

Medical Benefit		Effective Date: 01/01/14	Next Review Date: 09/20
Preauthorization	No	Review Dates: 02/07, 03/08, 03/09, 03/10, 01/11, 01/12, 09/12, 09/13, 09/14, 09/15, 09/16, 09/17, 09/18, 09/19	

This protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

DESCRIPTION

Idiopathic environmental intolerance (formerly known as multiple chemical sensitivities) is typically characterized by recurrent, nonspecific symptoms that the patient or clinician believes are provoked by low levels of exposure to chemical, biologic, or physical agents in food or the environment. Reported symptoms are wide-ranging, and there are not clearly established diagnostic criteria. Various tests (e.g., nutritional assessment) and treatments (e.g., immunoglobulin therapy [IVIg]) have been proposed.

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 people or those with chronic disease and aiding in the diagnosis of disease in patients with nonspecific symptoms.

SUMMARY OF EVIDENCE

IDIOPATHIC ENVIRONMENTAL INTOLERANCE

There is a lack of clear diagnostic criteria for idiopathic environmental intolerance and a lack of evidence on the diagnostic accuracy of laboratory or other tests for this condition. Overall, studies using existing criteria have not found that subjects diagnosed with the condition can reliably distinguish between chemical exposure and placebo. Moreover, studies have not consistently found that low-level electromagnetic field exposure affects objective outcomes (e.g., heart rate or cognitive function). In addition, there is a lack of controlled studies to evaluate treatments for idiopathic environmental intolerance. Thus, all tests and treatments for this condition are considered investigational.

Micronutrients

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 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.

POLICY

Laboratory tests designed to affirm the diagnosis of idiopathic environmental intolerance are considered **investigational**.

Treatments for idiopathic environmental intolerance, including but not limited to neutralizing therapy of chemical and food extracts, avoidance therapy, and elimination diets are considered **investigational**.

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

Note: This guideline does not address any potential pharmacologic treatments; refer to Pharmacy and Therapeutics Guidelines.

POLICY GUIDELINES

Laboratory tests for the diagnosis of idiopathic environmental intolerance may be broadly subdivided into those intended to rule out specific diseases with well-defined presentations and diagnostic criteria and those tests designed to affirm the diagnosis of idiopathic environmental intolerance. For example, a basic diagnostic workup, including a standard panel of chemistry tests and blood workup, would be considered appropriate as an initial diagnostic step, even in patients with nonspecific symptoms, to rule out well defined illnesses. Additional tests may be considered medically necessary in patients with more specific symptoms, suggestive, for example, of an autoimmune connective tissue disease, or infectious mononucleosis. A variety of psychiatric or psychologic assessments may be performed to assess underlying conditions. However, at the present time, no specific tests can confirm the diagnosis of idiopathic environmental intolerance, and thus, a large battery of tests performed for a patient with nonspecific symptoms must be reviewed carefully for medical necessity. For example, the following should be reviewed closely, particularly when ordered simultaneously: laboratory tests of immune function (i.e., lymphocyte transformation, deregulation of the 2,5A RNase L antiviral pathway), lymphocyte subsets (e.g., natural killer cells, CD4, CD8), immunoglobulin levels (e.g., IgG, IgE), levels of trace minerals in the serum or urine (e.g., selenium, manganese, mercury), antibodies for a variety of infectious agents simultaneously, allergy services (including provocation testing), positron emission tomography scans, or neuropsychologic testing and elaborate nutritional assessment, including intracellular micronutrient assays.

In addition, such treatments as IVIg therapy, provocation therapy, or counseling regarding specific avoidance environments or elimination diets would be considered investigational in the absence of specific symptoms.

BACKGROUND

IDIOPATHIC ENVIRONMENTAL INTOLERANCE

Idiopathic environmental intolerance has been labeled in a variety of ways over time. The original term, *clinical ecology*, was replaced by the term *multiple chemical sensitivity* (MCS). More recently, MCS has been replaced by *idiopathic environmental intolerance*, a term that reflects the uncertain nature of the condition and its relationship to chemical exposure. The central focus of the condition is patient reporting of recurrent, nonspecific symptoms referable to multiple organ systems that the patient believes are provoked by exposure to low levels

of chemical, biologic, or physical agents. The most common environmental exposures include perfumes and scented products, pesticides, domestic and industrial solvents, new carpets, car exhaust, gasoline and diesel fumes, urban air pollution, cigarette smoke, plastics, and formaldehyde. Certain foods, food additives, drugs, electromagnetic fields, and mercury in dental fillings have also been reported as triggering events. However symptoms do not bear any relationship to established toxic effects of the specific chemical and occur at concentrations far below those expected to elicit toxicity.

Reported symptoms are markedly variable but generally involve the central nervous system, respiratory and mucosal irritation, or gastrointestinal symptoms. Symptoms may include fatigue, difficulty concentrating, depressed mood, memory loss, weakness, dizziness, headaches, heat intolerance, and arthralgia. In contrast to the frequently debilitating symptomatology, no specific and consistent abnormalities are noted on laboratory or other diagnostic testing. Other primarily subjectively defined disorders have symptoms that overlap with idiopathic environmental intolerance, including chronic fatigue syndrome, sick building syndrome, fibromyalgia, irritable bowel syndrome, and Gulf War syndrome. A diagnosis of intestinal dysbiosis could be considered within the category of idiopathic environmental intolerance. (Intestinal dysbiosis is addressed separately in the Fecal Analysis in the Diagnosis of Intestinal Dysbiosis Protocol.)

The variable nature of the reported symptoms and the lack of recognized pathologic abnormalities make it extremely difficult to establish objective diagnostic criteria for the condition, which further hinders research into both the causes and appropriate treatment. Various causes for idiopathic environmental intolerances have been proposed; these have prompted different diagnostic and treatment approaches. Some believe that the condition is an unrecognized form of allergy or immunologic hypersensitivity. Advocates of this etiology may recommend a large series of immunologic tests, including a variety of provocation-neutralization tests and a panel of immunologic tests, including immune function tests (e.g., deregulation of the 2,5A RNase L antiviral pathway in peripheral mononuclear blood cells) and levels of lymphocyte subsets (i.e., natural killer cells, CD8 cells). Proposed therapies have included avoidance of environmental and/or dietary exposures. Immune globulin may be recommended for injection or sublingual drops of “neutralizing” chemical and food extracts. Others have proposed that exposure to toxic substances may have prompted the immunologic abnormality and, based on this theory, testing of levels of environmental chemicals in the blood, urine, or fat may be suggested. Detailed nutritional analyses have also been performed, including blood, urine, and intracellular levels of trace minerals. Such elaborate nutritional assessments may also be performed in asymptomatic subjects. For example, Functional Intracellular Analysis (FIA™) is a series of laboratory tests offered by SpectraCell Labs that measure the intracellular levels of micronutrients, such as vitamins, minerals, and antioxidants in lymphocytes.

In some instances, symptoms may appear to coincide after exposure to a viral illness (particularly common in the related condition of chronic fatigue syndrome); supporters of this theory may recommend a wide variety of tests to detect antibodies or antigens of various viruses. Some have also suggested that hypersensitivity to *Candida* may present with a similar array of subjective complaints and thus recommend testing for *Candida* in the stool or urine. Finally, it has also been proposed that idiopathic environmental intolerance is a manifestation of a psychiatric disease or personality disorder based in part on results of psychologic/psychiatric interviews.

It should be noted that some environmentally caused illnesses can be well-characterized by their clinical presentation and laboratory tests. For example, in certain instances, “sick building” syndrome can be traced back to exposure of microorganisms related to air-handling systems. However, in contrast to idiopathic environmental intolerances, these patients experience a limited range of symptoms, and those symptoms only occur in the affected building.

MICRONUTRIENTS

Vitamin Deficiencies

“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 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. Also, some commercial laboratories offer panels of vitamin and mineral testing that also use serum analysis.

Diagnostic Testing

This protocol 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 intra- 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 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, B1, B2, B3, B6, B12, 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.

REGULATORY STATUS

No specific U.S. Food and Drug Administration approval or clearance of a test for idiopathic environmental intolerance was found.

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 the CLIA.

Laboratories that offer LDTs must be licensed by the 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.

RELATED PROTOCOL

Fecal Analysis in the Diagnosis of Intestinal Dysbiosis

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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