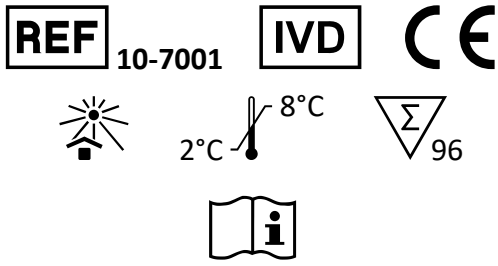
NF-light® (Neurofilament light) ELISA for CSF samples

Enzyme-Linked Immunosorbent Assay for quantification of Neurofilament light for CSF samples

Instructions for Use



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1. Revision history of instructions for use

Changes from the previous version **2021-11** to actual version **2026-03**
All Chapters – Updated
Chapter 5 – Updated and additional data
Chapter 7 – Additional Chapter: Warnings and Precautions
Chapter 10 – Updated material list
Chapter 12 – Updated / Additional information
Chapter 15 – Updated / Additional information
Chapter 16 – Updated / Additional information
Chapter 17 – Updated and additional data
Chapter 19 – Updated bibliography

2. Intended purpose

NF-light® ELISA is a non-automated in vitro diagnostic device intended for quantitative determinations of human Neurofilament light (NF-L) protein in cerebrospinal fluid (CSF). Increased NF-L levels indicate nerve cell degradation, and the result is used as an **aid to diagnosis** of neurological diseases such as amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), dementias and Parkinson's disease (PD). The results from this assay must be used together with other clinical observations and patient history as NF-L is an unspecific biomarker for neuronal damage. The intended test population is people > 18 years who are suspected of suffering from a neurological disease.

The kit is intended for professional use, i.e. should be used by clinical laboratory personnel trained in ELISA technology and in vitro diagnostic procedures.

3. Notice to user

If a serious incident occurs in relation to this device, the incident should be reported to the manufacturer and to the appropriate local competent authority of the member state in which the user and/or patient is established. To report to the manufacturer, see contact details at the end of this instruction.

4. Background

Neurofilaments are the main cytoskeletal constituents in neuronal cells. They are important for the maintenance of the neuronal calibre and morphological integrity, which affect the velocity and fidelity of neuronal transmissions. Three different neurofilament chains exist, named according to their size. These are Neurofilament light, medium, and heavy respectively. The Neurofilament light constitutes the backbone to which the heavier chains co-assemble, forming the neurofilament fibre [1]. Following injuries of nerve cells due to direct trauma or slow degenerative processes, the content of the cell is released into the surrounding compartment allowing quantitative determinations of the neuronal proteins. Increased levels of NF-L have been found in various degenerative diseases such as Amyotrophic lateral sclerosis, Alzheimer's disease, and Multiple sclerosis [2 – 4].

5. Method description

The UmanDiagnostics NF-light® ELISA assay is an enzymatic immunoassay designed for quantitative measurements of NF-L in human cerebrospinal fluid. The test uses two highly specific non-competing monoclonal antibodies [5]. The capture antibody is coated on a solid surface and binds the sample NF-L. The secondary/detection antibody is biotin conjugated and addition of HRP-conjugated Streptavidin allows for quantitative measurements by enzymatic turn-over of a colourless substrate (TMB) to a coloured product. The absorbance values can be correlated to the amount of NF-L in the sample by using a calibrator curve.

Calibrator curve quantification interval:	125 pg/ml – 2500 pg/ml
Calibrator curve interval:	50 pg/ml – 5000 pg/ml
LoB	16 pg/ml
LoD	25 pg/ml
LoQ	62 pg/ml
Precision: Intra-Assay CV%	< 3%
Precision: Inter-Assay CV%	< 6%
Incubation time:	2 hours and 30 minutes
Sample size:	50 µl/replicate
Minimum dilution of sample:	2x

6. Important information!

- The product should be used strictly in accordance with this instruction for use (IFU). Follow good laboratory practice and safety guidelines. Wear lab coats, disposable gloves, and protective glasses when necessary.
- In case of severe damage to the kit package, please contact your supplier in written form no later than one week after receiving the kit. Do not use damaged components. Please keep the damaged components stored for complaint-related issues. Lost vacuum for the plate has no negative effect on assay performance.
- NF-light® ELISA is for in vitro diagnostic use only and is not for internal use in humans or animals.
- Do not mix reagents of different lots.

7. Warnings and precautions ⚠

- There are no substances in the kit of animal or human origin that present a risk of infection.
- All samples to be analysed should be considered potentially contagious. Therefore, take appropriate safety measures when handling and disposing biological samples. In case of spillage, immediately disinfect with 0.5% sodium hypochlorite or equivalent.
- Dispose of all material which has been in contact with samples and reagents in accordance with country, state, and local regulations.
- **Warning (H290, H315, H319, P280, P305+P351+P338, P337+P313, P390)**
  Stop Solution may be corrosive to metals. Causes skin irritation. Causes serious eye irritation. Wear chemically resistant protective gloves and eye protection. IF IN EYES: Rinse cautiously with water for several minutes. If applicable and possible, remove contact lenses and continue rinsing. If eye irritation persists: Get medical advice/attention. Absorb spillage to prevent material damage. The Material Safety Data Sheet for this product is available on UmanDiagnostics website and can also be sent by email upon request.

8. Shelf-life and storage of reagents

Store the kit at + 2 – 8 °C and keep away from heat or direct sunlight. Do not freeze the components.
Reconstituted Calibrator and Positive Control should be used immediately and cannot be re-used.
Once opened, the kit should be used within 4 weeks.
An opened plate should be sealed with tape to avoid excess humidity and stored at + 2 – 8 °C.
The shelf-life of the kit is printed on the kit box label and can also be found on the included certificate of analysis (CoA).

9. Sample collection and storage

After lumbar puncture, the samples should be kept at - 80 °C in polypropylene tubes. Repetitive freeze-thawing should be avoided. The sample stability has been evaluated for 5 different clinical samples. The sample reactivity following different treatments was compared to the same sample stored at - 80 °C.

		Mean % of - 80 °C control	**Mean % interval**
Freeze-thawing	≤ 4 cycles	98.0	96 – 101
Storage	+ 5 – 8 °C ≤ 1 week	99.7	95 – 108
	24 h at RT (+ 22 °C)	100	91 – 106
	- 20 °C 1 month	95.8	89 – 109

10. Materials

Kit components provided:

Cap colour	Short name	Full name	Description	Quantity
N/A	Plate	Anti-NF-L Plate	Pre-coated with mouse anti-NF-L monoclonal antibody, covered with a lid and sealed in plastic pouch with desiccant.	12 x 8 wells
Grey	**Stop**	Stop Solution	Diluted H_2SO_4 (8% v/v).	1 x 6 ml
Black	**TMB**	TMB Substrate	Tetramethylbenzidine substrate.	1 x 12 ml
Black	**ELISA-Dil**	ELISA Diluent	Aqueous buffered solution with detergent.	1 x 40 ml
Red	**ConjDil**	Conjugate Diluent	Aqueous buffered biotin free stabilizing solution.	1 x 12 ml
Red	**Conj**	Conjugate	Streptavidin Horseradish peroxidase conjugate in aqueous buffered biotin-free stabilizing solution. Dilute according to label.	1 x 350 µl
Black	**Det**	Detector Ab	Biotin labelled anti-NF-L monoclonal antibody in aqueous buffered biotin-free stabilizing solution. Dilute according to label.	1 x 300 µl
Green	**bNFL-Cal**	bNF-L Calibrator	Reconstitute according to the vial label. (Contains bovine spongiform encephalopathy-, foot and mouth disease negative bovine material of German origin).	2 vials
White	**Pos Ctrl**	hrNF-L Positive Control	Recombinant Human NF-L, to be reconstituted according to the vial label.	2 vials
White	**Wash**	Wash Buffer	10x Aqueous buffered solution with detergent.	2 x 40 ml

Additional material provided:
15 ml tube for conjugate dilution, 2 pcs

Not included essential equipment:
Microtiter plate reader 450 nm (reference wavelength 620 – 650 nm)
Micropipettes 10 – 1000 µl
Vortex mixer
Orbital ELISA tabletop shaker (**800 rpm**)
Deionized water
Wash bottle, automated, or semi-automated microtiter plate wash system
Pipette tips and timer
Polystyrene or polypropylene tubes for calibrator and sample dilution

11. Assay procedure

Preparation and important notes:

- All assay reagents should be brought to room temperature (RT, + 18 – 25 °C) prior to use.
- The kit has been designed to be able to be used at two separate analysis occasions. If the kit is intended to be used at two occasions, not more than 500 µl extra volume of conjugate and detector antibody working solutions should be prepared. The conjugate and detector micro tubes should be centrifuged prior to use, to allow for sufficient reagent volumes at the second analysis occasion.
- It is advised to run samples and calibrators in duplicate. If large deviations occur between replicates, please re-assay.
- A plate lid is provided with the kit. This should be used to cover the plate during incubation steps, to protect from contamination. All incubation steps should be performed at room temperature.

- During the incubation steps, use an **orbital ELISA tabletop shaker** at **800 rpm**. **Agitation of the plate at 800 rpm is of UTMOST IMPORTANCE to obtain reliable results**. Incubation at a lower frequency will cause lowered absorbances and unreliable results.

- **Use the supplied 15 ml Sarstedt tube (62.554.502) when preparing the conjugate solution. Other tubes may have a negative impact on conjugate activity, causing the overall absorbance level to drop and the sample read-outs to be unreliable. Note however that reagent reservoirs may be used to facilitate pipetting in all steps.**

- Make sure there are no bubbles in the wells prior to measuring the absorbance.

Preparation of wash buffer 1x:
Dilute the total content of one **Wash** bottle with deionized water to a final volume of 400 ml. Diluted, unused **Wash** can be stored at room temperature and should be used within two months. The 10x **Wash** can appear opalescent due to high salt concentration (no effect on assay performance).

Reconstitution of calibrator and positive control:
Immediately before use, reconstitute the **bNFL-Cal** and **Pos Ctrl** according to the label on each respective vial with **ELISA-Dil.** Vortex briefly and keep in room temperature. **Pos Ctrl** should not be diluted further. **bNFL-Cal** and **Pos Ctrl** cannot be re-used. The reconstituted **bNFL-Cal** has a concentration of 5000 pg/ml. The concentration of the **Pos Ctrl** can be found on the CoA.

Preparation of calibrator dilution series:
A calibrator curve should be included on every plate analysed. The highest calibrator point (5000 pg/ml) is obtained by reconstituting one vial of lyophilized **bNFL-Cal** with the volume of **ELISA-Dil** indicated on the vial label. Label seven micro tubes, one for each calibrator point (that is 2500 pg/ml, 1250 pg/ml, 500 pg/ml, 250 pg/ml, 125 pg/ml, 50 pg/ml), and one for the zero calibrator, excluding 5000 pg/ml which is used directly from the vial. Dilute the reconstituted calibrator according to the table below using **ELISA-Dil**.

Make a serial dilution as described below.

Tube no.	Concentration pg/ml	Volume ELISA-Dil	Volume calibrator from tube no.
bNFL-Cal (Vial)	5000	Reconstitute with **ELISA-Dil** according to the Calibrator vial label	
1	2500	300 µl	300 µl (vial)
2	1250	300 µl	300 µl (1)
3	500	360 µl	240 µl (2)
4	250	300 µl	300 µl (3)
5	125	300 µl	300 µl (4)
6	50	360 µl	240 µl (5)
7	0	300 µl	0 µl

Assay overview:

Washing **3 x 300 µl**			
bNFL-Cal (Directly from vial and tubes no. 1 – 6) **Addition of 100 µl**	**ELISA-Dil** Zero Calibrator (tube no. 7) **Addition of 100 µl**	**Pos Ctrl** Directly from vial **Addition of 100 µl**	**CSF-samples / Internal Control sample** (1+1 dilution) **Addition of 100 µl**
Incubation 1 hour, 800 rpm			
Washing **3 x 300 µl**			
Addition of 100 µl Detector Ab 1x			
Incubation 45 minutes, 800 rpm			
Washing **3 x 300 µl**			
Addition of 100 µl Conjugate 1x			
Incubation 30 minutes, 800 rpm			
Washing **3 x 300 µl**			
Addition of 100 µl TMB			
Incubation 15 minutes, 800 rpm			
Addition of 50 µl Stop			
Read the plate at 450 nm (reference wavelength 620 – 650 nm) directly after adding the Stop Solution			

Detailed assay protocol:

1. **bNFL-Cal**, reconstituted and diluted according to the Calibrator dilution table and reconstituted **Pos Ctrl**, are ready to use (i.e., no further dilution should be made).
2. Dilute the CSF samples with equal amount (1+1) of **ELISA-Dil** to a total minimum volume of 210 µl.
3. Wash the wells to be used with **Wash** 1x (3 x 300 µl). Washing could be performed either by an automated washer or by manual pipetting. If washing manually, make sure to remove excess wash buffer between each wash by tapping the plate against absorbent paper. Remaining wash buffer and/or insufficient washing could affect the reactivity of the subsequent reagent.
4. Add 100 µl per well of the following: calibrator points (Directly from vial and tubes no. 1 – 6), zero calibrator (tube no. 7), positive control (vial), and samples. Add in duplicate.
   → Incubate 1 hour at RT with agitation (800 rpm).
5. Wash the wells with **Wash** 1x (3 x 300 µl), see point 3.
6. Directly before use, prepare the required volume (100 µl / well) of **Det 1x** by diluting the concentrated **Det** with **ELISA-Dil**. Mix thoroughly by inverting the tube or by vortexing.
   → Add 100 µl of freshly diluted **Det** to each well.
   → Incubate 45 minutes at RT with agitation (800 rpm).
7. Wash the wells with **Wash** 1x (3 x 300 µl), see point 3.
8. Directly before use, prepare the required volume (100 µl / well) of **Conj 1x** in the **supplied Sarstedt 15 ml tube** by diluting according to the vial label with **ConjDil** to 1x. Mix thoroughly by inverting the tube or by vortexing.
   → Add 100 µl of newly diluted **Conj** to each well.
   → Incubate 30 minutes at RT with agitation (800 rpm).
9. Wash the wells with **Wash** buffer 1x (3 x 300 µl), see point 3.
10. Add 100 µl of **TMB** to each well.
    → Incubate 15 minutes at RT with agitation (800 rpm).
11. Add 50 µl of **Stop** to each well and read the absorbance at 450 nm (reference wavelength 620 – 650 nm).

    The Stop Solution contains diluted sulfuric acid and is corrosive.

12. Calculation of results

The results can be calculated automatically by using an immunoassay software package. **A $1/y^2$– weighted 4-parameter algorithm provides the best curve fit** (see a typical calibrator curve below). If no such immunoassay software is available, the concentration of NF-L is calculated from plotting average OD at (λ450 minus λ620 – 650 reference) against the known calibrator concentrations in e.g. Excel. *Please note that such a model will not be as accurate in the lower end of the curve as a 4 parameter model*. Plot a lin-log calibrator curve from the absorbance (y-axis) and the concentration (x-axis). Add a linear trendline and use the trendline equation to manually calculate the concentration of your samples from their respective absorbance.
For all calculations, please note the following:

- The zero calibrator absorbance should not be subtracted from the measurement data. It should be used only as an indicator of the background levels, which should be compared to expected values on the CoA.
- **The sample read-outs from the curve must be multiplied by the dilution factor of the sample in order to obtain the concentration in the original sample**.
- The quantification interval of the curve is between 125 and 2500 pg/ml. Samples that fall above this interval should be diluted accordingly and re-analysed. Samples that fall below this interval are too low to be accurately quantified by this method. See section 12 for more details.

The concentration from the calibrator curve should be multiplied by 2 to obtain the concentration in the sample (due to dilution 1+1 before analysis).

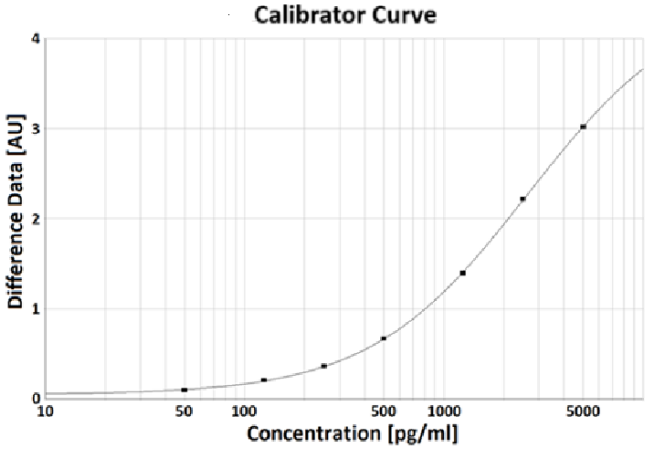
13. Quality control

In order to verify the assay performance, the following criteria should be fulfilled for each analysis occasion. Note that absorbances refer to difference data (λ 450 minus λ reference).

- The curve should have an appearance as shown in the figure below.
- The **Pos Ctrl** should have a concentration within the acceptance criterion stated on the CoA (the concentration should be determined directly from the calibrator curve, do not multiply by any dilution factor).
- The absorbance for 5000 pg/ml should be > 2.0 AU.
- The zero calibrator absorbance should be < 0.1 AU.

Internal control samples from healthy controls and/or samples containing elevated levels from patients should be established if the kit is used in clinical routine analysis. It is recommended that at least one control sample in the concentration interval 1000 – 3000 pg/ml is established. Control samples can be prepared by pooling samples of cerebrospinal fluid and analysing the pool repeatedly to establish concentration levels and acceptance criteria. The pool should be aliquoted and stored at - 80 °C.

Below, a typical calibrator curve at time of release is shown, and approximate absorbance values given.



Calibrator level (pg/ml)	% of signal for 5000 pg/ml
5000 (anchor point)	100
2500	71
1250	44
500	20
250	11
125	5.7
50 (anchor point)	2.7

14. Measuring interval

The calibrator curve covers the interval 50 – 5000 pg/ml NF-L. The 5000 pg/ml and 50 pg/ml calibrators serve as anchor points and quantification should be performed within the interval 125 – 2500 pg/ml of the calibrator curve, taking into account the dilution factor (2) of the sample, this corresponds to 250 – 5000 pg/ml of NF-L in the original sample. Extrapolation beyond the curve is not allowed with the implication that samples outside of the curve must be further diluted and re-measured.

15. Limitations of use

For clinical samples, the following criteria should be taken into consideration:

- In case of any diagnostic procedure, the results from this assay must be interpreted together with other clinical findings.
- Do not compare results from this assay with those obtained using kits from other manufacturers.
- NF-L levels are markedly elevated in atypical PD compared to PD [6].
- Different types of dementia are associated with different levels of NF-L [7].

Potential interference from heterophilic antibodies might cause erroneous results. Patients who have been regularly exposed to animals or have received immunotherapy or diagnostic procedures utilizing immunoglobulins or immunoglobulin fragments may produce human anti-animal antibodies, e.g. HAMA, that interfere with this immunoassay. Another potential source of interference is if patients have received biotin therapy. Carefully evaluate results if the samples are suspected of having these types of interferences.

16. Clinical performance

Levels of NF-L in CSF have been analysed for 35 different neurological and psychiatric conditions using UmanDiagnostics NF-light® ELISA kit. The meta study was based on 47 data sets and included data from 10 059 individuals. The results showed that NF-L levels were elevated when compared to healthy controls for most of the conditions. The highest levels of NF-L were found in Cognitively impaired HIV-positive individuals, ALS, frontotemporal dementia, and Huntington disease [8]. Other studies have further demonstrated the clinical utility of NF-L for ALS [9], dementias [10], MS [11] and PD [12].

The levels of healthy controls are dependent on age and gender. In healthy controls, NF-L levels in CSF are known to increase with age due to neuronal degradation. Experience from clinical routine analysis since the early development of the product has resulted in the following cut-off levels:

Age		**Reference value**
Adults	< 30 years	< 380 pg/ml
	30 – < 40 years	< 560 pg/ml
	40 – < 60 years	< 890 pg/ml
	≥ 60 years	< 1850 pg/ml

The results are only valid if the test has been performed according to the instructions for use and must be correlated to other clinical observations and diagnostic tests. The user must strictly adhere to the rules of GLP (Good Laboratory Practice) or other applicable standards/laws.

17. Performance characteristics

Traceability of Calibrator

The test is standardized using internal quality control samples of cerebrospinal fluid from patients (pooled samples). No reference method or standard reference material is commercially available. Below, typical batch-to-batch variation for the absorbance and QC samples are shown.

Kit lot	**Abs 5000 pg/ml (AU)**	**Conc. QC sample 1 (pg/ml)**	**Conc. QC sample 2 (pg/ml)**	**Conc. QC sample 3 (pg/ml)**
70940/70950	3.26	2179	1332	-
70966/70976	3.23	2289	1458	2303
70986/70996	3.16	2242	1475	2307
71017/71027	3.29	2169	1415	2196
71037/71047	3.22	-	1475	2200
71068CE/71069RUO	3.18	2270	1471	2253
71092CE/71093RUO	3.24	2309	1448	2223
Mean:	**3.23**	**2243**	**1439**	**2247**
SD:	**0.04**	**58**	**52**	**49**
CV:	**1.4%**	**2.6%**	**3.6%**	**2.2%**

Analytical Specificity

Interference and cross-reactivity seen in the table below were determined according to Clinical and Laboratory Standards Institute (CLSI) guideline EP07 [13].

Substance	**Concentration of substance**	**Bias due to substance**
Biotin	191 ng/ml	3.8%
Haemoglobin	27 ng/ml	6.4%
Direct bilirubin	3 mg/dl	3.1%
Indirect bilirubin	2 mg/ml	0.1%
Albumin	0.3 g/dl	4.6%
Neurofilament Medium	50000 pg/ml	-0.7%
Neurofilament Heavy	50000 pg/ml	0.5%
Tau	2500 pg/ml	0.7%

Analytical Sensitivity
Limit of Blank (LoB) 16 pg/ml.
Limit of Detection (LoD) 25 pg/ml.
Limit of Quantitation (LoQ) 62 pg/ml.
LoB and LoD were determined as described in CLSI guideline EP17-A2 [14]. LoQ was determined using blank results obtained during LoB assessment and calculated as $mean_{blank} + 10 \times SD_{blank}$.

Precision
Intra-assay precision: 2.8% (Concentration interval 239 – 4223 pg/ml).
Inter-assay precision: 6.0% (Concentration interval 242 – 4938 pg/ml).
Inter-lot precision: 1 of 5 Samples 19.2% (304 pg/ml), 4 of 5 Samples 4.7% (730 – 4753 pg/ml).
Intra-assay precision was determined as the average % CV from 20 replicate measurements of five CSF samples.
Inter-assay precision was determined as described in CLSI guideline EP05-A3 [15]. Inter-assay samples were assayed in a 5x2x2 design with three separate lots. The average of the results is presented.
Inter-lot precision was determined using results obtained during inter-assay assessment and was calculated as the % CV for the respective samples. The maximum self-allowed inter-lot precision is CV ≤ 20 % for samples < 500 pg/ml and CV ≤ 10 % for samples ≥ 500 pg/ml.

Dilution linearity
There is dilution linearity in the concentration interval 53 – 21 000 pg/ml.

Parallelism
Dilution of CSF samples follows the same trend as dilution of spiked samples. Dilution does not affect concentration determination of endogenous NF-L in the investigated concentration interval 171 – 6900 pg/ml.

Recovery
The recovery in the investigated NF-L concentration interval 1700 – 6800 pg/ml is between 88 and 108 %.

Accuracy
It has not been possible to compare the results for this assay with any other method as no CE marked kit for CSF or standard reference material for NF-L are available.

18. Warranty

The performance data presented here was obtained using the described assay procedure. Any change or modification in the procedure not recommended by UmanDiagnostics AB may affect the results, in which event UmanDiagnostics AB disclaims all warranties, expressed, implied or statutory, including the implied warranty of merchantability and fitness for use. UmanDiagnostics AB and its authorized distributors, in such event, shall not be liable for any damages, whether direct, indirect, or consequential.

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20. Symbols used

REF	Catalogue number
	Use by date
LOT	Lot number
	Contains sufficient for <n> tests
CONTROL +	Positive control
	Do not re-use
IVD	In Vitro Diagnostic medical device
	Consult instructions for use
	Keep away from sunlight
	Temperature limit
	Manufacturer
	Country of manufacture
	Caution!
	Harmful

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