Healthy Blue

Medical Policy

Subject:	Serum Biomarker Tests for Multiple Sclerosis		
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Description/Scope

This document addresses serum biomarker tests for multiple sclerosis (MS). Examples are:

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

Serum 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:

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

Rationale

Currently, there are no serum 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 serum 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.

Other serum 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 (Atkas, 2020; Cai, 2018; Calabresi, 2021; Hanninen, 2020; Russo, 2020; Williams, 2022). 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 serum 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 serum 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, serum 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]

ICD-10 Diagnosis	
	All diagnoses, including the following:
G35	Multiple sclerosis
G37.9	Demyelinating disease of central nervous system, unspecified

References

Peer Reviewed Publications:

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3. 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.
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12. 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.
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14. 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.
15. 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.

16. 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.
17. 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.
18. 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.
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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 21, 2022.

Index

Glycan-Based Test
gMS Dx Antibody/Marker
gMS Pro EDSS Blood Test
Multiple Sclerosis Biomarkers
Serum Biomarker Tests for Multiple Sclerosis
Serum Neurofilament Light Chain

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
Reviewed	08/11/2022	Medical Policy & Technology Assessment Committee (MPTAC) review. Description/Scope, Rationale, References, and Websites sections updated.
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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."

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