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Real-World Utilization of a Proteomic Biomarker Panel for Assessing Multiple Sclerosis Disease Activity in an Academic Multiple Sclerosis Clinic with a Diverse Patient Population

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Introduction

Conventional monitoring of patients with multiple sclerosis (MS) is performed using both clinical and radiographic assessments. The Multiple Sclerosis Disease Activity (MSDA) test is a commercially available multi-protein blood test. It has been analytically[1] and clinically validated[2].

The MSDA test measures 18 proteins to determine 4 disease pathway scores (i.e. Immune Modulation, Neuroinflammation, Myelin Biology, and Neuroaxonal Integrity) (Figure 2 & 3) and an overall Disease Activity score scaled from 1.0-10.0 with thresholds corresponding to Low, Moderate, and High disease activity.

Clinical validation is relative to gadolinium positive (Gd +) lesions on magnetic resonance imaging (MRI). The timing of utilizing the MSDA test and specific use cases/situations may depend on patient- and provider-specific preferences.

Objectives

The aim of the study was to assess the feasibility and real-world utility of the MSDA in diverse populations within the setting of an academic MS clinic in the southeastern United States.

Methods

Retrospective chart review was conducted at a single academic center. For all patients (n = 90) that received the MSDA from September 2022 to August 2023, relevant patient data was reviewed (see Table 1-3). A total of 90 blood samples were collected. Five samples were longitudinal (i.e. contained two data points). Data was reviewed including age, sex, race, age, EDSS, disease duration, DMT, presence or absence of recent evidence of disease activity by MRI change (new or active lesion), progressing symptoms, or recent clinical relapse. Patients were selected to receive the test at the discretion of the ordering provider.

Participants

Demographics (n = 90)	
Age (mean ± SD)	43 ± 12
Sex (% Female, % Male)	81%, 19%
Ethnicity (% Hispanic or Latino, % Not Hispanic or Latino)	0%, 100%
Race (% African American, % Asian, % Caucasian)	43%, 1%, 56%
BMI (mean ± SD)	32 ± 8
Smoking (% Yes, % No, % Former)	20%, 73%, 7%

Table 1: Participant Demographics. BMI = Body Mass Index

Radiographic Status (n = 86)	
Recent MRI Activity (± 60 days) (% Yes, % No)	15%, 85%
Gd+ Lesions	
0 (%)	91%
1 (%)	2%
≥2 (%)	7%
New or Enlarging T2 Lesions (% Yes, % No)	9%, 91%

Table 2: Radiographic Status. Recent MRI activity is defined as Gd+ and/or new T2 lesions ± 60 days of MSDA draw.

Clinical Status (n = 90)	
Type of DMT	
No Current DMT (%)	27%
Alemtuzumab (%)	3%
Dimethyl fumarate (%)	7%
Diroximel fumarate (%)	9%
Fingolimod (%)	2%
Glatiramer acetate (%)	2%
IFN beta 1a (%)	2%
Leflunomide (%)	1%
Natalizumab (%)	11%
Ocrelizumab (%)	23%
Ofatumumab (%)	7%
Ozanimod (%)	1%
Pegylated IFN (%)	1%
Siponimod (%)	1%
Teriflunomide (%)	3%
EDSS (mean ± SD)	3.97 ± 1.76
Disease Duration (mean ± SD years)	11 ± 9
Clinical Status (% Stable, % Recent Relapse, % Progressing)	71%, 15%, 14%

Table 3: Clinical Status. Recent relapse is defined as clinician-determined relapse ± 60 days of examination. EDSS = Expanded Disability Status Scale.

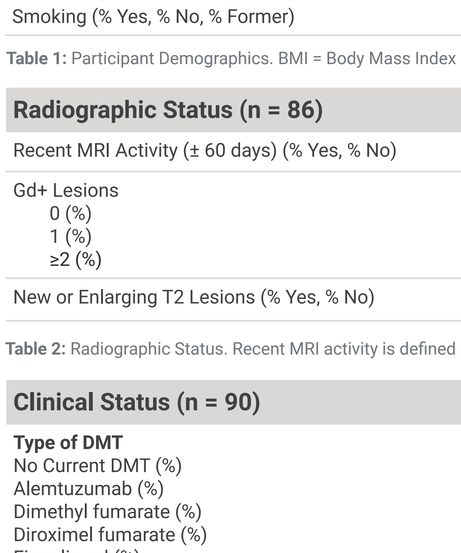


Figure 1: Population breakdown of disease course. RIS, radiographically isolated syndrome; CIS, clinically isolated syndrome; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis.

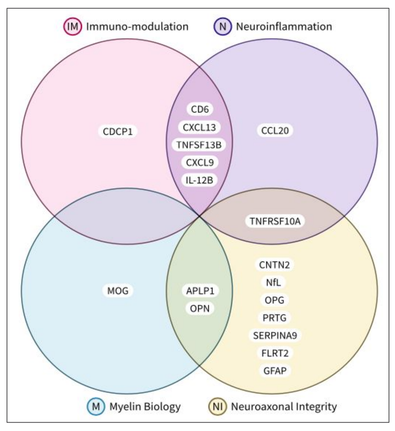


Figure 2. MSDA pathways and protein biomarkers

Biomarker	Pathways	Concentration	MS Range*	Percentile (1)
NfL Neurofilament Light	NI	7.35 pg/mL	3.5–42 pg/mL	34th
GFAP Glial Fibrillary Acidic Protein	NI	32.07 pg/mL	24 –220 pg/mL	6th
SERPINA9 Serpin Family A Member 9	NI	50.72 pg/mL	12–160 pg/mL	59th
FLRT2 Leucine-rich repeat transmembrane protein	NI	105.77 pg/mL	63–180 pg/mL	52nd
CNTN2 Contactin 2	NI	1.61 ng/mL	0.65–3.3 ng/mL	67th
PRTG Protogenin	NI	116.56 pg/mL	71–180 pg/mL	54th
OPN Osteopontin	NI M	22.75 ng/mL	9.5–39 ng/mL	73th
MOG Myelin Oligodendrocyte Glycoprotein	M	19.68 pg/mL	12–47 pg/mL	31st
CXCL9 Monokine Induced by Gamma Interferon	IM N	32.95 pg/mL	17–250 pg/mL	32nd
CXCL13 C-X-C Motif Chemokine Ligand 13	IM N	51.64 pg/mL	22–190 pg/mL	51st
CD6 Cluster of Differentiation 6	IM N	141.99 pg/mL	46–250 pg/mL	74th
CCL20 MIP-3 alpha	N	10.10 pg/mL	2.1–52 pg/mL	73rd
APLP1(2) Amyloid Beta Precursor Like Protein 1	NI M	12.04 pg/mL	5.5–22 pg/mL	57th
OPG(2) Osteoprotegerin	NI	0.82 pg/mL	0.41–1.4 pg/mL	70th
TNFRSF10A(2) TRAIL-R1	NI N	4.51 pg/mL	2.8–9.7 pg/mL	38th
TNFSF13B(2) BAFF	IM N	8.09 pg/mL	2.3–10 pg/mL	40th
IL-12B(2) Interleukin 12B	IM N	43.74 pg/mL	28–280 pg/mL	11th
CDCP1(2) CUB domain-containing protein 1	IM	169.86 pg/mL	28–230 pg/mL	93rd

Figure 3. Left = MSDA biomarkers directly correlated with disease activity. Right = MSDA biomarkers inversely correlated with disease activity. (1) = Subject's biomarker percentile relative to levels in MS patient samples from which the MS ranges were determined. (2) = Biomarker is inversely correlated with disease activity, therefore a lower concentration was associated with a higher level of disease activity in validation studies. *Example above is of mock data.

Results

Population Overview

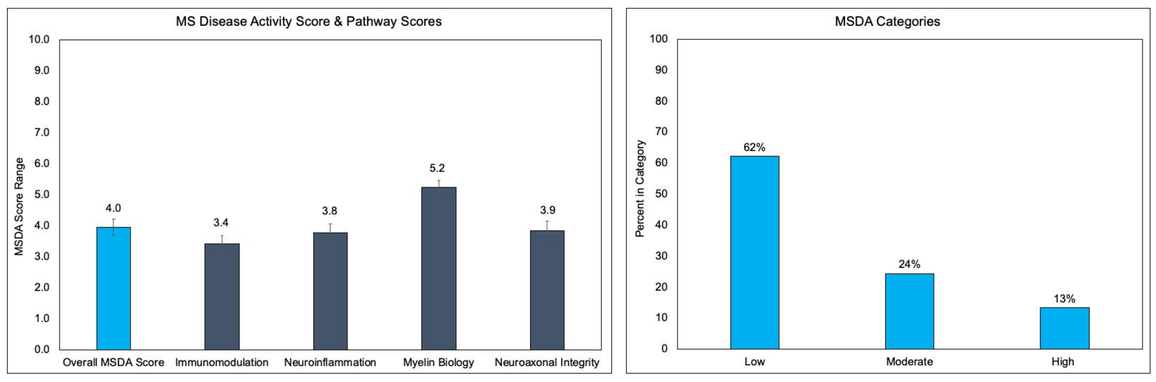


Figure 4: Left = MSDA overall score and pathway scores (n = 90). The categories are defined as low, moderate, and high with ranges of 1.0 - 4.0, 4.5 - 7.0, and 7.5 - 10.0, respectively. A score in the moderate/high range is ~4.5 times more likely to have ≥ 1 Gd+ lesion(s) as compared to the low range. A score in the high range is ~21 times more likely to have ≥ 2 Gd+ lesions. Right = Percent of participants (n = 90) in each MSDA category.

Concordance of Results

- Of the twelve "High" MSDA scoring patients, seven of eleven with reviewable MRIs had evidence of recent Gd (+) MRI activity.
- Eleven of the twelve "High" scorers had either recent objective clinical disease activity and/or MRI activity. The single high scorer with no clinical or radiographic correlate was a few weeks post-partum, not on DMT, with a history of highly active disease, and new, nonenhancing T2 lesions on MRI.
- Two of the twelve "High" scorers had elevated MSDA scores prior to clinical or radiographic evidence of disease activity.

Case Series Highlights

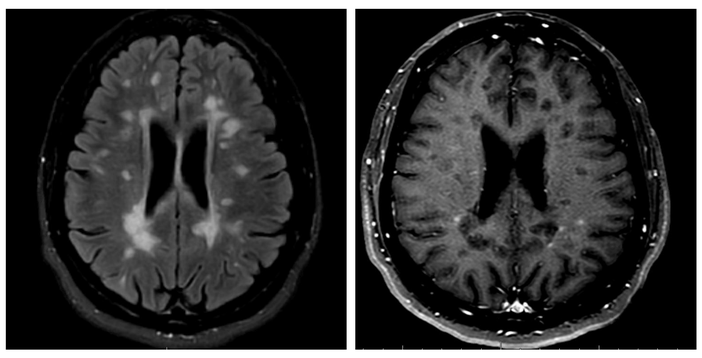
CLINICAL IMPRESSIONS

MRI

High Score Preceding Relapse

33 year old female, newly diagnosed and started on treatment with dimethyl fumarate one year prior. Patient was clinically stable at time of MSDA, which was performed for a baseline score while on dimethyl fumarate. 12 days following the test, the patient reported new onset of bilateral lower extremity numbness and poor balance. MRI showed multiple enhancing lesions. The patient was transitioned to ocrelizumab.

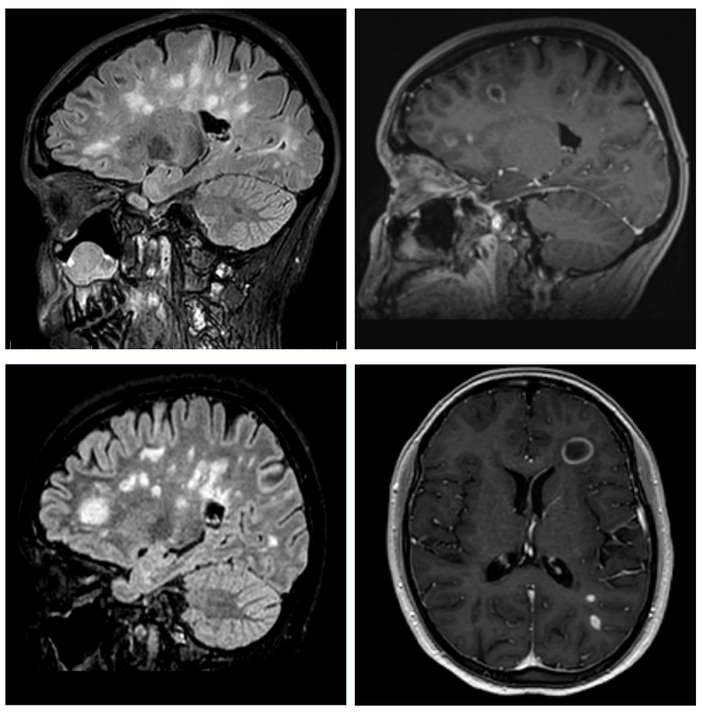
MSDA Score 8.5 High



Minimally Symptomatic MS

31 year old female who presented to the emergency department for headache. MRI brain with and without contrast showed multifocal lesions in a classical distribution for a demyelinating process. Work-up was all suggestive of a demyelinating etiology. She subsequently reported a subacute onset of facial numbness, but was otherwise clinically asymptomatic at the time of initial imaging.

MSDA Score 9.5 High



Highly Active Disease

21 year old female presenting with recent onset left-sided optic neuritis and lower extremity weakness. She is naïve to treatment including steroids. MSDA was obtained six weeks after baseline MRI.

MSDA Score 10.0 High

Conclusions

The MSDA test was a reliable indicator of recent objective disease activity when used in routine clinical practice within an academic MS clinic. All patients with high scores had evidence of recent disease activity, including two examples of elevated MSDA scores that preceded future clinical and radiographic manifestations of disease activity. Future directions with this research will include sub analyses of this diverse patient population.

Disclosures: William Kilgo serves on the speaker bureaus of Biogen, Genentech, and TG Therapeutics. Akhil Padarti has nothing to disclose. Patricia Izbicki, Jim Eubanks, Angela Sanchez, and Ferhan Qureshi are employees of Octave Bioscience.

References: 1. Qureshi F, Hu W, Loh L, et al. Analytical validation of a multi-protein, serum-based assay for disease activity assessments in multiple sclerosis. *Proteomics Clin Appl*. 2023;17(3):e2200018. doi:10.1002/prca.202200018 **2.** Chitnis T, Foley J, Ionete C, et al. Clinical validation of a multi-protein, serum-based assay for disease activity assessments in multiple sclerosis. *Clin Immunol*. 2023;253:109688. doi:10.1016/j.clim.2023.109688