



# Kansas City

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## Intracellular Micronutrient Analysis

**Policy Number:** 2.04.73

**Last Review:** 1/2014

**Origination:** 1/2013

**Next Review:** 1/2015

### **Policy**

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Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for intracellular micronutrient analysis. This is considered investigational.

### **When Policy Topic is covered**

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Not Applicable

### **When Policy Topic is not covered**

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

### **Considerations**

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This testing is currently only available through two reference laboratories: SpectraCell Laboratories (Houston, TX) and IntraCellular Diagnostics (Medford, OR).

### **Description of Procedure or Service**

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

### **Background**

"Micronutrients" is a collective term used to describe essential vitamins and minerals. Adequate intake of micronutrients is important to the maintenance of 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 United States; most individuals 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 policy addresses a novel laboratory test that measures the intracellular levels of micronutrients. This testing is known as intracellular micronutrient analysis and is also called micronutrient testing and functional intracellular analysis. Advocates claim that intracellular nutrient status is superior to serum testing. This is because intracellular levels may reflect more stable micronutrient levels over longer time periods compared to serum levels, since intracellular levels are not influenced by recent nutrition intake. However, this is not a widely accepted view, as the relationship 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 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, etc. The test offered by IntraCellular Diagnostics evaluates epithelial cells from buccal swabs and assesses levels of magnesium, calcium, potassium, phosphorous, sodium, and chloride, as well as ratios between various combinations of these minerals. 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 are as follows:

- 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 includes an evaluation of total antioxidant function.

### **Regulatory Status**

Intracellular micronutrient testing is offered by companies SpectraCell and IntraCellular Diagnostics, which have Clinical Laboratories Improvement Amendments (CLIA) accredited laboratories. SpectraCell's micronutrient panel test and the IntraCellular Diagnostics ExaTest have not been through the FDA approval process.

### **Rationale**

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#### **Literature Review**

This policy was created with a search of the MEDLINE database through May 2011. The policy was updated regularly with literature searches; the most recent search of the MEDLINE database was conducted for the period May 2012 through June 21, 2013. Following is a summary of the key literature to date.

One proposed use of intracellular micronutrient testing is as a screening test in individuals who do not have signs or symptoms of nutritional deficiency. The appropriate study design to evaluate the clinical benefit of a screening test is a randomized controlled trial (RCT) comparing health outcomes in a screened and unscreened population. No such studies were identified in the literature search. In addition, no controlled observational (non-randomized) studies were identified.

In 2010, Houston published an article on screening asymptomatic patients using micronutrient testing. (1) The article was primarily a review but presented data on one center's experience with micronutrient testing in the management of hypertensive patients. 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 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.

Intracellular micronutrient testing is also proposed to aid in the diagnosis of patients with generalized symptoms with no identified disease source. No studies were identified evaluating this potential application of intracellular micronutrient testing.

Another possible application of intracellular micronutrient testing is as an alternative to serum testing for the diagnosis of specific nutritional deficiencies in patients with signs or symptoms of a nutritional disorder. A related application would be using intracellular micronutrient testing instead of serum testing for asymptomatic patients who have been diagnosed with a disease associated with a specific nutritional deficiency. No studies comparing the diagnostic accuracy or clinical utility of intracellular versus serum testing were identified for any particular micronutrient in either of the above patient populations.

There are, however, some published data from the 1990s by Haigney and colleagues examining intracellular and serum magnesium levels in patients with heart disease. (Magnesium sulfate is an accepted treatment in selected patients with ventricular arrhythmias.) In a study with 40 patients referred for arrhythmia evaluation, there was a statistically significant correlation between intracellular magnesium levels and increased QT interval dispersion (dQT), defined as the difference between the longest and shortest QT interval. (2) The correlation was  $r: 0.22$ ,  $p < 0.022$ . There was not a significant correlation between serum magnesium and the dQT;  $r: 0.03$ ,  $p > 0.05$ . Another study by this research team included 18 patients admitted to the hospital for cardiac surgery, 21 control patients admitted with acute medical illnesses, and 15 healthy controls. (3) The mean serum magnesium levels were within the normal range for the cardiac surgery patients ( $1.87 \pm 0.06$  milliequivalents per liter [mEq/L]). However, the mean intracellular magnesium level was significantly lower in cardiac surgery patients than healthy volunteers ( $32.1 \pm 0.2$  vs.  $33.7 \pm 0.5$  mEq/L, respectively),  $p < 0.001$ . The Haigney et al. studies did not assess the accuracy of intracellular versus serum testing of magnesium levels and did not evaluate the impact of testing on health outcomes.

### **Summary**

No studies were identified that evaluated the accuracy or clinical utility of intracellular micronutrient testing compared to standard testing for vitamin or mineral levels. In addition, no controlled studies were identified that evaluated the health impact of any potential clinical application of intracellular micronutrient testing including diagnosing patients with generalized symptoms or screening individuals for nutrient deficiencies. Limited data are available on correlations between serum and intracellular micronutrient levels. Thus, due to the lack of evidence that intracellular micronutrient testing improves the net health outcome, the technology is considered investigational.

### **Practice Guidelines and Position Statements**

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

### **Medicare National Coverage**

No national coverage determination.

### **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.
2. Haigney MC, Berger R, Schulman S et al. Tissue magnesium levels and the arrhythmic substrate in humans. *J Cardiovasc Electrophysiol* 1997; 8(9):980-6.
3. Haigney MC, Silver B, Tanglao E et al. Noninvasive measurement of tissue magnesium and correlation with cardiac levels. *Circulation* 1995; 92(8):2190-7.

### **Billing Coding/Physician Documentation Information**

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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, etc.) along with multiple units of not otherwise specified (i.e., 84591) or unlisted (i.e., 84999) codes for elements of the panel which don't have specific codes.

According to SpectraCell Laboratories, their total antioxidant function testing (which they call SPECTROX®) is reported using CPT code 86353.

IntraCellular Diagnostics uses electron microscopy for which CPT code 88348 might be reported.

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**Additional Policy Key Words**

N/A

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**Policy Implementation/Update Information**

1/1/13	New policy; considered investigational.
1/1/14	No policy statement changes.

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