Large-scale Serum Proteomic Profiling Identifies Novel Biomarkers of Disability Progression in Multiple Sclerosis: Insights from the Graz MS Study

Gargi Datta[1], Elisa Toy[1], Maria Martinez-Serrat[2,3], Shannon McCurdy[1], Alexander Hari[1], Srushti Tiwari[1], Matt Burrill[1], Jonathan Verrier[1], Cansu Tafrali[2,3], Rina Demjaha[2,3], Daniela Pinter[2,4], Bettina Heschl[2], Anna Damulina[2,3], Edith Hofer[5], Stefan Ropele[2], Christian Enzinger[2], Ferhan Qureshi[1], Wayne Hu[1], David M. Brazel[1], Terrie Livingston[1], Michael Khalil[2,3]

[1]Octave Bioscience, Inc, Menlo Park, CA, USA. [2]Department of Neurology, Medical University of Graz, Graz, Austria [3]Neurology Biomarker Research Unit, Medical University of Graz, Graz, Austria [4]Research Unit for Neuronal Plasticity and Repair, Medical University of Graz, Austria [5]Institute for Medical Informatics, Statistics and Documentation, Medical University of Graz, Austria

P1345

Introduction

Large-scale proteomic platforms enable high-dimensional profiling that can identify novel biomarkers of disease progression beyond conventional targeted approaches. The Graz MS cohort evaluates clinical, neuroimaging parameters and biochemical dimensions of MS to uncover mechanisms driving disease progression.

Objectives

Identify serum proteomic biomarkers associated with MS disability progression in the Graz MS study.

Methods

Data from a longitudinal observational cohort of 90 MS patients reflecting real-world clinical practice (561 serum samples) were analyzed across Alamar NULISAseq (CNS 120 + Inflammation (INF) combined; 380 biomarkers) and Olink Reveal (1034 biomarkers) panels to generate log2 relative quantifications.[1,2,3]

Confirmed disability worsening (CDW) was defined with a 6-month Expanded Disability Status Scale (EDSS) confirmation period.[4]

Number of samples		561
Number of patients		90 (one without baseline)
Age at baseline	Mean ± sd (range)	32 ± 8 (18-50)
Sex (%)	Female	56 (63%)
	Male	33 (34%)
EDSS	Median (range); IQR	1.5 (0-7); 2.5 (0-2.5)
Had EDSS worsening	Y	28 (31.5%)
	N	61 (68.5%)
Had a CDW event	Y	21 (23.6%)
	N	68 (76.4%)
Time to first CDW in years	Median (range); IQR	2.8 (0.9-13.4); 5.3 (1.9-7.2)

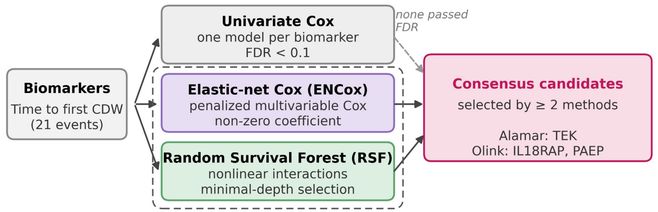
Table 1: Patient Demographics

References: [1] Ma XJ, et al. Development of NULISA™ CNS Disease Panel 120 for comprehensive proteomic profiling of neurodegenerative diseases. Alzheimers Dement. 2025 Jan 9;20(Suppl 2):e089847.
[2] Alamar Biosciences. NULISAseq™ Inflammation Panel AQ: Absolute Quantification for Comprehensive Profiling of Immune and Inflammatory Biomarkers. 2025. Alamar Biosciences, Fremont, CA
[3] van der Burgt YEM, et al. Brief Evaluation of Olink Reveal Proximity Extension Assay for High-Throughput Proteomics: A Case Study Using NIST SRM 1950 and Two Spike-In Protein Standards. J Proteome Res. 2025 Oct 3;24(10):5292-5296.
[4] Kappos L, et al. Contribution of relapse-independent progression vs relapse-associated worsening to overall confirmed disability accumulation in typical relapsing multiple sclerosis in a pooled analysis of 2 randomized clinical trials. JAMA Neurol. 2020;77(9):1132-1140.

Disclosure: G. Datta, E. Toy, S. McCurdy, A. Hari, S. Tiwari, J. Verrier, W. Hu, D. Brazel, T. Livingston,are an employee of Octave Bioscience. M. Martinez-Serrat: nothing to disclose. C. Tafrali has received travel funding and speaker honoraria from Merck. R. Demjaha has received travel funding from Janssen, Novartis and Sanofi. D. Pinter is a member of the advisory board for "Cognition and MS" for Novartis and has received speaking honoraria from Biogen, Novartis, MedAhead and Bristol-Myers Squibb. B. Heschl: nothing to disclose. A. Damulina has participated in meetings sponsored by, received speaker honoraria or travel funding from Sanofi-Aventis, Novartis and Janssen. E. Hofer: nothing to disclose. S. Ropele: nothing to disclose. C. Enzinger has received funding for traveling and speaker honoraria from Biogen Idec, Bayer Schering Pharma, Merck Serono, Novartis, Genzyme and Teva Pharmaceutical Industries Ltd./Sanofi-Aventis, Shire; received research support from Merck Serono, Biogen Idec, and Teva Pharmaceutical Industries Ltd./Sanofi-Aventis; and serves on scientific advisory boards for Bayer Schering Pharma, Biogen Idec, Merck Serono, Novartis, Genzyme, Roche, and Teva Pharmaceutical Industries Ltd./Sanofi- Aventis. M. Khalil has received travel funding and speaker honoraria from Bayer, Biogen, Novartis, Merck, Sanofi and Teva and serves on scientific advisory boards for Biogen, Bristol-Myers Squibb, Gilead, Merck, Novartis, Alexion, Amgen and Roche. He received research grants from Biogen, Novartis and Teva.

CDW and EDSS worsening were assessed using statistical and machine learning approaches. All models were adjusted for age, sex, and DMT. False Discovery Rate (FDR) correction was applied for multiple testing (FDR<0.1).

- **Confirmed Disability Worsening |** Biomarker-CDW associations were assessed using three methods:



- **EDSS worsening |** Per-biomarker ordinary least squares (OLS) models identified biomarkers differentially abundant between patients with and without EDSS worsening at first worsening or last visit.

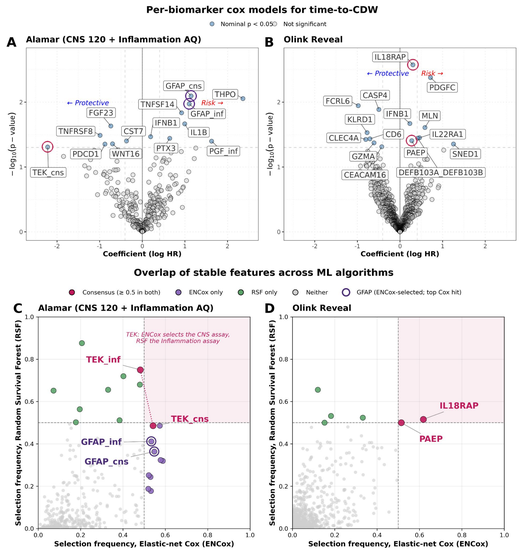


Figure 1: Biomarker associations with time to CDW. (A, B) Per-biomarker Cox models for Alamar and Olink; dashed line, p = 0.05. (C, D) Bootstrap selection frequencies for ENCox and RSF; dashed lines, 0.5 threshold. Crimson, consensus candidates selected by both methods; purple ring, GFAP.

Results

Participants had a mean age 32 years, follow-up 9.4 years, 63% female (Table 1).

- **Confirmed Disability Worsening |** In Olink, IL18RAP (SF_{ENCox}=0.62, SF_{RSF}=0.52) and PAEP (SF_{ENCox}=0.51,SF_{RSF}=0.50) were consensus candidates across ENCox and RSF; IL18RAP was also the top Cox hit (HR=1.4[1.1,1.7], p<0.01, FDR>0.2). In Alamar, TEK (SF^{CNS}_{ENCox}=0.54, SF^{INF}_{RSF}=0.75) was a consensus candidate. GFAP was selected by ENCox (SF^{CNS}_{ENCox}=0.55; SF^{INF}_{ENCox}=0.53) and was the top Cox hit for both panels (CNS: HR=3.1 [1.4, 7.3]; INF: HR=3.0 [1.3, 7.0]; both p<0.05, FDR>0.2). Neither Cox hit was FDR significant. (Figure 1)
- **EDSS worsening |** OLS identified APOE, pTau-181, pTau-231, and pTau-217 (β=-0.4[-0.6,-0.2],0.5[0.2,0.8],0.5[0.2,0.8],0.4[0.2,0.6]; FDR<0.05) as associated with EDSS worsening in Alamar; no Olink candidates were selected. (Figure 2)

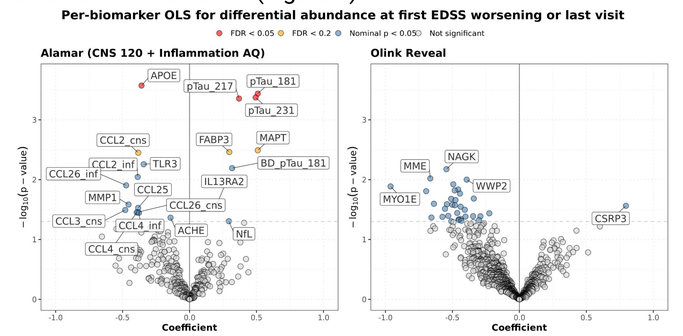


Figure 2: EDSS worsening differential abundance in Graz longitudinal, comparing worsened and non-worsened participants (per-biomarker ordinary least squares), shown as volcano plots of coefficient with $-\log_{10}(p)$.

Conclusions

Several candidate biomarkers were identified across Olink and Alamar panels. Non-overlapping CDW and EDSS worsening signatures may reflect differing biological processes for confirmed versus unconfirmed disability worsening. These findings support large-scale proteomics for MS progression biomarker discovery and warrant independent validation.

Presented at the 10th Joint ACTRIMS-ECTRIMS meeting (MSToronto), October 21-23, 2026 in Toronto, Canada.