Guidelines for collaborating studies on biomarkers within the BIOMS-eu network

Please fill in the following points and sustain your arguments with data and references.

To be completed by BioMS-eu:
Date of receipt proposal by BioMS-eu: 24th November 2022
BioMS-eu project number: BIOMS-2022_1

1. Name and address of applicant: Ahmed Abdelhak (UCSF/ University of Ulm) and Hayrettin Tumani (University of Ulm)

2. Application date: Nov. 24.2022

3. Title and project description

Participant-level meta-analysis on the predictive value of blood GFAP in Progressive Multiple Sclerosis

Reliable prediction of disability accumulation is a significant unmet need in people with progressive multiple sclerosis (pwPMS). Numerous clinical, MRI, and other imaging modalities failed to reliably reflect and predict confirmed disability progression (CDP) in MS in general, not to mention pwPMS. Body fluid biomarkers hold the potential to reflect the contribution of specific pathophysiological components to CDP. One of the most promising biomarkers, glial fibrillary acidic proteins (GFAP), has shown a consistent elevation in PMS (compared to relapsing MS) and association with disease severity parameters. Most importantly, initial studies revealed promising predictive value for baseline GFAP in regard to future CDP in a number of independent cohorts. However, those initial results were hampered by the limited number of patients with primary or secondary PMS.

In this project, we propose leveraging the available cohorts into a single, large, participant-level meta-analysis exploring the predictive value of blood GFAP for CDP (with or without imposed relapse activity) in pwPMS. Participating centers will be asked to provide blood GFAP values, longitudinally available EDSS scores, and another optional set of clinical and imaging data.

4. Description of methods:

a. Description of assay characteristics, including intra- and inter-assay CV, linearity, recovery, limit of detection, batch-to-batch reproducibility (max 0.5 page).

The current gold standard GFAP assay is the commercial assay from Quanterix (in singleplex or multiplex kits). Blood GFAP values measured by any of those assays can be included in the analysis.

b. What kind of material (CSF, serum, plasma, DNA, urine)

The analysis will include available GFAP data from serum or plasma. Centers willing to participate in the study will have options to either measure GFAP values using the commercial GFAP assay from Quanterix (in singleplex or multiplex kits) or send their blood samples to the University Hospital of Ulm (EU), or the University of California San Francisco (USA) for GFAP measurement.

Diagnoses, Number of patients per patient group, type of controls (Teunissen et al. MSJ 2013), rationale behind this number and power-analysis. What is the minimal number per patient group that a center should provide?

Diagnosis: Primary (McDonald criteria 2017) or secondary progressive MS (either clinical or based on Lohrscheider criteria). Cases labeled "RRMS" by the treating physician can be included if they already fulfill the following Lohrscheider criteria BEFORE the date/visit of sample collection: Disability progression of 1 EDSS point (EDSS ≤ 5.5) or 0.5 EDSS points (EDSS ≥ 6.0) in the absence of a relapse, Minimum EDSS = 4.0, Pyramidal Functional systems score = 2.0, Confirmed 3 months of progression. No controls will be needed for this analysis. A minimum follow-up period of one year (with at least 3x longitudinally collected EDSS scores) is required.

Treatment: treated and untreated/ treatment-naïve pwPMS will be included in this analysis. Statistical consideration will be applied to address the effect of the treatment category on CDP and GFAP levels.

The minimum number needed per center will be 25 patients (to facilitate center recruitment while aiming to have a sufficient sample size. The University of Ulm (for the EmBioProMS study group) will participate with GFAP values from > 200 PMS patients.

d. Clinical data (duration or severity of disease, MRI scan etc.)

Obligatory:

- At least 12 months of follow-up with three EDSS scores with at least 3 months between each are required. Longer follow-ups are preferred.

- History and date of relapses, if any.

- DMT treatment at sampling and during the follow-up period.

- Data regarding the GFAP kit used for the measurement and the machine (HD-1/ HD-X) to correct for any less characterized analytical variations that are unknown.

Optional:

- MRI parameters: T2 lesion count (volume in mm3 if available) and the number of contrast-enhancing lesions at the time of sample collection.

- Body mass index at the time of measuring GFAP/ sample collection.

e. Pre-analytical requirements of the samples (-20 °C, -80 °C). Effect of freezing/thawing. Two or more times, thawed material may be supplied unless convincing arguments for the negative effects of thawing.

- The analysis focuses on available GFAP values. If centers wish to send samples to measure, we will ask for serum/ plasma to be stored at -80. Freezing/thawing has been shown to have minimal effect on GFAP values in serum

f. Sample volume needed.

- for new measurements ONLY: 100 µl is the minimum required volume. 200 µl is preferred (in case of repetition of the measurements due to high %CV in the initial run). Otherwise the analysis aims to leverage available GFAP values.

5. Sample handling at the investigating center:

a. Expected storage time of the samples in your lab until the study is finished.

- ~ 3 months

b. Are samples being sent back to respective participating centers after the study is finished?

- Delivered volumes are expected to be consumed for any new GFAP measurements. Therefore, there will be no need to send residual volumes (~10-20 µl) to the centers unless explicitly required by the centers.

6. Names of researchers and/or technicians participating.

- Ahmed Abdelhak and Hayrettin Tumani will be coordinating the analysis. PIs from the participating centers are welcome to contribute to the initial data analysis and statistical consideration. All participating PIs will be invited to help design and draft the final manuscript.

7. Please describe in detail how the participating centers will be compensated for their input (e.g. financial compensation (price per sample?), compensation in natura, sharing intellectual property, co-authorship (which position?)).

- co-authorship will be offered to each participating center (2 authorships). A third co-authorship will be offered if a center contributes with more than 50 samples. Statisticians involved in the analysis will be offered co-authorship, regardless of the number of co-authorships offered to their center. All steering committee members will be added as co-authors unless they state otherwise. The positions will be determined based on the number of samples contributed to the final analysis.

8. Intention to publish in international refereed journals. This should be confirmed.

- we confirm the intention to publish in a high-impact journal giving the anticipated high relevance for clinical practice and clinical trials design.

9. Procedure:

Within two weeks after receipt of the research proposal, the steering committee of BioMS-eu will give their recommendation for collaboration. Next, BioMS-eu members will be invited by the BioMS-eu steering committee to participate in the study.

In case of financial compensation, each member will propose a price per sample to the BioMS-eu management. Next, one uniform price will be established and discussed with the party that requests for samples. Collaborative agreements will be made with every participant. 10-20% overhead for BioMS-management will be included in the price. Copies of agreements will be sent to the BioMS-eu management.

10. General principles:

a. Each BioMS-eu center can decide to participate in a particular study.

b. The study should be in agreement with the aims of BioMS, i.e. obtaining biomarkers for diagnosis, prognosis and therapy response in MS and related diseases.

c. The legal requirements for the study must be met by all participating centers (ethical vote, MTA, DTA, etc.).

d. Each center has the responsibility to check if collaboration with a commercial party is possible under the current ethical protocols and can decide for collaboration likewise.

e. Samples and patient data have been collected according to the BioMS-guidelines (Teunissen et al, Neurology 2009).

f. Please do consider the possibility that assays can be performed in the laboratories of the BioMS-eu partners. This will facilitate performance in agreement with ethical guidelines of several partners or obtaining ethical permission and reduce the costs.

g. Samples will be provided coded, and pseudonymized or anonymized clinical data will be shared at exchange of raw data.

h. If many centers are willing to participate with equal quality samples, prioritization will occur on a first come first serve basis.