CJD), peripheral neuropathies (PN), traumatic brain injury (TBI) or ischemic damage including cardiac arrest. For each clinical laboratory participating in this work, we collected information on the COU, pre-analytical and analytical methods, use of cutoffs, and the interpretation and reporting of results. This information was shared and reviewed among clinical laboratories to generate informative fact sheets, aiding in the implementation of these important clinical measurements.

2 | METHODS

2.1 | Partners involved

Centers and laboratories specialized in the biological diagnosis of neurodegenerative diseases were contacted through the French Society of Clinical Biology (SFBC, https://www.sfbc-asso.fr/), the ISTAART BBB-PIA (Biofluid Based Biomarkers PIA [Professional Interest Area] of the Alzheimer's Association), or the Society for Neurochemistry and Clinical CSF analysis (http://www.neurochem.info/). A total of 38 centers from 18 different countries (Austria, Belgium [3], Brazil [2], Canada, France [7], Germany, Greece, Italy [9], Japan, Netherlands, Poland, Portugal, Spain [5], Switzerland, Turkey, United Kingdom [2], United States of America, Sweden) provided different levels of information regarding their practice. For the interpretation of the surveys, each laboratory was anonymized. No personal or clinical patient data were used for this project, which therefore did not require ethical clearance. Data were collected between January 2023 and June 2024.

2.2 | Inquiries and data processing

A brief 12-question survey focused on NfL measurement was created and distributed to various clinical centers for recruitment. It was designed for online completion, with an automatic copy sent to the Montpellier center, which oversaw the analysis of the collected data. The survey included questions regarding the COU, the biological fluid used (blood, CSF, etc.), and the analytical methods implemented for such analysis. The questionnaire also addressed how pathological/normal NfL thresholds are defined, and the possible consideration of other clinical parameters (height, weight, age, ethnic background, potential comorbidities, etc.).

For each clinical laboratory participating in this work, we collected information on the COU, pre-analytical and analytical methods, use of cutoffs, and the interpretation and reporting of results. This information was shared and reviewed among clinical laboratories to generate informative fact sheets, aiding in the implementation of these important clinical measurements.

RESEARCH IN CONTEXT

1. **Systematic review**: Neurofilament light chain (NfL) is a key biomarker in neurology, indicating neuronal damage with applications across neurodegenerative, inflammatory, traumatic, and vascular disorders. However, standardization and clinical translation challenges lead to inconsistencies in reporting, cut-off values, and interpretation. This study systematically examines these issues and proposes harmonization strategies to support NfL's routine clinical use.
2. **Interpretation**: Providing a unique international perspective, this manuscript includes contributions from 38 expert centers across 18 countries, integrating insights from key opinion leaders in NfL implementation across diverse clinical contexts. We further propose a reference sheet specific to each clinical context.
3. **Future directions**: Several hurdles still need to be overcome before NfL can be widely used in clinical practice. In this work, we propose the basis for future regulatory and clinical guidelines, guaranteeing the reliability and comparability of NfL measurements between institutions and clinical indications.

Based on COU, subgroups of laboratories were then formed, each led by a coordinator, to gather additional information (e.g., type of fluid, assays, population tested). Post-analytical data were also collected, including analyte cutoff values, use of normative data, and additional details, such as the presence of comorbidities. These elements were compiled into different specification sheets, which were collectively shared and refined to reach a consensus.

2.3 | Role of the funding/sponsoring source

This research received no specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The study supporters had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

3 | RESULTS

3.1 | Initial survey sent and COU

The responses to the questionnaire initially sent to the centers are presented in Figure 1. Figure 1A shows that most centers (71%) have implemented NfL measurement for the diagnosis of FTD and AD, and 61% for the diagnosis or prognosis of ALS and MS. A total of 45% of centers have implemented NfL measurement or differential

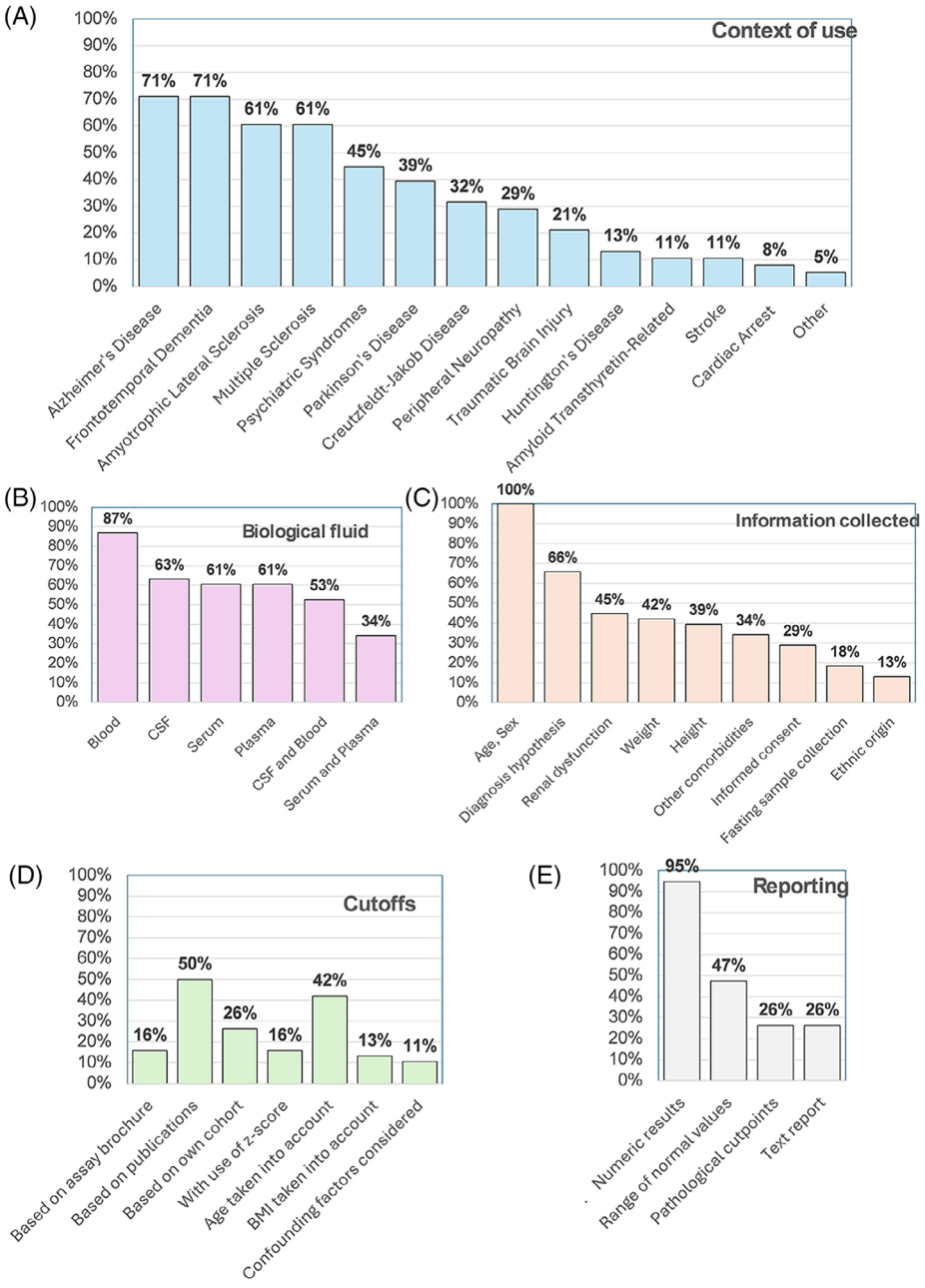

FIGURE 1 (A) The COU across participating centers. (B) An overview of the biological fluids utilized for NfL assessment across the participating centers. (C–E) The post-analytical analysis of NfL measurements, specifically addressing the clinical data used for result interpretation (C), the definition of cutoff values (D), and the reporting of results (E). COU, context of use; NfL, neurofilament light chain.

diagnosis of FTD-PS, 39% for PD, and 32% for CJD. Less than 30% have implemented this measurement in the other COU tested. In general, laboratories use NfL in two or more COU.

3.2 | Pre-analytical and analytical conditions overview

Standard operating procedures (SOPs) for pre-analytical sample handling for NfL quantification have already been proposed[19,24] and are, in fact, utilized by 100% of the centers.

The detection of NfL biomarkers indicates that nearly 90% of laboratories use blood for their analyses (Figure 1B). There is an equal distribution between the use of serum and plasma, with 34% of centers using both. A total of 53% of the participating centers analyze both CSF and blood (Figure 1B).

Analytical platforms for the analysis of NfL show varying usage patterns influenced by the emergence of new diagnostic kits, as illustrated in Figure S1, panels A and B. In 2023, most centers used Simoa Quanterix and enzyme-linked immunosorbent assay (ELISA) UmanDiagnostics for NfL quantification. This distribution evolved in 2024, with the majority using Lumipulse Fujirebio.

Furthermore, these analyses are often funded using funds from research projects. (47%), Figure S1, panel C. Some laboratories provide these tests fee-for-service, with partial reimbursement by insurance and social security systems (16%) in some instances. However, in other cases, the full cost may fall on the patient (around 20%). The analysis was free of charge in less than 20% of the centers.

Information on the patient's sex and age is systematically requested as part of clinical biology analyses (Figure 1C). However, only two-thirds of laboratories request the diagnostic hypothesis.

Additionally, some laboratories collect other data such as renal function (45%), weight (42%), and height (39%), which can act as confounding factors. Finally, one-third of laboratories require informed consent, highlighting that the analysis of neurological biomarkers is not yet considered a routine procedure, Figure 1C.

3.3 | Post-analytical procedures overview

The definition of cutoffs by the centers was based on the information given by manufacturers in 16% of centers, on literature (50%), or their own cohort (26%), Figure 1D. Some laboratories mentioned considering supplemental clinical information, such as BMI (13%) or age (42%). The Z-score definition was used in 16% of the centers, and other comorbidities were considered in 11% of them, Figure 1D. Results are mostly reported as numerical values (95%), accompanied by ranges of normal values (47%), Figure 1E. Around a third of laboratories also provide specific thresholds and explanatory comments.

3.4 | Clinical practice according to the different COUs

To summarize the information across different COUs, we have compiled a summary based on each subgroup of clinicians and biologists, as outlined in Table 1A. Additionally, we have created reference sheets for each indication, and by adopting a consensus-driven approach, we formulated a standardized strategy for the utilization and reporting of NfL results across different centers, tailored to their respective COU (Tables 1B–1J). These sheets include key details such as clinical indications, population, gold standard, and alternative methods, as well as recommendations for prescription and reporting.

4 | DISCUSSION

The quantification of NfL in blood and CSF has shown potential in supporting clinical decision-making for the evaluation of various neurological disorders.[95–99] There is, however, a diversity of practices between centers, essentially linked to COUs (see Tables), analytical methods,[10,100–102] the indication of confounding factors such as age and sex[103] or BMI,[15] genetic data (presence of a known pathogenic mutation), consideration of comorbidities such as renal dysfunction, determination of cutoffs, or use of interpretation scales. Only two-

TABLE 1A Reference sheet common to all contexts of use (COUs)

Clinical indications: Answer to a medical need that will impact: Diagnostic confidence/care of the patient/treatment strategy.

Population: It is extremely important that the population being tested corresponds to the one with the specific medical need. Otherwise, the risk of false-negative and false-positive results increases, and low positive and negative predictive values are obtained.

Gold standard, other alternatives: Ideally, the performance of measurements needs to match or even surpass the gold standard. However, even without achieving this, Nf, especially in blood, could be valuable if integrated into a meaningful patient clinical pathway.

Prescription: In all cases, to ensure a proper interpretation of the results, the prescription needs to include the COU. Age and sex or also always included with the prescription. BMI and renal function for blood measurement influence blood NfL levels and, depending on the COU, are recommended. Timing for measurement with regard to the pathology, as well as the frequency of measurement, are dependent on the different COUs.

Analytical aspect, cutoffs, and performances

- SOP for pre-analytical sample handling for NfL quantification[19,24]
- Normal values based on the NfL norms are available.[12,25,26] These values differ depending on the assays and technology used, especially in the absence of standardization of the assay.[20] Based on these norms, it is possible to define cutoffs that indicate a generic pathological situation. Specific high cutoffs may be established for diagnosis, prognosis, or therapeutic response/follow-up. The method for defining these cutoffs varies among laboratories, relying on published information, Z-scores, in-house cohorts, or vendor brochures (see Figure 1, panel D).
- BV and RCV: BV, a foundational concept in clinical chemistry, is crucial to ensure the safe implementation of diagnostic markers and to minimize misclassification risks in laboratory medicine.[27] European Federation of Clinical Chemistry and Laboratory Medicine EFM provides biological variability values (https://biologicalvariation.eu/) and a Web-based calculator that allows the calculation of RCV for each analyte based on the laboratory's APS.[28]
- Cutoffs need to be adapted to the NfL determination method used and potentially the clinical situation. The conversion equation can be obtained from studies reporting on the determination of NfL with different methods from the same samples[12,20]
- Confounder to be included in most COUs: Age/BMI (> 30)/Renal Insufficiency if eGFR < 60 mL/min

Reporting: Text reporting is not always provided; however, it is advisable to include this information for medical interpretation. The transmission of results to patients is becoming increasingly common and, depending on regulations, may even be compulsory. Given the impact of NfL values on the diagnosis of very severe diseases, it is recommended to organize a consultation to discuss the findings before transmitting the report to the patients.

Abbreviations: APS, analytical performance specifications; BMI, body mass index; BV, biological variation; COU, context of use; eGFR, estimated glomerular filtration rate; Nf, neurofilaments; NfL, neurofilament light chain; RCV, reference change value; SOP, standard operating procedure.

TABLE 1B Reference sheet for FTD and PS

Clinical indications:
- Differential diagnosis[29–31]
- FTD prognosis (marker of disease severity)[32]
- Conversion into the symptomatic stage in FTD genetic forms (presymptomatic mutation carriers)[33]
- Inclusion criterion supporting participant stratification in trials[34]
- Response to treatment in clinical trial (secondary outcome measure[35])

Population:
- Middle-aged and older adults
- Consulting tertiary centers (memory and psychiatric units)
- With an ambiguous clinical presentation between FTD and PS

Gold standard, other alternatives:
- Genetic screening for familial forms[33]
- Clinical International consensus criteria[36,37]
- Application of DSM-5 clinical criteria[25]

Prescription:
- Measurement performed in both CSF and blood. CSF is often available, as its analysis for other neurodegenerative diseases is commonly performed in this population.

Timing of NfL analysis:
- Following initial clinical/cognitive/imaging evaluation.

Analytical aspect, cutoffs, and performances: See the section for all COUs.
Reported clinical performance:
ROC AUC between FTD and PPS 0.850, sensitivity 80%, and specificity 85%[38]
ROC AUC between FTD and PPS 0.868, sensitivity 80%, and specificity 79.5%[39]

Reporting:
If in the range of normal values:
NfL concentration is in the normal range. Does not support the diagnosis of FTD.
If just above pathological cutoff (± 20%)
NfL with moderate pathological value. We expect in most FTD higher value.
If clearly pathological ≥ ± 20%
NfL concentration compatible with a diagnosis of FTD.
The cutoffs have to be adapted to the age of the patients.

Conclusion:
NfL measurement represents a clear added value in distinguishing FTD from PS and is one of the earliest uses of this analyte. It was initially measured in CSF, where it achieved high performance, and has been more recently used in blood, offering a less invasive approach but potentially lower performance. The differential diagnosis between FTD and PPS is crucial for proposing the best patient care.
NfL is a reliable biomarker for tracking disease progression and severity in FTD. However, when distinguishing FTD from other neurodegenerative conditions like AD—particularly in the early stages—its interpretation should be supported by additional clinical data and biomarkers, such as CSF AD markers or Amyloid PET imaging.

Abbreviations: AD, Alzheimer's disease; AUC, area under the curve; COU, context of use; CSF, cerebrospinal fluid; DSM, Diagnostic and Statistical Manual of Mental Disorders, Revision 5; FTD, frontotemporal dementia; NfL, Neurofilament light chain; PS, psychiatric syndromes; ROC, receiver operating characteristics curve.

TABLE 1C Reference sheet for ALS

Clinical indications:
- Prognostic information[10,40,41]
- Monitoring of treatment[42]
- Clinical monitoring in presymptomatic subjects[43]
- Diagnosis (exclusion of ALS mimics) and/or clinical and genetic subtype of ALS[10]

Population:
- Adults
- Consulting Tertiary centers with possible ALS
- With diagnosis already established (prognosis)

Gold standard, other alternatives:
GCC[44]
Clinical signs of lower or upper motor neuron degeneration, progressive spread of signs/Electrophysiological signs/neuroimaging (MRI-DTI of pyramidal tracts).
Genetic screening for familial forms

Prescription:Indication of onset of symptoms and ALS-FRS-R score: optional. Measurement is mostly performed in blood since CSF is often not a routine exam for these patients. However, CSF is available when intrathecal therapy is implemented.**Timing of NfL analysis**:
- At the time of diagnosis, if an ambiguous situation.
- When the ALS diagnosis is established (prognosis)
- In the follow-up of treatment (at each clinical evaluation)

Analytical aspect, cutoffs, and performances: See the section for all COUs.**Reported clinical performance**:
- ROC AUC between ALS and ALS mimics 0.88, sensitivity 83%, and specificity 85%. Prognosis: Hazard ratio 4.56[10]
- AUC between ALS and other conditions: 0.873, 85.5% sensitivity and 81.8% specificity[45]

Reporting:
If in the range of normal values:
NfL concentration is in the normal range. Not compatible with a diagnosis of ALS
If just above pathological cutoff (± 20%)
NfL with moderate pathological value. We expect in most ALS a higher value.
If clearly pathological (≥ ± 20%) or above the selected ALS cutoff
NfL concentration compatible with a diagnosis of ALS
If largely above the pathological cutoff (± 100%) or above the selected prognosis ALS cutoff
Compatible with an ALS diagnosis with poor prognosis.
The report may indicate stable, increasing, or decreasing values when serial measurements are performed, particularly in the follow-up of treatment (e.g., in genetic forms), where it provides an estimation of efficacy.

Conclusion:
Diagnosing ALS in specialized centers is typically not a significant challenge. However, in a small percentage of cases (< 5%), distinguishing ALS from its mimics can be difficult. In these situations, NfL measurement provides added diagnostic value. The primary role of NfL in ALS lies in its prognostic significance. Elevated NfL levels serve as an independent and highly accurate prognostic marker, often indicating a survival time of less than 1 year. This information is essential for guiding patient management.

Abbreviations: ALS, amyotrophic lateral sclerosis; AUC, area under the curve; COU, context of use; CSF, cerebrospinal fluid; GCC, Gold Coast Criteria; NfL, neurofilament light chain; ROC, receiver operating characteristics curve.

TABLE 1D Reference sheet for MS

Clinical indications:
- Evaluation of response to disease-modifying therapy[46]
- Marker to prescreen MRI scans[47]
- Guide treatment escalation and de-escalation[48]
- Capture residual disease activity[48]
- Prognostic information in NMSOD[49] and MOG-AD[50]

Population:
- Young adults and adults
- Patients in a clinical context of MS and/or NMSOD/MOG-AD, with diagnosis already established (monitoring, prognosis).

Gold standard, other alternatives:
- Emerging McDonald Criteria 2024 (not yet officially published): Proposed at the ECTRIMS 2024 Congress, the updated McDonald criteria are currently under discussion and reflect ongoing advances in MS diagnosis. While their formal publication is pending, some components are already widely applied in clinical practice, particularly the kappa FLC index. Other elements, such as the central vein sign, remain under evaluation and are not yet universally implemented. The proposed criteria include:
  Neuroimaging: MRI T2 hyperintense lesions on MRI.
  CSF-specific OCB IgG and/or Kappa FLC index.
  CSF-specific OCB IgM.
  OCT
  Clinical signs of neurodegeneration.
  CMSC Consensus Statement on neurofilament biomarkers in MS[48]

Prescription: Measurement performed in both CSF and blood.When relevant, indicate treatment, clinical exacerbation.
Timing of NfL analysis:
- Baseline NfL (both CSF and Blood) at time of lumbar puncture[48]
- During relapse to capture increases neuronal-axonal injury, otherwise 3–4 months after relapse (blood).
- Resampling: after 6-month intervals, CSF re-evaluate at 5–10 years intervals, blood re-evaluate after age 60.

Analytical aspect, cutoffs, and performances: See the section for all COUs.
Reported clinical performance:
Z-score > 1.25, worsening odd ratio (OR) of 2.28, Z-score > 1.75, OR of 3.85[16]

Reporting:
Interpretation based on Z-Score:
If Z-score < 0.84 (80th percentile): NfL concentration is in the normal range.
If Z-score ≥ 0.84 and ≤ 1.5 (93.3rd percentile): NfL concentration slightly elevated.
If *z*-score > 1.5 and ≤ 2 (97.7th percentile): NfL concentration elevated.
If *z*-score > 2: NfL concentration strongly elevated.
Interpretation based on RCV (%: Percentage change between 2 consecutive samples; *RCV* for each laboratory based on BV and particular performance):
+No change (2nd sample = 1st sample): "**Nonsignificant changes** from previous result."
+Increases (2nd sample > 1st sample:
If % > RCV: "**Significant increase** compared to the previous result according to (*RCV*) for NfL in plasma/serum in accordance with EFML Biological Variation Database."
If % ≤ RCV: "**Nonsignificant increase** compared to the previous result according to (*RCV*) for NfL in plasma/serum in accordance with EFML Biological Variation Database."
+Decreases (2nd sample < 1st sample):
If % > RCV: "**Significant decrease** compared to the previous result according to (*RCV*) for NfL in plasma/serum in accordance with EFML Biological Variation Database."
If % ≤ RCV: "**Nonsignificant decrease** compared to the previous result according to (*RCV*) for NfL in plasma/serum in accordance with EFML Biological Variation Database."

Conclusion:
Determining NfL in the context of MS provides valuable information about the response to, and appropriate use of, disease-modifying therapy. It serves as a marker of neurodegeneration and can eventually capture residual disease activity. Additionally, it may offer prognostic information in NMOSD and MOG-AD and can be used as a marker for prescreening MRI scans.

Abbreviations: BV, biological variation; COU, context of use; CSF, cerebrospinal fluid; FLC, free light chain; MOG-AD, Myelin Oligodendrocyte Glycoprotein Antibody associated Diseases; MS, multiple sclerosis; NfL, neurofilament light chain; NMSOD, Neuromyelitis Optica Spectrum Disorder; OCB, Oligoclonal IgG Bands; OCT, optical coherence tomography; RCV, reference change value.

thirds of laboratories request the diagnostic hypothesis with the prescription, even though NfL values vary significantly depending on the diagnosis. This may be explained by the fact that in some countries, the interpretation of results is often left to the prescribing physician, with the laboratory playing a lesser role in this step.

In this work, we collected information from 38 centers located in 18 different countries. We first gathered information concerning COUs for NfL measurement from the centers involved and observed a large diversity of clinical contexts, in agreement with the nonspecific involvement of NfL in these pathologies.[95–97] Our study first highlights that SOPs for pre-analytical sample handling for NfL quantification[19,24] are implemented in all centers involved. We further assigned a coordinator for each clinical subgroup and asked them to propose a template summarizing the important points for the COU considered (technology used, use of quality control, comorbidities considered, cutoff definition, etc.). Our study highlights changes in analytical practices between 2023 and 2024, driven by the introduction of new kits and platforms. As more vendors begin offering NfL tests, eventually obtaining United States Food and Drug Administration (FDA)/ European Union's In Vitro Diagnostic Medical Device Regulation (EU IVDR) approval, this landscape is expected to continue evolving. In addition, it is also relevant to examine the refunding mechanisms for these analyses, as the specific regulations of different countries often influence them. These analyses are not yet fully considered routine: they are frequently funded through research projects, even when applied in clinical settings. Some laboratories offer these tests fee-for-service, with partial coverage by insurance and social security systems in certain cases. However, in other cases, patients may bear the cost entirely, which raises potential issues regarding equitable access to care (the analysis being free of charge in less than 20% of the centers).

NfL has emerged as a versatile biomarker with applications across a wide spectrum of neurological disorders.[5,97] Our international overview reveals variable levels of practice and evidence among the different COUs. Two COUs, for FTD and ALS, are well-

TABLE 1E Reference sheet for neurogenetic diseases

Clinical indications:Detection of the transition from the asymptomatic to the symptomatic phase of:
- ADAD[51]
- Down syndrome[51]
- Huntington disease[52]
- Creutzfeldt-Jakob disease (CJD, see also Table 1J)[53]
- Genetic motoneuron diseases (ALS, see also Table 1C, SMA,[54] HSP.[55]
- FTD (see also Table 1B)

Population:
- Adults and children
- Consulting tertiary centers
- With genetic diagnosis already established

Gold standard, other alternatives:
The detection of clinical signs may be challenging in some cases. For example, in Down syndrome, cognitive decline can be difficult to identify. Additionally, the appearance of significant clinical signs may occur later than the progression of the underlying pathological processes.

Prescription:
Measurement performed preferably in blood (longitudinal assessment).
Timing of NfL analysis:
NfL analysis should be conducted during the follow-up of mutation carriers prior to the expected onset of the clinical phase, which may vary and is dependent on individual factors.

Analytical aspect, cutoffs, and performances: See the section for all COUs.
Reported clinical performance:
ROC AUC of sNfL between (HSP patients from controls 0.81[55]
ROC AUC of sNfL between asymptomatic Down syndrome and Alzheimer's disease 0.88[56]
ROC AUC of sNfL between asymptomatic phase and disease onset in genetic CJD 0.88[57]

Reporting:
- Reports should emphasize that NfL results must be integrated with clinical, biological, and neuroimaging features (depending on the disease) and interpreted by a clinician experienced in the relevant condition.
- Individual serial measurements are recommended to capture significant modifications (increase) relative to the individual baseline level.

Conclusion:
NfL seems valuable for monitoring asymptomatic carriers of pathogenic mutations. Its utility lies in its ability to provide insights into the timing and progression of underlying pathological processes, offering potential for earlier intervention and better management strategies. It also represents an interesting biomarker to follow the therapeutic response.

Abbreviations: ADAD, autosomal dominant Alzheimer disease; ALS, amyotrophic lateral sclerosis; AUC, area under the curve; CJD, Creutzfeldt—Jakob disease; COU, context of use; FTD, frontotemporal dementia; HSP, hereditary spastic paraplegia; NfL, neurofilament light chain; ROC, receiver operating characteristics curve; SMA, spinal muscular atrophy.

TABLE 1F Reference sheet for parkinsonism

Clinical indications:
Differential diagnosis between PD and APS disorders[29], such as MSA,[58] PSP,[59] and CBS/CBD[60]
Prognostic in PD[61,62]

Population:
- Middle-aged and older adults
- Consulting tertiary centers (Movement disorder units)
- Patients with PD and with signs suggesting an atypical Parkinsonism[63]

Gold standard, other alternatives:
Gold standard: α-syn SAA in CSF or skin, immunodetection of α-syn in skin
Alternatives: clinical signs, neuroimaging (e.g., Dopaminergic DATscan,[64] MIBG scintigraphy, brain MRI)

Prescription:
Indication of cognitive status (NfL levels are higher in PDD than in PD, reducing the discriminative power with APS).
Timing of NfL analysis:
At the identification/appearance of Parkinsonism, when the diagnosis is uncertain.

Analytical aspect, cutoffs, and performances: See the section for all COUs.
NfL in plasma or serum, given that lumbar puncture is often not performed in Parkinsonism.
Limitation: co-pathologies and cognitive decline may increase NfL in PD, leading to false results supporting APS.
Reported clinical performance:
ROC AUC for CSF NfL between PD and atypical Parkinsonism 0.96, sensitivity 93.9% and specificity 90.8%, ROC AUC for plasma NfL 0.95, sensitivity 90.3% and specificity 91.7[65]
ROC AUC for distinguishing MSA from PD: NfL CSF: 0.97–0.99; plasma: 0.90–0.97[58,65,66]
ROC AUC for PD survival at 3-years in advanced stage: sNfL 0.91 corresponding to a sensitivity of 85.0% and a specificity of 85.7% (AUC 0.91, 95% CI: 0.85–0.97)[62]

Reporting:
- Report the accuracy of the test based on the analysis of in-house cohorts when available.
- Remind that NfL results should be interpreted cautiously in the presence of cognitive decline and confounding factors such as renal insufficiency (for blood NfL).

Conclusion:
NfL is a valuable biomarker for distinguishing PD from atypical Parkinsonism syndromes (APS), such as MSA, PSP, and CBS/CBD, as NfL levels are significantly higher in APS due to more pronounced neurodegeneration. Its noninvasive detection through blood testing aids in early diagnosis, differential diagnosis, and tracking disease progression (PD) when combined with clinical and imaging assessments.

Abbreviations: APS, atypical parkinsonism; CBD, corticobasal degeneration; CBS, corticobasal syndrome; CSF, cerebrospinal fluid; COU, context of use; MSA, multiple system atrophy; NfL, neurofilament light chain; PSP, progressive supranuclear palsy; SAA, seed amplification assay; SPD, Parkinson's disease.

TABLE 1G Reference sheet for CA

Clinical question:
- Neurological outcome after cardiac arrest.

Population:
- Comatose patients in the ICU within the first days following CA and resuscitation.

Gold standard, other alternatives:
Current international guidelines on neuroprognostication following cardiac arrest and resuscitation recommend a multimodal prognostication approach.[67–69] Strong predictors for a poor long-term neurological outcome (death, unresponsive wakefulness syndrome, minimally conscious state or severe neurological deficits with need for constant nursing care) are: Absent pupillary light reflex 72 h after cardiac arrest, early status myoclonus, absence of cortical median nerve SSEPs (N20), "highly malignant" EEG patterns, signs of severe hypoxic-ischemic encephalopathy in brain CT or MRI, serum neuron specific enolase concentration at 48 to 72 h after cardiac arrest above a critical threshold (60–90 mg/dl).[68]

Prescription:
- Measurement performed in blood
- Indication of the delay between cardiac arrest and sampling.

Timing of NfL analysis:
Within the first days (24–72 h) following cardiac arrest and resuscitation.

Analytical aspect, cutoffs, and performances: See the section for all COUs.
Very high levels of NfL are expected; therefore, the assay needs to have a high upper limit of detection and good linearity, especially if dilutions are necessary.

Reported clinical performance:
Determination of NfL serum concentration is not yet recommended as a routine test in neuroprognostication after cardiac arrest in international guidelines published in 2021 and 2023. Several moderate to large-sized studies ($n = 80–717$) on neuroprognostication after cardiac arrest by NfL serum concentration have been published.[70–76] These include cohorts from multicenter randomized trials with long-term outcomes.[71–73,76] In August 2024, there is no international consensus on cutoffs to predict the absence of severe HIE or poor neurological outcome after CA. The sensitivity to predict poor neurological outcome is in the range of 50%–60%.
Current evidence suggests that NfL serum concentration may be superior to NSE serum concentration in the prediction of poor neurological outcome after cardiac arrest.[71]

Reporting: (**cutoffs correspond to SIMOA v2 or Lumipulse methods; cutoffs need to be adapted to the assay used**)
if NfL ≥ 2000 pg/mL (SIMOA/Lumipulse) 24–72 h after CA
A severe HIE with poor neurological long-term outcome is likely. Note that consequences from neuroprognostic tests should always be drawn considering the clinical context and within a multimodal prognostication approach, according to guidelines for neuroprognostication after cardiac arrest.
if NfL ≤ 55pg/mL (SIMOA/Lumipulse) 24–72 h after CA
A severe HIE is very unlikely. If no other diseases cause a poor outcome, the neurological outcome of the patient will very likely be good. Note that patients with the very rapid increase in intracranial pressure with cessation of cerebral circulation (e.g., with severe intracranial hemorrhage leading to CA) may have low NfL serum concentrations despite severe brain damage.

(Continues)

TABLE 1G (Continued)

if NfL ≥ 55 pg/mL but ≤ 2000 pg/mL (SIMOA/Lumipulse) 24–72 h after CA
A severe hypoxic-ischemic encephalopathy may or may not be present, with a likelihood increasing from low to high values within this range.
Note that NfL serum concentration and other neuroprognostic tests capture the extent of HIE and not the outcome per se. Poor outcome for other reasons (e.g., severe cardiac disease) cannot be predicted by these markers, and thus, poor outcome despite low NfL serum concentration and absence of brain damage is not infrequent in this population.

Conclusion:
The determination of blood NfL levels holds significant potential as a neuroprognostic marker following CA. While very high or very low NfL concentrations within the first 24–72 h can provide valuable insights into the likelihood of severe HIE or favorable neurological outcomes, it is essential to interpret results within the framework of a multimodal prognostication approach. Current international guidelines emphasize the use of multiple predictors, as no single marker, including NfL, can provide absolute certainty in outcome prediction. In clinical practice, integrating NfL measurements with established methods like EEG, neuroimaging, and other biochemical markers remains crucial for comprehensive and accurate neuroprognostication.

Abbreviations: CA, cardiac arrest; COU, context of use; CT, computed tomography; EEG, electroencephalogram; HIE, hypoxic–ischemic encephalopathy; ICU, intensive care units; NfL, neurofilament light chain; NSE, Neuron-Specific Enolase; SIMOA, single-molecule array; SSEP, somatosensory evoked potential.

established,[25,104,105] with strong validation in multiple studies and proposed cutoffs and reporting guidelines.[10,106] In FTD, NfL can certainly be considered a valid biomarker useful to monitor disease progression and severity. However, the clinical diagnosis of FTD often proves challenging, due to the overlap of symptoms with those of other neurodegenerative conditions such as AD, especially in its frontal variant (fvAD) and in the early stages of disease. Studies have highlighted the overlap of behavioral and dysexecutive features characteristic of fvAD and bvFTD patients, leading to the frequent misdiagnosis of fvAD as bvFTD.[107] The presence of co-pathology AD after the age of 70 should also be considered. Therefore, NfL interpretation should require integration with other clinical data and biomarkers, as CSF AD biomarkers (Aβ42, Tau, pTau181) or amyloid PET.

The interest in MS is also well-advanced in terms of evidence.[108] In addition, blood NfL could represent a valuable prognosis marker in CA[109] with recent evidence suggesting superiority to the established biomarker neuron-specific enolase (NSE).[71] In various genetic conditions such as autosomal dominant Alzheimer disease (ADAD),[51] Down syndrome[51] or Huntington disease,[52] NfL levels show potential for early detection and monitoring of pre-symptomatic individuals; however, these applications require additional validation, which may be challenging due to the rarity of some of these diseases. For other COUs, such as peripheral neuropathy, Parkinsonism, or TBI, substantial additional validation studies will be necessary, emphasizing the need for further research to optimize its clinical application and timing.

TABLE 1H Reference sheet for PN

Clinical indications:
- Prognosis in GBS[77–79]
- Biomarker of chemotherapy-induced polyneuropathy[80–82]
- hATTR[83,84]
- Other neuropathies[85]

Population: Adult and children
- Consulting tertiary centers
- Patients with PN classified by clinical and laboratory-supported tests (e.g., neurophysiology, nerve biopsy).

Gold standard, other alternatives:
- History and examination by a qualified clinician identifying a PN
- Neurophysiology confirming electrophysiological neuropathy
- Nerve biopsy (where indicated)
- Genetic screening for familial forms

There is no unitary standardized diagnostic biomarker test specifically as a gold standard for peripheral neuropathy, as it is many things—see above.

Prescription:
- NfL quantification mostly in blood (lumbar puncture is not common in the COU)

Timing of NfL analysis:When the diagnosis is suspected or when the disease is present (GBS), for prognosis. Longitudinal assessment for mutation carriers.

Analytical aspect, cutoffs, and performances: See the section for all COUs.

Reported clinical performance:
In GBS, high sNfL is associated with a transfer to intensive care at an odds ratio of 2.4[86]
During oxaliplatin administration, sNfL levels increased with progression of PN at 6 months[82]
In all ATTR carriers who developed PN, sNfL increased before the onset of symptoms[84]

Reporting
Each disease has unique characteristics depending on the extent of PNS tissue affected, the specific parts of the PNS involved, and the rate of progression. The reporting needs, therefore to be adapted to the different PN.

Conclusion:
PN are diverse, with characteristics varying by extent, location, and progression of PNS involvement. NfL shows promise in specific conditions, including prognosis and early detection in different PN. NfL complements traditional diagnostic tools and requires tailored interpretation for each PN type.
Standardization and further research are needed to enhance its clinical utility in this COU.

Abbreviations: COU, context of use; GBS, Guillain-Barré syndrome; hATTR, hereditary ATTR amyloidosis; NfL, neurofilament light chain; PN, peripheral neuropathy; PNS, peripheral nervous system.

TABLE 1I Reference sheet for TBI

Clinical indications:
- Differential diagnosis (mild–moderate–severe TBI)[87]
- Prognosis (long-term outcome)[88]

Population: Adult and children
- Following TBI

Gold standard, other alternatives:
- CT imaging
- GFAP, UCH-L1
- Other alternatives: S100, NSE.

Prescription:
- Measurement performed preferably in blood
- Indication of trauma type (road traffic incident, incidental fall, sports injury)
- Indication of the delay between TBI and sampling.
- Glasgow Coma Scale and Score (3–8, 9–12, 13–14, 15)

For follow-up, neuro-imaging (CT, MRI): normal/pathological**Timing of NfL analysis**:At different time points after TBI.

Analytical aspect, cutoffs, and performances: See the section for all COUs.

Reported clinical performance:
ROC AUC of 0.89 to discriminate players who returned to play after concussion[87]
ROC AUC of 0.0.84, 0.92, and 0.92 for sNfL at 30 days to distinguish patients with mild, moderate, and severe TBI from controls[88]

Reporting:
NfL is not a good acute TBI marker, but it rises over days/weeks and only falls again after months, and sometimes remains above the control level even after years.
NfL is reported as a marker for long-term outcome and progressive neurodegeneration following TBI.

Conclusion:
NfL is not effective as an acute marker due to its delayed rise following TBI; however, its levels may provide valuable insights into long-term outcomes and progressive neurodegeneration associated with TBI. Nevertheless, additional studies are needed to further validate its clinical utility, optimize sampling strategies, and explore its potential applications across diverse patient populations and injury scenarios.

Abbreviations: AUC, area under the curve; COU, context of use; CT, computed tomography; GFAP, glial fibrillary acidic protein; NfL, neurofilament light chain; ROC, receiver operating characteristics curve TBI, traumatic brain injury.

Data supporting the interest in NfL originate from retrospective, cross-sectional, prospective, or real-life studies, depending on the COU, resulting in varying levels of evidence. There is a critical need to globally strengthen the level of evidence and establish cutoff definitions for different COUs to fully realize NfL's potential as a universal biomarker in neurology. Further collaborative efforts among laboratories and clinicians are essential to bridge these gaps and enhance their clinical utility.

Finally, it is noteworthy that although standardized reference values for NfL are currently lacking, several factors should guide its interpretation in clinical and research settings. Plasma NfL levels are influenced by physiological variables such as age and renal function. Levels tend to rise with age—especially after 60—likely reflecting increased prevalence of neuronal disease and comorbidities with age. Additionally, impaired renal clearance may lead to artificially elevated NfL levels, possibly due to reduced elimination via the kidneys.[110] Therefore, age and kidney function (e.g., eGFR or serum Cr) should be assessed alongside NfL, particularly in elderly or multimorbid patients.[4] NfL values

TABLE 1J Reference sheet for CJD

Clinical question:
- Diagnosis and prognosis of CJD[15,89–93]
- Monitoring prodromal stages in genetic forms (see also Table 1E)[53]

Population:
Adults with suspected CJD (characterized by rapidly progressive dementia of unknown etiology)

Gold standard, other alternatives:
Gold standard: neuropathological examination, international recommendations (clinical evaluation, prion RT-QuIC, neuroimaging, EEG, molecular diagnosis, PRNP genotyping)
Biological evidence seeding amplification assays (RT-QuIC/seeding assay)

Prescription:
- Measurement in blood and CSF
- Indication of the delay between sampling and the beginning of the clinical signs.

Timing of NfL analysis:
- at the time of CJD suspicion
- during the follow-up of mutation carriers

Analytical aspect, cutoffs, and performances: See the section for all COUs.
Reported clinical performance:
ROC AUC of sNfL between asymptomatic phase and disease onset in genetic CJD 0.88[94]
ROC AUC of CSF NfL between sporadic CJD compared to non-CJD 0.89[90]
ROC AUC of sNfL between sporadic CJD compared to the mixed neurological disease control group 0.91[91]

Reporting:
The report could highlight the increase in NfL concentration as an indicator of the transition to the clinical phase in mutation carriers. The high level of NfL associated with CJD cold also applies to the diagnostic element in favor of the disease when compared to differential diagnosis.

Conclusion:
NfL appears valuable for monitoring asymptomatic carriers. Measurement in blood, rather than in CSF as required for other biomarkers (such as tau, 14-3-3 protein, and RT-QuIC), represents a non-invasive and potentially valuable alternative for initial screening. However, a new tau biomarker (brain-derived tau) may be more relevant than NfL as a rapid first blood test for assessing RPD patients with suspected CJD.[93]

Abbreviations: AUC, area under the curve; CJD, Creutzfeldt–Jakob disease; COU, context of use; CSF, cerebrospinal fluid; NfL, neurofilament light chain; ROC, receiver operating characteristics curve.

should always be interpreted within a broader clinical and biological context, including disease phenotype, duration, and comorbidities, ideally using age- and renal function-matched control cohorts.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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