Anthem

# Medical Policy

**Subject:** Idiopathic Environmental Illness (IEI)
**Document #:** MED.00059
**Status:** Reviewed

**Publish Date:** 04/10/2024
**Last Review Date:** 02/15/2024

## Description/Scope

This document addresses idiopathic environmental illness (IEI) – also called clinical ecology or multiple chemical sensitivities (MCS). IEI is described as an acquired sensitivity to numerous chemically unrelated environmental substances resulting in a wide variety of non-specific symptoms such that an objective case definition is not possible.

**Note:** For additional information, please see the following:

- LAB.00027 Selected Blood, Serum and Cellular Allergy and Toxicity Tests

## Position Statement

**Investigational and Not Medically Necessary:**

Laboratory tests designed to affirm the diagnosis of idiopathic environmental illness are considered **investigational and not medically necessary.**

Treatment of idiopathic environmental illness with avoidance therapy, elimination diets, neutralizing therapy of chemical and food extracts, or medical therapy is considered **investigational and not medically necessary.**

## Rationale

The clinical entity of IEI has been controversial for decades, in part due to the lack of clear diagnostic criteria. Some observers have interpreted IEI as part of a spectrum of nonphysical illnesses characterized by multiple somatic complaints. Others see it as a distinct entity. The “candida hypersensitivity syndrome” has been claimed to be a similar illness, and many clinical ecologists view this alleged problem as an underlying cause of IEI, but there is no scientific proof that *Candida albicans* causes such a condition. The American Academy of Allergy, Asthma and Immunology (AAAAI) summarized their position in a 1999 statement as follows:

> IEI [idiopathic environmental illness] – 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. The patient experiences wide-ranging symptoms, but evidence of pathology or physiologic dysfunction in such patients has been lacking in studies to date. Because of the subjective nature of the illness, an objective case definition is not possible. Allergic, immunotoxic, neurotoxic, cytotoxic, psychologic, sociologic, and iatrogenic theories have been postulated for both etiology and production of symptoms, but 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.

The AAAAI has also strongly criticized the concept of "candidiasis hypersensitivity syndrome" and the diagnostic and treatment approaches used by proponents (Anderson, 1986). The AAAAI has indicated that the concept of candidiasis hypersensitivity is speculative and unproven, its basic elements would apply to almost all sick individuals at some time. Because its’ supposed symptoms are essentially universal, overuse of oral antifungal agents could lead to the development of resistant germs that could menace others, and neither impacted individuals nor doctors can determine effectiveness without controlled trials. The antifungal drug most often prescribed by proponents of "candidiasis hypersensitivity" is nystatin. In a double-blind trial, the antifungal drug nystatin did no better than a placebo in relieving systemic or psychological symptoms of "candidiasis hypersensitivity syndrome" (Graveling, 1999).

Bailer and colleagues (2005) performed a small, nonrandomized study of 152 participants to determine if IEI was a variant of somatoform disorders (SFD). Participants were divided into four cohorts with 23 subjects identified as IEI, 31 participants with IEI and SFD, 44 participants with SFD and 54 participants did not have either diagnosis, therefore called the “nonsomatoform control group (CG).” The study data included self-reported symptoms, interviews and medical evaluation including blood tests. The three cohorts had higher psychological symptoms and bodily complaints in addition to higher risk factors for somatic complaints when compared to the control group. The authors concluded the similarities of symptoms between IEI and SFD support the hypothesis that IEI is a variant of SFD (Bailer, 2005).

In a 2018 systematic review by Viziano and colleagues, the authors summarized the literature regarding sensory-related disturbances thought to be attributed to IEI. A total of 34 articles were included addressing olfactory alterations, hearing disturbances, vestibular alterations, and cognitive issues. The authors noted that different diagnostic criteria among the studies, lack of homogeneous symptom-related questionnaires and the general incidence of personality traits in control subjects led to biased studies. Further research is necessary to clarify whether sensory-related impairments specifically affect IEI conditions as opposed to a wide spectrum of associated disorders.

Driesen and colleagues (2020) performed a systematic review to explore what qualitative research has suggested about how people with multiple chemical sensitivity (MCS) perceive it to affect their social and occupational functioning. A total of 388 potential articles were identified but only 13 of the articles were eligible for inclusion. Studies were excluded if they were descriptive only, primarily concerned with environmental intolerances other than chemicals or focused on specific populations. Two studies recruited people with sensory hyperactivity (SHR) and 11 studies included individuals “with what appeared to be MCS.” Only 3 of the studies included participants who were reported to have been diagnosed by a physician; this information was unclear in the remaining studies. The duration of the illness ranged from 1 to 51 years in the 5 studies that reported a range. There were only 2 studies that reported

comorbidities. In studies that reported the relevant data (N=8), the participants mean ages ranged between 46 and 68.5 years. Limitations of the study were identified and noted that the findings should be interpreted with caution due to the following reasons. The review process, study selection, data extraction, synthesis of findings and quality reviews were primarily undertaken by one researcher which could have biased the findings. Another limitation noted was that across studies, participants were predominantly middle-to-older aged Caucasian and unemployed women who were recruited from clinics and support groups in the United States and Canada. The studies did not consider how experiences differed depending on factors such as comorbidities, or the duration and severity of the illness. In addition, it was indicated that the studies "lacked rigour in design, analysis and ethical reporting." Although it was concluded that the findings suggested that MCS does limit some individuals' social and occupational functioning, the results warrant further research, and the development of prevention and intervention strategies.

An Italian expert consensus document on diagnosis and treatment of MCS was published in 2021 by Damiani and colleagues. The recommendations were based on the results of a consensus exercise that involved MCS experts and medical and non-medical researchers in Italy. The panel recommended a number of laboratory tests to diagnose MCS but did not cite published studies to support their recommendations.

There have been few recent studies which address the diagnostic and treatment questions associated with IEI. These studies are small, lower quality studies which tend to suggest that there might be a complex disease process and that further studies might be able to uncover the effect of environmental intolerances in humans. The published literature leaves unresolved questions regarding the etiology of the condition, appropriate diagnostic criteria, and treatment strategies.

## Background/Overview

Idiopathic environment illness (IEI) has been labeled in a variety of ways over time including clinical ecology, multiple chemical sensitivity, universal allergy, 20$^{th}$ century disease, and cerebral allergy. The central focus of the condition is the individuals' description of recurrent, nonspecific symptoms referable to multiple organ systems which 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 implicated as triggering events. However, symptoms do not bear any relationship to established toxic effects of the specific chemical, and they occur at concentrations far below those expected to elicit toxicity.

Reported symptoms are variable, but symptoms are vague and can 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 which overlap with idiopathic environmental intolerance including chronic fatigue syndrome, sick building syndrome, fibromyalgia, irritable bowel syndrome, and Gulf War syndrome.

The variable nature of the reported symptoms and the lack of recognized pathologic abnormalities make it 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 etiologies for idiopathic environmental intolerances have been proposed, which have prompted different diagnostic and treatment approaches. An unrecognized form of allergy or immunologic hypersensitivity is a commonly proposed etiology. Advocates for 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 (that is., 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 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. It has also been proposed that idiopathic environmental illness is a manifestation of a psychiatric disease or personality disorder. Studies supporting this cause may include brain imaging studies (including PET scans) or psychologic/psychiatric interviews. In some instances, symptoms may appear to coincide after exposure to a viral illness (particularly common with chronic fatigue syndrome); supporters of this theory may recommend a wide variety of tests to detect antibodies or antigens of various viruses. Finally, some have 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.

Candida albicans is a fungus normally present on the skin and in the mouth, intestinal tract, and vagina. Under certain conditions, it can multiply and infect the surface of the skin or mucous membranes. However, some practitioners claim that even when clinical signs of infection are absent, yeast-related problems (referred to as candidiasis hypersensitivity) can cause or trigger multiple symptoms such as fatigue, irritability, constipation, diarrhea, abdominal bloating, mood swings, depression, anxiety, dizziness, unexpected weight gain, difficulty in concentrating, muscle and joint pain, cravings for sugar or alcoholic beverages, psoriasis, hives, respiratory and ear problems, menstrual problems, infertility, impotence, bladder infections, prostatitis, and "feeling bad all over."

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

Laboratory tests for the diagnosis of idiopathic environmental illness may be broadly subdivided into those intended to rule out specific diseases with well-defined presentations and diagnostic criteria, including those tests designed to affirm the diagnosis of idiopathic environmental illness. For example, a basic diagnostic work up, including a standard panel of chemistry tests and blood work up, would be considered appropriate as an initial diagnostic step, even in individuals with non-specific symptoms, to rule out well-defined illnesses. Additional tests may be appropriate in individuals with more specific symptoms suggestive, for example, of an autoimmune connective tissue disease or infectious mononucleosis. However, at the present time, no specific tests can confirm the diagnosis of idiopathic environmental illness, and thus a large battery of tests performed for an individual with non-specific symptoms must be reviewed carefully. For example, the following should be reviewed closely, particularly when ordered simultaneously: laboratory tests of immune function (that is, lymphocyte transformation), lymphocyte subsets (that is, natural killer cells, CD4, CD8, etc.), immunoglobulin levels (IgG, IgE, etc.), levels of trace minerals in the serum, hair or urine (that is, selenium, manganese,

mercury among others), antibodies for a variety of infectious agents simultaneously, allergy services (including provocation testing), PET scans, or neuropsychological testing.

Currently there is inadequate evidence to establish diagnostic criteria for idiopathic environmental illness, and inadequate evidence to validate specific treatments, including intravenous immune globulin (IVIG), avoidance therapy, elimination diets, neutralizing therapy of chemical and food extracts, or oral nystatin (to treat "candidiasis hypersensitivity syndrome").

## Definitions

"Candidiasis hypersensitivity syndrome" (also known as chronic Candidiasis, Candida-related complex, the yeast syndrome, yeast allergy, yeast overgrowth, or simply "Candida" or "yeast problem"): An alleged problem in which neither infection nor actual allergy is present, purported as an underlying cause of IEI.

Hypersensitivity: An exaggerated response by the immune system to a drug or other substance.

Intravenous Immune Globulin (IVIG): A substance obtained from human blood plasma, which contains immunoglobulins (immune antibodies) to protect against infectious agents that cause various diseases.

## Coding

*The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. 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.*

**When services are Investigational and Not Medically Necessary:**
When the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

**CPT**

| | |
|---|---|
| 99199 | Unlisted special service, procedure or report [when specified as testing or treatment of idiopathic environmental illness (IEI)] |

**ICD-10 Diagnosis**

| | |
|---|---|
| | All diagnoses [no specific diagnosis codes for IEI] |

## References

**Peer Reviewed Publications:**


1. Aaron LA, Buchwald D. A review of the evidence for overlap among unexplained clinical conditions. Ann Intern Med. 2001; 134(9 Pt 2):868-881.
2. Anderson JA, Chai Hyman, Claman HN, et al. Candidiasis hypersensitivity. J Allergy Clin Immun. 1986; 78(2):271-273.
3. Bailer J, Witthoft M, Paul C, et al. Evidence for overlap between idiopathic environmental intolerance and somatoform disorders. Psychosom Med. 2005; 67(6):921-929.
4. Barsky AJ, Borus JF. Functional somatic syndromes. Ann Intern Med. 1999; 130(11):910-921.
5. Cullen MR. The worker with multiple chemical sensitivities: an overview. Occup Med. 1987; 2(4):655-661.
6. Dismukes W, Wade JS, Lee JY, et al. A randomized double-blind trial of nystatin therapy for the candidiasis hypersensitivity syndrome. N Engl J Med. 1990; 323(25):1717-1723.
7. Driesen L, Patton R, John M. The impact of multiple chemical sensitivity on people's social and occupational functioning; a systematic review of qualitative research studies. J Psychosom Res. 2020; 132:1099964.
8. Graveling RA, Pilkington A, George JP, et al. A review of multiple chemical sensitivity. Occup Environ Med. 1999; 56(2):73-85.
9. Kjellqvist A, Palmquist E, Nordin S. Psychological symptoms and health-related quality of life in idiopathic environmental intolerance attributed to electromagnetic fields. J Psychosom Res. 2016; 84:8-12.
10. Johnson D, Colman I. The association between multiple chemical sensitivity and mental illness: Evidence from a nationally representative sample of Canadians. J Psychosom Res. 2017; 99:40-44.
11. Micarelli A, Viziano A, Genovesi G, et al. Lack of contralateral suppression in transient-evoked otoacoustic emissions in multiple chemical sensitivity: a clinical correlation study. Noise Health. 2016; 18(82):143-149.
12. Tran MT, Skovbjerg S, Arendt-Nielsen L, et al. Transcranial pulsed electromagnetic fields for multiple chemical sensitivity: study protocol for a randomized, double-blind, placebo-controlled trial. Trials. 2013; 14:256.
13. Viziano A, Micarelli A, Pasquantonio G, et al. Perspectives on multisensory perception disruption in idiopathic environmental intolerance: a systematic review. Int Arch Occup Environ Health. 2018; 91(8):923-935.


**Government Agency, Medical Society, and Other Authoritative Publications:**


1. American Academy of Allergy, Asthma, and Immunology (AAAAI) Board of Directors. Idiopathic Environmental Intolerances Position Statement (archived). Available at: https://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20and%20Parameters/Idiopathic-environmental-intolerances-1999.pdf. Accessed on November 13, 2023.
2. American Academy of Allergy, Asthma, and Immunology (AAAAI). Allergy diagnostic testing: an updated practice parameter. March 2008. Available at: https://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20and%20Parameters/allergydiagnostictesting.pdf. Accessed on November 13, 2023.
3. Damiani G, Alessandrini M, Caccamo D et al. Italian expert consensus on clinical and therapeutic management of multiple chemical sensitivity (MCS). Int J Environ Res Public Health. 2021 Oct 27; 18(21):11294.


## Websites for Additional Information

1. International Society for Environmentally Acquired Illness (ISEAI). ISEAI resources. Available at:https://iseai.org/resources/. Accessed on November 13, 2023.
2. American Academy of Environmental Medicine (AAWM). Available at: https://www.aaemonline.org/ . Accessed on November 13, 2023.
3. United States Department of Labor. Multiple Chemical Sensitivities. Available at: https://www.osha.gov/SLTC/multiplechemicalsensitivities/. Accessed on November 13, 2023.

## Index



## Document History

| Status | Date | Action |
|---|---|---|
| Reviewed | 02/15/2024 | Medical Policy & Technology Assessment Committee (MPTAC) review. Updated References and Websites sections. |
| Reviewed | 02/16/2023 | MPTAC review. Updated Rationale, References and Website sections. |
| Reviewed | 02/17/2022 | MPTAC review. Updated References and Website sections. |
| Reviewed | 02/11/2021 | MPTAC review. Updated References and Website sections. Updated Coding section to add 99199 NOC. |
| Revised | 02/20/2020 | MPTAC review. Removed specific drug names from Position Statement. Updated References section. |
| Reviewed | 03/21/2019 | MPTAC review. Updated Rationale and References sections. |
| Reviewed | 03/22/2018 | MPTAC review. The document header wording updated from “Current Effective Date” to “Publish Date.” Updated References section. |
| Reviewed | 05/04/2017 | MPTAC review. Updated Rationale, Background, References and Website sections. |
| Reviewed | 05/05/2016 | MPTAC review. Updated Description, Rationale, Background, Definitions, References and Websites sections. Removed ICD-9 codes from Coding section. |
| Reviewed | 05/07/2015 | MPTAC review. Updated Description, Rationale, References and Website sections. |
| Reviewed | 05/15/2014 | MPTAC review. Updated Rationale, Background, References and Websites sections. |
| Reviewed | 05/09/2013 | MPTAC review. Updated References and Websites. |
| Reviewed | 05/10/2012 | MPTAC review. Updated references and websites |
| Reviewed | 05/19/2011 | MPTAC review. Updated references and websites. |
| Reviewed | 05/13/2010 | MPTAC review. Updated references and websites. |
| Reviewed | 05/21/2009 | MPTAC review. References updated. |
| Reviewed | 05/15/2008 | MPTAC review. References and websites updated. Moved the informative “Note” from the Position Statement section to the “Background” section. |
| | 02/21/2008 | The phrase "investigational/not medically necessary" was clarified to read "investigational and not medically necessary." This change was approved at the November 29, 2007 MPTAC meeting. |
| Reviewed | 05/17/2007 | MPTAC review. Updated references and coding. |
| Reviewed | 06/08/2006 | MPTAC annual review. References updated. |
| Revised | 07/14/2005 | MPTAC review. Revision based on Pre-merger Anthem and Pre-merger WellPoint Harmonization. |

| Pre-Merger Organizations | Last Review Date | Document Number | Title |
|---|---|---|---|
| Anthem, Inc. (Related Policies)<br>MED.00015 Allergy Testing<br>MED.00001 Allergy Immunotherapy<br>DRUG.00013 IVIG | | | No prior document on IEI |
| WellPoint Health Networks, Inc. | 12/02/2004 | 2.01.20 | Diagnosis and Management of Idiopathic Environment Intolerance (Clinical Ecology) |

---

Applicable to Commercial HMO members in California: When a medical policy states a procedure or treatment is investigational, PMGs should not approve or deny the request. Instead, please fax the request to Anthem Blue Cross Grievance and Appeals at fax # 818-234-2767 or 818-234-3824. For questions, call G&A at 1-800-365-0609 and ask to speak with the Investigational Review Nurse.

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 eligibility for coverage. The member’s contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.