Corporate Medical Policy

Biomarker Testing for Multiple Sclerosis and Related Neurologic Diseases AHS – G2123

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Description of Procedure or Service

I. Policy Description

Multiple sclerosis (MS) is the most common immune-mediated inflammatory demyelinating disease of the central nervous system (CNS) defined by multifocal areas of demyelination with loss of oligodendrocytes and astroglial scarring. The most common presenting symptoms are sensory disturbances, followed by weakness and visual disturbances, but the disease has a highly variable pace and many atypical forms (Olek, 2017). Besides MS, acute CNS demyelination also occurs in acute disseminated encephalomyelitis (ADEM), optic neuritis, transverse myelitis, and neuromyelitis optica (Lotze, 2018). “Neuromyelitis optica (NMO, previously known as Devic disease) and neuromyelitis optica spectrum disorders (NMOSD) are inflammatory disorders of the central nervous system characterized by severe, immune-mediated demyelination and axonal damage predominantly targeting optic nerves and spinal cord (Glisson, 2018).”

II. Scientific Background

In the United States, the estimated prevalence is 100 to 150 per 100,000, for a total of 300,000 to 400,000 persons with MS (Anderson et al., 1992; Dilokthornsakul et al., 2016). The mean age of MS onset ranges from 28 to 31 years with clinical disease usually becoming apparent between the ages of 15 to 45 years, though onset rarely has been noted as early as the first years of life or as late as the seventh decade (Goodin, 2014). In most cases but not all the clinically isolated syndrome (CIS) as the first single clinical event 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. Primary progressive multiple sclerosis (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, and 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; Olek, 2017).

Worsening of disability due to MS is highly variable. The impact of MS varies according to a number of measures, including severity of signs and symptoms, frequency of relapses, rate of...
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worsening, and residual disability. Worsening of disability over time is probably the most important issue in MS for patients (Olek, 2017).

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, and the 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 of the application of the 2017 criteria (Hyun et al., 2018), the sensitivity is higher (83.6%), but the specificity is lower (85%).

Previously, neuromyelitis spectrum disorders (NMOSD) were considered a subset of MS; however, now NMOSD and NMO are recognized as having distinct features, specifically an NMOSD/NMO-specific antibody that bind aquaporin-4 (AQP4), which sets 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 (Glisson, 2018). NMO lesions are distinct from MS in that both AQP4 and its coupled glutamate transporter, EAAT2, are lost. “In vitro studies demonstrate that binding of NMO-IgG to astrocytic AQP4 initiates multiple potentially neuropathogenic mechanisms: complement activation, AQP4 and EAAT2 downregulation with disruption of water and glutamate homeostasis, enhanced blood-brain barrier permeability, plasma protein and granulocyte influx, and antibody-dependent cell-mediated cytotoxicity (Hinson, McKeon, & Lennon, 2010).”

In MS, qualitative assessment of cerebrospinal fluid (CSF) for oligoclonal IgG bands (OCBs) using isoelectric focusing is an important diagnostic CSF study 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 (Olek, 2017). The 2010 McDonald criteria note that positive CSF findings can provide supportive evidence that the underlying disorder is inflammatory demyelinating, and incorporate them into the criteria for primary progressive MS. However, in contrast to the earlier 2001 and 2005 McDonald criteria, the CSF findings are not incorporated into the 2010 criteria for dissemination in space (McDonald et al., 2001; Polman et al., 2005). The 2017 McDonald criteria allow the presence of CSF oligoclonal bands to substitute for the requirement of fulfilling dissemination in time (Thompson et al., 2018).

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, there are no validated biomarkers of MS, however there are many under consideration: microRNA, messenger RNA, lipids, autoantibodies, metabolites and proteins are 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).
Polman et al (2011) found that “Although increased IgG index or the presence of oligoclonal bands in the CSF support an MS diagnosis, and AQP4 antibody assays can help in the differential diagnosis process, there are still no specific biomarkers to confirm the diagnosis.”

Freedman (2012) evaluated the prognostic value of gMS-Classifier1 in a large study cohort of clinically isolated syndrome (CIS) patients. gMS-Classifier1 antibodies’ panel (anti-GAGA2, anti-GAGA3, anti-GAGA4 and anti-GAGA6) levels were measured blinded to clinical data. Subjects were classified as either ‘positive’ or ‘negative’ according to a classification rule. The authors found that “gMS-Classifier1 was not predictive for the time to clinically definite MS or time to MS according to the revised McDonald’s criteria, but did significantly predict an increased risk for confirmed disability progression.” They concluded that “we could not confirm previous results that gMS-Classifier1 can predict early conversion to MS in CIS.”

Brownlee et al (2017) concluded in their most recent review that “Research is also focused on novel CSF and body fluid biomarkers that are associated with the development of multiple sclerosis in patients with clinically isolated syndrome, including CSF IgM- oligoclonal bands, MRZ-specific IgG, \( \kappa \) free light chains, CXCL13, chitinase-3-like protein 1, and neurofilament light chain. However, their use in differentiating multiple sclerosis from other disorders is yet to be established.”

Olek (2017) also states in their review that “Initial studies suggested that antibodies to myelin oligodendrocyte glycoprotein (MOG) and myelin basic protein (MBP) were potential markers of MS disease activity and predictors of progression from a clinically isolated syndrome to MS. However, subsequent evidence suggests that these antibodies are not associated with an increased risk of progression to MS or with MS disease activity.”

Thompson et al (2018) in establishing the 2017 McDonald criteria reiterate that “Currently, no laboratory test in isolation confirms the diagnosis of multiple sclerosis. Although AQP4 serological testing generally differentiates NMOSDs from multiple sclerosis, less is known about the performance of testing for MOG antibodies. Other diagnostic biomarkers have been proposed to differentiate between multiple sclerosis phenotypes or to monitor CNS damage, but none has been shown to diagnose multiple sclerosis reliably in individual patients, representing a major unmet need and area for future research.”

III. State and Federal Regulations, as applicable

This test is considered a laboratory developed test (LDT); developed, validated and performed by individual laboratories.

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.

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

BCBSNC will provide coverage for biomarker testing for multiple sclerosis and related neurologic diseases when it is determined the medical criteria or reimbursement guidelines below are met.
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Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member’s benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When biomarker testing for multiple sclerosis and related neurologic diseases is covered

1. Reimbursement for 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 is allowed 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 intralesonal 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)

When biomarker testing for multiple sclerosis and related neurologic diseases is not covered

1. Reimbursement is not allowed for serum biomarker tests for multiple sclerosis.
2. Reimbursement is not allowed for ELISA, Western blot, immunohistochemistry or any other serum assays to test for NMOSD or MOG-EM.
3. Reimbursement is not allowed for cerebrospinal fluid (CSF) biomarker tests, including AQP4-IgG or MOG-IgG, for multiple sclerosis, NMOSD, or MOG-EM.

Policy Guidelines

A. Guidelines and Recommendations
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Practice Guidelines and Position Statements

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).”

The International Panel on Diagnosis of Multiple Sclerosis

The Panel reviewed the 2010 McDonald criteria and recommended: “in patients with a typical clinically isolated syndrome and clinical or MRI demonstration of dissemination in space, the presence of CSF-specific oligoclonal bands allows a diagnosis of multiple sclerosis; symptomatic lesions can be used to demonstrate dissemination in space or time in patients with supratentorial, infratentorial, or spinal cord syndrome; and cortical lesions can be used to demonstrate dissemination in space (Thompson et al., 2018).”

As substantial data on neuromyelitis optica spectrum disorders (NMOSDs) have shown that uncertainty can occur between the 2010 McDonald criteria and the 2015 International Panel for Neuromyelitis optica criteria and the treatments for each differ—in fact, MS treatments, such as interferon beta, fingolimod, and natalizumab can exacerbate NMOSDs, the Panel recommended that “NMOSDs should be considered in any patient being evaluated for multiple sclerosis. Serological testing for AQP4 and for MOG should be done in all patients with features suggesting NMOSDs (such as bilateral optic neuritis, severe brainstem involvement, longitudinally extensive spinal cord lesions, large cerebral lesions, or normal brain MRI or findings not fulfilling dissemination in space [DIS]), and considered in groups at higher risk of NMOSDs (such as African American, Asian, Latin American, and paediatric 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. An international panel released their recommendations concerning diagnosis and antibody testing in 2018. 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) targeting 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.
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- 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. Cerebrospinal fluid (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: World Health Organization (WHO)
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International Panel on NMOSD (Wingerchuk et al., 2015)

The International Panel on NMOSD notes that “Patients who fulfill NMOSD criteria but do not have detectable AQP4-IgG despite use of the best available assays, or for whom serologic testing is unavailable, sometimes represent a diagnostic challenge.” They recommend “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.
Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: 83520, 84182, 86255, 86256, 88341, 88342

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources


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VII. Policy Implementation/Update Information

1/1/19 New policy developed. BCBSNC will provide coverage for serum biomarker testing for multiple sclerosis and related neurologic diseases when it is determined to be medically necessary because the medical criteria and guidelines are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (sk)

10/29/19 Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed (gm)

11/26/19 Specialty Matched Consultant Advisory Panel review 10/16/2019. (sk)

12/10/19 Reviewed by Avalon 3rd Quarter CAB. No change in overall intent of policy. (sk)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.