P008

Association between Serum Biomarkers and Patient-Reported Outcome of Disability in Multiple Sclerosis

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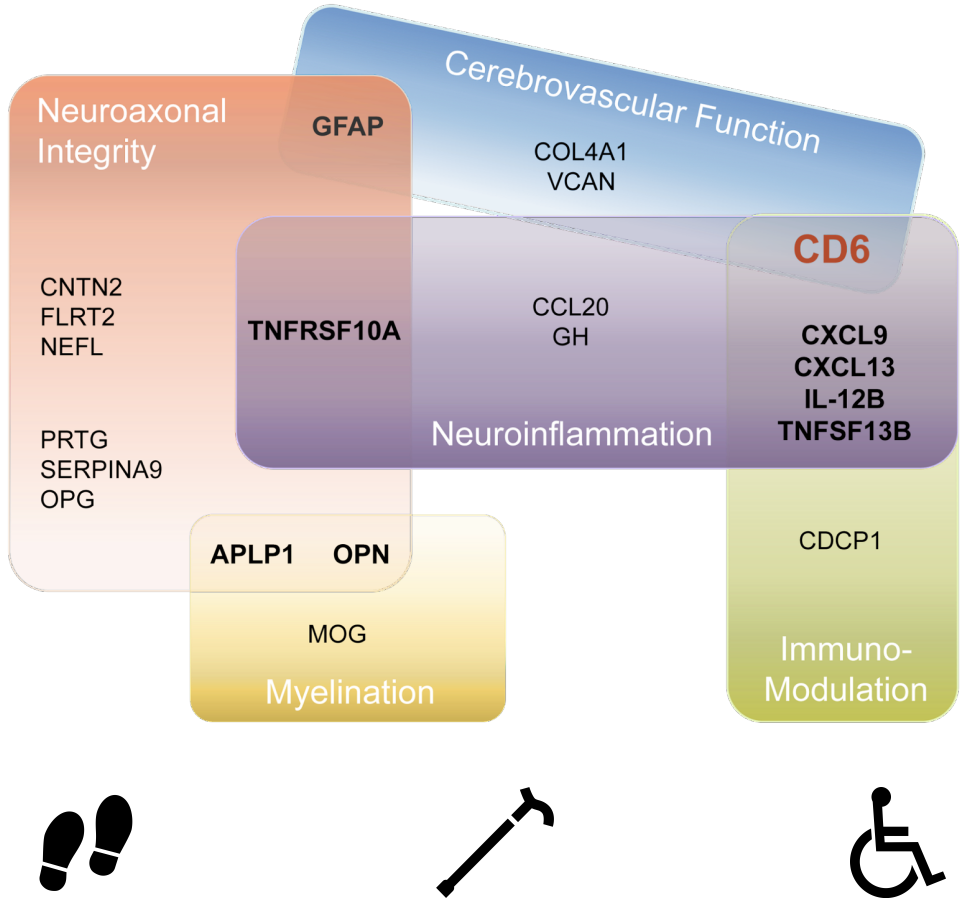
Background

- Biomarkers of neurological disability could inform disease worsening and severity in people with multiple sclerosis (MS).
- Few studies have examined blood biomarkers informative of patient-reported outcome (PRO) of disability such as the widely used Patient Determined Disease Steps (PDDS).
- Leveraging the Proximity Extension Assay (PEA) methodology on the Olink™ platform, we previously identified 21 proteins that are involved in key biological pathways in MS pathogenesis and are associated with MS inflammatory disease activity.
- In this study, we examined the associations between serum protein biomarker profiles and patient-reported disability in pwMS



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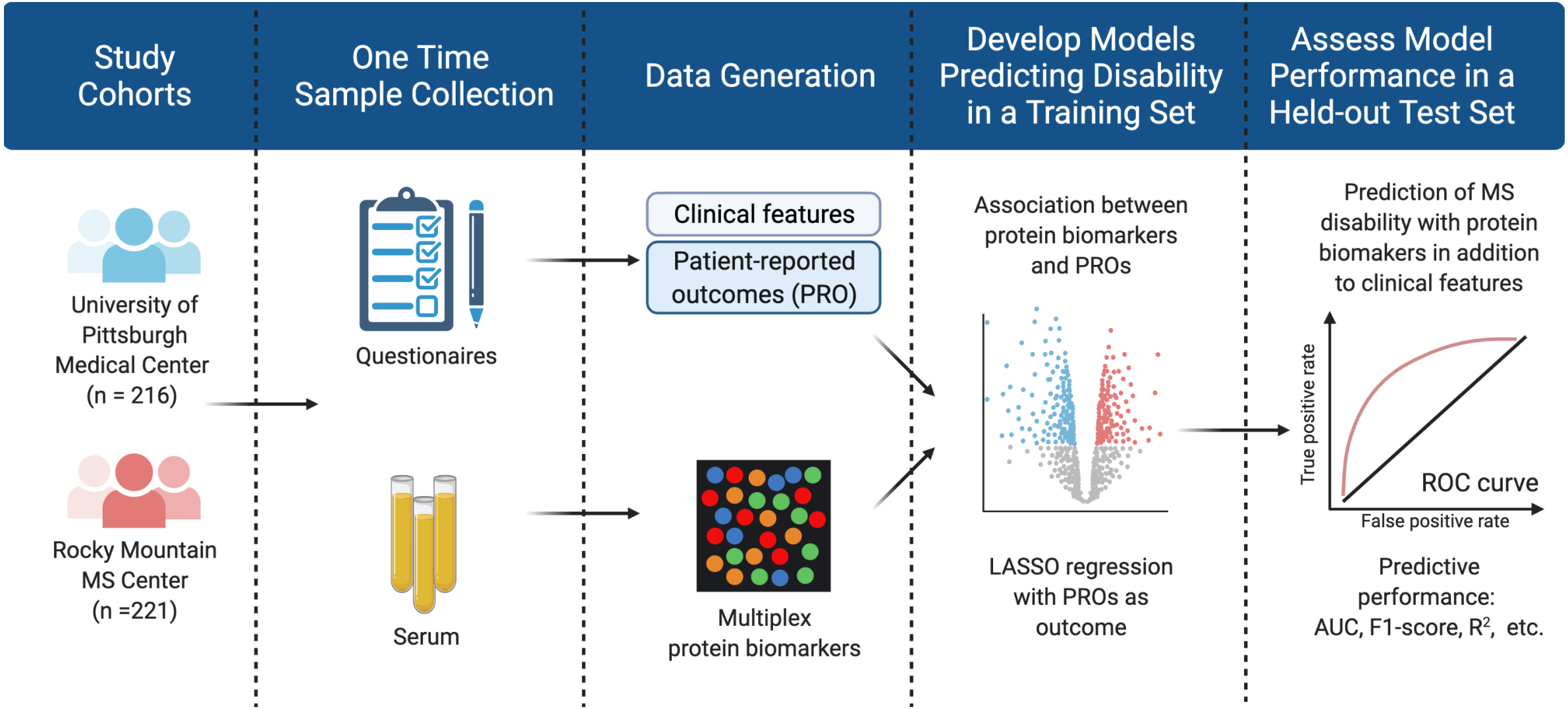
Study Design



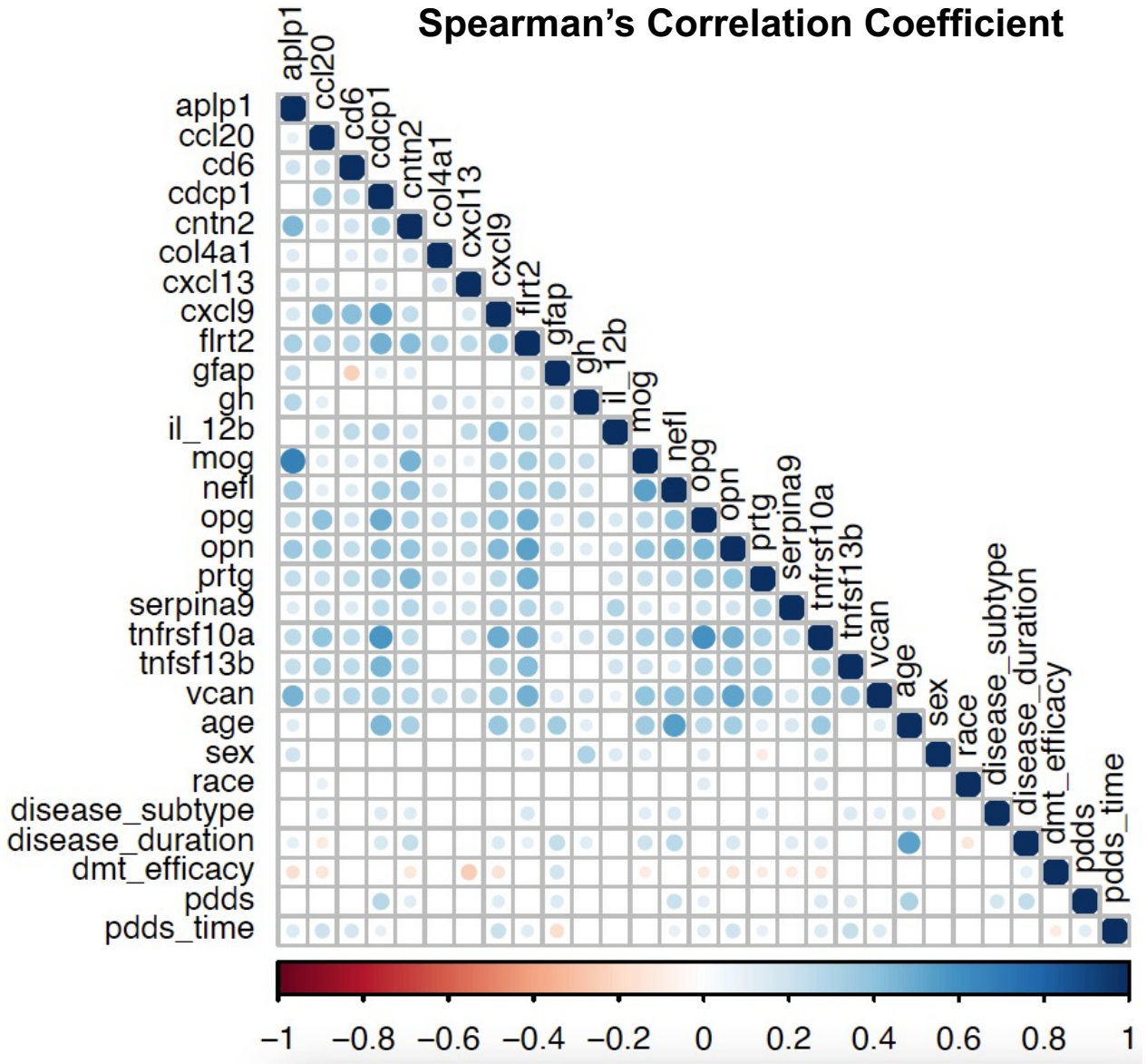
Cohort Characteristics

	UPMC (n = 216)	RMMSC (n = 221)
Age (years, mean ± SD)	48.4 ± 12.3	49.1 ± 12.4
Sex (n, % of cohort)		
Female	176 (81.5)	177 (80.0)
Male	40 (18.5)	44 (20.0)
Race/Ethnicity (White & Non-Hispanic, %)	197 (91.2)	208 (94.1)
Disease Duration (years, mean ± SD)	11.8 ± 9.7	13.8 ± 9.8
Disease Subtype[1] (n)	RRMS (191), PMS (14), CIS (1), RIS (4), NMO(6)	RRMS (217), PMS (4)
DMT Efficacy[2] (n, % of cohort)		
No DMT	40 (18.5)	9 (4.0)
Standard Efficacy	81 (37.5)	40 (18.1)
High Efficacy	95 (44.0)	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

[1]Disease Subtype: RRMS = relapse-remitting MS, PMS = progressive MS, CIS = clinical isolated syndrome, RIS = radiological isolated syndrome, NMO = neuromyelitis optica.
[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.

Correlation Structure of the Variables

- Levels of correlation between two variables with a significant p-value (<0.05) are shown with circles. Circle sizes correlate with the absolute values of correlation coefficients (blue = positively correlated, red = negatively correlated).
- Among all protein markers, **MOG and APLP1** have the strongest positive correlation (r = 0.67, p <0.0001), while **GFAP and CD6** have the strongest negative correlation (r = -0.22, p <0.0001).
- Among protein markers versus clinical markers, **NEFL and age** show the strongest positive correlation (r = 0.55, p <0.0001), **CXCL13 and DMT efficacy** have the strongest negative correlation (r = -0.24, p <0.0001).



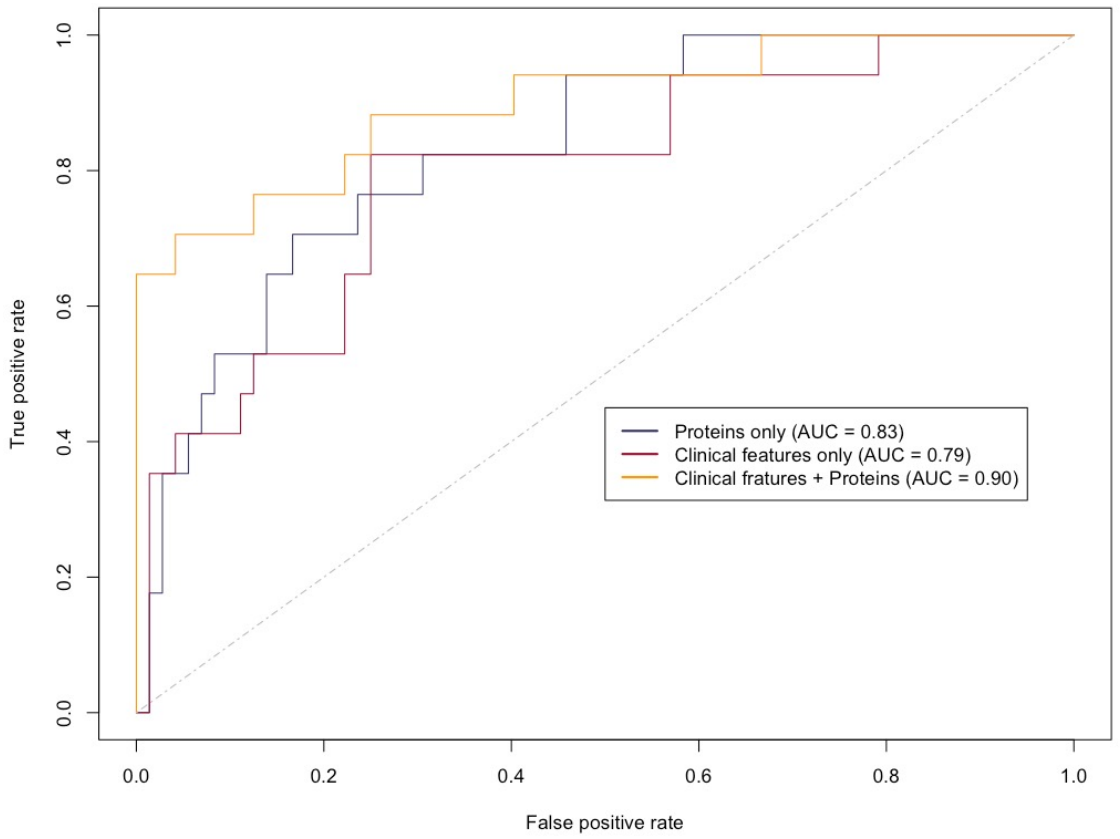
Build Predictive Models with LASSO Regression

- Samples were divided 80/20 first within each cohort, then combined into a training and a held-out test set (stratification by cohort was used due to significant imbalance in variables: DMT efficacy and PDDS time).
- The PDDS has nine ordinal levels ranging between 0 (normal) and 8 (bedridden). The milestone of 4 is a common threshold for classifying severe vs. mild/moderate disability. PDDS $\geq$ 4 indicates full time requirement for ambulatory assistance.
- We built models to predict either binary or ordinal PDDS using LASSO regression to reduce overfitting in three feature sets: (1) all clinical features; (2) all 21 serum proteins; (3) combined clinical and protein features.

Score	Disability level	Description
0	Normal	Mild, sensory symptoms with no limit on activity
1	Mild disability	Minor, noticeable symptoms that have only a small effect on lifestyle
2	Moderate disability	No limitations in walking ability but significant problems that limit daily activities in other ways
3	Gait disability	Interference with activities, especially walking
4	Early cane	Uses a cane or single crutch for walking all or part of the time; can walk 25 feet in 20 seconds without a cane or crutch
5	Late cane	Uses a cane or crutch to walk 25 feet
6	Bilateral support	Needs 2 canes, crutches, or a walker to walk 25 feet
7	Wheelchair/ scooter	Main form of mobility is a wheelchair
8	Bedridden	Unable to sit in a wheelchair for more than 1 hour

Abbreviation: PDDS, Patient-Determined Disease Steps.

Predictive Models of PDDS (Binary)



*Binary PDDS is classified as 0 (PDDS < 4) and 1 (PDDS ≥ 4). PDDS ≥ 4 indicates full time requirement for ambulatory assistance.

[1]Predictive Performance: All performance metrics were generated from the held-out test set.

[2]95% CI = 95% Confidence Interval.

	Predictive Performance[1]		
	Clinical Features Only	Proteins Only	Clinical Features + Proteins
AUC (95% CI)[2]	0.83 (0.75-0.91)	0.79 (0.73-0.84)	0.90 (0.81-0.99)
F1-score	0.50	0.54	0.71
Selected Features	Age	APLP1	CCL20
	Disease duration	CD6	CD6
	PDDS time	CDCP1	CDCP1
		CNTN2	CNTN2
		COL4A1	COL4A1
		CXCL9	CXCL9
		GFAP	GH
		GH	IL-12B
		IL-12B	MOG
		MOG	NEFL
		NEFL	PRTG
		PRTG	SERPINA9
		TNFRSF10B	TNFRSF10B
		VCAN	VCAN
			Age
			Sex
			Disease duration
			PDDS time

Predictive Models of PDDS (Ordinal)

	Predictive Performance[1]		
	Clinical Features only	Proteins only	Clinical Features + Proteins
R^2 (95% CI)[2]	0.18 (0.08-0.28)	0.19 (0.09-0.28)	0.28 (0.18-0.38)
Selected Features	Age	APLP1	APLP1
	Sex	CDCP1	CDCP1
	Race	COL4A1	COL4A1
	Disease duration	GFAP	GFAP
	DMT efficacy	IL-12B	IL-12B
	PDDS time	NEFL	NEFL
		OPG	OPG
		PRTG	PRTG
		VCAN	VCAN
			Age
			Sex
			Disease duration
			DMT efficacy

[1]Predictive Performance: All performance metrics were generated from the held-out test set. [2]95% CI = 95% Confidence Interval.

Coefficient of Algorithm-Selected Features in the Combined Models

- Using **binary PDDS** as outcome, **15** protein markers and **4** clinical features were retained in the LASSO logistic regression model.
- Using **ordinal PDDS** as outcome, **9** protein markers and **4** clinical features were retained in the LASSO linear regression model.
- Among all these selected features, both models included **5** protein markers (**CDCP1, IL-12B, NEFL, PRTG and VCAN**), as well as **3** clinical features (**age, sex, and disease duration**)*.

*Features that are selected by at least one model are presented in the table. Features shared by both models are highlighted in red.

	PDDS (Binary)	PDDS (Ordinal)
APLP1	.	-0.5282
CCL20	0.0059	.
CD6	-0.0118	.
CDCP1	0.0066	0.3386
CNTN2	0.0710	.
COL4A1	-0.0196	-0.1531
CXCL9	0.0285	.
GFAP	.	0.1147
GH	0.0354	.
IL-12B	-0.0528	-0.2232
MOG	-0.1149	.
NEFL	0.0102	0.1839
OPG	.	0.3684
PRTG	-0.0510	-0.4014
SERPINA9	-0.0056	.
TNFRSF10B	0.1401	.
VCAN	-0.1921	-0.8117
Age	0.0079	0.0338
Sex	-0.0772	-0.1896
Disease duration	0.0069	0.0212
DMT efficacy	.	0.1191
PDDS time	0.0003	.

Summary and Future Directions

- The addition of serum protein biomarkers to key clinical features improves the performance of predictive models of patient-reported MS disability status (PDDS) with clinically actionable accuracy.
- Model using binary PDDS as outcome and model using ordinal PDDS as outcome share 5 protein markers (CDCP1, IL-12B, NEFL, PRTG and VCAN), as well as 3 clinical features (age, sex, and disease duration).
- We will validate these findings using different PROs, including the multiple sclerosis rating scale revised (MSRS-R) and the Patient-Reported Outcomes Measurement Information System – Physical (PROMIS – Physical).

For questions, please contact Zongqi Xia: zxia1@pitt.edu and Fujun Zhang: fzhang@octavebio.com.