# Association between Serum Biomarker Profile and Real-World Evidence of Disability in Multiple Sclerosis

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## BACKGROUND

- Biomarkers could inform disease worsening and severity in people with multiple sclerosis (pwMS).
- Few studies have examined blood biomarkers informative of patient-reported outcome (PRO) of disability, such as Patient Determined Disease Steps (PDDS) and Patient-Reported Outcomes Measurement Information System (PROMIS) physical function, in pwMS.
- Leveraging a custom assay panel that uses the Proximity Extension Assay (PEA) methodology on the Olink™ platform, we previously identified 19 proteins that are involved in key biological pathways in MS pathogenesis and are associated with MS inflammatory disease activity.

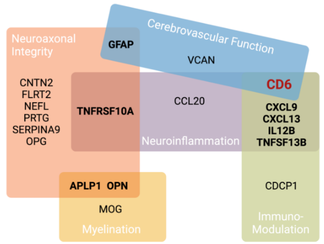
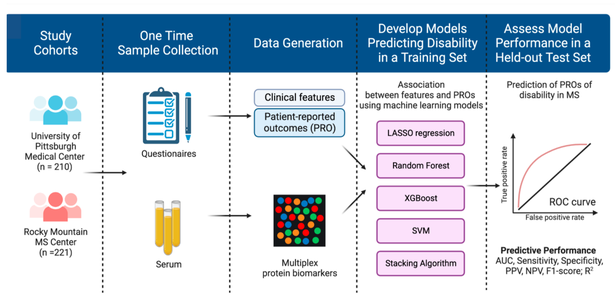



**Figure 1. The 19 serum protein biomarkers** are grouped into 5 functional pathways: Cerebrovascular Function, Immunomodulation, Myelination, Neuroaxonal Integrity, and Neuroinflammation.

## OBJECTIVE

In this study, we examined the associations between **serum protein biomarker profiles** and **patient-reported disability** in pwMS

## STUDY DESIGN



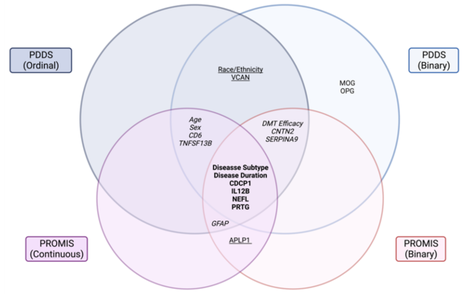

## RESULTS

### Table 1. Cohort Characteristics

| | UPMC (n = 210) | RMMSC (n = 221) |
|---|---|---|
| Age (years, mean ± SD) | 48.4 ± 12.3 | 49.1 ± 12.4 |
| Sex (n of female, % of cohort) | 172 (81.9) | 177 (80.0) |
| Race/Ethnicity (White & Non-Hispanic, %) | 192 (91.4) | 208 (94.1) |
| Disease Duration (years, mean ± SD) | 11.8 ± 9.7 | 13.8 ± 9.8 |
| Disease Subtype[1] (n) | CIS+RIS+RRMS (196), PMS (14) | RRMS (217), PMS (4) |
| DMT Efficacy[2] (n, % of cohort) | | |
| No DMT | 38 (18.1) | 9 (4.0) |
| Standard Efficacy | 79 (37.6) | 40 (18.1) |
| High Efficacy | 93 (44.3) | 172 (77.8) |
| PDDS (median, IQR) | 1 (3) | 1 (3) |
| PDDS < 4 (n, % of cohort) | 166 (75.9) | 185 (83.7) |
| PDDS Time[3] (days, mean ± SD) | 75.5 ± 98.4 | 0 ± 0 |
| PROMIS (mean, SD) | 43.8 ± 10.3 | - |
| PROMIS < 35 (n, % of cohort) | 37 (20.1) | - |
| PROMIS Time[4] (days, mean ± SD) | 350.2 ± 303.6 | - |

[1]Disease Subtype: RRMS = relapse-remitting MS, PMS = progressive MS, CIS = clinical isolated syndrome, RIS = radiological isolated syndrome; [2]DMT Efficacy was encoded as a variable with 0=None, 1=Standard Efficacy, 2=High Efficacy at time of serum draw. Natalizumab, mitoxantrone, alemtuzumab, rituximab, ocrelizumab, cladribine, and ofatumumab are considered high-efficacy therapies and every other approved drug is standard-efficacy; [3]PDDS Time is defined as the time interval between serum collection and the closest PDDS assessment after sample collection. All RMMSC samples were collected on the same day as the PDDS questionnaire was administered. PDDS = Patient Determined Disease Steps; [4]PROMIS Time is defined as the time interval between serum collection and the closest PROMIS assessment after sample collection. PROMIS = Patient-Reported Outcomes Measurement Information System

### Figure 2. LASSO-Selected Features across PROs




Features in **boldface**: shared by all 4 LASSO models; Features in *italics*: shared by 3 LASSO models; Features with underscore: shared by 2 LASSO models.

### Table 2. Model Predictive Performance | PDDS

Using PDDS as outcome, **combined models comprising all clinical and all protein features** performed better than models with all clinical features only *or* models with all protein features only.

| | PDDS Binary | | | PDDS Continuous | | |
|---|---|---|---|---|---|---|
| | Clinical Features Only | Proteins Only* | Clinical Features + Proteins | Clinical Features Only | Proteins Only* | Clinical Features + Proteins |
| AUC (95% CI) | 0.85 (0.77, 0.93) | 0.81 (0.71, 0.91) | 0.91 (0.85, 0.97) | | | |
| Sensitivity | 0.60 | 0.71 | 0.89 | | | |
| Specificity | 0.81 | 0.83 | 0.86 | | | |
| PPV | 0.16 | 0.26 | 0.42 | | | |
| NPV | 0.97 | 0.97 | 0.99 | | | |
| F1-score | 0.25 | 0.38 | 0.57 | | | |
| $R^2$ (95% CI) | | | | 0.20 (0.07, 0.33) | 0.28 (0.16, 0.40) | 0.31 (0.20, 0.41) |

### Table 3. Model Predictive Performance | PDDS (Binary)

Across all machine learning models, **combined clinical and protein features** performed better than the benchmark containing clinical features only.

| | LASSO | Random Forest | | | XGBoost | | | SVM | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Clinical Features + Proteins | Clinical Features Only | Proteins Only | Clinical Features + Proteins | Clinical Features Only | Proteins Only | Clinical Features + Proteins | Clinical Features Only | Proteins Only | Clinical Features + Proteins |
| AUC (95% CI) | 0.91 (0.85, 0.97) | 0.77 (0.65, 0.89) | 0.79 (0.68, 0.89) | 0.84 (0.73, 0.94) | 0.76 (0.64, 0.89) | 0.75 (0.64, 0.87) | 0.90 (0.83, 0.97) | 0.70 (0.56, 0.84) | 0.75 (0.62, 0.89) | 0.85 (0.76, 0.95) |
| Sensitivity | 0.89 | 0.50 | 0.45 | 0.48 | 0.58 | 0.46 | 0.67 | 0.60 | 0.80 | 0.88 |
| Specificity | 0.86 | 0.85 | 0.86 | 0.89 | 0.84 | 0.83 | 0.86 | 0.81 | 0.82 | 0.85 |
| PPV | 0.42 | 0.42 | 0.47 | 0.63 | 0.37 | 0.32 | 0.42 | 0.16 | 0.21 | 0.37 |
| NPV | 0.99 | 0.89 | 0.84 | 0.81 | 0.93 | 0.90 | 0.94 | 0.97 | 0.99 | 0.99 |
| F1-score | 0.57 | 0.46 | 0.46 | 0.55 | 0.45 | 0.37 | 0.52 | 0.25 | 0.33 | 0.52 |

### Table 4. Model Predictive Performance | PROMIS

Using PROMIS as outcome, **combined models comprising all clinical and all protein features** performed better than models with all clinical features only *or* models with all protein features only.

| | PROMIS Binary | | | PROMIS Continuous | | |
|---|---|---|---|---|---|---|
| | Clinical Features Only | Proteins Only* | Clinical Features + Proteins | Clinical Features Only | Proteins Only* | Clinical Features + Proteins |
| AUC (95% CI) | 0.80 (0.53, 1.00) | 0.81 (0.66, 0.96) | 0.90 (0.78, 1.00) | | | |
| Sensitivity | 0.89 | 0.89 | 0.93 | | | |
| Specificity | 1.00 | 0.30 | 0.57 | | | |
| PPV | 1.00 | 0.77 | 0.90 | | | |
| NPV | 0.33 | 0.50 | 0.67 | | | |
| F1-score | 0.94 | 0.83 | 0.92 | | | |
| $R^2$ (95% CI) | | | | 0.25 (0.06, 0.43) | 0.26 (0.16, 0.37) | 0.35 (0.29, 0.42) |

### Table 5. Model Predictive Performance | PROMIS (Binary)

Across all machine learning models, **combined clinical and protein features** performed better than the benchmark containing clinical features only.

| | LASSO | Random Forest | | | XGBoost | | | SVM | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Clinical Features + Proteins | Clinical Features Only | Proteins Only | Clinical Features + Proteins | Clinical Features Only | Proteins Only | Clinical Features + Proteins | Clinical Features Only | Proteins Only | Clinical Features + Proteins |
| AUC (95% CI) | 0.90 (0.78, 1.00) | 0.67 (0.38, 0.97) | 0.80 (0.61, 0.98) | 0.83 (0.68, 0.87) | 0.63 (0.31, 0.96) | 0.40 (0.14, 0.66) | 0.81 (0.65, 0.97) | 0.74 (0.49, 0.98) | 0.73 (0.52, 0.93) | 0.90 (0.80, 1.00) |
| Sensitivity | 0.93 | 0.90 | 0.87 | 0.90 | 0.86 | 0.84 | 0.90 | 0.91 | 0.86 | 0.86 |
| Specificity | 0.57 | 0.43 | 0.33 | 0.43 | 0.25 | 0.17 | 0.38 | 0.75 | 0.50 | 0.50 |
| PPV | 0.90 | 0.87 | 0.87 | 0.87 | 0.81 | 0.68 | 0.84 | 0.97 | 0.97 | 0.97 |
| NPV | 0.67 | 0.50 | 0.33 | 0.50 | 0.33 | 0.33 | 0.50 | 0.50 | 0.17 | 0.17 |
| F1-score | 0.92 | 0.89 | 0.87 | 0.89 | 0.83 | 0.75 | 0.87 | 0.94 | 0.91 | 0.91 |

## SUMMARY & FUTURE DIRECTIONS

- The addition of serum protein biomarkers to key clinical features improves the performance of predictive models of patient-reported MS disability status with clinically actionable accuracy.
- LASSO outperformed other machine learning models.
- Serum protein biomarkers that are informative of disease activity and progression (e.g, gad, ARR, EDSS) appear to also be predictive of real-world evidence of disability status.
- Future studies that include long-term follow-up from baseline clinical profile and serum biomarker profile ascertainment, incorporate objective functional testing in conjunction with PROs, would further establish the clinical utility of this integrated approach in monitoring individual MS disease trajectories, particularly in predicting relapse-free disability progression.

## ACKNOWLEDGEMENTS

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- Full manuscript is available at: https://www.medrxiv.org/content/10.1101/2022.10.21.22281364v1

## DISCLOSURE

F. Qureshi is an employee of Octave Bioscience.
F, Zhang was an employee of Octave Bioscience when the study was performed.
J. Foley has received research support from Biogen, Novartis, Adamas, Octave, Genentech, and Mallinckrodt. He received speakers' honoraria and acted as a consultant for EMD Serono, Genzyme, Novartis, Biogen, and Genentech. He has equity interest in Octave and is the founder of InterPro Biosciences.

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