Update on biomarkers in neuromyelitis optica

ABSTRACT

Neuromyelitis optica (NMO) (and NMO spectrum disorder [NMOSD]) is an inflammatory autoimmune disease of the CNS. It was first described in the 19th century by Gault and Devic, among others. NMO usually presents with acute or repeated episodes of optic neuritis (ON) and longitudinal transverse myelitis. It presents less commonly as a unique area postrema syndrome accompanied by intractable vomiting and hiccups. NMO/NMOSD may be monophasic; however, the frequency of truly monophasic disease is difficult to estimate, as interval attacks may last several years. The incidence of NMO is highest during the third to fourth decade of life, with a considerably higher frequency among females (female-to-male ratio as high as 9–10:1).

Detection of complement-fixing antibodies directed against aquaporin-4 (AQP4; also known as AQP4-IgG or NMO-IgG) in serum supports the diagnosis of seropositive NMO. However, whether AQP4-IgG levels correlate with disease activity, severity, response to therapy, or long-term outcomes is unclear. Moreover, biomarkers for patients with seronegative NMO have yet to be defined and validated. Collaborative international studies hold great promise for establishing and validating biomarkers that are useful in therapeutic trials and clinical management. In this review, we discuss known and potential biomarkers for NMO.

Neuromyelitis optica (NMO) (and NMO spectrum disorder [NMOSD]) is an inflammatory autoimmune disease of the CNS. It was first described in the 19th century by Gault and Devic, among others. NMO usually presents with acute or repeated episodes of optic neuritis (ON) and longitudinal transverse myelitis. It presents less commonly as a unique area postrema syndrome accompanied by intractable vomiting and hiccups. NMO/NMOSD may be monophasic; however, the frequency of truly monophasic disease is difficult to estimate, as interval attacks may last several years. The incidence of NMO is highest during the third to fourth decade of life, with a considerably higher frequency among females (female-to-male ratio as high as 9–10:1). Detection of complement-fixing antibodies directed against aquaporin-4 (AQP4; also known as AQP4-IgG or NMO-IgG) in the majority of patients with the NMO clinical syndrome has highlighted NMO/NMOSD as a distinct disease entity from multiple sclerosis (MS).

Extensive research has now established significant differences in the clinical, immunologic, histopathologic, and imaging characteristics between NMO/NMOSD and MS.

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GJCF-ICC&BR coinvestigators are listed at Neurology.org/nn.

Funding information and disclosures are provided at the end of the article. Go to Neurology.org/nn for full disclosure forms. The Article Processing Charge was paid by Guthy-Jackson Charitable Foundation.

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Presence of AQP4-IgG has also facilitated the diagnosis and early treatment of patients with NMO/NMOSD. However, studies correlating serum AQP4-IgG titers with disease activity, severity, outcome, and response to therapy have yielded inconsistent results.13–15 The search for additional biomarker candidates in NMO has resulted in several interesting leads, though they remain to be further validated.16,17 In this article, we will review the current landscape of biomarker(s)/biomarker candidates in NMO and NMOSD, consider their clinical implications, and propose potential analytic platforms for future NMO biomarker discovery, validation, and application.

DESIGN OF LITERATURE REVIEW Along with manual literature review by authors with expertise in the field, published peer-reviewed articles were interrogated to assess the current knowledge about biomarkers in NMO/NMOSD. A search of the PubMed database (National Center for Biotechnology Information, US National Library of Medicine) was performed using the query terms “biomarker,” “NMO,” “opticospinal multiple sclerosis (OSMS),” “blood,” “serum,” and “CSF.” NMO and NMOSD met the criteria proposed by Wingerchuk et al.18 The analysis included published literature up to 2014. Although it was not possible to cite every published report in this review, all of the meritorious efforts to discover and validate potential biomarkers in NMO/NMOSD are appreciated. Every effort was made to highlight universally accepted themes. See the figure for a summary of biomarker candidates in NMO and MS and their current evidence levels.

### I. AQP4-IgG AND OTHER SEROLOGIC MARKERS

AQP4-IgG/NMO-IgG. AQP4-IgG was the first proposed biomarker of NMO/NMOSD and has become a sine qua non of NMO diagnosis. Given
its high specificity, NMO-IgG was added as a supportive criterion in the revised 2006 NMO diagnostic criteria.\textsuperscript{18} To date, AQP4 is the main clinically approved biomarker for NMO. AQP4, the most abundant water channel in the CNS, is found predominantly on astrocyte foot processes forming the glia limitans of the blood-brain barrier (BBB) and around synapses at nodes of Ranvier.\textsuperscript{19} The AQP4 protein is highly expressed in the brainstem, hypothalamus, diencephalon, spinal cord, and optic nerves, correlating with the frequent distribution of NMO lesions.\textsuperscript{20} AQP4 is also found in kidney, stomach, placenta, and more isolated regions of the CNS (such as granular layer of the cerebellum, hippocampus, and globus pallidus), but most of these tissues are not known to be involved in NMO/NMOSD.\textsuperscript{21,22} Extensive experimental evidence supports an important contribution of AQP4-IgG to disease pathogenesis.\textsuperscript{23–26} It is evident that NMO-IgG from the systemic circulation enters the CNS through a disrupted BBB; however, it is also possible that anti-AQP4 is generated intrathecally.\textsuperscript{24,25,27} The latter scenario has implications for potential detection of AQP4-IgG in CSF vs serum. AQP4-IgG (primarily IgG1 subclass) binds avidly to AQP4, resulting in complement fixation, generation of chemotactic signals (e.g., C3a, C5a), immune cell infiltration, and subsequent loss of AQP4 and glial fibrillary acidic protein (GFAP) in astrocytes.\textsuperscript{28–31}

Detection of AQP4-IgG has improved over the past decade. First-generation tissue-based immunofluorescence assays had relatively low sensitivity (48%–54% for a single assay or 72% in a combination assay using recombinant human AQP4 ELISA and transfected cell-based assays [CBAs]) and specificity of up to 100%.\textsuperscript{32–34} Newer techniques, such as optimized immunohistochemistry assay, can detect AQP4-IgG with 74.8% sensitivity and 100% specificity.\textsuperscript{35} Antibody directed against the M23 isoform of AQP4 in orthogonal arrays has been reported to have the highest sensitivity for the diagnosis of NMO/NMOSD.\textsuperscript{36} Live CBAs, particularly those using the M1-AQP4 isoform as antigen, have had the lowest false-positive rates.\textsuperscript{37} The importance of assay methodology for the differential diagnosis of NMO vs MS has recently been underscored by the findings of Pittock et al.,\textsuperscript{38} suggesting caution in interpretation of results obtained using ELISA.

AQP4-IgG assessment can be helpful with disease monitoring in certain cases. AQP4-IgG is found in 74% of recurrent NMO cases,\textsuperscript{39} and initial seropositivity correlates with higher relapse rates than seronegative status.\textsuperscript{9} Of interest, AQP4-IgG can predate clinical symptoms by up to 10 years.\textsuperscript{40} Patients with NMO often benefit from plasmapheresis, presumably due to reduction in circulating AQP4-IgG and/or other circulating soluble factor(s).\textsuperscript{41,42} However, the utility of monitoring AQP4-IgG titers during a distinct clinical relapse is less clear. AQP4-IgG titers also may not predict extent of spinal disease.\textsuperscript{14,43} Immunosuppressive therapies (such as azathioprine, cyclophosphamide, or rituximab) can lower AQP4-IgG titers during remission; however, disease quiescence can occur with persistently high NMO-IgG titers.\textsuperscript{44} Currently, NMO-IgG titers do not appear to be a reliable indicator of disease activity or prognosis. Larger longitudinal studies will establish criteria for and usefulness of serial NMO-IgG testing.

Despite the clinical utility of AQP4-IgG in NMO diagnosis, several caveats preclude its use as a universal NMO biomarker. Approximately 20%–30% of patients with the clinical syndrome of NMO lack detectable AQP4-IgG, while in older studies up to 5%–10% of patients with MS were AQP4-IgG positive; however, seronegative cases have significantly decreased with the use of newer CBAs.\textsuperscript{7,45} AQP4-IgG seropositivity also varies widely based on geographic location and ethnicity. Among Caucasians, 56%–73% of patients with NMO/NMOSD are AQP4-IgG positive,\textsuperscript{9,46,47} whereas 33.3% of Caribbean patients, 47% of Italian patients, 63%–90% of Japanese patients, and 70%–76.9% of Chinese patients are seropositive.\textsuperscript{48–51} The wide variability in serostatus may reflect multiple factors, including ethnicity, sex, age, disease activity, immune therapies, and variations in assay techniques.\textsuperscript{52} Collectively, the complexities associated with use of AQP4-IgG as a standard biomarker in NMO/NMOSD emphasize the importance of optimization and standardization of assays and clinical diagnostic criteria.

**Anti-MOG and other autoantibodies in AQP4-IgG–seronegative cases.** Recently, additional autoantibodies have gained attention as candidate biomarkers of NMO/NMOSD, particularly in seronegative cases. Antibodies against myelin oligodendrocyte glycoprotein (MOG-IgG) have been observed in 20%–40% of pediatric patients with acute disseminated encephalomyelitis, ON, and relapsing demyelination disorders, including NMO/NMOSD.\textsuperscript{53–55} MOG localizes to the outer surface of oligodendrocytes and the myelin sheath.\textsuperscript{56} Mader et al.\textsuperscript{57} first reported anti–MOG-IgG in a proportion of AQP4-IgG–seronegative adult and pediatric patients with NMO/NMOSD. Most recently, Ramanathan et al.\textsuperscript{58} found a strong association between anti-MOG antibodies and bilateral relapsing ON in AQP4-IgG–seronegative patients (sensitivity 69%, specificity 99% in their retrospective adult patient cohort). In their study, MOG-IgG–seropositive patients tended to be younger females with a preceding infection and a relapsing course. Monophasic nature in anti-MOG–seropositive cases
II. B CELLS

B cell dysregulation appears to be at the core of NMO/NMOSD pathogenesis. For instance, B cells expressing anti-AQP4 antibodies in the CSF and elevated levels of circulating plasmablasts are found in patients with acutely active NMO. Specific B cell subsets have been implicated as potential biomarker candidates during relapses in patients with NMO. For example, CD138^+ HLA-DR^+ plasmablasts are more abundant in the peripheral blood of patients with NMO and are enriched in the fraction of CSF lymphocytes during a relapse. From a therapeutic standpoint, efficacy of an anti-CD20 monoclonal antibody (rituximab) may be related to the magnitude of B cell depletion and the repopulation of memory B cells. Interleukin (IL)-6 signaling plays an important role in antibody-producing plasmablast survival and has an impact on the germinal center maturation of memory B cells in NMO. Alternatively, inhibition of IL-6 signaling may inhibit T helper 17 (T_h17) cell differentiation, an effector T cell type implicated in NMO pathogenesis. Recent clinical studies also suggest that administration of a monoclonal antibody targeting the IL-6 receptor (tocilizumab) may have clinical benefits in NMO. Indeed, the depletion of proinflammatory IL-6–secreting B cells may underpin the therapeutic benefit of rituximab, as plasmablasts and plasma cells do not display CD20 and NMO-IgG titers are generally uninfluenced by rituximab therapy. Future focused analyses of B cell subsets (surface biomarkers, idiotype, and affinity maturation) will be necessary to identify and validate a prognostic or therapeutic B cell biomarker in NMO.

III. CYTOKINES, CHEMOKINES, AND OTHER MOLECULAR MARKERS OF INFLAMMATION

Circulating soluble mediators as well as B and T cell subsets, cells of myeloid lineage, and deposition of immunoglobulin (IgG and IgM) complement present in the target organ suggest the participation of multiple cell types in the pathogenesis of NMO. However, the timing and contribution of each player remain to be determined as we learn more about the pathogenesis of NMO. On the one hand, presence of autoantibodies, high levels of serum IL-5 and CCL24 (eotaxin-2), CCL26 (eotaxin-3) in the CSF, B-cell activating factor (BAFF) in serum and CSF, and infiltration of granulocytes suggest involvement of a T_h17 cellular immune response in NMO/NMOSD. In addition, there appears to be enhanced expression of T_h17-related (e.g., as IL-17A, IL-6) and T_h11-related (e.g., interferon [IFN]-γ) cytokines in some NMO/NMOSD cohorts. Increased levels of additional inflammatory mediators, including IL-1 receptor antagonist, IL-6, CCL8 (IL-8), IL-13, granulocyte colony-stimulating factor (GCSF), High Mobility Group Box 1 Protein, CXCL13 (BLC), CXCL10 (IP-10), and IL-13–responsive chitinase, have also been detected in the serum or CSF of patients with NMO. In addition, cytokine and chemokine profile differences between NMO/NMOSD and MS have been examined and may prove useful as future diagnostic biomarkers. Despite the differential expression of these inflammatory markers in the serum of patients with NMO, these markers are also observed in other systemic and inflammatory conditions; thus, the specificity and utility of these biomarkers in NMO remain to be investigated further.
optocarpinal lesions. Of interest, sera from relapsing patients with NMO induced permeability in an in vitro BBB model, which was reversed by application of an anti–VEGF-A–blocking antibody, suggesting the potential role of VEGF-A in NMO pathology.\(^{52}\) This effect was higher in sera from AQP4-IgG-seronegative patients with NMOSD than seropositive patients, implying factor(s) other than AQP4-IgG regulate BBB perturbation in NMO.

Other BBB-regulating factors include adhesion molecules, notably intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), which also play important roles in lymphocyte migration into the CNS.\(^{53-55}\) Higher CSF levels of soluble ICAM-1 and soluble VCAM-1 have been reported in patients with relapsing NMO compared with patients with MS or healthy controls and correlate with CSF albumin quotient.\(^{36}\) Collectively, markers of BBB breakdown present another avenue of potential biomarkers in NMO/NMOSD, and future studies are warranted to establish their sensitivity/specificity.

**V. TH LYMPHOCYTE RESPONSE IN NMO** Another body of emerging evidence points to critical roles for T lymphocyte subsets in the pathogenesis of NMO/NMOSD. There appears to be a direct relationship between T activation, expansion, and enhanced expression of Th1, Th17 cytokines, and APQ4-specific T cells.\(^{47}\) Furthermore, presence of APQ4-specific T cells has been observed.\(^{38,39}\) IFN-γ–producing T cells were overrepresented compared with IL-4–expressing lymphocytes in the peripheral blood mononuclear cells in patients with OSMS during relapse.\(^{40,41}\) Elevated IL-17 (from Th17 cells) and CXCL8 levels in CSF were also observed in patients with OSMS and correlated with extent of spinal cord lesions in NMO.\(^{42}\) IL-17, IFN-γ, and GCSF levels were elevated in the CSF of patients with OSMS regardless of their AQP4-IgG serostatus.\(^{43}\) Recent findings also suggest that CD4+: CD8+ T cell ratios may be of interest in understanding NMO/NMOSD pathogenesis and therapeutic efficacy, as shown by reduction in ratio following rituximab therapy during NMO relapse.\(^{44}\) Moreover, regulatory T cell expansion also correlated with NMO remission following anti–CD20 therapy.\(^{45}\) However, a comprehensive analysis of the expression, function, and fate of T cell subsets and their corresponding inflammatory mediators in NMO remains to be conducted.

**VI. CNS PROTEINS AS BIOMARKERS** CNS proteins are detected in sera and CSF of patients with NMO/NMOSD, likely as part of compromised BBB and tissue damage. Neurofilament (NF) heavy-chain levels have been implicated in inflammatory optic neuropathies in NMO/NMOSD, with high serum NF levels correlating with poor clinical outcome.\(^{46}\) In addition, GFAP and S100B are astrocytic markers detected in the CSF in several inflammatory CNS disorders, including NMO, and are both elevated in AQP4-IgG–seropositive patients.\(^{47-49}\) CSF and serum levels of S100B correlated with active NMO disease, suggesting that S100B may be a potential biomarker of acute relapse in seropositive NMO. IL-6 and GFAP may also correlate with onset of NMO attack.\(^{50}\) Other studies have suggested that CSF haptoglobin levels may be a biomarker candidate for diagnosis or disease severity in NMO.\(^{51}\)

**VII. GENETIC BIOMARKERS** To date, as in most autoimmune conditions, there is no direct relationship between any individual gene or gene locus and NMO/NMOSD, suggesting multifactorial etiology with interplay from environmental triggers. Genetic susceptibility loci include HLA-DPB1,\(^{52}\) HLA-DRB1*03:01,\(^{53,54}\) PD-1.3A allele of PTPN22,\(^{45}\) and CD226 Gly307Ser.\(^{56}\) CYP7A1 gene G/G genotype compared with T/G genotype may have a protective gene dose-dependent effect on the risk of NMO.\(^{57}\) It is interesting that the HLA-DRB1*1501 allele, which is associated with MS, does not appear to be associated with NMO.\(^{58}\) Also, no common single nucleotide polymorphism in AQP4 appears to be associated with NMO.\(^{59}\) Hence, although all of the above examples offer reasonable insights, additional studies in larger cohorts are necessary to explore potential genetic contributions to NMO/NMOSD.

**VIII. COMPOSITE BIOMARKER EVALUATION** Beyond assessment of individual biomarkers, it may be useful to explore composite biomarkers and/or biomarker signatures in a complex disease such as NMO/NMOSD. Pattern analysis applied to proteomic data from NMO/NMOSD and MS has suggested composite signatures that differentiate these diseases, especially during relapse.\(^{60}\) Similarly, mass spectrometry and proteome network analyses have been used to generate hypothetical composite biomarkers for potential investigation in NMO/NMOSD,\(^{61}\) MS,\(^{62}\) and systemic lupus erythematosus.\(^{63}\) As with all biomarker discovery or validation efforts, optimal study design is paramount, and any definitive interpretations or conclusions will await prospective masked investigations, preferably among ideally matched and sufficiently large patient cohorts and using optimally standardized methods.

**IX. RELATIONSHIP TO CLINICAL DISABILITY** Beyond insights into molecular or cellular immunopathology of NMO/NMOSD, further biomarkers are needed to
help predict disease activity and outcomes. Current potential markers include BAFF, a proliferation-inducing ligand, and osteopontin, which correlate with disability in NMO but not MS. In addition, CSF levels of CXCL13 (BLC) appear to be elevated in direct proportion to relapse rates and correlate with disability in patients with NMO. While more investigation will be necessary to ascertain their clinical relevance, the intersection of biomarkers and disease status represents an important and unmet patient need.

**CONCLUSION** Sensitive and specific biomarkers are essential for diagnosis, prediction of relapses, prognosis of disease course, and therapeutic response in NMO. If validated, biomarker candidates identified in recent studies will pave the way to a better understanding of NMO pathogenesis. Moreover, they hold promise for greater diagnostic accuracy and individualized care. AQP4-IgG is the best biomarker of NMO to date; however, standardization and optimization of assays are needed. Future investigation into anti-MOG and other non-AQP4 autoantibodies should adjudicate whether these are clinically useful, especially in the context of AQP4-IgG–seronegative cases. Prospective research into T and B lymphocyte immunobiology, cytokine and chemokine profiles, antioxidants, markers of CNS and BBB damage, and genomics/proteomics are expected to accelerate biomarker discovery and validation. In this regard, collaborative longitudinal international biomarker studies with sufficient sample sizes to ensure statistical power should enhance methodological standardization and promote consistent diagnostic accuracy worldwide. In turn, these advances will support the most informative clinical trials to improve therapies and address unmet needs for patients with NMO and NMOSD. Although beyond the scope of the current review, future efforts should also include delineation of the utility of imaging and post mortem neuropathologic examination in predicting clinical disability in NMO/NMOSD.

**AUTHOR CONTRIBUTIONS**

Esther Melamed: drafting/revising the manuscript, study supervision. Michael Levy: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval. Patrick J. Waters: drafting/revising the manuscript, study concept or design, analysis or interpretation of data. Douglas K. Sato: drafting/revising the manuscript, study concept or design, analysis or interpretation of data. Jeffrey L. Bennett: drafting/revising the manuscript. Gareath R. Johns: drafting/revising the manuscript. Douglas C. Hooper: drafting/revising the manuscript, study concept or design. Albert Saiz: drafting/revising the manuscript. Amit Bar-Or: drafting/revising the manuscript, study concept or design. Albert Stevens: drafting/revising the manuscript. Lahkar Pandit: drafting/revising the manuscript, study concept or design. Maria Isabel Leite: drafting/revising the manuscript, intellectual contribution. Nasrin Asgari: drafting/revising the manuscript, analysis or interpretation of data. Najib Kissani: drafting/revising the manuscript. Romain Marignier: drafting/revising the manuscript. Sven Jarius: drafting/revising the manuscript. John Marcellini: analysis or interpretation of data, acquisition of data, statistical analysis. Terry J. Smith: drafting/revising the manuscript. Michael R. Yeaman: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, statistical analysis, study supervision. May H. Han: drafting/revising the manuscript, analysis or interpretation of data.

**STUDY FUNDING**

No targeted funding reported.

**DISCLOSURE**

E. Melamed reports no disclosures. M. Levy is on the scientific advisory board for Asterias, Chugai, and Alexion; is on the editorial board for Multiple Sclerosis and Related Disorders; holds a patent for aquaporin-4 sequence that elicits pathogenic T cell response in animal model of neuromyelitis optica; has consulted for Guédipoint Global, GersonLehrman Group, and Cowen Group; and received research support from Viropharma/Shire, Acorda, ApoPharma, Sanofi, Genzyme, Aplylam, Alexion, Terumo BCT, National Institute of Neurological Disorders and Stroke, and Guthy-Jackson Charitable Foundation. P.J. Waters received speaker honoraria from Biogen Idec Japan and Euroimmun AG; is a review editor for *Frontiers in Molecular Innate Immunity;* holds patents for assays for the detection of antibodies to Igλ, Casp2, Tag-1, Gabaar; and receives royalty payments for CASPR2, LGI1, TAG-1, GABAAR. D.K. Sato received speaker honoraria from Novartis, is an associate editor for *Arquivos de Neuro-Psiquiatria,* and received research support from Ministry of Education, Culture, Sports, Science & Technology in Japan, Japanese Government Scholarship Program, Japan Society for the Promotion of Science, and CAPES/Brasil. J.L. Bennett is on the editorial board for *Journal of Neuro-ophthalmology, Multiple Sclerosis, and Neurology: Neurommunology & Neuroinflammation;* holds a patent for compositions and methods for the treatment of neuromyelitis optica; has consulted for EMD-Serono, Questcor Pharmaceuticals, Aplylam Pharmaceuticals, Medimmune, Abbvie, Novartis, Chugai, Genzyme, and Genentech; received research support from Questcor, Novartis, NIH, and Guthy-Jackson Foundation; holds stock in Apsara Therapeutics; and receives license fees and rights for future royalty payments from Aquaporumab. G.R. John is on the scientific advisory board for Genzyme and Teva; received travel funding and/or speaker honoraria from National Multiple Sclerosis Society, Guthy-Jackson Charitable Foundation, and Teva; and receives research support from Teva, Genzyme, Novartis, National Institute of Neurological Disorders and Stroke, National Multiple Sclerosis Society, and Guthy-Jackson Charitable Foundation. D.C. Hooper is on the editorial board for *Journal of Immunology Research and Scientific Reports;* holds patents for Urane in the treatment of neurodegenerative disease, Human rabies monoclonal antibodies for post-exposure prophylaxis, recombinant rabies vaccines, and reagent for immune modulation; received research support from NIH/NIAID and Albert Stevens Foundation; holds stock in Forer Laboratories; receives license fees from human rabies monoclonal antibodies, Crucell Inc, Rabies vaccines, IDT; and receives royalty payments for human rabies monoclonal antibodies, Crucell Inc/Sano-Fasteur. Albert Saiz is on the scientific advisory board for Biogen Idec and Merck-Serono; received travel funding and/or speaker honoraria from Bayer-Scherin, Merck-Serono, Biogen, Sanofi-Aventis, Teva, and Novartis; and has consulted for Bayer-Scherin, Merck-Serono, Biogen, Sanofi-Aventis, Teva, and Novartis. A. Bar-Or is on the scientific advisory board for Diogenes, Ono Pharmacia, Receptos, Roche, Novartis, GSK, and Guthy-Jackson Greater Good Foundation; is on the editorial board for *Neurology and Clinical and Experimental Neurommunology;* has consulted for and received travel funding and/or speaker honoraria from Diogenix, Ono Pharmacia, Receptos, Roche, Novartis, and GSK; and has consulted for Bayer-Scherin, Merck-Serono, Biogen, Sanofi-Aventis, Teva, and Novartis. H.J. Kim received travel funding and/or speaker honoraria from Bayer-Scherin, Biogen, Genzyme, Merck-Serono, Novartis, Teva-Handok, and UCB; is on the editorial board for *Multiple Sclerosis Journal;* and has consulted for Bayer-Scherin, Biogen, Genzyme, Medimmune, Merck-Serono, Novartis, Teva-Handok, and UCB. L. Pandit reports no disclosures. M.I. Leite received travel funding and honoraria from Biogen Idec Japan, Novartis, and Genzyme. N. Asgari received research support from The Vejle...
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Update on biomarkers in neuromyelitis optica
*Neurol Neuroimmunol Neuroinflamm* 2015;2;
DOI 10.1212/NXI.0000000000000134

This information is current as of July 23, 2015