Serum Biomarker Testing for Multiple Sclerosis and Related Neurologic Diseases

Policy Number: AHS – G2123 – Serum Biomarker Testing for Multiple Sclerosis and Related Neurologic Diseases	Prior Policy Name and Number, as applicable: AHS – G2123 – Serum Biomarker Tests for Multiple Sclerosis
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I. Policy Description

Multiple sclerosis (MS) is the most common immune-mediated inflammatory demyelinating disease of the central nervous system (CNS) and is defined by multifocal areas of demyelination with loss of oligodendrocytes and astroglial scarring. The most commonly present symptom is sensory disturbances, followed by weakness and visual disturbances. However, the disease has a highly variable pace and many atypical forms (M. Olek, 2019). Besides MS, acute CNS demyelination also occurs in acute disseminated encephalomyelitis (ADEM), optic neuritis, transverse myelitis, and neuromyelitis optica (Lotze, 2019).

Neuromyelitis optica and neuromyelitis optica spectrum disorders (NMOSD) are inflammatory disorders of the CNS characterized by severe, immune-mediated demyelination and axonal damage predominantly targeting the optic nerves and spinal cord. Previously considered a subset of MS, this set of disorders is now recognized as its own clinical entity with its own unique immunologic features (Glisson, 2019).

II. Related Policies

Policy Number	Policy Title

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request

1. Cerebrospinal fluid (CSF) and serum oligoclonal band analysis **MEETS COVERAGE CRITERIA** for multiple sclerosis in any of the following situations

   a. Atypical clinical, laboratory, or imaging features; OR

b. An atypical clinically isolated syndrome such as but not limited to, primary progressive multiple sclerosis or relapsing-remitting course; OR

c. Belongs to a population in which MS is less common, such as but not limited to, children, older individuals, or non-Caucasians; OR

d. Insufficient clinical or imaging evidence for diagnosis

2. Serum indirect fluorescence assay or fluorescence-activated cell sorting (FACS) assay of aquaporin-4-IgG (AQP4-IgG) and myelin oligodendrocyte glycoprotein (MOG-IgG) in cases of suspected NMOSD, including NMO, or MOG-EM **MEET COVERAGE CRITERIA** when the following conditions are met:

   a. Monophasic or relapsing acute optic neuritis, myelitis, brainstem encephalitis, encephalitis, or any combination thereof; AND

   b. Radiological or electrophysiological findings compatible with CNS demyelination; AND

   c. At least one of the following:

      i. Belong to a higher risk population—African American, Latin American, Asian, or pediatric; OR

      ii. Abnormal MRI depicting extensive optic nerve lesion, extensive spinal cord lesion or atrophy, or large confluent T2 brain lesions; OR

      iii. Prominent papilledema/papillitis/optic disc swelling during acute optic neuritis; OR

      iv. Neutrophilic CSF pleocytosis; OR

      v. Histopathology finding primary demyelination with intralesional complement and IgG deposits or previous diagnosis of "pattern II MS"; OR

      vi. Simultaneous bilateral acute optic neuritis; OR

      vii. Severe visual deficit or blindness in one or both eyes during or after acute optic neuritis; OR

      viii. Severe or frequent episodes of acute myelitis or brainstem encephalitis; OR

      ix. Permanent sphincter and/or erectile disorder after myelitis; OR

      x. Previous diagnosis of acute disseminated encephalomyelitis (ADEM)

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of a patient's illness.

3. Serum biomarker tests for multiple sclerosis **DO NOT MEET COVERAGE CRITERIA** in all other situations.

4. ELISA, Western blot, immunohistochemistry or any other serum assays to test for NMOSD or MOG-EM **DO NOT MEET COVERAGE CRITERIA**.

5. All other cerebrospinal fluid (CSF) biomarker tests, including AQP4-IgG or MOG-IgG, for multiple sclerosis, NMOSD, or MOG-EM **DO NOT MEET COVERAGE CRITERIA.**

IV. Scientific Background

In the United States, the estimated prevalence of multiple sclerosis (MS) is 100 to 150 per 100,000 individuals, totaling 300,000 to 400,000 persons with MS (Anderson et al., 1992; Dilokthornsakul et al., 2016). The mean age of MS onset is 28 to 31 years of age with clinical disease usually becoming apparent between the ages of 15 to 45 years, though in rare instances, onset has been noted as early as the first years of life or as late as the seventh decade (Goodin, 2014). In most, but not all, cases, a patient presents with a clinically isolated syndrome (CIS) as the first single clinical event. This CIS preludes a clinically definite MS (Lublin et al., 2014). The pattern and course of MS is then further categorized into several clinical subtypes (Lublin & Reingold, 1996; Lublin et al., 2014): Relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), and primary progressive MS (PPMS). RRMS is the most common type of disease course (85 to 90 percent of cases at onset (Weinshenker, 1994)) and is characterized by clearly defined relapses with full recovery, or with sequelae and residual deficit upon recovery. The transition from RRMS to SPMS usually occurs 10 to 20 years after disease onset (Eriksson, Andersen, & Runmarker, 2003). SPMS is characterized by an initial RRMS disease course followed by gradual worsening with or without occasional relapses, minor remissions, and plateaus. PPMS is characterized by progressive accumulation of disability from disease onset with occasional plateaus, temporary minor improvements, or acute relapses still consistent with the definition. A diagnosis of PPMS is made exclusively on patient history: there are no imaging or exam findings that distinguish PPMS from RRMS. PPMS represents about 10 percent of MS cases at disease onset (Koch, Kingwell, Rieckmann, & Tremlett, 2009; M. Olek, 2019). Worsening of disability due to MS is highly variable. The impact of MS varies according to several measures, including severity of signs and symptoms, frequency of relapses, rate of worsening, and residual disability. Worsening of disability over time is a critical issue for MS patients (M. Olek, 2019). Current treatments can delay the progression of the disease. However, this delay is only achievable if treatment starts at the beginning of the disease. Thus, it is essential that a proper diagnosis is made as early as possible, allowing for early treatment and as much delay as possible in symptom progression (Sapko et al., 2020).

MS is primarily diagnosed clinically. The core requirement for the diagnosis is the demonstration of central nervous system lesion dissemination in time and space, based upon either clinical findings alone or a combination of clinical and MRI findings. The history and physical examination are most important for diagnostic purposes. MRI is the test of choice to support the clinical diagnosis of MS (Filippi & Rocca, 2011). The McDonald diagnostic criteria include specific MRI criteria for the demonstration of lesions dissemination in time and space; however, the McDonald criteria are not intended for distinguishing MS from other neurologic conditions (Brownlee, Hardy, Fazekas, & Miller, 2017). The sensitivity and specificity of MRI for the diagnosis of MS varies widely in different studies. This variation is probably due to differences among the studies in MRI criteria and patient populations (Offenbacher et al., 1993; Schaffler et al., 2011). Using the 2010 McDonald criteria, the sensitivity and specificity were approximately 53 and 87 percent, respectively (Rovira et al., 2009). In the first studies applying the 2017 criteria (Hyun et al., 2018), the sensitivity is higher (83.6%), but the specificity is lower (85%).

Qualitative assessment of cerebrospinal fluid (CSF) for oligoclonal IgG bands (OCBs) using isoelectric focusing can be an important diagnostic tool when determining a diagnosis of MS. Elevation of the CSF immunoglobulin level relative to other protein components is a common finding in patients with MS and suggests intrathecal synthesis. The immunoglobulin increase is predominantly IgG, although the synthesis of IgM and IgA is also increased (M. Olek, 2019). A positive finding is defined by "finding of either oligoclonal bands different from any such bands in serum, or by an increased IgG index" and can be measured by features such as percentage of total protein or total albumin. Up to 95% of clinically definite MS cases will have these oligoclonal bands (M. Olek, Howard, Jonathan, 2019).

The 2017 McDonald criteria allows for the presence of CSF oligoclonal bands to substitute for the diagnostic requirement of fulfilling dissemination in time. However, Thompson notes that "currently, no laboratory test in isolation confirms the diagnosis of multiple sclerosis" (Thompson et al., 2018). Luzzio et al also note that in a review of four guidelines from the Consortium of Multiple Sclerosis Centers, the European Academy of Neurology, and the Magnetic Resonance Imaging in MS Network, MRI is the "imaging procedure of choice for confirming MS and monitoring disease progression in the brain and spinal cord" (Luzzio, 2019).

Neuromyelitis optica spectrum disorders (NMOSD, also known as Devic disease or neuromyelitis optica, NMO) are a range of conditions that are characterized by symptoms similar to MS; namely demyelination and axonal damage to structures of the central nervous system, such as the spinal cord. Previously, NMOSD were considered a subset of MS; however, now NMOSD and NMO are recognized as having distinct features, specifically the presence of a NMOSD/NMO-specific antibody that binds aquaporin-4 (AQP4), setting these apart from relapsing-remitting MS. AQP4 is a water channel protein primarily located in the spinal cord gray matter. NMO-IgG (or anti-AQP4) is involved in the pathogenesis of NMOSD/NMO. This antibody selectively binds AQP4, differing from MS in that the loss of AQP4 expression is unrelated to the stage of demyelination. The presence of this antibody is

incorporated into the current diagnostic criteria for NMOSD and can differentiate MS cases from NMOSD cases (Glisson, 2019).

Clinical Utility and Validity

There is a strong unmet clinical need for objective body fluid biomarkers to assist early diagnosis and estimate long-term prognosis, monitor treatment response, and predict potential adverse effects in MS. Currently, no biomarkers of MS have been validated; however, many are under consideration: microRNA (miRNA), messenger RNA (mRNA), lipids, autoantibodies, metabolites, and proteins all have been reported to have potential as possible biomarkers (Comabella & Montalban, 2014; Comabella, Sastre-Garriga, & Montalban, 2016; El Ayoubi & Khoury, 2017; Lim et al., 2017; Raphael, Webb, Stuve, Haskins, & Forsthuber, 2015; Teunissen, Malekzadeh, Leurs, Bridel, & Killestein, 2015).

Fryer et al. (2014) compared three assays for measuring aquaporin-4 IgG: ELISA, fixed cell-based fluorescence (CBA), and live cell-based fluorescence (FACS, M1 and M23 versions). Four groups of patients were measured with these assays. In Group 1 (n = 388), FACS was optimal, with the highest area under the curve. In Group 2, FACS identified the highest percentage of neuromyelitis optica spectrum disorders, identifying 23 (M1) and 24 (M23) of 30 patients. In Group 3, all four assays identified true negatives at an approximate 85% success rate (5 of 31 positives). In Group 4, all four assays identified true positives in 40 of 41 samples. The authors noted that "aquaporin-4-transfected CBAs, particularly M1-FACS, perform optimally in aiding NMOSD serologic diagnosis" (Fryer et al., 2014).

Jitprapaikulsan et al. (2018) evaluated the prognostic value of aquaporin-4 IgG and myelin oligodendrocyte glycoprotein IgG (MOG) in patients with recurrent optic neuritis (rON). 246 patients were studied and autoantibodies were detected in 32% of these patients (aquaporin-4 in 19%, MOG in 13%). 186 patients had rON only and 60 patients had "additional inflammatory demyelinating attacks" (rON plus). Of the 186 rON only patients, 27 were positive for MOG, 24 were positive for aquaporin-4, and 110 were negative for both. In the rON plus group, 23 were positive for aquaporin-4, 4 were positive for MOG, and 11 were negative for both. The authors noted that 5 years after optic neuritis onset, 59% of aquaporin-4 positive patients and 12% of MOG positive patients were estimated to have "severe visual loss". The authors concluded that "aquaporin-4 IgG seropositivity predicts a worse visual outcome than MOG IgG1 seropositivity, double seronegativity, or MS diagnosis. Myelin oligodendrocyte glycoprotein IgG1 is associated with a greater relapse rate but better visual outcomes" (Jitprapaikulsan et al., 2018).

Sotirchos and colleagues (2019) compared 31 healthy controls with individuals with one of three types of optic neuritis (ON): 48 individuals with aquaporin-4 IgG-associated ON (AQP4-ON), 16 individuals with myelin oligodendrocyte glycoprotein-IgG-associated ON (MOG-ON), and 40 individuals with MS-associated ON (MS-ON). The authors note, "AQP4-ON eyes exhibited worse high-contrast letter acuity (HCLA) compared to MOG-ON (-22.3 ± 3.9 letters; $p < 0.001$) and MS-ON eyes (-21.7 ± 4.0 letters; $p < 0.001$). Macular ganglion cell + inner plexiform layer (GCIPL) thickness was lower, as compared to MS-ON, in AQP4-ON (-9.1 ± 2.0 μm; $p < 0.001$) and MOG-ON (-7.6 ± 2.2 μm; $p = 0.001$) eyes. Lower GCIPL

thickness was associated with worse HCLA in AQP4-ON (-16.5 ± 1.5 letters per 10 µm decrease; $p < 0.001$) and MS-ON eyes (-8.5 ± 2.3 letters per 10 µm decrease; $p < 0.001$), but not in MOG-ON eyes (-5.2 ± 3.8 letters per 10 µm decrease; $p = 0.17$), and these relationships differed between the AQP4-ON and other ON groups ($p < 0.01$ for interaction)." These data indicate that AQP4-IgG seropositivity suggests worse visual outcomes than those occurring after MOG-ON or even MS-ON (Sotirchos et al., 2019).

Cantó et al. (2019) evaluated neurofilament light chain's (NfL) ability to "serve as a reliable biomarker of disease worsening for patients with multiple sclerosis (MS)". 607 patients with MS were included and assessed over a period of 12 years. Serum NfL was measured, and disability progression was the primary clinical outcome (defined as "clinically significant worsening on the Expanded Disability Status Scale (EDSS) score and brain fraction atrophy"). Baseline measurements of NfL showed significant association with EDSS score, MS subtype, and treatment status. Worsening EDSS scores and changes of NfL levels over time were found to be correlated. The baseline NfL measurement was also found to be associated with approximately 11.6% of brain fraction atrophy over 10 years, increasing to 18% after multivariable analysis. Furthermore, active treatment was associated with declining levels of NfL, with "high-potency treatments" associated with the greatest decrease out of all of the treatments assessed. Overall, the authors concluded that they had confirmed a significant association of serum NfL with clinical outcomes of MS. However, they also acknowledged that "further prospective studies are necessary to assess the assay's utility for decision-making in individual patients" (Cantó et al., 2019).

Gil-Perotin et al. (2019) evaluated the combined biomarker profile of NfL and chitinase3-like1 (CHI3L1) and its ability to provide prognostic information for patients with MS. 157 MS patients were included, with 99 RRMS patients, 35 SPMS patients, and 23 PPMS patients. Disease activity was defined by "clinical relapse and/or gadolinium-enhanced lesions (GEL) in MRI within 90 days from CSF collection". Levels of both biomarkers were found to be higher in MS patients compared to non-MS patients. Elevated NfL was associated with clinical relapse and GEL in RRMS and SPMS patients and high CHI3L1 levels were characteristic of progressive disease. The authors also found the combined profile useful for differentiating between MS subtypes, with high NfL and low CHI3L1 often indicating a RRMS stage. They found that elevation of both biomarkers indicates disease progression. Overall, the authors concluded these biomarkers were useful for disease activity and progression and that the biomarker profile can discriminate between MS subtypes (Gil-Perotin et al., 2019).

Martin et al. (2019) performed a meta-analysis to evaluate the CSF levels of NfL to determine "whether, and to what degree, CSF NfL levels differentiate MS from controls, or the subtypes or stages of MS from each other". The authors identified 14 articles for inclusion in their meta-analysis. NfL levels were higher in MS patients (746) than controls (435) (mean of 1965.8 ng/L in MS patients compared to 578.3 ng/L in healthy controls). Mean NfL levels were found to be higher in 176 patients with relapsing disease (mean = 2124.8ng/L) compared to 92 patients with progressive disease (mean = 1121.4ng/L). The authors also found that patients with relapsing disease (138 in this cohort) had approximately double the levels of CSF NfL compared to patients in remission (268), with an average of 3080.6ng/L in the relapsing cohort

compared to 1541.7ng/L in the remission cohort. Overall, the authors concluded that CSF NfL correlates with MS activity throughout the course of disease, that relapse was strongly associated with elevated CSF NfL levels, and that CSF NfL may be useful as a measure of activity (Martin, McGlasson, Hunt, & Overell, 2019).

Simonsen et al. (2020) performed a retrospective study investigating if analysis of IgG index could safely predict oligoclonal band (OCB) findings. 1295 MS patients were included, with 93.8% of them positive for OCBs. Of 842 MS patients with known IgG status and known OCB status, 93.3% were oligoclonal band positive and 76.7% were found to have an elevated IgG profile. The authors found the positive predictive value of elevated IgG based on positive OCBs to be 99.4%, and the negative predictive value of normal IgG based on negative OCBs to be 26.5%. The authors concluded that an IgG index of >0.7 has a positive predictive value of >99% for OCBs (Simonsen et al., 2020).

V. Guidelines and Recommendations

International Advisory Committee on Clinical Trials in Multiple Sclerosis (Lublin et al., 2014)

In 2014, the International Advisory Committee on Clinical Trials in Multiple Sclerosis, jointly sponsored by the U.S. National Multiple Sclerosis Society, the European Committee for Treatment and Research in Multiple Sclerosis, and the MS Phenotype Group, re-examined MS phenotypes, exploring clinical, imaging, and biomarker advances through working groups and literature searches. The committee concluded that "To date, there are no clear clinical, imaging, immunologic or pathologic criteria to determine the transition point when RRMS [relapse-remitting MS] converts to SPMS [secondary progressive MS]; the transition is usually gradual. This has limited our ability to study the imaging and biomarker characteristics that may distinguish this course (Lublin et al., 2014)." In 2020, the committee updated this policy for clarity, summarizing with "the committee urges clinicians, investigators, and regulators to consistently and fully use the 2013 phenotype characterizations by (1) using the full definition of activity, that is, the occurrence of a relapse or new activity on an MRI scan (a gadolinium-enhancing lesion or a new/unequivocally enlarging T2 lesion); (2) framing activity and progression in time; and (3) using the terms worsening and progressing or disease progression more precisely when describing MS course."(Lublin et al., 2020)

The International Panel on Diagnosis of Multiple Sclerosis (Thompson et al., 2018)

The Panel reviewed the 2010 McDonald criteria and recommended: "In a patient with a typical clinically isolated syndrome and fulfilment of clinical or MRI criteria for dissemination in space and no better explanation for the clinical presentation, demonstration of CSF-specific oligoclonal bands in the absence of other CSF findings atypical of multiple sclerosis allows a diagnosis of this disease to be made." The Panel goes on to state that "CSF oligoclonal bands are an independent predictor of the risk of a second attack when controlling for demographic, clinical, treatment, and MRI variables" and that in the absence of atypical CSF findings, demonstration of these CSF OCBs can allow for a diagnosis of MS to be made. The Panel remarks that inclusion of this CSF criterion can substitute for the traditional "dissemination in

time" criterion, but that no laboratory test in isolation can confirm an MS diagnosis (Thompson et al., 2018).

CSF examination is "strongly recommended" in some circumstances for MS diagnosis, and the Panel remarks that the threshold for additional testing should be low. Those circumstances are as follows:

- "when clinical and brain MRI evidence supporting a diagnosis of multiple sclerosis is insufficient, particularly if initiation of long-term disease-modifying therapies are being considered"
- "when there is a presentation other than a typical clinically isolated syndrome, including patients with a progressive course at onset (primary progressive multiple sclerosis)"
- "when there are clinical, imaging, or laboratory features atypical of MS"
- "in populations in which diagnosing MS is less common (for example, children, older individuals, or non-Caucasians)".

The Panel does emphasize that it is essential for CSF to be paired with another serum sample when analyzed to demonstrate that the OCBs are unique to the CSF (Thompson et al., 2018).

The treatments for these very similar conditions (MS and NMOSD) differ, as some MS treatments (interferon beta, fingolimod, and natalizumab) can exacerbate NMOSDs. Therefore, the Panel recommended that "NMOSDs should be considered in any patient being evaluated for multiple sclerosis". The Panel notes that aquaporin-4 serological testing "generally differentiates" NMOSD from MS (Thompson et al., 2018). Serological testing for AQP4 and for MOG should be done in all patients with features suggesting NMOSDs (severe brainstem involvement, bilateral optic neuritis, longitudinally extensive spinal cord lesions, large cerebral lesions, or a normal brain MRI or findings not fulfilling dissemination in space [DIS]), and considered in groups at higher risk of NMOSDs (African American, Asian, Latin American, and pediatric populations) (Thompson et al., 2018).

International Panel on MOG Encephalomyelitis (Jarius et al., 2018)

Human myelin oligodendrocyte glycoprotein (MOG-IgG)-associated encephalomyelitis (MOG-EM) is considered a unique disease from MS and other NMOSD, but MOG-EM has often been misdiagnosed as MS in the past. In 2018, an international panel released their recommendations concerning diagnosis and antibody testing. They state their purpose with the following: "To lessen the hazard of overdiagnosing MOG-EM, which may lead to inappropriate treatment, more selective criteria for MOG-IgG testing are urgently needed. In this paper, we propose indications for MOG-IgG testing based on expert consensus. In addition, we give a list of conditions atypical for MOG-EM ("red flags") that should prompt physicians to challenge a positive MOG-IgG test result. Finally, we provide recommendations regarding assay methodology, specimen sampling and data interpretation."

They list the following recommendations:

- Assay: Indirect fluorescence assays, including fluorescence-activated cell sorting (FACS) that targets full-length human MOG (IgG-specific), are the gold standards. The use of either IgM or IgA antibodies are less specific and can result in both false-negative results due to high-affinity IgG displacing IgM and false-positive results due to cross-reactivity with rheumatoid factors.
- Immunohistochemistry is NOT recommended because it is "less sensitive than cell-based assays, limited data available on specificity, [and] sensitivity depends on tissue donor species."
- Peptide-based ELISA and Western blot are NOT recommended because they are "insufficiently specific, obsolete".
- Biomaterial: Serum is the recommended specimen of choice. CSF is "not usually required" because "MOG-IgG is produced mostly extrathecally, resulting in lower CSF than serum titers".
- Timing of testing: Serum concentration of MOG-IgG is highest during an acute attack and/or while not receiving immunosuppressive treatment. MOG-IgG concentration may decrease during remission. "If MOG-IgG test is negative but MOG-EM is still suspected, re-testing during acute attacks, during treatment-free intervals, or 1-3 months after plasma exchange (or IVIG [intravenous immunoglobulin treatment]) is recommended."
- "Given the very low pre-test probability, we recommend against general MOG-IgG testing in patients with a progressive disease course."
- "In practice, many patients diagnosed with AQP4-IgG-negative NMOSD according to the IPND 2015 criteria will meet also the criteria for MOG-IgG testing…and should thus be tested. However, MOG-IgG testing should not be restricted to patients with AQP4-IgG-negative NMOSD."

The table below outlines the recommendation on the criteria required for testing:

Table 1 Recommended indications for MOG-IgG testing in patients presenting with acute CNS demyelination of putative autoimmune etiology

1. Monophasic or relapsing acute optic neuritis, myelitis, brainstem encephalitis, encephalitis, or any combination thereof,
and
2. radiological or, only in patients with a history of optic neuritis, electrophysiological (VEP) findings compatible with CNS demyelination,
and
3. at least one of the following findings:

MRI
- a. Longitudinally extensive spinal cord lesion (≥3 VS, contiguous) on MRI (so-called LETM)[a,b]
- b. Longitudinally extensive spinal cord atrophy (≥3 VS, contiguous) on MRI in patients with a history compatible with acute myelitis[a]
- c. Conus medullaris lesions, especially if present at onset[c]
- d. Longitudinally extensive optic nerve lesion (e.g., >1/2 of the length of the pre-chiasmal optic nerve, T2 or T1/Gd)[d]
- e. Perioptic Gd enhancement during acute ON[e]
- f. Normal supratentorial MRI in patients with acute ON, myelitis and/or brainstem encephalitis
- g. Brain MRI abnormal but no lesion adjacent to a lateral ventricle that is ovoid/round or associated with an inferior temporal lobe lesion and no Dawson's finger-type or juxtacortical U fiber lesion (Matthews-Jurynczyk criteria[f])
- h. Large, confluent T2 brain lesions suggestive of ADEM

Fundoscopy
- i. Prominent papilledema/papillitis/optic disc swelling during acute ON

CSF
- j. Neutrophilic CSF pleocytosis[g] or CSF WCC > 50/µl[h]
- k. No CSF-restricted OCB as detected by IEF at first or any follow-up examination[i] (applies to continental European patients only)

Histopathology
- l. Primary demyelination with intralesional complement and IgG deposits
- m. Previous diagnosis of "pattern II MS"[j]

Clinical findings
- n. Simultaneous bilateral acute ON
- o. Unusually high ON frequency or disease mainly characterized by recurrent ON
- p. Particularly severe visual deficit/blindness in one or both eyes during or after acute ON
- q. Particularly severe or frequent episodes of acute myelitis or brainstem encephalitis
- r. Permanent sphincter and/or erectile disorder after myelitis
- s. Patients diagnosed with "ADEM", "recurrent ADEM", "multiphasic ADEM" or "ADEM-ON"
- t. Acute respiratory insufficiency, disturbance of consciousness, behavioral changes, or epileptic seizures (radiological signs of demyelination required)
- u. Disease started within 4 days to ~4 weeks after vaccination
- v. Otherwise unexplained intractable nausea and vomiting or intractable hiccups (compatible with area postrema syndrome)[a]
- w. Co-existing teratoma or NMDAR encephalitis (low evidence[k])

Treatment response
- x. Frequent flare-ups after IVMP, or steroid-dependent symptoms[l] (including CRION)
- y. Clear increase in relapse rate following treatment with IFN-beta or natalizumab in patients diagnosed with MS (low evidence)

Note that these recommendations are primarily intended for use in adults and adolescents. Indications for MOG-IgG testing in young children need not to be as rigorous

International Panel on NMOSD (Wingerchuk et al., 2015)

The International Panel on NMOSD recommends "testing with cell-based serum assays (microscopy or flow cytometry-based detection) whenever possible because they optimize autoantibody detection (mean sensitivity 76.7% in a pooled analysis; 0.1% false-positive rate in a MS clinic cohort)." They state that ELISA and indirect immunofluorescence assays have lower sensitivity and "strongly" recommend "interpretative caution if such assays are used and when low-titer positive ELISA results are detected in individuals who present with NMOSD clinical symptoms less commonly associated with AQP4-IgG (e.g., presentations other than recurrent optic neuritis, myelitis with LETM, or area postrema syndrome) or in situations where clinical evidence suggests a viable alternate diagnosis. Confirmatory testing is recommended, ideally using 1 or more different AQP4-IgG assay techniques. Cell-based assay has the best current sensitivity and specificity and samples may need to be referred to a specialized laboratory." The table below outlines the NMOSD diagnostic criteria for adult patients.

Table 1 NMOSD diagnostic criteria for adult patients

Diagnostic criteria for NMOSD with AQP4-IgG

1. At least 1 core clinical characteristic
2. Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended)
3. Exclusion of alternative diagnoses[a]

Diagnostic criteria for NMOSD without AQP4-IgG or NMOSD with unknown AQP4-IgG status

1. At least 2 core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements:
   a. At least 1 core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome
   b. Dissemination in space (2 or more different core clinical characteristics)
   c. Fulfillment of additional MRI requirements, as applicable
2. Negative tests for AQP4-IgG using best available detection method, or testing unavailable
3. Exclusion of alternative diagnoses[a]

Core clinical characteristics

1. Optic neuritis
2. Acute myelitis
3. Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting
4. Acute brainstem syndrome
5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions (figure 3)
6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions (figure 3)

VI. State and Federal Regulations, as applicable

A search on the FDA website on July 14, 2021 yielded no results for "myelin oligodendrocyte glycoprotein", "oligoclonal band", or "neurofilament light chain" (FDA, 2021). A search on the FDA website on the same date for "aquaporin-4" yielded one result, the KRONUS Aquaporin-4 Autoantibody (AQP4Ab) ELISA Assay. The indication for use is as follows: "The KRONUS Aquaporin-4 Autoantibody (AQP4Ab) ELISA Assay is for the semi-quantitative determination of autoantibodies to Aquaporin-4 in human serum. The KRONUS Aquaporin-4 Autoantibody (AQP4Ab) ELISA Assay may be useful as an aid in the diagnosis of Neuromyelitis Optica (NMO) and Neuromyelitis Optica Spectrum Disorders (NMOSD). The KRONUS Aquaporin-4 Autoantibody (AQP4Ab) ELISA Assay is not to be used alone and is to be used in conjunction with other clinical, laboratory, and radiological (e.g. MRI) findings" (FDA, 2016).

Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

VII. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified
83916	Oligoclonal immune (oligoclonal bands)
84182	Protein; Western Blot, with interpretation and report, blood or other body fluid, immunological probe for band identification, each
86255	Fluorescent noninfectious agent antibody; screen, each antibody
86256	Fluorescent noninfectious agent antibody; titer, each antibody
88341	Immunohistochemistry or immunocytochemistry, per specimen; each additional single antibody stain procedure (List separately in addition to code for primary procedure)
88342	Immunohistochemistry or immunocytochemistry, per specimen; initial single antibody stain procedure

Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

VIII. Evidence-based Scientific References

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