Serum Biomarker Tests for Multiple Sclerosis

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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers serum biomarker tests for multiple sclerosis (MS) are considered **investigational*** in all situations.

Background/Overview

Serum antibodies to polysaccharide-containing molecules, called glycans, and other serum biomarkers are potential biomarker testes for the diagnosis and prognosis of MS. Multiple sclerosis is diagnosed according to criteria that incorporate clinical symptoms and magnetic resonance imaging (MRI) and cerebrospinal fluid findings. Currently, there is no biomarker available to inform diagnosis or prognosis. A serum biomarker is particularly desirable because of ease of repeat measurements.

Disease Description

Estimated prevalence of MS in North America varies regionally and ranges from 240 of 100,000 in Canada to 191 of 100,000 in Minnesota and 40 of 100,000 in Texas. Women are affected twice as often as men, and median age of onset is 24 years. Most patients (85%) have the relapsing remitting form of MS (RRMS), and of these, 60% to 70% will progress to secondary progressive MS, usually 10 to 30 years after disease onset. Rarer forms are primary progressive MS and progressive relapsing MS.

Multiple sclerosis is characterized by destruction of myelin in the central nervous system.

symptoms are diverse and may include cognitive, speech, or vision deficits; numbness; pain; weakness or dyscoordination; and bowel or bladder dysfunction. Diagnosis is made by clinical symptoms, typical MRI findings, and oligoclonal antibodies in the cerebrospinal fluid according to current McDonald criteria. Diagnosis requires 2 clinical episodes occurring at 2 discreet points in time, or 1 clinical episode (CIS, defined next) with MRI lesions indicating development at 2 discreet points in time (ie, simultaneous appearance of old and new lesions). Disability progression is quantified in practice and in clinical trials by the Kurtzke Expanded Disability Status Scale (EDSS). Patients with scores less than 5 are fully ambulatory; scores of 5 to 10 are defined by incrementally decreasing ability to walk.

The term clinically isolated syndrome (CIS) describes patients who have suffered a first episode suggestive of MS but do not meet diagnostic criteria for definite MS. Studies indicated that early treatment with interferon beta-1b (IFNβ-1b) may delay relapse (ie, a second episode), although long-term disability outcomes were unaffected.

In addition to IFNβ-1b, 8 other disease-modifying drugs are currently U.S. Food and Drug Administration (FDA)–approved for first- or second-line treatment of MS with varying degrees of efficacy for reducing relapses and preventing neurologic deterioration. First-line treatments include self-injectable drugs (interferon and glatiramer acetate) and newer oral agents, such as fingolimod, teriflunomide, and dimethyl fumarate. Choice of first-line agent depends on severity of initial presentation, patient preference, and adverse effect profile. Patients with more active or refractory disease are more likely to tolerate greater risk for greater efficacy, for example with second- or third-line agents, natalizumab and alemtuzumab.

Biomarkers
Glycominds Ltd., based in Israel, markets the diagnostic test, gMS®‡ Dx, for patients with a first episode or CIS, and the multi-marker prognostic test, gMS Pro EDSS, for predicting deterioration in patients diagnosed with MS. Both tests are based on detection of serum antibodies to glycans, which are polysaccharide- or carbohydrate-containing molecules on the surface of immune and other cells. gMS Dx detects immunoglobulin M (IgM) antibodies to the disaccharide glycan, glucose (α1,4)glucose(α) (GAGA4), and gMS Pro EDSS detects IgM antibodies to GAGA2, -3, -4, and -6.

These anti-glycan antibodies are thought to interfere with normal function of the immune system. Temperature controls are implemented during assay runs to prevent IgM precipitation.

Several other serum biomarkers for MS have been investigated, but no other commercially-available tests were identified.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

The FDA-approved tests for serum biomarkers in MS are currently unavailable. Glycominds Ltd offered gMS Dx and gMS Pro EDSS as laboratory-developed (in-house) tests at its Clinical Laboratory Improvement Act (CLIA)–certified laboratory in Simi Valley, California. However, current status of the tests is unknown because links to the company website are inactive, and ordering information is not readily available through the parent company, Coronis Partners. Although commercial versions of other biomarker assays were not identified, clinical laboratories may offer in-house assays to measure serum biomarkers in MS.

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratories offering such tests as a clinical service must meet general regulatory standards of CLIA and must be licensed by CLIA for high-complexity testing.

Rationale/Source

Serum antibodies to polysaccharide-containing molecules, called glycans, and other serum biomarkers are potential biomarker tests for the diagnosis and prognosis of multiple sclerosis (MS). MS is diagnosed according to criteria that incorporate clinical symptoms and magnetic resonance imaging and cerebrospinal fluid findings. Currently, there is no biomarker available to inform diagnosis or prognosis. A serum biomarker is particularly desirable because of ease of repeat measurements.

For individuals who have signs and/or symptoms of MS who receive serum biomarker tests for MS, the evidence includes cross-sectional studies of diagnostic accuracy and cohort studies. Relevant outcomes are test accuracy and validity, other test performance measures, symptoms, functional

outcomes, health status measures, and quality of life. Antibodies to glycan molecules are thought to impair immune function. They include antibodies to 1 (glucose[α1,4]glucose[α] [GAGA4]) or several (GAGA2, -3, -4, and - 6) glycan molecules. The gMS Dx and gMS Pro EDSS tests may aid in the diagnosis and prognosis in MS, respectively. Tests for serum levels of other potential MS biomarkers, including but not limited to apoptosis-related molecules, intercellular adhesion molecules, and myelin peptides, have also been described. Current evidence for these other biomarkers makes it difficult to assess their utility in diagnosis and prognosis. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Practice Guidelines and Position Statements

Multiple Sclerosis Think Tank

In 2013, the Multiple Sclerosis Think Tank, a group of approximately 40 hospital neurologists in France, published consensus recommendations for serum tests useful to diagnose MS. Recommendations were developed by systematic review of the literature and a Delphi consensus process. Panelists concurred that "there is currently no useful biological blood test for the positive diagnosis of MS."

International Advisory Committee on Clinical Trials in Multiple Sclerosis

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, published results of its deliberations on the MS clinical course descriptions in light of current evidence for improved descriptive terminology (eg, incorporating evidence for serum and other biomarkers). The Committee concluded: "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."

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

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Policy History

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10/02/2014	Medical Policy Committee review
10/15/2014	Medical Policy Implementation Committee approval. New policy.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
10/08/2015	Medical Policy Committee review
10/21/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/06/2016	Medical Policy Committee review. Recommend archiving policy.
10/19/2016	Medical Policy Implementation Committee approval. Archived.
02/06/2020	Medical Policy Committee review
02/12/2020	Medical Policy Implementation Committee approval. Policy reactivated from archive status as investigational to track BCBSA's policy archived in July 2016.
02/04/2021	Medical Policy Committee review
02/10/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 02/2022

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	84999
HCPCS	No codes
ICD-10 Diagnosis	G35

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*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

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