Anthem

Medical Policy

Subject: Blood-based Biomarker Tests for Multiple Sclerosis
Document #: LAB.00028
Status: Revised
Publish Date: 09/27/2023
Last Review Date: 08/10/2023

Description/Scope

This document addresses blood-based biomarker tests for multiple sclerosis (MS). Examples are:

- gMS® Dx (Glycominds, Simi Valley, CA)
- gMS® Pro EDSS (Glycominds, Simi Valley, CA)
- Neurofilament light chain

Blood-based biomarker tests for MS are blood tests designed to either expedite the diagnosis of MS or as a prognostic tool to measure the risk for rapid progression of disability in individuals with relapsing-remitting MS (RRMS) or clinically isolated syndrome (CIS).

Position Statement

Investigational and Not Medically Necessary:

Blood-based biomarker tests for multiple sclerosis are considered **investigational and not medically necessary** for all uses.

Rationale

Currently, there are no blood-based biomarker tests for MS that have been proven to confirm the diagnosis of MS or measure risk for progression. Examples of tests marketed for these uses include the gMS Dx and gMS Pro EDSS. In addition, there are other blood-based biomarkers for MS under investigation.

The gMS Dx is a blood test designed to be used as a companion to magnetic resonance imaging (MRI) in suspected cases of MS at the first neurological event and for individuals with CIS in order to expedite the diagnosis of RRMS. The gMS Dx test measures the levels of IgM antibodies to the glycan structure GAGA 4 and reportedly “rules-in” the diagnosis of RRMS. The gMS Pro EDSS test is designed to be used as a tool to identify individuals with CIS and RRMS who are at risk for rapid disability progression. This test measures the levels of four GAGA molecules (anti-GAGA2, anti-GAGA3, anti-GAGA4 and anti-GAGA6).

Early reports showed potential promise for the gMS Dx (GAGA4) antibody/marker for use as an aid in the diagnosis or prognosis of MS (Brettschneider, 2009; Freedman, 2009; Schwartz, 2006) . However, outcomes from these studies have not been confirmed, and large, well-designed trials are warranted to validate findings.

Freedman and colleagues (2012) suggested that at least one of a panel of four α-glucose IgM antibodies (gMS-Classifier 1) in individuals with CIS is associated with imminent early relapse of the disease within 2 years. As a result, investigators studied the prognostic value of gMS-Classifier 1 (gMS Pro EDSS) in a large cohort study of individuals with CIS from a 5-year trial of the MS drug betaseron (BEtaseron® in Newly Emerging multiple sclerosis For Initial Treatment [BENEFIT]) which was designed to evaluate the impact of early versus delayed interferon-β-1b (IFNβ-1b; Betaseron) treatment in individuals with a first neurological event suggestive of MS. A total of 258 subjects (61% of total), with a minimum of 2 ml baseline serum, were eligible for the biomarker study. Levels of the gMS-Classifier 1 antibodies panel (anti-GAGA2, anti-GAGA3, anti-GAGA4 and anti-GAGA6 [gMS Pro EDSS]) were measured blinded to clinical data. The investigators were not able to verify that gMS-Classifier 1 could predict early conversion to MS in CIS. It was also noted that raised titers of these antibodies may have predicted an increased risk for disability progression, although additional study is needed.

The use of serum neurofilament light chain (sNfL) is being investigated as a biomarker of neuronal damage in individuals with multiple sclerosis. It has been proposed that the biomarker be used to monitor disease activity, response to drug therapy and to prognosticate the course of the disease in individuals with multiple sclerosis (Atkas, 2020; Benkert, 2022; Cai, 2018; Calabresi, 2021; Hanninen, 2020; Russo, 2020).

Seiberl and colleagues (2023) explored the impact of cladribine (CLAD) on sNfL and the potential of sNfL as a predictor of long-term treatment response. Data were collected from a prospective, real-world CLAD cohort. Researchers measured sNfL at baseline (BL-sNfL) and 12 months (12MosNfL) after starting CLAD. Clinical and radiological assessments determined fulfilment of “no evidence of disease activity” (NEDA-3). BL-sNfL, 12M-sNfL and BL/12M sNfL ratio (sNfL-ratio) were measured as predictors for treatment response. A total of 14 participants were followed for a median of 41.5 months (range 24.0–50.0). NEDA-3 was met by 71%, 57% and 36% for a period of 12, 24 and 36 months, respectively. Researchers observed clinical relapses in 4 (29%), MRI activity in 6 (43%) and EDSS progression in 5 (36%) subjects. CLAD notably reduced sNfL (BL-sNfL: mean 24.7 pg/mL (SD ± 23.8); 12Mo-sNfL: mean 8.8 pg/mL (SD ± 6.2); p=0.0008). The researchers found no correlation between BL-sNfL, 12Mo-sNfL and ratio-sNfL and the time until loss of NEDA-3, the occurrence of relapses, MRI activity, EDSS progression, treatment switch or sustained NEDA-3. While the researchers confirmed that CLAD reduces neuroaxonal damage in individuals with MS as determined by sNfL, sNfL results at baseline and at 12 months failed to predict clinical and radiological treatment. The authors concluded that long-term sNfL assessments in larger studies are necessary to explore the predictive utility of sNfL in individuals treated with immune reconstitution therapies.

Williams and colleagues (2022) evaluated the relationship between longitudinal changes in cognition and baseline sNfL in individuals with secondary progressive multiple sclerosis (SPMS). Participants from the MS-STAT trial (NCT00647348) underwent a detailed neuropsychological test battery at baseline, 12 and 24 months. Linear mixed models were used to assess the relationships between cognition, sNfL, T2 lesion volume (T2LV) and normalised regional brain volumes. A total of 110 participants had sufficient sNfL, MRI and neuropsychometric data to be included in the primary analysis, 101 of whom had a minimum of at least one follow-up cognitive assessment. Median age and Expanded Disability Status Score (EDSS) were 51 and 6.0, respectively. The researchers found that each doubling of baseline sNfL was associated with a 0.010 [0.003–0.017] point per month more rapid decline in WASI Full Scale IQ Z-score (p=0.008), independent of T2LV and normalised regional volumes. Additionally, lower baseline volume of the transverse

temporal gyrus was associated with poorer current cognitive performance (0.362 [0.026–0.698] point reduction per mL, p=0.035), but not change in cognition. The results were supported by secondary analyses of individual cognitive components. The authors concluded that elevations in sNfL are associated with more rapid cognitive decline, irrespective of T2LV and regional normalised volumes.

In 2017, Novakova and colleagues reported the results of a study that examined the effects of disease activity, disability, and disease-modifying therapies (DMTs) on sNfL and the correlation between NfL concentrations in serum and CSF in MS. NfL concentrations were measured using paired serum and CSF samples (n=521) from 373 participants: MS (n=286); other neurological conditions (n=45); and healthly controls (n=42). In 138 subjects with MS, the serum and CSF samples were collected prior to and after DMT treatment with a median interval of 12 months. The CSF NfL concentration was determined with the UmanDiagnostics NF-light enzyme-linked immunosorbent assay (ELISA). The serum NfL concentration was quantified with an in-house ultrasensitive single-molecule array assay. In MS, the association between serum and CSF NfL was r = 0.62 (p<0.001). Serum concentrations were notably higher in participants with RRMS (16.9 ng/L) and in subjects with progressive MS (23 ng/L) than in the healthy controls (10.5 ng/L, p<0.001 and p<0.001, respectively). Treatment with DMT lowered median serum NfL levels from 18.6 (interquartile range [IQR] 12.6 to 32.7) ng/L to 15.7 (IQR 9.6 to 22.7) ng/L (p<0.001). Subjects with radiologic activity or with relapse had significantly higher serum NfL levels than the individuals in remission (p<0.001) or those without new lesions on MRI (p<0.001). The authors concluded that serum and CSF NfL levels were highly correlated and that serum blood sampling can replace CSF taps for this particular marker. However, the researchers also issued the following caution:

> The high correlation between serum and CSF NFL suggests that the temporal course of serum NFL is similar to that described for CSF NFL. However, this has to be further investigated in prospective studies. In monitoring of the effect of DMT on axonal damage, a 3-month interval between blood tests for monitoring serum NFL would reveal the occurrence of new disease activity. However, we cannot determine from our data whether this would detect a stepwise accumulation of T2 lesions, accumulation of disability, or conversion to a progressive disease course. There is a need for long-term follow-up studies to collect data on the correlation between NFL concentrations over time and such outcomes.

While early studies suggest that there may be an association between serum NfL concentration and response to therapy and disease progression in individuals with MS, it is important to note that NfL is not specific to MS. Additional studes are needed to establish its clinical utility as a biomarker for MS.

Other blood-based biomarker tests for MS currently under investigation include but are not limited to: anti-KIR4 antibodies (Brickshawana, 2014; Brill, 2015; Navas-Madroñal, 2017), antiphospholipid antibodies (Koudriavtseva, 2014; Merashli, 2017), anti-myelin antibodies (Findling, 2014), osteopontin matrix protein biomarker (Agah, 2018), microRNAs (Regev, 2018), and neurofilament light chain levels in plasma (Abdelhak, 2022; Hendricks, 2019; Sejbaek, 2019). However, these tests have not been proven to confirm a diagnosis of MS or alter disease management.

The Multiple Sclerosis Think Tank, a group of approximately 40 hospital neurologists in France, published 2013 consensus recommendations for blood-based tests useful to diagnose MS. Recommendations were developed by systematic review of the literature and a consensus process. The authors reported that “there is currently no useful biological blood test for the positive diagnosis of MS.”

In 2014, the Advisory Committee on Clinical Trials in MS, the U.S. National Multiple Sclerosis Society, the European Committee for Treatment and Research in MS, and other experts (the MS Phenotype Group) published a re-examination of MS clinical course descriptions (Lublin, 2014). The authors indicated that there may be markers of disease activity (other than clinical exacerbations or MRI-detected lesions) but “there is insufficient evidence for including them at this time.” Additionally, the committee stated:

> To date, there are no clear clinical, imaging, immunologic, or pathologic criteria to determine the transition point when RRMS 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.

In conclusion, there is insufficient evidence in the published literature to support the efficacy and clinical utility of blood-based biomarker tests to either expedite the diagnosis of MS or measure the risk for rapid progression of disability in individuals with RRMS, CIS, or any other condition.

Background/Overview

MS is an autoimmune disease of the central nervous system (CNS). During the MS disease process, inflammation of nervous tissue causes the loss of myelin, a fatty material that acts as a protective insulation for the nerve fibers in the brain and spinal cord. This demyelination leaves multiple areas of hard, scarred tissue (plaques) along the covering of the nerve cells. Another characteristic of MS is the destruction of axons, which are the long filaments that carry electric impulses away from a nerve cell. Demyelination and axon destruction disrupts the ability of the nerves to conduct electrical impulses to and from the brain and produces various symptoms. Common symptoms of the disease include fatigue, numbness, coordination and balance problems, bowel and bladder dysfunction, emotional and cognitive changes, spasticity, vision problems, dizziness, sexual dysfunction, and pain. Classifications of MS are relapsing-remitting (RRMS), primary progressive (PPMS), progressive relapsing (PRMS), and secondary progressive MS (SPMS). Most individuals with MS have a relapsing course, and their first attack may present as a CIS. A CIS is a single demyelinating episode with consistent MRI findings (indicating inflammation/demyelination in one site in the CNS). Individuals with CIS are at high risk for developing clinically definite MS.

As technology related to the diagnosis and treatment of MS continues to be studied, blood-based biomarker tests for use in the diagnosis or prognosis of the disease may evolve. However, at this time there is insufficient evidence in the published literature to support the use of the gMS Dx and gMS Pro EDSS, or any other biomarker test for MS, in routine clinical practice.

The gMS Dx and gMS Pro EDSS laboratory tests are performed in a single laboratory which is certified under the federal Clinical Laboratory Improvement Amendments (CLIA) of 1988. Premarket approval from the U.S. Food and Drug Administration (FDA) is not required when the assay is performed in a CLIA certified laboratory. Currently, the status of the gMS Dx and gMS Pro EDSS tests is unknown because the product website link is inactive, and information is not readily available through the parent company, Coronis Partners. Commercial versions of other biomarker assays were not identified.

Definitions

Clinically isolated syndrome (CIS): A first neurologic event that is suggestive of demyelination, accompanied by multiple, clinically “silent” (asymptomatic) lesions on MRI that are typical of MS. Individuals with this syndrome are at high risk for developing clinically definite MS.

Relapsing-remitting MS (RRMS): A clinical course of MS characterized by clearly defined, acute relapses with full or partial recovery;

no disease progression or worsening of disability develops between relapses.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:
When the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT

84999	Unlisted chemistry procedure [when specified as a biomarker test for MS, e.g., gMS Dx Antibody/Marker, gMS Pro EDSS test, or other biomarker test]
0361U	Neurofilament light chain, digital immunoassay, plasma, quantitative Neurofilament Light Chain (NfL), Mayo Clinic, Mayo Clinic

ICD-10 Diagnosis

	All diagnoses, including the following:
G35	Multiple sclerosis
G37.9	Demyelinating disease of central nervous system, unspecified

References

Peer Reviewed Publications:

1. Abdelhak A, Cordano C, Boscardin WJ, et al. Plasma neurofilament light chain levels suggest neuroaxonal stability following therapeutic remyelination in people with multiple sclerosis. J Neurol Neurosurg Psychiatry. 2022: jnnp-2022-329221.
2. Agah E, Zardoui A, Saghazadeh A, et al. Osteopontin (OPN) as a CSF and blood biomarker for multiple sclerosis: a systematic review and meta-analysis. PLoS One. 2018; 13(1):e0190252.
3. Aktas O, Renner A, Huss Aet al. Serum neurofilament light chain: No clear relation to cognition and neuropsychiatric symptoms in stable MS. Neurol Neuroimmunol Neuroinflamm. 2020 Sep 24; 7(6):e885.
4. Benkert P, Meier S, Schaedelin S, et al. Serum neurofilament light chain for individual prognostication of disease activity in people with multiple sclerosis: a retrospective modelling and validation study. Lancet Neurol. 2022; 21(3):246-257.
5. Brettschneider J, Jaskowski TD, Tumani H, et al. Serum anti-GAGA4 IgM antibodies differentiate relapsing remitting and secondary progressive multiple sclerosis from primary progressive multiple sclerosis and other neurological diseases. J Neuroimmunol. 2009; 217(1-2):95-101.
6. Brickshawana A, Hinson SR, Romero MF, et al. Investigation of the KIR4.1 potassium channel as a putative antigen in patients with multiple sclerosis: a comparative study. Lancet Neurol. 2014; 13(8):795-806.
7. Brill L, Goldberg L, Karni A, et al. Increased anti-KIR4.1 antibodies in multiple sclerosis: Could it be a marker of disease relapse? Mult Scler. 2015; 21(5):572-579.
8. Cai L, Huang J. Neurofilament light chain as a biological marker for multiple sclerosis: a meta-analysis study. Neuropsychiatr Dis Treat. 2018; 14:2241-2254.
9. Calabresi PA, Arnold DL, Sangurdekar D, et al. Temporal profile of serum neurofilament light in multiple sclerosis: Implications for patient monitoring. Mult Scler. 2021; 27(10):1497-1505.
10. Findling O, Durot I, Weck A, et al. Antimyelin antibodies as predictors of disability after clinically isolated syndrome. Int J Neurosci. 2014; 124(8):567-572.
11. Freedman MS, Laks J, Dotan N, et al. Anti-alpha-glucose-based glycan IgM antibodies predict relapse activity in multiple sclerosis after the first neurological event. Mult Scler. 2009; 15(4):422-430.
12. Freedman MS, Metzig C, Kappos L, et al. Predictive nature of IgM anti-α-glucose serum biomarker for relapse activity and EDSS progression in CIS patients: a BENEFIT study analysis. Mult Scler. 2012; 18(7):966-973.
13. Hanninen K, Jaaskelainen O, Herukka SK, Soilu-Hanninen M. Vitamin D supplementation and serum neurofilament light chain in interferon-beta-1b-treated MS patients. Brain Behav. 2020 Sep; 10(9):e01772.
14. Hendricks R, Baker D, Brumm J, Det al. Establishment of neurofilament light chain Simoa assay in cerebrospinal fluid and blood. Bioanalysis. 2019; 11(15):1405-1418.
15. Koudriavtseva T, D'Agosto G, Mandoj C, et al. High frequency of antiphospholipid antibodies in relapse of multiple sclerosis: a possible indicator of inflammatory-thrombotic processes. Neurol Sci. 2014; 35(11):1737-1741.
16. Merashli M, Alves JD, Gentile F, Ames PRJ. Relevance of antiphospholipid antibodies in multiple sclerosis: a systematic review and meta analysis. Semin Arthritis Rheum. 2017; 46(6):810-818.
17. Navas-Madroñal M, Valero-Mut A, Martínez-Zapata MJ, et al. Absence of antibodies against KIR4.1 in multiple sclerosis: A three-technique approach and systematic review. PLoS One. 2017; 12(4): e0175538.
18. Novakova L, Zetterberg H, Sundström P, et al. Monitoring disease activity in multiple sclerosis using serum neurofilament light protein. Neurology. 2017; 89(22):2230-2237.
19. Ouallet JC, Bodiguel E, Bensa C, et al; Groupe de Re´flexion sur la Scle´rose en Plaques: GRESE. Recommendations for useful serum testing with suspected multiple sclerosis. Rev Neurol (Paris). 2013; 169(1):37-46.
20. Regev K, Healy BC, Paul A, et al. Identification of MS-specific serum miRNAs in an international multicenter study. Neurol Neuroimmunol Neuroinflamm. 2018; 5(5):e491.
21. Russo M, Gonzalez CT, Healy BC, et al. Temporal association of sNfL and gad-enhancing lesions in multiple sclerosis. Ann Clin Transl Neurol. 2020; 7(6):945-955.
22. Schwarz M, Spector L, Gortler M, et al. Serum anti-Glc(alpha1,4)Glc(alpha) antibodies as a biomarker for relapsing-remitting multiple sclerosis. J Neurol Sci. 2006; 244(1-2):59-68.
23. Seiberl M, Feige J, Hilpold P, et al. Serum neurofilament light chain as biomarker for cladribine-treated multiple sclerosis patients in a real-world setting. Int J Mol Sci. 2023; 24(4):4067.
24. Sejbaek T, Nielsen HH, Penner N, et al. Dimethyl fumarate decreases neurofilament light chain in CSF and blood of treatment naïve relapsing MS patients. J Neurol Neurosurg Psychiatry. 201; 90(12):1324-1330.
25. Williams TE, Holdsworth KP, Nicholas JM, et al. Assessing neurofilaments as biomarkers of neuroprotection in progressive multiple sclerosis: from the MS-STAT randomized controlled trial. Neurol Neuroimmunol Neuroinflamm. 2022 Mar; 9(2):e1130.

Government Agency, Medical Society, and Other Authoritative Publications:

1. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology.

2014; 83(3):278-286.

Websites for Additional Information

1. National Multiple Sclerosis Society. About MS. Available at:http://www.nationalmssociety.org/about-multiple-sclerosis/index.aspx. Accessed on June 5, 2023.

Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Revised	08/10/2023	Medical Policy & Technology Assessment Committee (MPTAC) review. Expanded scope of document from serum to blood-based biomarker testing for multiple sclerosis (MS). Changed title to Blood-based Biomarker Tests for Multiple Sclerosis. Revised position statement to indicate blood-based biomarker tests for multiple sclerosis are considered investigational and not medically necessary for all uses. Updated Rationale, References, Websites for Additional Information and Index sections. Updated Coding section, added 0361U.
Reviewed	08/11/2022	MPTAC review. Description/Scope, Rationale, References, and Websites sections updated.
Reviewed	08/12/2021	MPTAC review. Rationale, References, Websites and Index sections updated.
Reviewed	08/13/2020	MPTAC review. Rationale, References and Websites sections updated.
Reviewed	08/22/2019	MPTAC review. Rationale, References and Websites sections updated.
Reviewed	09/13/2018	MPTAC review. Rationale, References and Websites sections updated.
Reviewed	11/02/2017	MPTAC review. Description/Scope, Rationale, Background/Overview, Definitions and References sections updated. The document header wording updated from “Current Effective Date” to “Publish Date.”
Reviewed	11/03/2016	MPTAC review. Rationale and References sections updated.
Revised	11/05/2015	MPTAC review. Brand names removed from position statement and Title of document. Description, Rationale, Background and Reference sections updated. Removed ICD-9 codes from Coding section.
Reviewed	11/13/2014	MPTAC review. Description, Background and Reference sections updated.
Reviewed	11/14/2013	MPTAC review. Rationale, Background and Definition sections updated.
New	11/08/2012	MPTAC review. Initial document development.

Applicable to Commercial HMO members in California: When a medical policy states a procedure or treatment is investigational, PMGs should not approve or deny the request. Instead, please fax the request to Anthem Blue Cross Grievance and Appeals at fax # 818-234-2767 or 818-234-3824. For questions, call G&A at 1-800-365-0609 and ask to speak with the Investigational Review Nurse.

Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member’s contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.