Application of serum NfL and GFAP as Biomarkers in the Clinical Management of Multiple Sclerosis (NeuroFilMS): A Protocol of a prospective observational study

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Introduction

Background: Multiple sclerosis (MS), the most common autoimmune disease of the CNS, is driven by inflammatory and neurodegenerative processes leading to heterogeneous disease courses. Fluid biomarkers play an increasingly important role in the management of neurological disorders, aiding in diagnosis, prognosis, and therapeutic monitoring. Advances in ultrasensitive assay techniques have enabled precise quantification of serum neurofilament light chain (sNfL) (1-3) and serum glial fibrillary acidic protein (sGFAP) (5-6), highlighting their potential as dynamic biomarkers for detecting neuroaxonal injury, disease activity and worsening progression in MS.

Objectives

In the NeuroFilMS study, sNfL is being investigated prospectively as a prognostic biomarker for clinical and radiological disease activity in relapsing MS, while sGFAP is retrospectively explored as a marker of disease progression. The aim is to assess whether longitudinal monitoring of sNfL can inform diagnostic and therapeutic decisions in treatment of people with MS (pwMS) and whether retrospective sGFAP measurements provide additional insights into disease progression. The study additionally aims to evaluate the comparability of different assay methods. Specific objectives include:

1.To determine the association of sNfL and sGFAP levels with clinical and radiological disease activity and disability progression.
2.To assess the predictive value of sNfL for treatment response under different DMTs.
3.To evaluate the feasibility of integrating sNfL measurement into routine clinical care.

Patients and Methods

Study Design

NeuroFilMS is a prospective, observational, multicenter study that will be conducted across multiple MS study centers participating in the German Multiple Sclerosis Registry setup by the German MS Society ("MS Register"). (4) The study aims to enroll 1,500 pwMS diagnosed with relapsing MS. Participants will be randomized in a 2:1 ratio (n=1,000 vs. n=500) to either immediate sNfL reporting or delayed sNfL reporting to treating physicians, in order to evaluate how sNfL availability influences therapeutic decision-making in routine healthcare regarding diagnostics and therapy decisions (Figure 1).

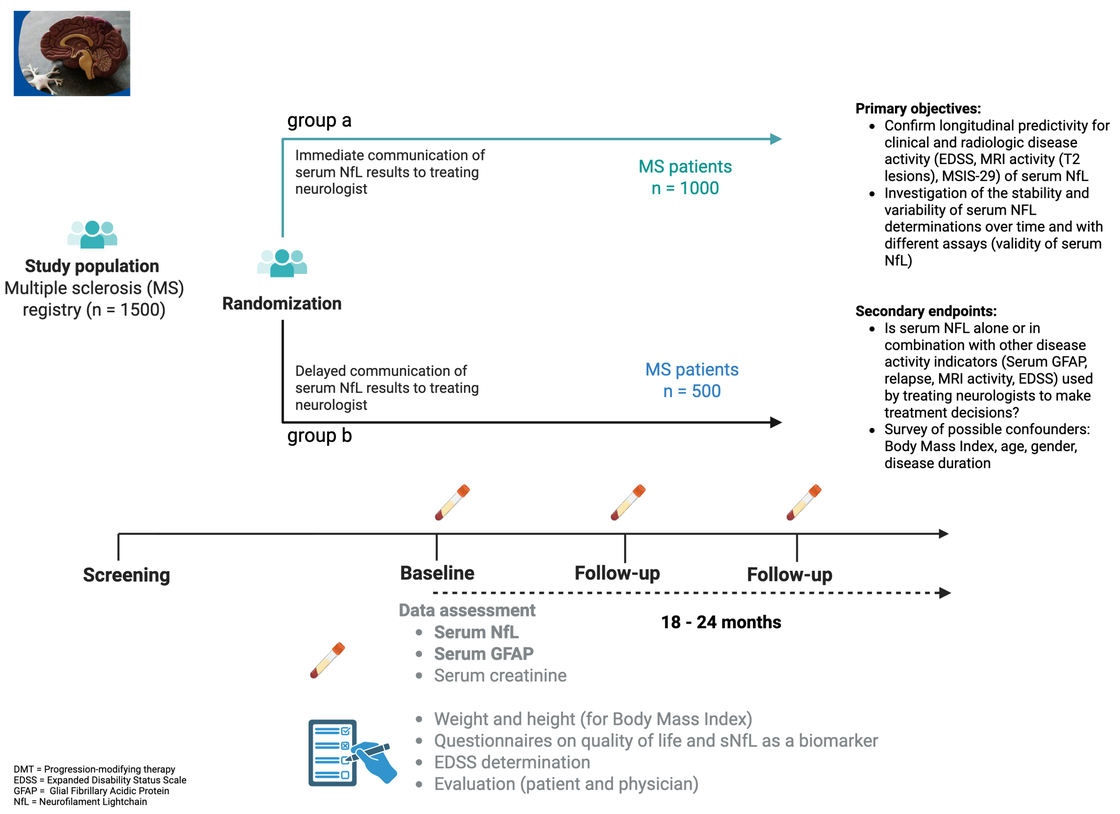

Figure 1: Study Design of the NeuroFilMS Study.

Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
- Age between 18 and 60 years	- Non-relapsing MS course
- Confirmed diagnosis of relapsing MS (RRMS or SPMS)	- Age below 18 or above 60 years
- Written informed consent for participation in both the sNfL study and the MS Registry	- Inability or unwillingness to provide written informed consent
- Stable disease-modifying therapy for at least six months or no DMT in the past six months	- Unstable treatment (recent DMT change within the past six months)
- Inclusion of de novo patients (directly after diagnosis) is permissible	- Significant comorbid conditions that may interfere with study assessments or biomarker measurements
	- Pregnant or breastfeeding women*
	-Traumatic brain injury or severe accident in the last 3 months before inclusion
	- Current desire to have children
	- Participation in interventional clinical trials**

*Pregnancy: Women who are pregnant or breastfeeding at the time of enrollment will be excluded to avoid potential confounding effects on biomarker levels.

**Concurrent participation in other studies: while participation in multiple observational studies is permitted, patients enrolled in interventional clinical trials will be excluded to prevent overlapping effects of different treatments on study outcomes.

Table 1: Inclusion and Exclusion Criteria

Primary Outcomes

- **Longitudinal predictivity of sNfL and sGFAP for clinical and radiologic disease activity (EDSS, MRI T2 lesions)**
- **Stability and variability of sNfL over time and between different assays**

Secondary Outcomes

- Does sNfL influence treatment decisions, alone or in combination with other disease activity indicators (relapses, MRI acitivity, EDSS)?
- Confounder survey: BMI, age, gender, disease duration
- Questionnaires (evaluation of sNfL use in healthcare (patients and physicians), HAQUAMS, MSIS-29)

Ethics

The study has received ethical approval by the Clinical Ethics Committee Charité (EA4/136/24) at 01.10.2024 and will be conducted in accordance with the provisions of the Declaration of Helsinki and the guidelines for good clinical practice set forth by the International Conference on Harmonization. The study is registered at Germany Registry for Clinical Studies, DRKS00034337 at 11.04.2025.

Results

The following study centers are currently participating in the NeuroFilMS study and as of 12 September 2025, 159 patients have been recruited:

center	name
1	Charité - Universitätsmedizin Berlin, outpatient clinic for multiple sclerosis ("MS-Ambulanz Charité CCM")
2	Stuttgart: Neurologicum am Berliner Platz
3	Charité - Universitätsmedizin Berlin, Hochschulambulanz der Charité Berlin Buch, ECRC
4	Krankenhaus der Barmherzigen Brüder Trier, Abteilung für Neurologie und Neurophysiologie
5	Immanuel Klinik Rüdersdorf – Multiple Sclerosis Outpatient Clinic ("MS-Ambulanz")
6	Bad Homburg: meinmedicum MVZ; Dr. Schöll, Dr. Steidl & Kollegen GbR
7	Klinikum Ibbenbüren, Klinik für Neurologie
8	Pforzheim: Praxis für Neurologie und Psychiatrie
9	Universitätsklinikum Mannheim GmbH, Klinik für Neurologie
10	NeuroMed Campus Nelles, Köln
11	St. Josefs-Krankenhaus Potsdam
12	Universitätsklinikum Heidelberg, Neurologie

Conclusions

Expected Impact: There is a paucity of validated serum biomarkers for the precise assessment of disease activity and degeneration in MS. sNfL and sGFAP have the potential to be cost-effective, easily accessible, and low-burden biomarkers, potentially enabling faster and more precise therapeutic decisions. Additionally, the study will evaluate the intra-individual variability of sNfL measurements over time and across different laboratory testing methods, ensuring its robustness for clinical use.

Conclusion: sNfL and sGFAP have the potential to serve as cost-effective, biomarkers in the future, contributing in a timely manner to diagnostic and therapeutic decision-making in relapsing MS.

Disclosures

RR, SS, AR and LSB receive funding from a Novartis research grant. AS has no personal pecuniary interests to disclose, other than being the lead of the German MS Registry, which receives (project) funding from a range of public and corporate sponsors, recently including The German Innovation Fund (G-BA), The German Retirement Insurance, The German MS Trust, The German MS Society, Bristol Myers Squibb, Merck Healthcare Germany GmbH, Novartis Pharma GmbH, Roche Pharma AG and TG Therapeutics/Neuraxpharm. PS received speaker's honoraria, travel support and/or served on advisory boards by Alexion, Roche, and UCB. MN reports research support from argenx, Cellerys, Merck (EMD Serono), Novartis, neuraxpharm and Roche. HWR and LS received speaker fees, research support, travel support, and/or served on advisory boards by Argenx, Neuraxpharm, Merck, Roche, Novartis. JK received speaker fees, research support, travel support, and/or served on advisory boards by Swiss MS Society, Swiss National Research Foundation (320030_189140/1), University of Basel, Progressive MS Alliance, Bayer, Biogen, Bristol Myers Squibb, Celgene, Merck, Novartis, Octave Bioscience, Roche, Sanofi. HT received honoraria as a consultant/speaker and/or for events sponsored by Alexion, Bayer, Biogen, Bristol-Myers Squibb, Celgene, Diamed, Fresenius, Fujirebio, GlaxoSmithKline, Horizon, Janssen-Cilag, Merck, Novartis, Roche, Sanofi-Genzyme, Siemens, Teva and Viatris. No conflicts are relevant to the study. FP served on the scientific advisory boards of Novartis and MedImmune; received travel funding and/or speaker honoraria from Bayer, Novartis, Biogen, Teva, Sanofi-Aventis/Genzyme, Merck Serono, Alexion, Chugai, MedImmune, and Shire; is an associate editor of Neurology: Neuroimmunology & Neuroinflammation; is an academic editor of PLOS ONE; consulted for Sanofi Genzyme, Biogen, MedImmune, Shire, and Alexion; received research support from Bayer, Novartis, Biogen, Teva, Sanofi-Aventis/Genzyme, Alexion, and Merck Serono; and received research support from the German Research Council, Werth Stiftung of the City of Cologne, German Ministry of Education and Research, Arthur Arnstein Stiftung Berlin, EU FP7 Framework Programme, Arthur Arnstein Foundation Berlin, the Guthy-Jackson Charitable Foundation, and the National Multiple Sclerosis Society (NMSS). FP is also supported by the Deutsche Forschungsgemeinschaft (DFG, Excellence Cluster 257), the Bundesministerium für Bildung und Forschung (Competence Network Multiple Sclerosis, KKNMS), and the Guthy-Jackson Charitable Foundation.
Funding statement/ Acknowledgements: The study is supported by Novartis and Roche. We thank all participating patients and study centers.

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ePoster Number P1545