2.04.136	Nutrient/Nutritional Panel Testing		
Original Policy Date:	January 1, 2016	**Effective Date:**	March 1, 2020
Section:	2.0 Medicine	**Page:**	Page 1 of 9

Policy Statement

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

Policy Guidelines

There are no specific codes for these panels of tests. Tests in the panel that have specific CPT codes would be reported using those codes such as folic acid (82746), magnesium (83735), manganese (83785), vitamin A (84590), and zinc (84630). There are codes for testing multiple amino acids—82128 for qualitative testing and 82136 for quantitative testing. The unlisted chemistry code 84999 would be used once for the other tests in the panel that do not have specific codes (or are used incorrectly with multiple units).

Description

Multimarker nutritional panel testing is proposed for patients with certain chronic conditions (e.g., mood disorders, fibromyalgia, unexplained fatigue) as well as for healthy individuals seeking to optimize health and/or fitness.

Related Policies

- Cardiovascular Risk Panels
- Homocysteine Testing in the Screening, Diagnosis, and Management of Cardiovascular Disease and Venous Thromboembolic Disease
- Intracellular Micronutrient Analysis

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

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. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.

Rationale

Background

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 DNA damage) and nutrient elements (see Table 1).[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 B1, riboflavin B2, niacin B3, pyridoxine B6, biotin B7, folic acid B9, cobalamin B12	Vitamin A, vitamin B1, vitamin B2, vitamin B3, vitamin B6, vitamin B12, 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

Literature Review

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.

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 the use of 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 PICOs 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.

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

Comparators

The following practice is currently being used to manage mood disorders, fibromyalgia, unexplained fatigue, or healthy individuals seeking to optimize health and fitness: 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.

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.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess the clinical validity of nutrient/nutritional panel testing to evaluate patients with mood disorders, fibromyalgia, or unexplained fatigue, or among healthy individuals seeking to optimize health and fitness, studies should report sensitivity, specificity, positive and negative predictive values. Additionally, studies reporting false-positive rates and false-negative rates are informative.
- To assess the clinical utility of nutrient/nutritional panel testing to evaluate the conditions listed above, studies should demonstrate how the results of the panel tests impacted treatment decisions and the overall management of the patient.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires a 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
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

No RCTs were identified that assessed the clinical utility of nutrient/nutritional panel testing for mood disorders, fibromyalgia, chronic fatigue, or optimization of health and fitness.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

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 (e.g., with nutritional supplements) improves health outcomes; and (3) evidence that, if there is sufficient evidence on the first two items, panel testing is more appropriate than testing for specific nutrients.

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 in 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 (95% CI)
Depression				
Petridou et al (2015)[2,]	Folate and vitamin B_{12}	11	No	Odds of having depression significantly associated with low folate and vitamin B levels: • Folate: OR=1.27 (1.07 to 1.43) • Vitamin B: OR=1.20 (1.02 to 1.42)
Cheungpasitporn et al (2015)[3,]	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 (1.01 to 1.79; I^2=33%) Pooled RR excluding the cross-sectional studies: • 1.38 (0.92 to 2.07; I^2=24%)
Swardfager et al (2013)[4,]	Zinc	17	No	Mean serum zinc concentrations of -1.85 µmol/L (-2.52 to -1.19 µmol/L) in depressed patients vs nondepressed controls (p<0.001)
Anglin et al (2013)[5,]	Vitamin D	14	No	Cross-sectional studies: • OR of depression, highest vs lowest vitamin D categories: 1.31 (1.00 to 1.71; p=0.03) Prospective series: • Risk of depression significantly higher in patients with lower vitamin D (HR=2.21; 1.40 to 3.49; p=0.028)
Fibromyalgia				
Hsiao et al (2015)[6,]	Vitamin D	12	No	Significantly higher odds of hypovitaminosis D among patients with chronic pain including fibromyalgia vs control group: • Crude OR=1.63 (1.20 to 2.23) • Adjusted OR=1.41 (1.00 to 2.00)
Daniel and Pitotta (2011)[7,]	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

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 outcomes 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 (95% CI)
Depression				
Gowda et al (2015)[8,]	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; -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
Taylor et al (2003)[9]	Folic acid (alone or as adjunctive treatment) vs antidepressant medication	3 RCTs	No	Difference in HDRS scores significantly lower in patients taking folic acid plus antidepressants vs antidepressants alone (MD= -2.65; -4.93 to -0.038)

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 levels (mean age, 29 years; 53% women).[10] The outcome was measured using the Fatigue Assessment Scale. The vitamin D group had a significantly greater decrease in mean (standard deviation) Fatigue Assessment Scale score (-3.3, standard deviation=5.3) than the placebo group (-0.8, standard deviation=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 the Fatigue Assessment Scale correlated with the rise in 25-hydroxyvitamin 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 RCTs have suggested that folate might have a role as a supplement to other therapies in patients with depression. However, it is unclear whether folate supplement would benefit both people with normal folate levels and those with folate deficiency. A meta-analysis of RCTs 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. The 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.

Supplemental Information

Practice Guidelines and Position Statements

No guidelines or statements were identified.

U.S. Preventive Services Task Force Recommendations

The U.S. Preventive Services Task Force has not addressed nutritional panel testing. The Task Force has made several recommendations addressing screening for individual nutrients. The Task Force concluded that there is insufficient evidence to recommend for or against screening for iron deficiency anemia in asymptomatic children and vitamin D deficiency in asymptomatic adults.[11,12,] Screening for iron deficiency anemia is recommended in asymptomatic pregnant women.

Medicare National Coverage

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.

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in October 2019 did not identify any ongoing or unpublished trials that would likely influence this review.

References

1. Genova Diagnostics. NutrEval FMV. 2015; https://www.gdx.net/product/nutreval-fmv-nutritional-test-blood-urine. Accessed November 1, 2018.
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3. Cheungpasitporn W, Thongprayoon C, Mao MA, et al. Hypomagnesaemia linked to depression: a systematic review and meta-analysis. Intern Med J. Apr 2015;45(4):436-440. PMID 25827510
4. Swardfager W, Herrmann N, Mazereeuw G, et al. Zinc in depression: a meta-analysis. Biol Psychiatry. Dec 15 2013;74(12):872-878. PMID 23806573
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6. Hsiao MY, Hung CY, Chang KV, et al. Is serum hypovitaminosis D associated with chronic widespread pain including fibromyalgia? A meta-analysis of observational studies. Pain Physician. Sep-Oct 2015;18(5):E877-887. PMID 26431141
7. Daniel D, Pirotta MV. Fibromyalgia--should we be testing and treating for vitamin D deficiency? Aust Fam Physician. Sep 2011;40(9):712-716. PMID 21894281
8. Gowda U, Mutowo MP, Smith BJ, et al. Vitamin D supplementation to reduce depression in adults: meta-analysis of randomized controlled trials. Nutrition. Mar 2015;31(3):421-429. PMID 25701329
9. Taylor MJ, Carney S, Geddes J, et al. Folate for depressive disorders. Cochrane Database Syst Rev. Jun 2003(2):CD003390. PMID 12804463
10. Nowak A, Boesch L, Andres E, et al. Effect of vitamin D3 on self-perceived fatigue: A double-blind randomized placebo-controlled trial. Medicine (Baltimore). Dec 2016;95(52):e5353. PMID 28033244
11. U.S. Preventive Services Task Force (USPSTF). Iron Deficiency Anemia: Screening. 2006; http://www.uspreventiveservicestaskforce.org/Page/Topic/recommendation-summary/iron-deficiency-anemia-screening. Accessed November 1, 2018.

12. U.S. Preventive Services Task Force (USPSTF). Vitamin D Deficiency: Screening. 2014; http://www.uspreventiveservicestaskforce.org/Page/Topic/recommendation-summary/vitamin-d-deficiency-screening. Accessed November 1, 2018.
13. Blue Cross Blue Shield Association. Medical Policy Reference Manual, No. 2.04.136 (December 2019).

Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

IE
The following services may be considered investigational.

Type	Code	Description
CPT®	82128	Amino acids; multiple, qualitative, each specimen
	82136	Amino acids, 2 to 5 amino acids, quantitative, each specimen
	82746	Folic acid; serum
	83735	Magnesium
	83785	Manganese
	84590	Vitamin A
	84630	Zinc
	84999	Unlisted chemistry procedure
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
01/01/2016	BCBSA Medical Policy Adoption
03/01/2016	Administrative Update (Correction to Documentation for Clinical Review section)
06/01/2017	Policy revision without position change
02/01/2018	Policy revision without position change
02/01/2019	Policy revision without position change
03/01/2020	Annual review. No change to policy statement. Literature review updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and

effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.