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| 2.04.73 Intracellular Micronutrient Analysis | |
| Original Policy Date: August 29, 2014 | Effective Date: March 1, 2024 |
| Section: 2.0 Medicine | Page: Page 1 of 8 |

Policy Statement

I. Intracellular micronutrient panel testing is considered **investigational**.

NOTE: Refer to [Appendix A](#) to see the policy statement changes (if any) from the previous version.

Policy Guidelines

There is no specific CPT code for this panel of testing.

The specific CPT codes for each of the elements of the panel would most likely be reported (e.g., 84590 for vitamin A, 82310 for calcium, 82725 for oleic acid) along with 1 unit of a not otherwise specified (i.e., 84591) or unlisted (i.e., 84999) code for the balance of the panel, which does not have specific codes.

According to SpectraCell Laboratories, their total antioxidant function testing (which they call SPECTROX®) is reported using the following CPT code:

- **86353:** Lymphocyte transformation, mitogen (phytomitogen) or antigen induced blastogenesis

IntraCellular Diagnostics uses electron microscopy for which the following CPT code might be reported:

- **88348:** Electron microscopy, diagnostic

Description

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.

Related Policies

- N/A

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. Intracellular micronutrient panel testing is offered by SpectraCell Laboratories and IntraCellular Diagnostics 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

"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.

Diagnostic Testing

This evidence review evaluates 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 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 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 (EXA Test[®]) evaluates epithelial cells from buccal swabs and assesses levels of intracellular mineral electrolyte (i.e., magnesium, calcium, potassium, phosphorus, sodium, chloride).¹ SpectraCell Laboratories offers a panel of tests that evaluates the intracellular status of micronutrients within lymphocytes in blood samples.² The micronutrients measured by the test include:

- Vitamins: A, B₁, B₂, B₃, B₆, B₁₂, C, D, K; biotin, folate, pantothenic acid
- Minerals: calcium, magnesium, manganese, 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 may include SPECTROX[™] for evaluation of the total antioxidant function and IMMUNIDEX[™] for immune response score.

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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Intracellular Micronutrient Analysis**Clinical Context and Test Purpose**

The purpose of diagnostic testing of individuals 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 following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with chronic diseases or with nonspecific generalized symptoms.

Interventions

The test being considered is intracellular micronutrient analysis.

Comparators

The following practices are currently being used to identify micronutrient deficiencies: serum testing for individual 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 the 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

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 (e.g., 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.³ 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 vs 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 an 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 the 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: Clinically Useful

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.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to

guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

No guidelines or statements were identified.

U.S. Preventive Services Task Force Recommendations

Not applicable.

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 2023 did not identify any ongoing or unpublished trials that would likely influence this review.

References

1. IntraCellular Diagnostics. Mitochondria: Exploration of Intracellular Space. Accessed November 20, 2023. <https://www.exatest.com/>
2. SpectraCell Laboratories. Micronutrient Test. Accessed November 20, 2023. <https://spectracell.sitewrench.com/search-tests>
3. 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): 165-83. PMID 20400494

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.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

| Type | Code | Description |
|-------|-------|--|
| CPT® | 82310 | Calcium; total |
| | 82725 | Fatty acids, nonesterified |
| | 84590 | Vitamin A |
| | 84591 | Vitamin, not otherwise specified |
| | 84999 | Unlisted chemistry procedure |
| | 86353 | Lymphocyte transformation, mitogen (phytomitogen) or antigen induced blastogenesis |
| | 88348 | Electron microscopy, diagnostic |
| 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 |
|----------------|--|
| 08/29/2014 | BCBSA Medical Policy adoption |
| 01/01/2017 | Policy revision without position change |
| 05/01/2017 | Policy revision without position change |
| 05/01/2018 | 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. |
| 03/01/2024 | Policy reactivated. Previously archived from 09/01/2020 to 02/29/2024. |

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 and Feedback (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.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue

Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

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.

Appendix A

| POLICY STATEMENT | |
|--|--|
| BEFORE | AFTER <i>Blue font: Verbiage Changes/Additions</i> |
| Reactivated Policy Policy Statement: N/A | <i>Intracellular Micronutrient Analysis 2.04.73</i> Policy Statement: I. <i>Intracellular micronutrient panel testing is considered investigational.</i> |