BlueCross BlueShield Minnesota

Blue Cross Blue Shield of Minnesota Medical Policy

Medical Policy:	VI-59-005
Topic:	Expanded Gastrointestinal Biomarker Panels
Section:	Laboratory
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A variety of conditions have been attributed to dysbiosis (imbalance) of the gut microbiota or imbalance of nutritional and metabolic biomarkers. Examples of these conditions include chronic intestinal disorders (e.g., Crohn's disease and irritable bowel syndrome), inflammatory or autoimmune disorders, food allergy, atopic eczema, unexplained fatigue, arthritis, ankylosing spondylitis, and neuropsychiatric syndromes including mood disorders and autism.

Reference laboratories may offer comprehensive testing of various aspects of digestion, absorption, microbiology, and metabolic markers. Examples include several tests by Genova Diagnostics, including the Comprehensive Digestive Stool Analysis (CDSA)™ and CDSA 2.0™ tests that evaluate a stool sample for markers of digestion/absorption, gut metabolism, and microbiology. Genova's GI Effects® Comprehensive Stool Profile is a multianalyte stool assay that uses polymerase chain reaction (PCR) to quantify 26 commensal gut bacteria and standard biochemical and culture methods to measure levels of other stool components (eg, lipids, fecal occult blood) and potential pathogens (ova and parasites, opportunistic bacteria, yeast). The test is purported to optimize management of gut health and to differentiate IBS from inflammatory bowel disease (IBD). Genova Diagnostics also offers nutritional/nutrient panel testing. Including the NutrEval® FMV, which involves analysis of first morning voiding (FMV) urine and blood samples and provides information on more than over 125 biomarkers and 40 antioxidants, vitamins, minerals, essential fatty acids, and amino acids. Genova Diagnostics also offers nutritional/nutrient panel testing using the Metabolomix+ Test which combines a variety of tests to analyze key nutritional biomarkers, including organic acids, amino acids, and oxidative stress markers.

Additional antibody and serology tests are being studied in the management of gastrointestinal conditions. IBSchek by Commonwealth Diagnostics and ibs-smart by Gemelli Biotech measure the levels of antibodies, anti-CdtB and anti-vinculin, in those suspected of irritable bowel syndrome. Cytolethal distending toxin B (CdtB) is produced by bacteria that cause acute gastroenteritis. CdtB and vinculin/vincilin IgG are novel biomarkers being studied for their role in ruling in and differentiating IBS with diarrhea (IBS-D) from other causes of diarrhea including inflammatory bowel disease.

SpectraCell Laboratories offers a micronutrient test that measures functional deficiencies at the cellular level. The test assesses how well the body uses 33 vitamins, minerals, amino and fatty acids, antioxidants, and metabolites. SpectraCell categorizes test results into adequate, borderline, and deficient, and offers supplementation suggestions based on each patient's deficiencies.

Cellular Micronutrient Assay from Cell Science Systems offers a micronutrient test that measures vitamins, amino acids, minerals, and other nutrients such as carnitine, alpha-ketoglutarate, choline, glutathione, and inositol. By measuring intracellular levels of micronutrients, the test is intended to provide insight into the long-term nutritional status (6 months) versus the short-term variability of serum nutrient levels.

Commercially available, laboratory-developed tests, such as those listed above, are regulated under the Clinical Laboratory Improvement Amendments (CLIA). Premarket approval from the U.S. Food and Drug Administration (FDA) is not required when the assay is performed in a laboratory that is licensed by CLIA for high-complexity testing.

This policy is designed to address medical guidelines that are appropriate for the majority of individuals with a particular disease, illness, or condition. Each person's unique clinical circumstances may warrant individual consideration, based on review of applicable medical records.

Policy Position *Coverage is subject to the specific terms of the member's benefit plan.*

Expanded gastrointestinal biomarker panels are considered **EXPERIMENTAL/INVESTIGATIVE** for all indications, including but not limited to evaluation of intestinal dysbiosis, irritable bowel syndrome, malabsorption, or small intestinal overgrowth of bacteria, and nutrition status, due to the lack of clinical evidence demonstrating an impact on improved health outcomes.

Procedure Codes

0164U 0176U 81479 81599 Multiple codes apply

Links

Summary of Evidence

No high quality studies were identified on the diagnostic accuracy of expanded biomarker panels compared with another diagnostic approach or that compared health outcomes in patients managed with and without expanded panels. No studies were identified that directly informed the use of expanded panels in the evaluation of intestinal dysbiosis, malabsorption, or small intestinal bacterial overgrowth. There have not been any studies published to date linking testing for dysbiosis with any specific treatment or other clinical utility. The evidence is insufficient to determine the effects of the technology on health outcomes.

There is no evidence on any indication to suggest that nutritional panel testing improves the net health outcome compared with testing for one or several individual nutrients. Moreover, with nutritional panel testing, there is a potential for incidental findings that could cause harm. Examples of potential harms include unnecessary confirmatory tests, unnecessary treatments provided for clinically insignificant conditions, and toxicity related to supplementation, or interactions between nutritional supplements and prescription medication. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have mood disorders, fibromyalgia, or unexplained fatigue, or healthy individuals who seek to optimize health and fitness who receive nutritional panel testing, the evidence includes several systematic reviews and randomized controlled trials (RCTs) on the association between a single condition and a single nutrient and on the treatment of specific conditions with nutritional supplements. Relevant outcomes are symptoms, change in disease status and functional outcomes.

Rationale

There is no direct evidence on the health benefits of nutritional panel testing for any condition, including testing healthy individuals, and no evidence that nutritional panel testing is superior to testing for individual nutrients for any condion. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

While the literature includes much discussion regarding the relationship between intestinal microflora and various disorders, intestinal dysbiosis as a specific disorder is poorly defined. A literature search revealed no published studies establishing diagnostic criteria for this disorder. The gastrointestinal symptoms attributed to intestinal dysbiosis (for example, bloating, flatulence, diarrhea or constipation) overlap in part with irritable bowel syndrome and small intestinal bacterial overgrowth syndrome. No studies in the published literature have been identified describing stool analysis for bacterial flora or metabolic products as a diagnostic technique for irritable bowel syndrome or small intestine bacterial overgrowth.

The American College of Gastroenterology published practice guidelines on Crohn’s disease and celiac disease. Guidelines on management of Crohn’s disease in adults were published in 2018. Recommendations for routine laboratory testing include:

- Initial laboratory investigation should include evaluation for inflammation, anemia, dehydration, and malnutrition.
- In patients who have symptoms of active Crohn's disease, stool testing should be performed to include feval pathogens. Clostridium difficile testing, and may include studeies that identify gut inflammation such as a fecal calprotectin.

Routine use of serologic markers of IBD to establish the diagnosis of Crohn’s disease is not indicated. Genetic testing, an optional component of some extended GI panels, is not indicated to establish a diagnosis of Crohn’s. The ACG notes that certain genetic variants are associated with different phenotypic expressions in Crohn’s disease but testing remains a research tool.

Each of these recommendations are characterized as summary statements due to lack of available clinical trial data, These are descriptive statements and not associated with evidence-based ratings. Expanded biomarker panel testing is not addressed.

AGA Clinical Practice Guideline on the Role of Biomarkers for the Management of Ulcerative Colitis (2023)
In patients with UC in symptomatic remission, the panel suggests the use of a biomarker- and symptom-based monitoring strategy over a symptom-based monitoring strategy. For patients in symptomatic remission, the panel suggests using fecal calprotectin <150 µg/g, normal fecal lactoferrin, and/or normal CRP to rule out active inflammation and avoid routine endoscopic assessment of disease. In patients with UC with moderate to severe symptoms, the panel suggests using fecal calprotectin >150 µg/g, elevated fecal lactoferrin, or elevated CRP to inform treatment decisions and avoid routine endoscopic assessment of disease. However, in patients in symptomatic remission but elevated biomarkers, and in patients with moderate to severe symptoms with normal biomarkers, the panel suggests endoscopic assessment of disease to inform treatment decisions. In patients with UC with mild symptoms, the panel suggests endoscopic assessment of disease activity to inform treatment decisions. The panel identified the use of a biomarker-based monitoring strategy over an endoscopy-based monitoring strategy as a knowledge gap. The panel also proposed key implementation considerations for optimal use of biomarkers, and identified areas for future research. Large panels with nonspecific biomarkers and nutrient analysis are not recommended within this guideline.

No other professional society guidelines were identified that included recommendations on testing addressed in this policy.

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Medicaid products may provide different coverage for certain services, which may be addressed in different policies. For Minnesota Health Care Program (MHCP) policies, please consult the MHCP Provider Manual website.

Medicare products may provide different coverage for certain services, which may be addressed in different policies. For Medicare National Coverage Determinations (NCD), Local Coverage Determinations (LCD), and/or Local Coverage Articles, please consult CMS, National Government Services, or CGS websites.

Note that services with specific coverage criteria may be reviewed retrospectively to determine if criteria are being met. Retrospective denial of claims may result if criteria are not met.

Blue Cross and Blue Shield of Minnesota reserves the right to revise, update and/or add to its medical policies at any time without notice. Codes listed on this policy are included for informational purposes only and are subject to change without notice. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement.

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ATENCIÓN: Si usted habla español, servicios de asistencia lingüística, de forma gratuita, están disponibles para usted. Llame al número en la parte posterior de su tarjeta de identificación (TTY: 711).

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