Nutrient/Nutritional Panel Testing

Policy # 00469
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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.

Note: Intracellular Micronutrient Analysis is addressed separately in medical policy 00311.

Note: Cardiovascular Risk Panels is addressed separately in medical policy 00398.

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 nutrient/nutritional panel testing for all indications including but not limited to testing for nutritional deficiencies in patients with mood disorders, fibromyalgia, unexplained fatigue and healthy individuals to be **investigational.***

Background/Overview

Nutritional panel testing aims to identify nutritional deficiencies that will lead to personalized nutritional supplement recommendations. Testing is proposed both for healthy individuals to optimize health and for patients with chronic conditions (e.g., mood disorders, fibromyalgia, chronic fatigue) to specify supplements that will ameliorate symptoms.

Genova Diagnostics offers nutritional/nutrient panel testing. Among tests this company offers is NutrEval FMV, which involves analysis of urine and blood samples and provides information on more than 100 markers including organic acids, amino acids, fatty acids, markers of oxidative stress (direct measurement of glutathione and CoQ10, and markers of oxidative injury and deoxyribonucleic acid [DNA] damage) and nutrient elements (see Table 1).

Genova Diagnostics produces a report that includes test results categorized as normal, borderline, and high need, along with recommendations for supplements and dosages for items categorized as high need. NutrEval FMV patient reports can recommend supplementation or any of the nutrients listed in Table 1 if they are found to be areas of high need.

A related test, the ONE (Optimal Nutritional Evaluation) FMV also by Genova Diagnostics, limits testing to the organic acid, amino acid, and oxidative stress marker categories.

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 (see Table 1). SpectraCell categorizes test results into adequate, borderline, and deficient, and offers supplementation suggestions based on each patient's deficiencies.

Table 1. Components of the NutrEval FMV Test

Category	NutrEval	SpectraCell Nutrient Testing
B vitamins	Thiamin B_1, riboflavin B_2, niacin B_3, pyridoxine B_6, biotin B_7, folic acid B_9, cobalamin B_{12}	Vitamin A, vitamin B_1, vitamin B_2, vitamin B_3, vitamin B_6, vitamin B_{12}, biotin, folate, pantothenate, vitamin C, vitamin D, vitamin K
Minerals	Magnesium, manganese, molybdenum, zinc	Calcium, magnesium, manganese, zinc, copper
Fatty acids	Omega-3-oils	Oleic acid
Digestive support	Probiotics, pancreatic enzymes	
Other vitamins	Vitamin D	
Amino acids	Arginine, asparagine, cysteine, glutamine, glycine, histidine, isoleucine, leucine, lycine, methionine, phenylalanine, serine, taurine, threonine, tryptophan, tyrosine, valine	Asparagine, glutamine, serine

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Nutrient/nutritional panel testing using urine and/or blood samples is offered (e.g., NutrEval FMV® and ONE FMV® by Genova Diagnostics; micronutrient testing by SpectraCell)‡ under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. FDA has chosen not to require any regulatory review of this test.

Centers for Medicare and Medicaid Services (CMS)

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Direct evidence that nutrient/nutritional panel testing improves health outcomes would consist of randomized controlled trials that compare outcomes in patients managed with and without

nutrient/nutritional panel testing. In the absence of direct evidence, a chain of evidence can be examined. Nutrient/nutritional panel tests are specifically targeted at patients with mood disorders, fibromyalgia, and chronic fatigue so that this review will focus on those conditions. The following is a summary of the key literature.

NUTRIENT/NUTRITIONAL PANEL TESTING

Clinical Context and Test Purpose

The purpose of nutrient/nutritional panel testing in patients who have mood disorders, fibromyalgia, or unexplained fatigue or in healthy individuals seeking to optimize health and fitness is to inform a decision whether the patient might benefit from specific nutrient supplementation.

The question addressed in this evidence review is: Does nutrient/nutritional panel testing, to identify nutrient deficiencies, result in improved health outcomes among patients with mood disorders, fibromyalgia, or unexplained fatigue or among healthy individuals seeking to optimize health and fitness compared with standard of care.

The following PICOTS were used to select literature to inform this review.

Patients

The relevant populations of interest are patients with mood disorders, fibromyalgia, or unexplained fatigue, or healthy individuals seeking to optimize health and fitness.

Interventions

The relevant intervention of interest is nutrient/nutritional panel testing.

Comparators

The relevant comparator of interest is standard of care.

Outcomes

The potential beneficial outcomes of primary interest would be an improvement in symptoms, change in disease status, and functional outcomes. The potential harmful outcomes are those resulting from a false test result. False-positive or false-negative test results can lead to the initiation of unnecessary treatment and adverse events from that overtreatment or undertreatment.

Timing

Nutrient/nutritional panel testing might be conducted before or after starting specific therapy for the specific conditions addressed herein or as a screening test for healthy individuals seeking to optimize health and fitness.

Setting
Ordering and interpreting nutrient/nutritional panel testing should be done by physicians in an outpatient or inpatient setting.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid
Evidence to support the clinical validity of nutrient/nutritional panel testing would require studies that report the sensitivity, specificity, and positive and negative predictive values of these tests in detecting nutritional deficiency compared with a criterion standard test, preferably among the study population of interest. Currently, there is no literature reporting on the clinical validity of nutrient/nutritional panel tests in this target population.

Clinically Useful
The chain of evidence to support the clinical utility of the use of nutrient/nutritional panel testing would consist of: (1) evidence that specific nutritional deficiencies included in the panel test are significantly associated with mood disorders, fibromyalgia, and/or chronic fatigue; (2) evidence that, in patients with mood disorders, fibromyalgia, and/or chronic fatigue, treatment of a patient found to have specific nutritional deficiencies (eg, with nutritional supplements) improves health outcomes; and (3) evidence that, if there is sufficient evidence on the first 2 items, panel testing is more appropriate than testing for specific nutrients.

No studies were identified that directly evaluated the impact of nutrient/nutritional panel testing on health outcomes. Evidence for a chain of evidence is examined next.

Mood Disorders, Fibromyalgia, or Unexplained Fatigue
Several systematic reviews and meta-analyses evaluating associations between the indications of interest and specific nutrient deficiencies were identified, and they are described in Table 2. No systematic reviews or meta-analyses were identified on the association between nutritional deficiencies and unexplained fatigue. A limitation of all reviews is that, although they compared low and high levels of nutrient levels, none addressed whether these low levels constituted actual deficiencies in a particular nutrient.

Table 2. Systematic Reviews on the Association Between Nutritional Deficiencies and Mood Disorders, Fibromyalgia, and Unexplained Fatigue

Study	Nutrient	No. of Studies	Specified Cutoff for Nutrient Deficiency	Key Findings
Depression				
Swardfager et al (2013)	Zinc	17	No	Mean serum zinc concentrations of -1.85 µmol/L (95% CI, -2.52 to -1.19 µmol/L) in depressed patients vs nondepressed controls (p<0.001)

Study	Nutrient	No. of Studies	Specified Cutoff for Nutrient Deficiency	Key Findings
Anglin et al (2013)	Vitamin D	14	No	Cross-sectional studies: • OR of depression, highest vs lowest vitamin D categories: 1.31 (95% CI, 1.00 to 1.71; p=0.03) Prospective series: • Risk of developing depression significantly higher in patients with lower vitamin D (HR=2.21; 95% CI, 1.40 to 3.49; p=0.028)
Petridou et al (2015)	Folate and vitamin B_{12}	11	No	Odds of having depression significantly associated with low folate and vitamin B levels: • Folate: OR=1.27 (95% CI, 1.07 to 1.43) • Vitamin B: OR=1.20 (95% CI, 1.02 to 1.42)
Cheungpasitporn et al (2015)	Magnesium	6	No	Pooled RR of depression in patients with hypomagnesemia (3 cohort studies, 2 cross-sectional studies, 1 case-control study combined; N=19,137 patients): • 1.34 (95% CI, 1.01 to 1.79; I^2=33%) Pooled RR excluding the cross-sectional studies: • 1.38 (95% CI, 0.92 to 2.07; I^2=24%)
Fibromyalgia				
Daniel and Pitotta (2011)	Vitamin D		No	No pooled analyses. Lower quality studies tended to find positive associations between fibromyalgia and low vitamin D levels; studies with control groups found no significant associations; larger population-based studies had mixed findings
Hsiao et al (2015)	Vitamin D	12	No	Significantly higher odds of hypovitaminosis D among patients with chronic pain including fibromyalgia vs control group: • Crude OR=1.63 (95% CI, 1.20 to 2.23) • Adjusted OR=1.41 (95% CI, 1.00 to 2.00)

CI: confidence interval; HR: hazard ratio; OR: odds ratio; RR: relative risk.

Subsection Summary: Mood Disorders, Fibromyalgia, or Unexplained Fatigue

Evidence from multiple systematic reviews and meta-analyses of observational studies have indicated an association between deficiency of nutrients (vitamin B_{12}, vitamin D, folate, magnesium, zinc) and different outcomes (depression, fibromyalgia). There is no evidence whether screening for these nutrient deficiencies results in improved health outcome compared with no screening.

Treatment of Mood Disorders, Fibromyalgia, or Unexplained Fatigue in Patients With Nutritional Deficiencies

Several systematic reviews and meta-analyses evaluating health outcomes in patients with depression treated with nutritional supplementation were identified, and they are described in Table 3. A limitation of all of the reviews is that they did not require patients to have an established deficiency of any nutrient. No systematic reviews or meta-analyses were identified on nutritional interventions in patients with fibromyalgia or unexplained fatigue.

Table 3. Systematic Reviews on Interventions for Patients With Mood Disorders, Fibromyalgia, and/or Unexplained Fatigue Diagnosed With Nutritional Deficiencies

Study	Intervention and Comparator	No. and Type of Studies	Patients Diagnosed With Nutritional Deficiencies	Key Findings
Depression				
Taylor et al (2003)	Folic acid (alone or as adjunctive treatment) vs antidepressant mediation	3 RCTs	No	Difference in HDRS scores significantly lower in patients taking folic acid plus antidepressants vs antidepressants alone (MD = -2.65; 95% CI, -4.93 to -0.038)
Gowda et al (2015)	Vitamin D	9 RCTs	• No in overall analysis • Yes in subgroup analysis	• No significant difference found in depression after supplementation with vitamin D vs placebo (SMD=0.28; 95% CI, -0.14 to 0.69) • No significant difference found in depression with vitamin D vs placebo in patients with baseline vitamin D >50 nmol/L or in patients with baseline vitamin D <50 nmol/L

CI: confidence interval; HDRS: Hamilton Depression Rating Scale; MD: mean difference; RCT: randomized controlled trial; SMD: standard mean difference.

Nowak et al (2016) conducted a single-center, double-blind, placebo-controlled trial to determine whether a single vitamin D dose would reduce fatigue after 30 days among 120 otherwise healthy persons with low serum 25-hydroxyvitamin D (25(OH)D) levels (mean age, 29 years; 53% women). The outcome was measured using the Fatigue Assessment Scale. The vitamin D group had a significantly greater decrease in mean (standard deviation [SD]) Fatigue Assessment Scale score (-3.3, SD=5.3) than the placebo group (-0.8, SD=5.3; p=0.01). Improvements were reported more frequently in the vitamin D group (42 [72%]) than in placebo group (31 [50%]; p=0.01; odds ratio, 2.63; 95% confidence interval for odds ratio, 1.23 to 5.62). Among all participants, improvement in Fatigue Assessment Scale correlated with the rise in 25(OH)D levels (r=0.22, p=0.02).

Subsection Summary: Treatment of Mood Disorders, Fibromyalgia, or Unexplained Fatigue in Patients With Nutritional Deficiencies

A systematic review and meta-analysis of randomized controlled trials have suggested that folate might have a role as a supplement to other therapies. However, it is unclear whether folate supplement would benefit both people with normal folate level and those with folate deficiency. A meta-analysis of randomized controlled trials has suggested no significant benefit of vitamin D supplementation vs placebo in the case of depression. There is no evidence whether screening for these nutrient deficiencies (vs no screening) would result in significant improvement in outcomes.

Panel Testing vs Testing for Individual Nutrients

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. This includes patients with mood disorders, fibromyalgia, and/or unexplained fatigue, as well as healthy individuals seeking to optimize health and/or fitness. 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.

SUMMARY OF EVIDENCE

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 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. There was no evidence of associations between fibromyalgia or unexplained fatigue and nutrient deficiencies. Systematic reviews have found statistically significant associations between depression and levels of several nutrients; however, there is no evidence that nutrient supplementation for patients with depression improves health outcomes. Also, 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 condition. The evidence is insufficient to determine the effects of the technology on health outcomes.

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Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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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	All related diagnoses

*****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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