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 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® (First Morning Void), 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).

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>
<thead>
<tr>
<th>Table 1. Components of the NutrEval FMV® Test</th>
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</thead>
<tbody>
<tr>
<td>Category</td>
</tr>
<tr>
<td>B vitamins</td>
</tr>
<tr>
<td>Minerals</td>
</tr>
<tr>
<td>Fatty acids</td>
</tr>
<tr>
<td>Digestive support</td>
</tr>
<tr>
<td>Other vitamins</td>
</tr>
<tr>
<td>Amino acids</td>
</tr>
</tbody>
</table>

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.

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Nutrient</th>
<th>No. of Studies</th>
<th>Specified Cutoff for Nutrient Deficiency</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swardfager et al (2013)</td>
<td>Zinc</td>
<td>17</td>
<td>No</td>
<td>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&lt;0.001)</td>
</tr>
<tr>
<td>Anglin et al (2013)</td>
<td>Vitamin D</td>
<td>14</td>
<td>No</td>
<td>Cross-sectional studies:</td>
</tr>
<tr>
<td>Petridou et al (2015)</td>
<td>Folate and vitamin B12</td>
<td>11</td>
<td>No</td>
<td>Odds of having depression significantly associated with low folate and vitamin B levels:</td>
</tr>
<tr>
<td>Cheungpasitpom et al (2015)</td>
<td>Magnesium</td>
<td>6</td>
<td>No</td>
<td>Pooled RR of depression in patients with hypomagnesemia (3 cohort studies, 2 cross-sectional studies, 1 case-control study combined; N=19,137 patients):</td>
</tr>
</tbody>
</table>

Fibromyalgia
2.04.136 Nutrient/Nutritional Panel Testing
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<table>
<thead>
<tr>
<th>Study</th>
<th>Nutrient</th>
<th>No. of Studies</th>
<th>Specified Cutoff for Nutrient Deficiency</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daniel and Pitotta (2011)</td>
<td>Vitamin D</td>
<td>No</td>
<td>No</td>
<td>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</td>
</tr>
</tbody>
</table>
| 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 B12, 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention and Comparator</th>
<th>No. and Type of Studies</th>
<th>Patients Diagnosed with Nutritional Deficiencies</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taylor et al (2003)</td>
<td>Folic acid (alone or as adjunctive treatment) vs antidepressant mediation</td>
<td>3 RCTs</td>
<td>No</td>
<td>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)</td>
</tr>
</tbody>
</table>
| Gowda et al (2015)           | Vitamin D                  | 9 RCTs                  | • No in overall 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

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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.

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. Screening for iron deficiency anemia is recommended in 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 November 2017 did not identify any ongoing or unpublished trials that would likely influence this review.

References


6. 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


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 a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.
IE
The following services may be considered investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>82128</td>
<td>Amino acids; multiple, qualitative, each specimen</td>
</tr>
<tr>
<td>CPT</td>
<td>82136</td>
<td>Amino acids, 2 to 5 amino acids, quantitative, each specimen</td>
</tr>
<tr>
<td>CPT</td>
<td>82746</td>
<td>Folic acid; serum</td>
</tr>
<tr>
<td>CPT</td>
<td>83735</td>
<td>Magnesium</td>
</tr>
<tr>
<td>CPT</td>
<td>83785</td>
<td>Manganese</td>
</tr>
<tr>
<td>CPT</td>
<td>84590</td>
<td>Vitamin A</td>
</tr>
<tr>
<td>CPT</td>
<td>84630</td>
<td>Zinc</td>
</tr>
<tr>
<td>CPT</td>
<td>84999</td>
<td>Unlisted chemistry procedure</td>
</tr>
</tbody>
</table>

HCPCS None
ICD-10 Procedure None
ICD-10 Diagnosis All Diagnoses

Policy History

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

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>01/01/2016</td>
<td>BCBSA Medical Policy Adoption</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>03/01/2016</td>
<td>Administrative Update (Correction to Documentation for Clinical Review section)</td>
<td>Administrative Review</td>
</tr>
<tr>
<td>06/01/2017</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>02/01/2018</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
</tbody>
</table>

Definitions of Decision Determinations

Medically Necessary: A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

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. Please call (800) 541-6652 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.