Intracellular Micronutrient Analysis

Policy # 00311
Original Effective Date: 08/17/2011
Current Effective Date: 12/20/2017

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.

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 intracellular micronutrient panel testing to be **investigational.***

Background/Overview

"Micronutrients" collectively refer to essential vitamins and minerals necessary in trace amounts for health. Clinical deficiency states (states occurring after prolonged consumption of a diet lacking the nutrient that is treated by adding the nutrient to the diet) have been reported for vitamins A, B_1, B_{12}, C, and D, selenium, and other micronutrients. Classic nutritional deficiency diseases are uncommon in the United States; most people derive sufficient nutrition from their diets alone or in combination with over-the-counter multivitamins. Laboratory tests are available for individual micronutrients and are generally used to confirm suspected micronutrient deficiencies. Testing is performed by serum analysis using standardized values for defining normal and deficient states. In addition, some commercial laboratories offer panels of vitamin and mineral testing that also use serum analysis.

This evidence review addresses a laboratory tests that measure the intracellular levels of micronutrients. This testing, also known as intracellular micronutrient analysis, micronutrient testing, or functional intracellular analysis, is sometimes claimed to be superior to serum testing because intracellular levels reflect more stable micronutrient levels over longer time periods than serum levels, because intracellular levels are not influenced by recent nutrition intake. However, the relation between serum and intracellular levels of micronutrients is complex. The balance of intra- and extracellular levels depend on a number of factors, including the physiology of cellular transport mechanisms and the individual cell type.

At least 2 commercial laboratories offer intracellular testing for micronutrients. Laboratories perform a panel of tests evaluating the intracellular level of various micronutrients (e.g., minerals, vitamins, amino acids, fatty acids). The test offered by IntraCellular Diagnostics evaluates epithelial cells from buccal swabs and assesses levels of intracellular mineral electrolyte (i.e., magnesium, calcium, potassium, phosphorous, sodium, chloride). SpectraCell Laboratories offers a panel of tests that evaluates the intracellular status of micronutrients within lymphocytes in blood samples. The micronutrients measured by the test include:

- Vitamins: A, B_1, B_2, B_3, B_6, B_{12}, C, D, K; biotin, folate, pantothenic acid
- Minerals: calcium, magnesium, zinc, copper
- Antioxidants: α-lipoic acid, coenzyme Q10, cysteine, glutathione, selenium, vitamin E
- Amino acids: asparagine, glutamine, serine

- Carbohydrate metabolism: chromium, fructose sensitivity, glucose-insulin metabolism
- Fatty acids: oleic acid
- Metabolites: choline, inositol, carnitine.

The SpectraCell micronutrient panel also evaluates total antioxidant function.

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 (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Intracellular micronutrient testing, offered by SpectraCell and IntraCellular Diagnostics, is available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA 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 (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

INTRACELLULAR MICRONUTRIENT ANALYSIS

Clinical Context and Test Purpose

The purpose of diagnostic testing of patients who have chronic diseases or nonspecific generalized symptoms is to identify micronutrient deficiencies, not indicated by specific signs and/or symptoms, that would inform management decisions and improve health outcomes.

The question addressed in this evidence review is: Does intracellular micronutrient analysis testing improve health outcomes in individuals with chronic diseases or nonspecific generalized symptoms?

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

Patients
The relevant populations of interest are patients with chronic diseases or nonspecific generalized symptoms.

Interventions
Intracellular micronutrient analysis.

Comparators
Serum testing for nutritional deficiencies or standard management without nutritional testing.

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Outcomes
The general outcomes of interest are test accuracy, symptoms, and change in disease status.

Timing
Short- and long-term symptom improvement and change in disease status; the time frame will vary depending on the chronic disease affecting the patient.

Setting
Testing can be ordered in primary care or specialty setting.

Analytic Validity
No studies on analytic validity were identified.

Clinical Validity
No studies on the sensitivity and specificity of intracellular micronutrient analysis tests compared with a reference standard (e.g., serum testing) were identified.

Clinical Utility

Direct Evidence
We did not identify any studies reporting on the clinical utility of intracellular micronutrient analysis. The ideal study would be a randomized controlled trial evaluating health outcomes in patients who did and did not undergo intracellular micronutrient testing.

Chain of Evidence
Absent direct evidence, a chain of evidence to demonstrate improved outcomes would require data that intracellular micronutrient testing can identify individuals with micronutrient deficiencies who would not otherwise be identified, that treatments are available for these patients that would not otherwise be given, and that these treatments improve health outcomes.

An observational study by Houston (2010) provided some data relevant to a chain of evidence. The study described a single center's experience with micronutrient testing in the management of hypertension. A total of 3338 patients treated over 5 years received micronutrient testing. Among the 3338 patients, 671 (20%) were considered to have hypertension (defined as blood pressure >140/90 mm Hg). The author stated that there were differences in levels of many micronutrients in the hypertensive versus nonhypertensive populations but did not report the specific micronutrients for which levels differed. Hypertensive patients identified as having micronutrient deficiencies were treated with high-dose therapy of appropriate supplements, as well as with recommendations on optimal diet, exercise, and weight management. The author reported that, after 6 months, 62% of the hypertensive population had succeeded in reaching their blood pressure goals and had tapered and discontinued hypertensive medication. The article did not report micronutrient levels before or after treatment and did not report 6-month blood pressure data for a comparison group of hypertensive patients who did not undergo micronutrient testing.

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Section Summary: Clinical Utility
There is no direct evidence that intracellular micronutrient analysis improves health outcomes in patients with chronic diseases or nonspecific generalized symptoms. Moreover, there are insufficient data to construct a chain of evidence that intracellular micronutrient testing would likely lead to identifying patients whose health outcomes would be improved compared with alternative approaches to patient management.

SUMMARY OF EVIDENCE
For individuals who have chronic diseases or nonspecific generalized symptoms who receive intracellular micronutrient analysis, the evidence includes observational studies. Relevant outcomes are test accuracy, symptoms, and change in disease status. No studies were identified that evaluated the analytic validity, clinical validity, or clinical utility of intracellular micronutrient testing compared with standard testing for vitamin or mineral levels. Limited data from observational studies are available on correlations between serum and intracellular micronutrient levels. No randomized controlled trials or other comparative studies were identified evaluating the direct health impact of intracellular micronutrient testing. Moreover, there are insufficient data to construct a chain of evidence that intracellular micronutrient testing would likely lead to identifying patients whose health outcomes would be improved compared with alternative approaches to patient management. The evidence is insufficient to determine the effects of the technology on health outcomes.

References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, "Intracellular Micronutrient Analysis", 2.04.73, 3:2017.
2. Houston MC. The role of cellular micronutrient analysis, nutraceuticals, vitamins, antioxidants and minerals in the prevention and treatment of hypertension and cardiovascular disease. Ther Adv Cardiovasc Dis. Jun 2010;4(3):165-183. PMID 20400494

Policy History

Original Effective Date: 08/17/2011
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08/04/2011	Medical Policy Committee review
08/17/2011	Medical Policy Implementation Committee approval. New policy.
08/02/2012	Medical Policy Committee review
08/15/2012	Medical Policy Implementation Committee approval. No change to coverage.
09/05/2013	Medical Policy Committee review
09/18/2013	Medical Policy Implementation Committee approval. No change to coverage.
09/04/2014	Medical Policy Committee review
09/17/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/03/2015	Medical Policy Committee review
09/23/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/01/2016	Medical Policy Committee review
12/21/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
12/07/2017	Medical Policy Committee review
12/20/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 12/2018

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Coding

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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	82310, 82725, 84999, 86353, 88348, 84590
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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