

Reimbursement Policy

Biomarker Testing for Multiple Sclerosis and Related Neurologic Diseases

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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.¹ Besides MS, acute CNS demyelination also occurs in acute disseminated encephalomyelitis (ADEM), optic neuritis, transverse myelitis, and neuromyelitis optica.²

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.³

II. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the "Applicable State and Federal Regulations" section of this policy document.

- 1) For the diagnosis of multiple sclerosis (MS), cerebrospinal fluid (CSF) and serum oligoclonal band analysis **MEETS COVERAGE CRITERIA** in **any** of the following situations:
 - a) For individuals with atypical clinical, laboratory, or imaging features.
 - b) For individuals with an atypical, clinically isolated syndrome, including, but not limited to, primary progressive multiple sclerosis or relapsing-remitting course.
 - c) For individuals belonging to a population in which MS is less common (e.g., children, older individuals).
 - d) For individuals with insufficient clinical or imaging evidence for diagnosis.

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- 2) In cases of suspected neuromyelitis optica spectrum disorders (NMOSD) or myelin oligodendrocyte glycoprotein-immunoglobulin G (MOG-IgG)-associated encephalomyelitis (MOG-EM), serum indirect fluorescence assay or fluorescence-activated cell sorting (FACS) assay of aquaporin-4-IgG (AQP4-IgG) and MOG-IgG **MEET COVERAGE CRITERIA** when **all** of the following conditions are met:
- a) The individual has monophasic or relapsing acute optic neuritis, myelitis, brainstem encephalitis, encephalitis, or any combination thereof;
 - b) The individuals have radiological or electrophysiological findings compatible with central nervous system (CNS) demyelination;
 - c) The individual has at least one of the following:
 - i) Belongs to a higher risk population (e.g, pediatric).
 - ii) Has an abnormal MRI depicting extensive optic nerve lesion, extensive spinal cord lesion or atrophy, or large confluent T2 brain lesions.
 - iii) Has prominent papilledema/papillitis/optic disc swelling during acute optic neuritis.
 - iv) Has neutrophilic CSF pleocytosis.
 - v) Has a histopathology finding of primary demyelination with intralesional complement and IgG deposits or has a previous diagnosis of “pattern II MS”.
 - vi) Has simultaneous bilateral acute optic neuritis.
 - vii) Has a severe visual deficit or blindness in one or both eyes during or after acute optic neuritis.
 - viii) Has severe or frequent episodes of acute myelitis or brainstem encephalitis.
 - ix) Has permanent sphincter and/or erectile disorder after myelitis.
 - x) Has a 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 an individual's illness.

- 3) In all other situations, serum biomarker tests for multiple sclerosis **DO NOT MEET COVERAGE CRITERIA**.
- 4) ELISA, Western blot, immunohistochemistry, or any other serum assays to test for NMOSD or MOG-EM **DO NOT MEET COVERAGE CRITERIA**.
- 5) For the diagnosis of MS, NMOSD, or MOG-EM, all other cerebrospinal fluid (CSF) biomarker tests, including AQP4-IgG or MOG-IgG, **DO NOT MEET COVERAGE CRITERIA**.

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III. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: <https://www.cms.gov/medicare-coverage-database/search.aspx>. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

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). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

In 2016, the FDA approved 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.”⁴¹

IV. 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
83884	Neurofilament light chain (NfL)
83916	Oligoclonal immune (oligoclonal bands)
84182	Protein; Western Blot, with interpretation and report, blood or other body fluid, immunological probe for band identification, each
86051	Aquaporin-4 (neuromyelitis optica [NMO]) antibody; enzyme-linked immunosorbent immunoassay (ELISA)
86052	Aquaporin-4 (neuromyelitis optica [NMO]) antibody; cell-based immunofluorescence assay (CBA), each
86053	Aquaporin-4 (neuromyelitis optica [NMO]) antibody; flow cytometry (ie, fluorescence-activated cell sorting [FACS]), each

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86362	Myelin oligodendrocyte glycoprotein (MOG-IgG1) antibody; cell-based immunofluorescence assay (CBA), each
86363	Myelin oligodendrocyte glycoprotein (MOG-IgG1) antibody; flow cytometry (ie, fluorescence-activated cell sorting [FACS]), each
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
0443U	Neurofilament light chain (Nfl), ultra-sensitive immunoassay, serum or cerebrospinal fluid Proprietary test: Neurofilament Light Chain (NfL) Lab/Manufacturer: Neuromuscular Clinical Laboratory at Washington University in St. Louis School of Medicine, Neuromuscular Clinical Laboratory at Washington University in St. Louis School of Medicine

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

V. Evidence-based Scientific References

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VI. Revision History

Revision Date	Summary of Changes
09/04/2025	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria. Title changed from “Serum Biomarker Testing for Multiple Sclerosis and Related Neurologic Diseases” to “Biomarker Testing for Multiple Sclerosis and Related Neurologic Diseases”, as policy addresses CSF and serum biomarkers Revised CPT code description for CPT code 84182, 0443U
12/04/2024	Off-cycle coding modification: Added CPT code 83884 (effective date 1/1/2025).