Serum Biomarker Tests for Multiple Sclerosis
Archived Medical Policy

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Policy # 00433
Original Effective Date: 10/15/2014
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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 tests 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. 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 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.

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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\textsuperscript{®} 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**

**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.
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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.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD).

Rationale/Source

gMS Dx Test
In 2006, Schwarz et al screened sera from 107 patients in Israel diagnosed with relapsing-remitting multiple sclerosis (RRMS) for antibodies to 76 glycan molecules. Sera were analyzed by immunofluorescence assay using the GlycoChip (Glycominds; Lod, Israel) glycan array. Antibody levels in patients with RRMS were compared with levels in patients with primary progressive MS (PPMS) (n=16); patients with other neurologic diseases, including inflammatory (eg, Guillain-Barré syndrome, myasthenia gravis) and noninflammatory (eg, Parkinson disease, Huntington disease,) neurologic diseases (n=50); and patients with other autoimmune diseases (rheumatoid arthritis, Crohn disease) (n=27). No differences between groups were observed for immunoglobulin G (IgG) and immunoglobulin A (IgA) antibodies. IgM binding to glycans containing free glucose residues (eg, disaccharide glycan, [GAGA4]) best discriminated RRMS patients from other groups; anti-GAGA4 antibody levels were significantly higher in patients with RRMS compared with patients with other neurologic disease (ANOVA, p<0.001) and patients with other autoimmune diseases (ANOVA, p=0.02). No difference between patients with RRMS and PPMS was observed. Coefficients of variation for repeated anti-GAGA4 IgM measurements were approximately 8% for quadruple intraplate measurements and 22% for interplate measurements. Area under the receiver operating characteristic (ROC) curve for discriminating patients with MS (RRMS or PPMS) from patients with other neurologic diseases was 0.765 (95% confidence interval [CI], 0.673 to 0.865). Using a cutoff value for anti-GAGA4 IgM positivity (normalized for total IgM) of 2.1 ´ 10^3 relative fluorescence units (RFU)/(µg total IgM/mL serum)³, sensitivity was 57%, and specificity was 85%.

In 2009, Brettschneider et al retrospectively analyzed sera from 2 cohorts of patients: Cohort 1 (n=778) comprised 648 U.S. patients with MS (77% RRMS), 30 patients in Germany who had other neurologic disease (suspected neuropsychiatric lupus), and 100 healthy controls from the U.S.; cohort 2 (n=126) comprised 91 U.S. patients with MS (91% RRMS) and 35 U.S. patients with other inflammatory (eg, Guillain-Barré syndrome) and noninflammatory (eg, amyotrophic lateral sclerosis) neurologic diseases. Anti-GAGA4 IgM levels were assessed in all patients by enzyme immunoassay and were higher in MS patients compared with controls, although differences reached statistical significance only in cohort 1. Area under the curve (AUC) for discriminating MS patients from patients with other neurologic diseases was 0.903 in cohort 1 and 0.812 in cohort 2. For discriminating MS patients from healthy controls (cohort 1), AUC was

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0.651. Sensitivity and specificity were determined for the combined cohort of 739 patients with MS and 65 patients with other neurologic diseases using a cutoff determined by anti-GAGA4 IgM levels in the upper 15 percentile of healthy controls (50 enzyme immunoassay units [EU]/[mg total IgM/mL serum]). Sensitivity was 34%; specificity was 99%; positive likelihood ratio was 21.9; and negative likelihood ratio was 0.67.

Freedman et al (2009) retrospectively assessed sera drawn at the time of presentation with a first episode suggestive of MS in 3 patient cohorts in Canada and Belgium. Cohort 1 (n=88) comprised 44 patients later diagnosed with RRMS and 44 age- and sex-matched patients who had other neurologic diseases; cohort 2 (n=252) comprised 167 patients later diagnosed with RRMS and 85 patients with other neurologic diseases; cohort 3 is discussed next. Enzyme-linked immunosorbent assay (ELISA) was used to measure anti-GAGA4 IgM, and values were normalized to total IgM, although 2 different normalizing algorithms were used. In cohort 1, cutoff value was determined by mean optical density (OD) plus 2 standard deviations in the control group (0.53 OD/total IgM RFU - 10^6; in cohort 2, cutoff value was determined by ROC analysis to achieve 90% specificity for RRMS (42 EU/[mg total IgM/mL serum]). Coefficients of variation for intra- and interplate measurements were 11% and 15%, respectively. In cohort 1 and cohort 2, respectively, sensitivity was 27% and 26%; specificity was 98% and 91%; positive predictive value (PPV) was 92% and 85%; and negative predictive value (NPV) was 52% and 39%. In cohort 1, 16 (80%) of 20 patients with antibody titers above the median had a second clinical attack within 2 years, compared with 10 (47%) of 21 patients with antibody titers at or below the median (odds ratio, 4.4 [95% CI, 1.1 to 17.7]; Fisher exact test, p=0.05).

Section Summary
Three studies indicated that anti-GAGA4 IgM antibody levels may be higher in patients with RRMS compared with patients with a variety of other neurologic diseases and healthy controls. Although the test demonstrated high specificity, suggesting that it may be useful to confirm a diagnosis of MS, estimated specificity ranged from 85% to 99%, different assay methodologies were used (fluorescence immunoassay and enzyme immunoassay), and cutoffs were data-driven. Further, prospective studies demonstrating improved health outcomes in patients who may have MS (eg, presenting with a first episode CIS) and who are treated according to test results are lacking. The anti-GAGA4 IgM test (gMS Dx) therefore is considered in an early stage of development and investigational for all uses.

gMS Pro Expanded Disability Status Scale Test
Freedman et al conducted 2 exploratory analyses of an IgM antibody panel to GAGA2, -3, -4, and -6 for predicting disease progression in patients presenting with a first episode. The first study comprised cohort 3 of the study previously reviewed. Sera drawn at the time of first presentation in 100 patients were analyzed by immunofluorescence assay. Coefficients of variation were 8% to 12% for intraslide measurements and 15% to 22% for interslide measurements. Cutoffs for each antigen were calculated as mean values plus 1,
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1.5, or 2 SD to optimize performance (4.0 RFU [sample ÷ reference sample], 4.5 RFU, 4.5 RFU, and 4.3 RFU for anti-GAGA2, -GAGA3, -GAGA4, and -GAGA6 IgM, respectively). Samples were considered positive if at least 1 result exceeded the cutoff for 1 of the 4 antibodies. Results in 58 patients who had early relapse (≤24 months) were compared with results in 42 patients who had late relapse (>24 months). For detecting early relapse, sensitivity was 38%; specificity was 88%; PPV was 82%; and NPV was 51%.

The second study prospectively assessed sera from patients presenting with a first episode suggestive of MS who were enrolled in an international trial assessing early versus delayed initiation of IFNβ-1b (BENEFIT). IgM antibodies to GAGA2, -3, -4, and -6 were measured by enzyme immunoassay in 286 patients (61% of enrolled patients) who had at least 2 mL of serum available. A total of 177 patients (62%) were randomized to IFNβ-1b for 2 years, and 109 patients (38%) were randomized to placebo; 255 (89%) of 286 patients enrolled in a follow-up phase with open-label IFNβ-1b and were followed for up to 5 years. The primary outcome was the ability of the test to predict early (<24 months) relapse. Cutoffs for each antigen were calculated as mean values plus 1.4 SD, 1.8 SD, 0.8 SD, and 1.7 SD, for anti-GAGA2, -3, -4, and -6, respectively (148.8 EU, 164.6 EU, 133.6 EU, and 168.1 EU for anti-GAGA2, -3, -4, and -6, respectively). Samples were considered positive if at least 1 result exceeded the cutoff for 1 of the 4 antibodies. Sensitivity was 21%, specificity was 83%, PPV was 38%, and NPV was 68%. For secondary outcomes, the risk of confirmed disability progression, defined as a 1-point increase on the EDSS scale confirmed over 6 months or more, was significantly greater for patients classified as positive compared with patients classified as negative (hazard ratio, 2.05 [95% CI, 1.2 to 3.5]; log-rank test, p=0.009). However, statistical significance was lost when results were controlled for baseline EDSS or examined only in the group who received IFNβ-1b from the start of the trial. The assay panel also had no significant predictive value for conversion to MS satisfying McDonald criteria, 2005 version, for annualized relapse rates, or for MRI findings. The authors concluded that baseline EDSS, presence of oligoclonal bands, and MRI findings remain the best predictors of disease progression and stated, “All current first-line, disease-modifying medications reduce the risk for subsequent attacks and lower MRI activity, and have shown benefit in patients at CIS, so it is unlikely that CIS patients would not be treated with one of these agents, obviating the need for a baseline biomarker predicting early relapse.”

**Section Summary**

Two studies in patients presenting with a first episode suggestive of MS indicated that a panel of anti-GAGA IgM antibodies is not useful for predicting relapse or clinical course. Because different assay methods were used and cutoffs were data-driven, the gMS Pro EDSS test is considered in an early stage of development and investigational for all uses.
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Investigational Serum Biomarkers
Several other serum biomarkers for MS have been investigated. These have been reviewed recently elsewhere and include the factors listed in Table 1. Serum levels of several factors have been shown to change (increase or decrease) during relapses. None have been shown conclusively to alter disease management.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Significance</th>
<th>Citation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-KIR4 antibodies</td>
<td>Associated with disease activity</td>
<td>Brill (2015)</td>
</tr>
<tr>
<td>Anti-myelin antibodies</td>
<td>Limited prognostic value in patients with CIS</td>
<td>Findling (2014)</td>
</tr>
<tr>
<td>Antiphospholipid antibody</td>
<td>Associated with disease activity</td>
<td>Koudriavtseva (2014)</td>
</tr>
<tr>
<td>Anti-transferrin antibodies</td>
<td>Associated with disease vs healthy controls</td>
<td>Colomba (2014)</td>
</tr>
<tr>
<td>Apoptosis-related molecules</td>
<td>Inconsistent evidence for association with disease activity</td>
<td>Moreno (2013)</td>
</tr>
<tr>
<td>Chemokine (C-X-C motif) ligand 16 (CXCL16)</td>
<td>Associated with disease activity</td>
<td>Holmoy (20130</td>
</tr>
<tr>
<td>Complement regulator factor H</td>
<td>Associated with disease activity</td>
<td>Ingram (2010)</td>
</tr>
<tr>
<td>Epstein Barr virus antibodies^a</td>
<td>Associated with disease activity and treatment response</td>
<td>Kvistad (2014)</td>
</tr>
<tr>
<td>Endogenous secretory RAGE</td>
<td>Associated with disease activity</td>
<td>Stemberg (2014)</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>May be involved in myelin repair</td>
<td>Girori (20130</td>
</tr>
<tr>
<td>Human herpesvirus 6A/B</td>
<td>Associated with disease activity</td>
<td>Ortega-Madueño (2014)</td>
</tr>
<tr>
<td>Inflammatory mediators/cytokines^c</td>
<td>Inconsistent evidence for associations with disease activity and treatment response</td>
<td>Dimisianos (2014)</td>
</tr>
<tr>
<td>Intercellular adhesion molecules</td>
<td>Associated with endothelial cell activation; useful for defining active disease</td>
<td>Hartung (1995)</td>
</tr>
<tr>
<td>Ischemia-modified albumin</td>
<td>Associated with disease vs healthy controls</td>
<td>Aydin (2014)</td>
</tr>
<tr>
<td>Lactic acid</td>
<td>Associated with disease progression</td>
<td>Amorini (2014)</td>
</tr>
<tr>
<td>Macrophage-derived chemokines</td>
<td>Associated with disease in women</td>
<td>Jafarzadeh (2014)</td>
</tr>
<tr>
<td>Metabolic profile^g</td>
<td>May distinguish RRMS from progressive MS</td>
<td>Dickens (2014)</td>
</tr>
<tr>
<td>Metalloproteinases</td>
<td>Associated with breakdown of the blood-brain barrier; useful for defining active disease</td>
<td>Waubant (1999)</td>
</tr>
<tr>
<td>Myelin peptides^1</td>
<td>Inconsistent evidence for predicting early relapse after first episode</td>
<td>Berger (2003)</td>
</tr>
<tr>
<td>Osteopontin</td>
<td>Serum levels not associated with disease activity</td>
<td>Kivisakk (2013)</td>
</tr>
</tbody>
</table>
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<tbody>
<tr>
<td>Phospholipase A2</td>
<td>No association with disease course</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uric acid</td>
<td>Associated with disease activity</td>
<td></td>
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</table>

Shimizu (2013)
Phospholipase A2
No association with disease course

Siroos (2013)
Uric acid
Associated with disease activity

Moccia (2014)

CIS: clinically isolated syndrome; EBV: Epstein-Barr virus; IFN: interferon; Ig: immunoglobulin; RAGE: receptor for advanced glycation end products; TNF: tumor necrosis factor.

a Soluble Fas, Fas-ligand, and soluble TNF-related apoptosis-inducing ligand (sTRAIL).
b Anti-EBV nuclear antigen 1 IgG, anti-EBV viral capsid antigen IgM.
c IFN-γ, TNF-α, IL-1, IL-6, IL-10, IL-17, C-reactive protein, and soluble TNF receptor 2 (sTNF-R2).
d CCL22, CD163.
e Serum fatty acids, phosphocholine, N-acetyl glycoproteins, glucose, and β-hydroxybutyrate.
f Myelin oligodendrocyte glycoprotein, myelin basic protein.

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in June 2016 did not identify any ongoing or unpublished trials that would likely influence this review.

Summary
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[a][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.

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10/02/2014 Medical Policy Committee review
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.
Next Scheduled Review Date: Archived medical policy

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<td>ICD-10 Diagnosis</td>
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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:
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