| BLUE CROSS OF NORTHEASTERN PA<br>"BCNEPA"<br>MEDICAL POLICY BULLETIN | **MANUAL:** MEDICAL POLICY |
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| | **REFERENCE NO.:** MPO-134-0002 |
| **EFFECTIVE DATE**<br>July 1, 2014 | **SUBJECT:** Serum Biomarker Tests for Multiple Sclerosis |

**Blue Cross of Northeastern Pennsylvania ("BCNEPA") Medical Policy**

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical policy and claims payment policy are applied. Policies are provided for informational purposes only and are developed to assist in administering plan benefits and do not constitute medical advice.

Treating providers are solely responsible for medical advice and treatment. Policies are based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease.

Medical practices and information are constantly changing and BCNEPA may review and revise its medical policies periodically. Also, due to the rapid pace of changing technology and the advent of new medical procedures, BCNEPA may not have a policy to address every procedure.

In those cases, BCNEPA may review other sources of information including, but not limited to, current medical literature and other medical resources, such as Technology Evaluation Center Assessments (TEC) published by the Blue Cross Blue Shield Association. BCNEPA may also consult with health care providers possessing particular expertise in the services at issue.

## DESCRIPTION:

Serum antibodies to polysaccharide-containing molecules, called glycans, and other potential serum biomarkers are in development for the diagnosis of multiple sclerosis (MS). These include 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.

## BENEFIT POLICY STATEMENT:

BCNEPA makes decisions on coverage based on Policy Bulletins, benefit plan documents, and the member's medical history and condition. Benefits may vary based on product line, group or contract, therefore, Member benefits must be verified. In the event of a conflict between the Member's benefit plan document and topics addressed in Medical Policy Bulletins (i.e., specific contract exclusions), the Member's benefit plan document always supersedes the information in the Medical Policy Bulletins. BCNEPA determines medical necessity only if the benefit exists and no contract exclusions are applicable.

Benefits are determined by the terms of the Member's specific benefit plan document [i.e., the Fully Insured policy, the Administrative Services Only (ASO) agreement applicable to the Self-Funded Plan Participant, or the Individual Policy] that is in effect at the time services are rendered.

**BACKGROUND:**

Disease Description

Estimated prevalence of MS in North America varies regionally and ranges from 240/100,000 in Canada to 191/100,000 in Minnesota and 40/100,000 in Texas. (1) 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. (2) Rarer forms are primary progressive MS and progressive relapsing MS.

MS is characterized by destruction of myelin in the central nervous system. Progressive focal demyelination eventually leads to axonal degeneration and cumulative physical and cognitive disabilities. Because any area of the brain, optic nerve, or spinal cord can be affected, 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 magnetic resonance imaging (MRI) findings, and oligoclonal antibodies in the cerebrospinal fluid according to current McDonald criteria. (3) 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. (4) 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. (5, 6)

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. (2, 7, 8)

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. (9) 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.

**MEDICAL POLICY STATEMENT:**

BCNEPA will not provide coverage for serum biomarker tests for multiple sclerosis as they are considered investigational in all situations.

**GUIDELINES:**

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.

**RATIONALE:**

Multiple sclerosis (MS) is diagnosed according to criteria that incorporate clinical symptoms and magnetic resonance imaging (MRI) and CSF findings. Because 2 clinical episodes are required for diagnosis, diagnosis and treatment may be delayed in patients presenting with a first clinical episode suggestive of MS. Currently, there is no biomarker available to inform diagnosis or prognosis. A serum biomarker is particularly desirable because of ease of repeat measurements.

Antibodies to glycan molecules are thought to impair immune function. Commercial assays are available to measure serum antibody levels to 1 (glucose [α1,4]glucose[α], also called GAGA4) or several (GAGA2, -3, -4, and -6) glycan molecules. These tests, gMS Dx and gMS Pro EDSS, are marketed to aid diagnosis and prognosis in MS, respectively. However, evidence indicates that these tests are in an early stage of development, and both are therefore considered investigational for all uses.

Tests for serum levels of other MS biomarkers currently in development, including but not limited to apoptosis-related molecules, intercellular adhesion molecules, and myelin peptides, are considered investigational.

**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. (15) 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.”

**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.

**DEFINITIONS:**

N/A

**CODING:**



- **The identification of a code in this section does not denote coverage or separate reimbursement.**
- Covered procedure codes are dependent upon meeting criteria of the policy and appropriate diagnosis code.
- The following list of codes may not be all-inclusive, and are subject to change at any time.
- Benefits are determined by the terms of the Member's specific benefit plan document [i.e., the Fully Insured policy, the Administrative Services Only (ASO) agreement applicable to the Self-Funded Plan Participant, or the Individual Policy] that is in effect at the time services are rendered.

**PROCEDURE CODES**

84999

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**APPROVALS:**

Approved by Vice President, Clinical Operations & Chief Medical Officer:

Signature: 
(Nina M. Taggart, MA, MD, MBA)

Date of Approval: June 16, 2014

**HISTORY:**

Original Development Date: (07/01/14)

Policy developed by: Medical Policy Department