Diagnosis and Management of Idiopathic Environmental Intolerance (i.e., Multiple Chemical Sensitivities)

Policy # 00367
Original Effective Date: 06/27/2013
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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.

Note: Fecal Analysis in the Diagnosis of Intestinal Dysbiosis is addressed separately in medical policy 00040 (Archived 12/20/2017).

Note: Intracellular Micronutrient Analysis is addressed separately in medical policy 00311.

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 laboratory tests designed to affirm the diagnosis of idiopathic environmental intolerance to be **investigational.***

Based on review of available data, the Company considers treatments for idiopathic environmental intolerance, including but not limited to immunoglobulin therapy (IVIg), neutralizing therapy of chemical and food extracts, avoidance therapy, elimination diets, and oral nystatin (to treat *Candida*) to be **investigational.***

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 medically 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/Overview

Idiopathic environmental intolerance 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. Reported symptoms are wide-ranging, and there are not clearly established diagnostic criteria. Various tests, e.g., nutritional assessment and treatment, e.g., IVIg, have been proposed.

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 (EMF), 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 in 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.

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 exposure, either or both in the environment or in the diet. 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 levels of trace minerals in the blood, urine, or intracellular levels. 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 psychological/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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

No specific U.S. FDA approval or clearance of a test for idiopathic environmental intolerance was found.

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

The clinical entity of idiopathic environmental intolerance has been controversial for decades, in part due to the lack of a set of reproducible diagnostic criteria. Absent a clear definition of the disorder, basic science research into the etiology of the disorder, appropriate laboratory tests, and identifications of effective treatment are obviously problematic. Published reviews and opinion pieces suggest controversy regarding the etiology of the condition, appropriate diagnostic criteria, and treatment strategies.

Diagnosis

No well-designed studies were identified in the literature searches that evaluated the ability of laboratory tests, nutritional assessments, or other diagnostic tests to accurately diagnose idiopathic environmental intolerance (or MCS).

Studies to date have focused on developing reliable criteria for characterizing idiopathic environmental intolerance and defining an optimal approach to diagnosing the condition. In 2006, Das-Munshi et al. published a systematic review of provocation studies in individuals with MCS. The investigators identified 37 studies that included a total of 784 patients who had been diagnosed with MCS. Blinding was inadequate in most cases. In 8 of 11 studies that were described as double-blind but likely had discernible odors, individuals with MCS had positive responses to provocation. However, of the 7 studies that used chemicals at or below the threshold of detectable odors, 6 failed to show consistent responses in patients with MCS after active provocation. In the 3 studies that used olfactory-masking agents to conceal the identity of the stimulus, none found associations between provocation and response. The authors concluded that persons with MCS react to chemical challenges when they can discern differences between active and sham substances, but when stimuli are adequately masked, individuals with MCS are unable to reliably identify active stimuli. The authors further commented that there may be psychological or behavioral factors leading individuals to have physiologic responses to stimuli when they are aware of the exposure. In reports from Europe, researchers have found that findings of psychological distress, the ability to express emotions, somatic attribution, amplification (susceptibility to sensation), and absorption (predisposition to become deeply immersed in sensory or mystical experiences) were related to the presence of idiopathic environmental intolerance.

In 2008, Bornschein and colleagues published the findings of a double-blind, placebo-controlled provocation study, conducted in Germany that included 20 patients with MCS and 17 healthy controls matched for age and gender. Patients with MCS met several sets of diagnostic criteria developed in the 1990s, including criteria for idiopathic environmental intolerances defined by the International Program for Chemical Safety. Specific eligibility criteria included reporting symptoms that usually arise and recede within a time span of 10 minutes after the beginning of exposure and MCS symptoms that can be provoked by organic solvents. Provocations took place in a “climate chamber” (room for climatologic and chemical provocations). Participants underwent 6 consecutive 15-minute sessions, each followed by a 15-minute break. Three sessions were exposures to solvents and the other 3 were exposure to placebo (clean air), in random order; patients and staff were blinded. The solvents were a mixture of 6 hydrocarbons found in common household solvents; to avoid the need for olfactory masking, room air concentrations were set below a detectable odor threshold. Only one participant failed to complete the provocation sessions. A positive reaction to exposure was defined as 1) the individual believed he or she had been exposed to an active agent; 2) there was an objective sign of a reaction, e.g., rash, increase in heart rate; or 3) symptom severity rose to 3 or 4 (on 4-point scale). Fifty percent of patients with MCS and 53% of matched controls showed a positive reaction in all 6 exposure sections. Eighty-two percent of controls and 50% of patients had 3 correct reactions. However, more patients than controls (30% versus 12%, respectively) reacted correctly more than 3 times. Considering only the subjective perception of exposure, 40% of patients and 35% of controls

voted correctly more than 3 times. Overall, study findings suggest that patients with MCS disorders cannot reliably distinguish between solvents and placebo.

Several systematic reviews of studies on the diagnosis of idiopathic environmental intolerance attributed to EMF have been published. A 2011 systematic review by Rubin and colleagues identified 29 studies which were single- or double-blind, exposed participants to EMF fields, and measured objective outcomes. Twenty of the 29 studies used outcomes related to the autonomic nervous system (e.g., heart rate or blood pressure). Two of 20 (10%) studies found a significant impact of EMF on function and the other 18 studies found no effect. The authors noted that findings of the 2 positive studies might have been influenced by the order of exposure e.g. including a sham exposure that was always first or second in a series of 3 or 4 consecutive exposures. None of the 4 studies measuring blood chemistry or 3 studies measuring brain physiology found a significant effect of EMF levels on outcomes. Seven studies tested cognitive function; 2 of 7 (29%) had at least one positive finding. The authors concluded that there is insufficient evidence suggesting that individuals with idiopathic environmental intolerance attributed to EMF experience their physiological reactions as a result of exposure to EMF.

In 2012, Baliatsas and colleagues reviewed 63 studies that included definitions or criteria for identifying individuals with idiopathic environmental intolerance related to EMF exposure. The major criteria used in the studies were: 1) attribution of non-specific physical symptoms to either various or specific sources of EMF (n=13 studies); 2) self-reported idiopathic environmental intolerance attributed to EMF exposure (or similar terms) (n=14 studies); 3) experience of symptoms during or within 24 hours after perceived or actual EMF exposure (n=10 studies); and 4) high score on a symptom scale (n=6). The review found considerable variation among studies in terms of definitions and criteria; uniform diagnostic criteria have not yet been developed.

Treatment
In 2012, Skovbjerg and colleagues in Denmark published a randomized non-blinded pilot study to evaluate mindfulness-based cognitive therapy to treat multiple chemical sensitivities. Thirty-seven individuals with self-reported symptoms attributed to exposure to common airborne chemicals, or with physician-diagnosed MCS were included. Participants were randomized to receive weekly group therapy for 8 weeks or usual care. At the 4-, 8- and 12-week follow-ups, no statistically significant differences were found between groups in the 2 main outcome measures, the Symptom Checklist-92 (SCL-92) and the Brief Illness Perception Questionnaire (Brief IPQ). For example, 8 weeks after the beginning of the intervention, mean scores on the somatization scale of the SCL-92 were 0.78 in the therapy group and 0.79 in the control group (p=0.59).

Summary
There is a lack of clear diagnostic criteria for idiopathic environmental intolerance (also known as multiple chemical sensitivities) 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 individuals 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.

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Policy History

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06/27/2013	Medical Policy Committee review
07/17/2013	Medical Policy Implementation Committee approval.
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08/23/2017 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/09/2018 Medical Policy Committee review
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Next Scheduled Review Date: 08/2019

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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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	84999, 86849
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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