Predictive Utility of Serum Protein Biomarkers from the Octave MSDA Panel for Optic Neuritis Events in People with Multiple Sclerosis

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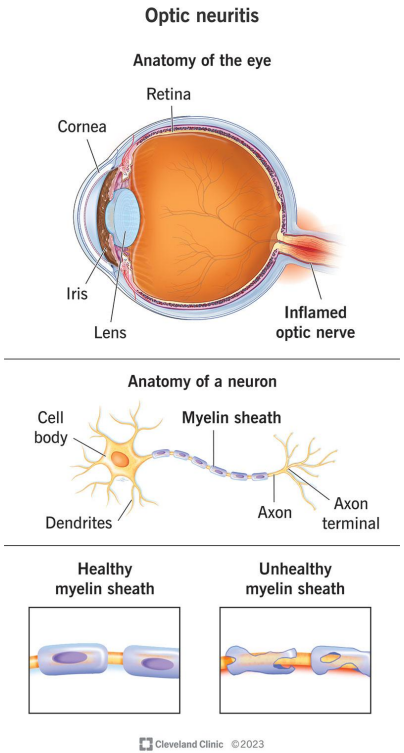
Disclosures

Kian Jalaleddini and Anisha Keshavan are former employees of Octave Bioscience. Dejan Jakimovski has nothing to disclose. Ferhan Qureshi, Shannon McCurdy and Atiyeh Ghoreyshi are employees of Octave Bioscience. Niels Bergsland has nothing to disclose. Michael Dwyer received compensation from Keystone Heart for consultant fees, and financial support for research activities from Bristol Myers Squibb, Mapi Pharma, Keystone Heart, Protembis and V-WAVE Medical, and received compensation from Keystone Heart for consultant fees and received financial support for research activities from Bristol Myers Squibb, Mapi Pharma, Keystone Heart, Protembis and V-WAVE Medical. Murali Ramanathan received research funding from the National Multiple Sclerosis Society, Department of Defense and National Institute of Neurological Diseases and Stroke. Bianca Weinstock-Guttman received honoraria for serving in advisory boards and educational programs from Biogen Idec, Novartis, Genentech, Genzyme and Sanofi, Janssen, Abbvie and Bayer and also received support for research activities from the National Institutes of Health, National Multiple Sclerosis Society, Department of Defense, and Biogen Idec, Novartis, Genentech, Genzyme and Sanofi. Ralph Benedict received honoraria, speaking, or consulting fees from Biogen, BMS, Celgene, EMD Serono, Genentech, Medday, Merck, Novartis, Roche, and Sanofi, and has received research support from Biogen, BMS, Genentech, Genzyme, and Novartis and has received royalties from Psychological Assessment resources, Inc. Robert Zivadinov has received personal compensation from Bristol Myers Squibb, EMD Serono, Sanofi, Keystone Heart, Protembis and Novartis for speaking and consultant fees, and received financial support for research activities from Sanofi, Novartis, Bristol Myers Squibb, Octave, Mapi Pharma, Keystone Heart, Protembis and V-WAVE Medical.

Background



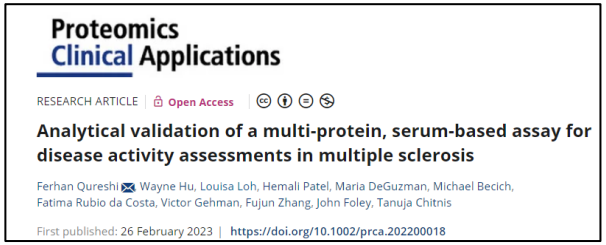
- Optic Neuritis (ON) is a common manifestation in multiple sclerosis (MS) that can affect patients' quality of life.
- The effectiveness of biomarkers in forecasting ON in MS remains underexplored, although studies exploring individual biomarker associations have been reported.[1]
- Multianalyte serum proteomic biomarker algorithms have demonstrated stronger associations versus individual biomarkers with MS endpoints of disease activity and disability status.[2]
- The prediction of ON using protein biomarkers could offer clinicians valuable insights into: disease activity, disease progression, and potentially guide therapeutic strategies

1. Kim, H.J., Lee, EJ., Kim, SY. *et al.* Serum proteins for monitoring and predicting visual function in patients with recent optic neuritis. *Sci Rep* 13, 5609 (2023). https://doi.org/10.1038/s41598-023-32748-5 2. Zhu, W., Chen, C., Hoyt, T. Association between serum multi-protein biomarker profile and real-world disability in multiple sclerosis, Brain Communications, Volume 6, Issue 1, 2024, fcad300, https://doi.org/10.1093/braincomms/fcad300

Objective

To assess the predictive power of serum protein biomarkers measured using the Octave Multiple Sclerosis Disease Activity (MSDA) immunoassay panel for predicting optic neuritis (ON) events in people with MS (pwMS) using machine learning models.

Methods: MSDA Assay Panel



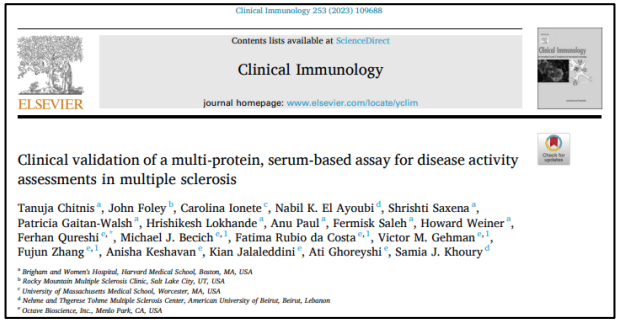
Proteomics Clinical Applications

RESEARCH ARTICLE | Open Access

Analytical validation of a multi-protein, serum-based assay for disease activity assessments in multiple sclerosis

Ferhan Qureshi, Wayne Hu, Louisa Loh, Hemali Patel, Maria DeGuzman, Michael Becich, Fatima Rubio da Costa, Victor Gehman, Fujun Zhang, John Foley, Tanuja Chitnis

First published: 26 February 2023 | https://doi.org/10.1002/prca.202200018



Clinical Immunology 253 (2023) 109688

Contents lists available at ScienceDirect

Clinical Immunology

journal homepage: www.elsevier.com/locate/yclim

Clinical validation of a multi-protein, serum-based assay for disease activity assessments in multiple sclerosis

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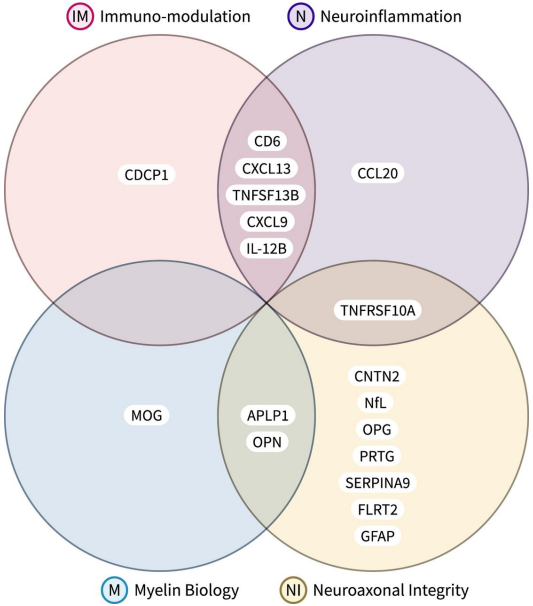

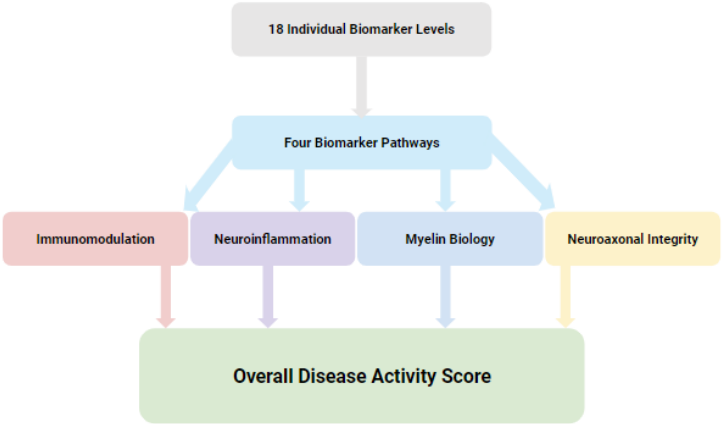

- Custom assay panel developed using PEA technology
- Clinically and analytically validated in serum for disease activity assessment in MS
- Measures 18 protein biomarkers
- Reports on 4 biological pathways
- Provides a quantitative, overall Disease Activity score (1-10)
- Routine clinical use in > 80 clinics across the US
- Leveraged by pharma for retrospective and prospective studies
- ***Panel can be utilized for biological insights from individual proteins and bespoke modeling relative to novel endpoints***

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Methods: CEG-MS Cohort

- CEG-MS is a longitudinal study that explored the cardiovascular, environmental and genetic factors in MS
- Serum samples from 202 CEG-MS study participants have been analyzed in the MSDA assay panel: Baseline serum and at the 5-year follow-up, if available.
- Inclusion criteria: (i) age of 18–75 years old (ii) diagnosed with MS or CIS per McDonald 2017 criteria; (iii) availability of baseline serum sample, MRI and clinical assessment within 30 days of each other; and (iv) availability of an MRI and clinical examination at ~5 years (±6 months) follow-up.
- Exclusion criteria: (i) having clinical relapse or receiving IV corticosteroid therapy within 30 days before the MRI and serum sampling, and (ii) pregnant or nursing mothers.
- The CEG-MS study and the retrospective proteomic analyses were approved by the IRB, all subjects provided informed consent.
- As the objective was prediction of future ON, 109 patients that did not have ON at baseline were used for this analysis.

Characteristic	Study Population n= 109
Female, n (%)	79 (72.5)
Age at baseline, mean (SD)	46.6 (11.8)
Disease duration, mean (SD)	10.8 (9)
Number of relapses , mean (SD)	1.1 (1.8)
BMI, mean (SD)	27.8 (5.9)
EDSS at baseline, median (IQR)	2.5 (2.5)
Optic neuritis, n (%)	10 (9.2)

CEG Cohort MSDA Assay Panel Investigations

ANNALS of Clinical and Translational Neurology
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Proteomic signatures of physical, cognitive, and imaging outcomes in multiple sclerosis

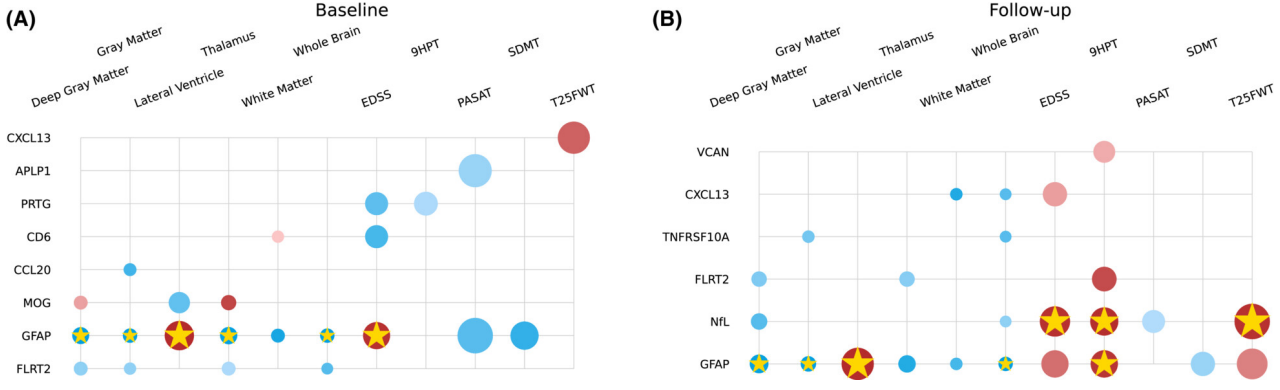
Kian Jalaleddini, Dejan Jakimovski, Anisha Keshavan, Shannon McCurdy, Kelly Leyden, Ferhan Qureshi, Atiyeh Ghoreyshi, Niels Bergsland, Michael G. Dwyer, Murali Ramanathan ... See all authors

First published: 17 January 2024 | https://doi.org/10.1002/acn3.51996

https://doi.org/10.1093/braincomms/fcad183 BRAIN COMMUNICATIONS 2023: Page 1 of 15 | 1
BRAIN COMMUNICATIONS

Proteomics and relationship with axonal pathology in multiple sclerosis: 5-year diffusion tensor imaging study

Dejan Jakimovski,[1] Ferhan Qureshi,[2] Murali Ramanathan,[3] Victor Gehman,[2] Anisha Keshavan,[2] Kelly Leyden,[2] Michael G. Dwyer,[1] Niels Bergsland,[1,4] Bianca Weinstock-Guttman[5] and Robert Zivadinov[1,6]



Cross-sectional single-protein model parameters with adjustment for age, sex, and BMI for baseline (left) and follow-up (right). The radius of each circle is proportional to the estimated standardized coefficient of the corresponding protein; red (blue) circles represent proteins with positive (negative) effects. The opacity of each circle represents the *p*-value; a *p*-value < 0.001 corresponds to full opacity, and a *p*-value of 0.05 corresponds to the least opacity. Biomarkers that survived the multiple comparison correction are marked with a gold star (*).

Proteomic associations derived from the MSDA immunoassay analysis of the CEG cohort have been extensively reported: Clinical (EDSS), MRI, Neurofunctional, OCT, DTI, CABF, ALV, etc.

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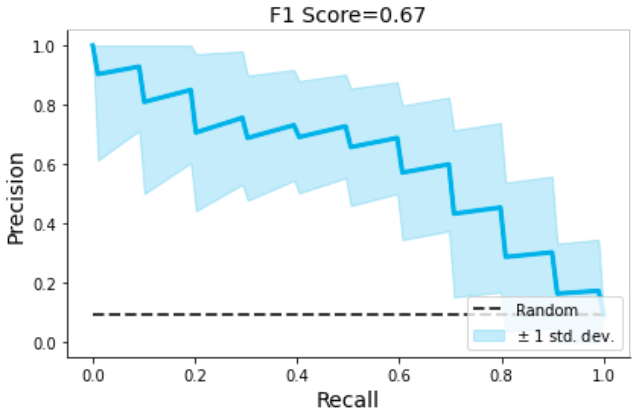
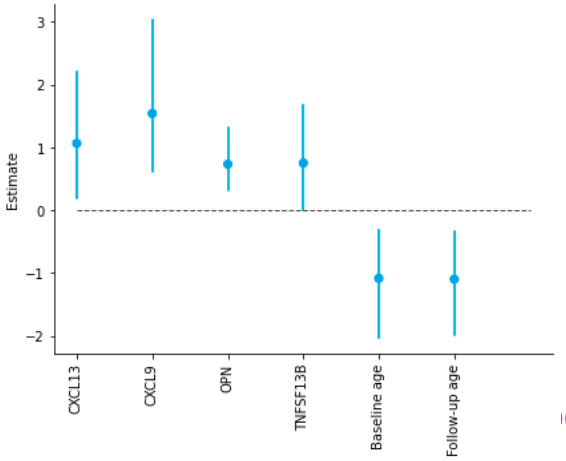
Results – Optic Neuritis Prediction

- Three machine learning models (Support Vector Machine, Logistic Regression, and Linear Discriminant Analysis) were trained to predict ON from baseline biomarkers and demographics in a leave-one-out cross-validation approach to optimize the F1-score.
- The top-performing model used a sequence of preprocessing with StandardScaler and feature selection, and a LDA model
- Validation classification metrics were:
  - F1: 0.67
  - Balanced Accuracy: 0.83
  - Sensitivity: 0.7
  - Specificity: 0.96
- The most influential features in the model were OPN, CXCL13, CXCL9, TNFSF13B, and age.





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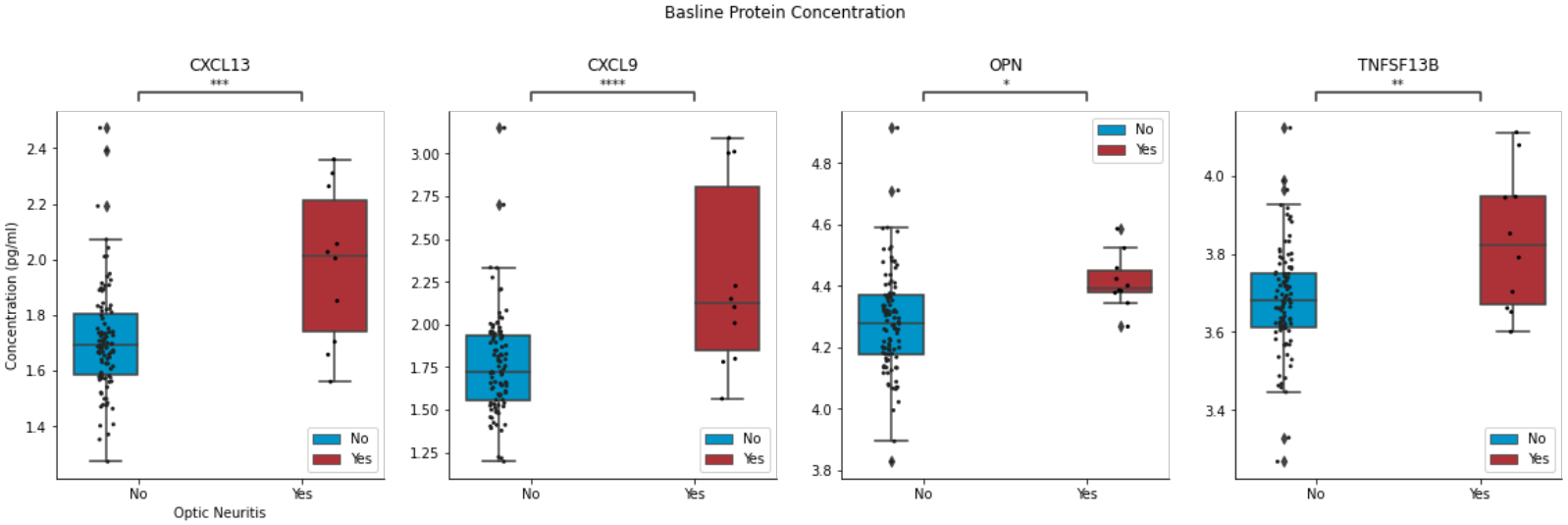
Results - Optic Neuritis Prediction (continued)

- Further inspection of the protein concentration changes suggested that elevations in the concentrations of CXCL13 ($p<0.001$), CXCL9 ($p<0.0001$), OPN ($p<0.05$), and TNFSF13B ($p<0.01$) were predictive of ON in the next 5 years.



Conclusions

- Multianalyte proteomic models that include key mediators in inflammatory processes are able to stratify pwMS regarding their risk of future ON occurrence.
- Protein biomarkers measured using the Octave MSDA assay panel can detect the heightened immune activation that precedes the onset of clinical manifestations, offering a window of opportunity for early intervention.

Acknowledgments

Octave Bioscience

Kian Jalaleddini

Anisha Keshavan

Ati Ghoreyshi

Shannon McCurdy

Elisa Sheng

Jim Eubanks

Wayne Hu

Louisa Loh

Srushti Tiwari

Alex Hari

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MS patients who contributed biospecimens and the research teams that collected and processed data from the CEG-MS cohort

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