
Medical Policy



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***Current Policy Effective Date: 1/1/21**
(See policy history boxes for previous effective dates)

Title: Intracellular Micronutrient Analysis

Description/Background

Commercial laboratories offer panels of tests evaluating intracellular levels of micronutrients (essential vitamins and minerals). Potential uses of these tests include screening for nutritional deficiencies in healthy people or those with chronic disease and aiding in the diagnosis of disease in patients with nonspecific symptoms.

Diagnostic Testing

This evidence review evaluates laboratory tests that measures 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 and 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 intracellular and extracellular levels depends on a number of factors, including the physiology of cellular transport mechanisms and the individual cell type.

At least two commercial laboratories offer intracellular testing for micronutrients. Laboratories perform a panel of tests evaluating the intracellular level of a variety of 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 (ie, magnesium, calcium, potassium, phosphorus, sodium, and 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, B₁, B₂, B₃, B₆, B₁₂, C, D, K; biotin, folate, pantothenic acid
- Minerals: calcium, magnesium, zinc, copper
- Antioxidants: alpha 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 may include SPECTROX™ for evaluation of the total antioxidant function.

Regulatory Status

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). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Medical Policy Statement

The clinical utility of intracellular micronutrient analysis has not been established. The medical literature has not shown that this testing demonstrates diagnostic accuracy to provide clinically relevant information when compared to other available diagnostic studies. Intracellular micronutrient analysis is experimental/ investigational.

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

N/A

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

N/A

Other codes (investigational, not medically necessary, etc.):

84999

86353

88348

Rationale

INTRACELLULAR MICRONUTRIENT ANALYSIS

Clinical Context and Test Purpose

“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, B₁, B₁₂, C, and D, selenium, and other micronutrients. Classic nutritional deficiency diseases are uncommon in the U. S.; 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. Also, some commercial laboratories offer panels of vitamin and mineral testing that also use serum analysis.

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 PICOs 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

The test being considered is intracellular micronutrient analysis. Testing can be ordered in primary care or specialty setting.

Comparators

The following practices are currently being used to identify micronutrient deficiencies: serum testing for nutritional deficiencies or standard management without nutritional testing.

Outcomes

The general outcomes of interest are symptoms and change in disease status. The timeframe for short- and long-term symptom improvement and change in disease status vary by the chronic disease affecting the patient.

Study Selection Criteria

For the evaluation of clinical validity of the intracellular micronutrient test panel, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard (describe the reference standard)
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

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

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).

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

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.

No evidence from randomized controlled trials was identified supporting the use of intracellular micronutrient analysis tests.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

An observational study by Houston (2010) provided some data relevant to a chain of evidence.⁽¹⁾ The study described a single center's experience with micronutrient testing in the management of hypertension. A total of 3,338 patients treated over 5 years received micronutrient testing. Among the 3,338 patients, 671 (20%) were considered to have hypertension (defined as blood pressure above 140/90 mm Hg). The author stated that there were differences in levels of many micronutrients in the hypertensive versus non-hypertensive 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 report did not provide data on micronutrient levels

before or after treatment or 6-month blood pressure data for a comparison group of hypertensive patients who did not undergo micronutrient testing.

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 symptoms and change in disease status. No studies were identified that evaluated the 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 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.

Supplemental Information

PRACTICE GUIDELINES AND POSITION STATEMENTS

No practice guidelines or position statements on intracellular micronutrient testing were identified.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

Government Regulations

National/Local:

Medicare has no national or local coverage determination on this topic.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

N/A

References

1. 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 2010; 4(3):165-83. PMID 20400494

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 7/31/20, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
5/1/10	3/16/10	2/16/10	Joint policy established
7/1/11	4/19/11	5/3/11	Policy revised: Title changed from "Functional Intracellular Analysis" to "Intracellular Micronutrient Analysis"; references updated. Description/background section revised to omit the names of specific entities or brand names. Rationale section modified from previous version of policy.
3/1/13	12/11/12	12/31/12	Routine maintenance; background, rationale and references revised.
7/1/14	4/10/14	4/15/14	Routine maintenance
7/1/15	4/24/15	5/8/15	Routine maintenance
7/1/16	4/19/16	4/19/16	Routine maintenance
1/1/17	10/11/16	10/11/16	Routine maintenance
1/1/18	10/19/17	10/19/17	Routine maintenance
1/1/19	10/16/18	10/16/18	Routine maintenance
1/1/20	10/15/19		Routine maintenance
1/1/21	10/20/20		Routine maintenance

Next Review Date: 4th Qtr, 2021

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: INTRACELLULAR MICRONUTRIENT ANALYSIS

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.