Name of Policy:
Diagnosis and Management of Idiopathic Environmental Intolerance (i.e., Clinical Ecology Multiple Chemical Sensitivities)

Policy #: 267       Latest Review Date: June 2014
Category: Medicine       Policy Grade: B

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. 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 that patient’s illness, injury or disease.
Description of Procedure or Service:
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., immunoglobulin therapy (IVIg), have been proposed.

Idiopathic environment 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). Most recently, it has been replaced by idiopathic environmental illness, a term that reflects the uncertain nature of the condition and its relationship to chemical exposure. The central focus of the condition is the fact that the patient describes recurrent, nonspecific symptoms referable to multiple organ systems that the sufferers believe 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 symptoms generally involve either 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. In addition to multiple-chemical-sensitivity, other terms used to describe idiopathic environmental intolerance include universal allergy, 20th century disease, or cerebral allergy. Other primarily subjectively defined disorders have symptoms that overlap with idiopathic environmental intolerance including chronic fatigue syndrome, sick building syndrome, fibromyalgia, and irritable bowel syndrome. Intestinal dysbiosis is a diagnosis that 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. One of the commonly quoted conceptual definitions, proposed by Cullen in 1987, includes the following elements:

- The syndrome is acquired after a documentable environmental exposure that may have caused objective evidence of health effects.
- Symptoms are referable to multiple organ systems and vary predictably in response to environmental stimuli.
• The symptoms occur in relation to measurable levels of chemical, but the levels are below those known to harm health.

• No objective evidence of organ damage can be found.

Various causes for idiopathic environmental intolerances have been proposed; these have prompted different diagnostic and treatment approaches. An unrecognized form of allergy or immunologic hypersensitivity is a commonly proposed cause. 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 and levels of lymphocyte subsets (i.e., natural killer cells, CD8 cells). Proposed therapies have included avoidance of exposure, either in the environment or in the diet. IVIg 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 illness 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 symptoms. However, in contrast to idiopathic environmental intolerances, these patients experience a limited range of symptoms, and they occur in the affected building only.

**Policy:**

**Laboratory tests designed to affirm the diagnosis of idiopathic environmental intolerance do not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and are considered **investigational.**

**Nutritional assessments, including intracellular analysis of micronutrients, do not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and are considered **investigational** in both asymptomatic persons and patients with symptoms suggestive of idiopathic environmental illness.
Treatment for idiopathic environmental intolerance, including but not limited to IVIg, neutralizing therapy of chemical and food extracts, avoidance therapy, elimination diets, and oral nystatin (to treat Candida) does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member’s contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

**Key Points:**
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 that are 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 non-specific 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 psychological 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 non-specific 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), 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), PET scans, or neuropsychologic testing and elaborate nutritional assessment including intracellular micronutrient assays.

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

This policy’s most recent literature review was performed through April 8, 2014. The following is a summary of the key literature.

The clinical entity of idiopathic environmental intolerance has been controversial for decades, in part due to 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 multiple chemical sensitivity [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 subjects 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 eight of 11 studies that were described as double-blind but likely had discernible odors, subjects with MCS had positive responses to provocation. However, of the seven studies that used chemicals at or below the threshold of detectable odors, six failed to show consistent responses in patients with MCS after active provocation. In the three 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, subjects with MCS are unable to reliably identify active stimuli. The authors further commented that there may be psychologic or behavioral factors leading subjects to have physiologic responses to stimuli when they are aware of the exposure. In reports from Europe, researchers have found that findings of psychologic distress, 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 et al 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 ten 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 six consecutive 15-minute sessions, each followed by a 15-minute break. Three sessions were exposures to solvents and the other three were exposure to placebo (clean air), in random order; patients and staff were blinded. The solvents were a mixture of six 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) subject believed he or she had been exposed to an active agent; 2) objective sign of a reaction, eg, 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 six exposure sections. Eighty-two percent of controls and 50% of patients had three correct reactions.
However, more patients than controls (30% versus 12%, respectively) reacted correctly more than three times. Considering only the subjective perception of exposure, 40% of patients and 35% of controls voted correctly more than three 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 electromagnetic fields (EMF) have been published. A 2011 systematic review by Rubin et al 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 two 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 three or four consecutive exposures. None of the four studies measuring blood chemistry or three studies measuring brain physiology found a significant effect of EMF levels on outcomes. Seven studies tested cognitive function; two of seven (29%) had at least one positive finding. The authors concluded that there is insufficient evidence suggesting that subjects with idiopathic environmental intolerance attributed to EMF experience their physiologic reactions as a result of exposure to EMF.

In 2012, Bialiatsas et al reviewed 63 studies that included definitions or criteria for identifying subjects with idiopathic environmental intolerance related to EMF exposure. The major criteria used in the studies were: 1) attribution of nonspecific 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 et al in Denmark published a randomized nonblinded pilot study to evaluate mindfulness-based cognitive therapy to treat multiple chemical sensitivities. Thirty-seven participants 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 eight weeks or usual care. At the four-, eight- and 12-week follow-ups, no statistically significant differences were found between groups in the two main outcome measures, the Symptom Checklist-92 (SCL-92) and the Brief Illness Perception Questionnaire (Brief IPQ). For example, eight 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 have not found that individuals diagnosed with the condition using existing criteria 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. There is also a lack of controlled studies evaluating treatments for idiopathic environmental intolerance. Thus, all tests and treatments for this condition are considered investigational.

**Practice Guidelines and Position Statements**

A variety of organizations have presented position papers on idiopathic environmental intolerance, previously referred to as MCS or clinical ecology.

In 1999, the American Academy of Allergy, Asthma and Immunology (AAAAI) issued a position statement on idiopathic environmental intolerance. This statement is still posted on the AAAAI website, but it has been archived. The summary of the position states:

IEI [idiopathic environmental intolerances]-also called environmental illness and multiple chemical sensitivities-has been postulated to be a disease unique to modern industrial society in which certain persons are said to acquire exquisite sensitivity to numerous chemically unrelated environmental substances… Because of the subjective nature of the illness, an objective case definition is not possible…there is an absence of scientific evidence to establish any of these mechanisms as definitive. Most studies to date, however, have found an excess of current and past psychopathology in patients with this diagnosis. The relationship of these findings to the patient's symptoms is also not apparent. Rigorously controlled studies to verify the patient's reported subjective sensitivity to specific environmental chemicals have yet to be done. Moreover, there is no evidence that these patients have any immunologic or neurologic abnormalities. In addition, no form of therapy has yet been shown to alter the patient's illness in a favorable way. A causal connection between environmental chemicals, foods, and/or drugs and the patient's symptoms continues to be speculative and cannot be based on the results of currently published scientific studies.

In 1999, the American College of Occupational and Environmental Medicine published a position statement that concluded, in part:

Although specific diagnostic test and treatment have not yet been demonstrated to be helpful, a generalized clinical approach useful in the management of other nonspecific medical syndromes can be adopted pending further scientific findings. This approach emphasizes 1) establishing a therapeutic alliance with a goal toward functional restoration; 2) performing a medical evaluation appropriate to the presenting complaints and physical findings; 3) avoiding ineffective, costly, and potentially hazardous, unproven diagnostic tests or remedies that may increase a patient’s distress or disease; 4) treating all diagnosable medical and psychological problems; 5) individualizing medical and behavioral coping strategies useful in managing symptoms; and 6) educating the patients about the current state of knowledge about MCS.

**Key Words:**

Allergy, clinical ecology, idiopathic environmental illness, idiopathic environmental intolerance, environmental medicine, multiple chemical sensitivities
Approved by Governing Bodies:
Not applicable

Benefit Application:
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply
FEP: Special benefit consideration may apply. Refer to member’s benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Coding:
CPT Codes: There are no specific CPT codes identified since a wide variety of codes could be reported.

References:
Policy History:
Medical Policy Group, June 2006 (3)
Medical Policy Administration Committee, June 2006
Available for comment June 3-July 17, 2006
Medical Policy Group, June 2008 (1)
Medical Policy Group, June 2010 (1): Policy updated
Medical Policy Group, June 2011 (3): Key Points & References Update
Medical Policy Group, May 2012 (3): 2012 Update to Description, Key Points & References
Medical Policy Panel, May 2013
Medical Policy Group, May 2013 (3): 2013 Updates to policy statement – minor wording changes (no change in content/intent), Key Points and References
Medical Policy Panel, May 2014
Medical Policy Group, June 2014 (3): 2014 Updates to Key Points, Key Words & References; no change in policy statement

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.