Multivariate Proteomic MS Disease Activity Test Results Surfaces Both Individual Patient and Clinical Practice Population Insights

F. Qureshi[1], T. Hoyt[2], A. Christensen[2], F. Rubio da Costa[1], V. Gehman[1], F. Zhang[1], D. Hughes[1], J. Foley[2]
[1]Octave Bioscience, Menlo Park, CA, [2]Rocky Mountain Multiple Sclerosis Clinic, Salt Lake City, UT.

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Background

- The availability of a validated blood-based assay to quantitatively assess disease activity and progression will significantly advance MS clinical care. Quantitative measurement of the level of disease activity in MS patients can provide insights for individual patients as well as for the entire population of patients treated within a clinical practice.
- A Multiple Sclerosis Disease Activity (MSDA) Test that measures the concentrations of 18 proteins used to determine 4 disease pathway scores (immune modulation, neuroinflammation, myelin biology and neuroaxonal integrity) and an overall disease activity score has been both analytically (Hu et al., 2021) and clinically validated (Chitnis et al., 2021).

Objective

- To evaluate the distributions of the MSDA Test disease activity scores observed in a population of MS patients from a clinical practice (Rocky Mountain Multiple Sclerosis Clinic) in the United States.

Methods

- 222 samples from a matched serum-MRI study (e.g serum draw and contrast enhancing MRI administered within 60 days of one another) were assayed in the MSDA Test. Patient sample demographics and characteristics are summarized in Table 1. For this study, the administration of intravenous solumedrol was utilized as a surrogate endpoint for clinically defined relapse status.
- In a separate clinical validation study (that included a subset of these matched serum-MRI study samples among 3 other retrospective cohorts) the MSDA test algorithm was found to significantly associate with both clinical and radiographic disease activity endpoints including the presence and count of gadolinium enhancing (Gd+) lesions , new and enlarging T2 (N/E T2) lesions and active/stable status (combined endpoint of Gd+ lesions, N/E T2 lesions, and relapse status as defined by the clinician at the time of the blood draw).
- The validated MSDA Test algorithm is a stacked classifier logistic regression model. Protein concentrations are demographically corrected for both age and sex using fixed coefficients that were established in the clinical validation study. The first layer of the model consists of 4 Disease Pathway Algorithms (restricted to subsets of 18 proteins pathophysiologically associated with one another). The second layer of the model utilizes the 4 Disease Pathway Algorithms as meta-features to determine an overall DA Score reflecting both the likelihood and severity of disease activity (see Figure 1). Thresholds were established for the DA score (scale = 1.0 to 10.0 with 0.5 intervals) corresponding to Low, Moderate and High levels of DA based on the presence and count of gadolinium enhanced lesions observed on the associated MRI (Low = 0 lesions, Moderate = 1 lesion, and High = ≥ 2 lesions).
- The 222 samples were assayed in the MSDA Test and then assigned to the 3 disease activity categories based on their observed disease activity score.

Results

- Of the 222 samples tested, 142 (64.0%) were observed to have disease activity scores in the Low category (1.0 to 4.0). 70 samples (31.5%) were observed to have disease activity scores in the Moderate category (4.5 to 7.0). 10 samples (4.5%) were observed to have disease activity scores in the High category (7.5 to 10.0). Results are presented in Figure 2.
- For each endpoint evaluated in the completed clinical validation study, the percentage of samples representing active MS increased alongside the score categorizations: Gd+ (L = 0.7%, M = 2.9%, H = 10.0%), N/E T2 Lesions (L = 2.8%, Moderate = 12.9%, High = 30.0%), and Active/Stable Status (L = 7.7%, M = 15.7%, H = 30.0%)
- The relationship between the overall Disease Activity Score and the 4 Disease Pathway Scores used as meta features in the algorithm is presented in Figure 3. The Disease Activity Score is strongly correlated with the Disease Pathway scores (immune modulation R2 = 0.843, neuroinflammation R2 = 0.816, myelin biology R2 = 0.550 and neuroaxonal integrity R2 = 0.787). The variance between the 4 pathway scores for individual samples may provide insights regarding which disease pathways are influencing the DA score categorization.

Conclusions

- The samples analyzed in the study reflected a well-controlled population of MS patients with the majority of patient samples (64.0%) categorized as having Low Disease Activity.
- Additional analysis will be performed in independent cohorts derived from other clinics and centers to compare the distributions observed in this study with other real world populations. For this cohort of samples, 74.4% of patients were treated with high efficacy biologic disease modifying therapies (natalizumab, ocrelizumab, and ofatumumab).
- The results from the MSDA Test can serve as a quantitative and objective tool to evaluate an individual patient's level of disease activity as well as to monitor the overall level of disease activity within a clinic's population.

References:

1) Hu et al. 2021: Analytical Validation of a Multivariate Proteomic Serum Based Assay for Disease Activity Assessments in Multiple Sclerosis, P010 ACTRIMS 2021 W. Hu[1], L. Loh[1], H. Patel[1], M. DeGuzman[1], M. Becich[1], F. Rubio da Costa[1], V. Gehman[1], E. Assarsson[2], S.Ohlsson[2], M. Lundberg[2], J. Bergman[2], N. Nordberg[2], F. Qureshi[1] [1]Octave Bioscience, Inc., Menlo Park, CA, USA; [2]Olink Proteomics, Uppsala, Sweden

2) Chitnis et al. 2021: Clinical Validation Study Results of a Multivariate Proteomic Serum Based Assay for Disease Activity Assessments in Multiple Sclerosis, P574 ECTRIMS 2021 T. Chitnis[1], J. Foley[5], C. Ionete[2], N. El Ayoubi[3], S. Saxena[1], P. Gaitan-Walsh[1], H. Lokhande[1], A. Paul[1], F. Saleh[1], H. Weiner[1], F. Qureshi[4], M. J. Becich[4], F. Rubio da Costa[4], V. M. Gehman[4], S. J. Khoury[3] [1]Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [2]University of Massachusetts Medical School, Worcester, MA; [3]American University of Beirut, Beirut, Lebanon; [4]Octave Bioscience, Menlo Park, CA; [5]Rocky Mountain Multiple Sclerosis Clinic, Salt Lake City, UT

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Figure 1. MSDA Stacked Classified Meta-Feature Algorithm

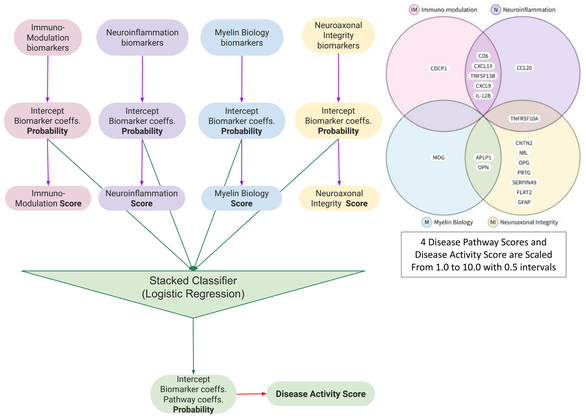
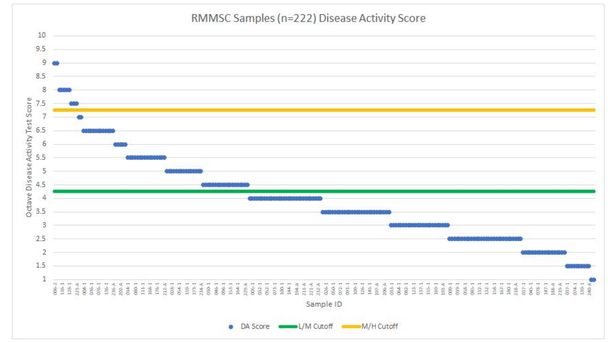


Table 1. Patients demographics and characteristics

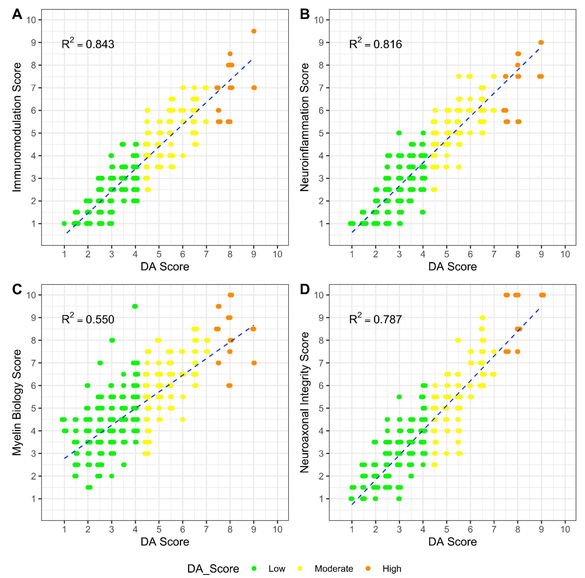
Variables	Low (n = 142)	Moderate (n = 70)	High (n = 10)	Total (n = 222)
Age				
Mean (SD)	50.2 (11.8)	46.7 (12.8)	51.5 (16.5)	49.2 (12.4)
Median (Min, Max)	51 (20, 76)	44.5 (25, 78)	48 (18, 76)	49 (18, 78)
Sex: n (%)				
Female	113 (79.6)	55 (78.6)	9 (90)	177 (79.7)
Male	29 (20.4)	15 (21.4)	1 (10)	45 (20.3)
Disease_duration				
Mean (SD)	14.0 (10.1)	13.1 (9.5)	15.9 (7.8)	13.8 (9.8)
Median (Min, Max)	12.6 (0.4, 47.0)	10.6 (0.8, 42.7)	15.8 (0.9, 25.9)	12.4 (0.4, 47.0)
PDDS				
Mean (SD)	1.6 (1.7)	1.9 (1.9)	2.3 (2.7)	1.7 (1.8)
Median (Min, Max)	1 (0, 7)	1 (0, 7)	1.5 (0, 7)	1 (0, 7)
Current DMT: n (%)				
dimethyl fumarate	19 (13.4)	8 (11.4)	1 (10)	28 (12.6)
glatiramer acetate	5 (13.4)	6 (8.6)	0 (0)	11 (5)
Interferon beta-1a	1 (0.7)	0 (0)	0 (0)	1 (0.5)
natalizumab	98 (69)	45 (64.3)	8 (80)	151 (68)
ocrelizumab	10 (7)	3 (4.3)	0 (0)	13 (5.9)
ofatumumab	0 (0)	1 (1.4)	0 (0)	1 (0.5)
peginterferon beta-1a	1 (0.7)	0 (0)	0 (0)	1 (0.5)
teriflunomide	2(1.4)	1 (1.4)	1 (10)	4 (1.8)
none	6 (4.2)	6 (8.6)	0 (0)	12 (5.4)
Gd Active: n (%)				
Y	1 (0.7)	2 (2.9)	1 (10)	4 (1.8)
N	141 (99.3)	66 (94.3)	9 (90)	214 (97.3)
NA	0 (0)	2 (2.9)	0 (0)	2 (0.9)
New/Enlarging Brain T2 Lesions: n (%)				
Y	4 (2.8)	9 (12.9)	3 (30)	16 (7.2)
N	136 (95.8)	60 (85.7)	7 (70)	203 (91.4)
NA	2 (1.4)	1 (1.4)	0 (0)	3 (1.4)
Active/Stable Status: n (%)				
Y	11 (7.7)	11 (15.7)	3 (30)	25 (11.3)
N	131 (92.3)	59 (84.3)	7 (70)	197 (88.7)

Figure 2. DA Scores sorted from Highest to Lowest Score (n=222)



DA Score Level	Sample Count	Percent
Low	142	64.0%
Moderate	70	31.5%
High	10	4.5%

Figure 3. Relationship between DA Score and Disease Pathway Scores



For questions, please contact Ferhan Qureshi: fqureshi@octavebio.com

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