I. Policy

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. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

II. Product Variations

This policy is applicable to all programs and products administered by Capital BlueCross unless otherwise indicated below.

FEP PPO*


III. Description/Background

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

At least 1 company, Genova Diagnostics, offers nutritional/nutrient panel testing. Among tests offered by this company is the NutrEval® FMV test, 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).

The company produces a report that includes test results divided into the categories 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 following nutrients, if they are found to be areas of high need.

Table 1. Components of the NutrEval Test

<table>
<thead>
<tr>
<th>Category</th>
<th>Nutrients</th>
</tr>
</thead>
<tbody>
<tr>
<td>B vitamins</td>
<td>Thiamin B₁, riboflavin B₂, niacin B₃, pyridoxine B₆, biotin B₇, folic acid B₉, cobalamin B₁₂</td>
</tr>
<tr>
<td>Minerals</td>
<td>Magnesium, manganese, molybdenum, zinc</td>
</tr>
<tr>
<td>Essential fatty acids</td>
<td>Omega-3-oils</td>
</tr>
<tr>
<td>Digestive support</td>
<td>Probiotics, pancreatic enzymes</td>
</tr>
<tr>
<td>Other vitamins</td>
<td>Vitamin D</td>
</tr>
<tr>
<td>Amino acids</td>
<td>Arginine, asparagine, cysteine, glutamine, glycine, histidine, isoleucine, leucine, lycine, methionine, phenylalanine, serine, taurine, threonine, tryptophan, tyrosine, valine</td>
</tr>
</tbody>
</table>

A related test, the ONE (Optimal Nutritional Evaluation) FMV™, involves testing limited to the organic acid, amino acid, and oxidative stress markers categories.

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

IV. RATIONALE

The evidence review was created with a literature review using MEDLINE through July 10, 2015.

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, an indirect chain of evidence can be examined. Nutrient/nutritional panel tests are particularly targeted to patients with mood disorders, fibromyalgia, and chronic fatigue, so these are the conditions that will be the focus of the evidence review.

An indirect chain of evidence to support 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 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 an indirect chain of evidence is examined next.

**Evidence on the Association Between Nutritional Deficiencies and 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 these 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 and Meta-Analyses on the Association Between Nutritional Deficiencies and Mood Disorders, Fibromyalgia, and Unexplained Fatigue**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Study</th>
<th>Nutrient</th>
<th>No. of Studies</th>
<th>Specified Cutoff Indicating Nutrient Deficiency</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mood disorders</td>
<td>Swardfager et al (2013)¹</td>
<td>Zinc</td>
<td>17</td>
<td>No</td>
<td>Mean serum zinc concentrations = -1.85 μmol/L (95% CI, -2.52 to -1.19) in depressed patients vs nondepressed controls (p&lt;0.001)</td>
</tr>
</tbody>
</table>
| Depression | Anglin et al (2013)²  | Vitamin D| 14             | No                                            | Cross-sectional studies:  
  • Odds of depression, highest vs lowest vitamin D categories: OR=1.31 (95% CI, 1.00 to 1.71; p=0.03)  
  • Prospective series |
### Evidence that Treatment of Patients With Mood Disorders, Fibromyalgia, or Unexplained Fatigue Found to Have Nutritional Deficiencies Improves Condition-Specific Symptoms

Several systematic reviews and meta-analyses evaluating health outcomes in patients with depression treated with nutritional supplementation were identified, and these 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 and Meta-Analyses on Interventions for Patients With Mood Disorders, Fibromyalgia, and/or Unexplained Fatigue Diagnosed With Nutritional Deficiencies

<table>
<thead>
<tr>
<th>Indication</th>
<th>Study</th>
<th>Intervention, Comparison Intervention</th>
<th>No. of Studies and Type</th>
<th>Patients Diagnosed With Nutritional Deficiencies</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mood disorders</td>
<td>Petridou et al (2015)³</td>
<td>Folate and vitamin B₁₂</td>
<td>11 No</td>
<td>Odds of having depression significantly associated with low folate and vitamin B levels:</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Folate: OR=1.27 (95% CI, 1.07 to 1.43)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Vitamin B: OR=1.20 (95% CI, 1.02 to 1.42)</td>
<td></td>
</tr>
</tbody>
</table>

CI: confidence interval; HR: hazard ratio; OR: odds ratio.
Depression  Taylor et al (2003)  3 RCTs  No  Difference in HDRS score significantly lower in patients taking folic acid plus antidepressants vs antidepressants alone (MD = -2.65; 95% CI, -4.93 to -0.038)

Depression  Gowda et al (2015)  9 RCTs
• No in overall analysis
• Yes in subanalysis
• 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
depression and levels of several nutrients; however, there was no evidence that treatment of depressed patients with nutrient supplementation improved health outcomes. In addition, there was no direct evidence on 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.

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 (USPSTF) has not addressed nutritional panel testing. USPSTF has several recommendations addressing screening for individual nutrients. They have 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 (NCD).

V. DEFINITIONS

N/A

VI. BENEFIT VARIATIONS

The existence of this medical policy does not mean that this service is a covered benefit under the member’s contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member’s individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member’s benefit information or contact Capital for benefit information.

VII. DISCLAIMER

Capital’s medical policies are developed to assist in administering a member’s benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this
medical policy and a member’s benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational; therefore not covered when used to report Nutrient-Nutritional Panel Testing:

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<tr>
<th>CPT Codes®</th>
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</table>


IX. REFERENCES

4. 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

X. POLICY HISTORY

<table>
<thead>
<tr>
<th>Policy Number</th>
<th>Date</th>
<th>Description</th>
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<tr>
<td>MP-2.334</td>
<td>CAC 9/29/15</td>
<td>New policy. BCBSA adopted. 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. Coding added.</td>
</tr>
<tr>
<td></td>
<td>Administrative 2/4/16</td>
<td>2016 coding update, removed end dated code.</td>
</tr>
<tr>
<td></td>
<td>CAC 11/29/16</td>
<td>Consensus review. No change to the policy statement. No new references added. FEP variation added to refer to the FEP medical policy manual. Variations reformatted. Coding reviewed.</td>
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