Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

***Current Policy Effective Date: 7/1/25**
(See policy history boxes for previous effective dates)

Title: Antigen Leukocyte Antibody Test

Description/Background

Intolerance of Environmental Agents or Food

Environmental illness refers to a physiologic reaction that is triggered by an exogenous agent, which can be ingested, inhaled, or absorbed through direct contact with skin. The physiologic reaction can be an immunologic response or a nonimmunologic response. An adverse physiologic reaction to exogenous antigens has been proposed to play a causative role in a wide variety of illnesses, including allergies, gastrointestinal tract disorders such as irritable bowel syndrome, eczema, chronic fatigue, and migraine headache.[1]

Food allergy is the most well-defined type of environmental illness and is estimated to affect 8% of children.[2] In most cases, true food allergy is characterized by a classic immunologic response (ie, an immunoglobulin E-mediated reaction in response to a specific protein allergen). Reactions can range from mild symptoms to life-threatening anaphylaxis. Current guidelines for the diagnosis and management of food allergies have been developed by the National Institute of Allergy and Infectious Disease.[3]

Food intolerance is a broader term that overlaps with food allergy but is less well-defined. Food intolerance refers to physiologic reactions that are triggered by a particular food but which are not immune-mediated.[2] It is hypothesized that physiologic reactions to food may manifest as a range of nonspecific symptoms, such as gastrointestinal complaints, headache, fatigue, and musculoskeletal complaints and that these symptoms may become chronic with repeated exposure. An example of food intolerance, distinguished from a true food allergy, is lactose intolerance, in which dairy products incite a nonimmunologic reaction that can lead to a constellation of gastrointestinal symptoms.

Treatment of environmental illness primarily involves avoidance of the inciting agent. Acute allergic reactions are treated in the same way as other types of allergies, with antihistamines, steroids, and supportive measures. In cases of a severe allergy where an agent cannot be definitively avoided, individuals can carry and self-administer auto-injectable epinephrine when needed. Prophylactic antihistamines can also be used to prevent or lessen reactions. Allergy immunotherapy may be appropriate for selected allergens.

For individuals with food intolerance that is not allergy based, identification of the inciting agent(s) can be difficult because the symptoms are chronic. Use of an elimination diet is considered the best way to identify intolerant agents. In an elimination diet, 1 specific food or food group is eliminated from the diet for a specified period, and symptoms are observed. Following the elimination period, a re-challenge can be performed to ascertain whether symptoms return. Elimination diets often need to be done sequentially with a large number of items, so the process can be lengthy and cumbersome.

Antigen Leukocyte Antibody Test

The Antigen Leukocyte Antibody Test (ALCAT) is intended to identify foods and other environmental agents for which an individual may be intolerant. It is not intended to diagnose food allergies.[4] The test is based on the theory that a substantial increase in leukocyte size and number is characteristic of an intolerant response. Identifying the specific inciting agent facilitates avoidance of that agent, which may lead to a reduction in symptoms. In this regard, ALCAT testing has been used as a tool for developing an elimination diet that targets the most likely offending agents.

The test is performed by taking a sample of blood, which is first treated to remove the red blood cells and then tested to determine the baseline number and size of leukocytes and platelets. Measurement of size and count of cells is performed by the Coulter technique, which is a standard technique in clinical hematology. Next, a small quantity of blood is incubated with multiple agents. Following exposures, change in the number and size of cells is determined for each exposure. A 10% increase in the size of leukocytes is considered characteristic of a response to an intolerant agent.

The ALCAT website (Cell Sciences Systems) lists 11 separate panels consisting of various combinations of foods, herbs, food additives/coloring, and environmental chemicals. The total number of agents tested in these panels ranges from 70-357.[4]

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. The ALCAT is available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Medical Policy Statement

The Antigen Leukocyte Antibody Test (ALCAT) is considered **experimental/investigational**. There is a lack of published research on the diagnostic accuracy of the test; therefore, it is not possible to determine the sensitivity, specificity, and/or predictive value of the test compared with alternatives.

Inclusionary and Exclusionary Guidelines

N/A

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

N/A

Other codes (investigational, not medically necessary, etc.):

83516*

*This billing code is a non-specific code and may be used to bill for a variety of tests. When this code represents the antigen leukocyte antibody test, the code is considered experimental/investigational.

Note: Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

Rationale

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

ANTIGEN LEUKOCYTE ANTIBODY TEST

Clinical Context and Test Purpose

The purpose of the Antigen Leukocyte Antibody Test (ALCAT) in individuals with a suspected intolerance of environmental agents or food is to inform a decision whether to pursue additional diagnostic testing, initiate treatment, or lifestyle and diet management.

The following PICOT was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with suspected intolerance to environmental agents or food.

Interventions
The test being considered is ALCAT

Comparators
The following tests and practices are currently being used to make decisions about diagnosing suspected intolerance of environmental agents or food: antigen or allergen skin testing, antigen or allergen in vitro assays, and elimination dietary changes

Outcomes
The general outcomes of interest are confirming intolerance to an environmental agent or food and selecting an appropriate intervention. The timing of interest may range from 4 weeks to evaluate test results to 1 to 2 years to evaluate reductions in morbid events and medication use.

Study Selection Criteria
For the evaluation of clinical validity of the ALCAT, studies that met the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard (describe the reference standard)
- Individual/sample clinical characteristics were described
- Individual/sample selection criteria were described.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence
There is not a widely accepted criterion standard test for food and environmental intolerance. The double-blind food challenge test may be considered an appropriate reference standard, but there are deficiencies in the definitions and interpretation of food challenge results. No published studies identified have reported on the sensitivity and specificity of ALCAT compared with a double-blind food challenge. One study by Buczylko et al (1995) compared ALCAT with cytotoxic testing, which is not a test routinely used in clinical care at present, in 56

children between the ages of 6 months and 16 years.[5] This study reported that results of the 2 tests were consistent in two-thirds of patients.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

No RCTs evaluating the clinical utility of ALCAT in a population with suspected intolerance of environmental agents or food were identified.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Randomized Controlled Trials
A RCT by Kaats et al (1996) evaluated the use of ALCAT in facilitating weight loss, changes in body composition, and health symptoms.[6] One hundred patients were recruited through an advertisement in a fitness newspaper. Eligibility criteria included at least 2 symptoms that had a “severe effect,” as measured by the Disease Symptoms Inventory (DSI). Patients were randomized to ALCAT testing followed by dietary modifications or to a control group that was instructed to pursue a diet of their own choosing. The ALCAT group received dietary guidance on dietary changes that were recommended based on ALCAT results. Outcomes were measured after 4 weeks of the intervention and included changes in weight, body composition and symptoms on the DSI. Eight participants were lost to follow-up, 7 in the control group and 1 in the ALCAT group.

There was a greater reduction in weight in the ALCAT group compared with the control group (-1.04 kg vs +0.32 kg, $p<.001$), as well as a greater reduction in the percent body fat (-1.2% vs +0.7%, $p<.001$). There were also significantly better scores on the final DSI outcomes for the ALCAT group. Of 20 symptoms included on the DSI, the final scores were significantly better for the ALCAT group on 18 of 20 symptoms. The results of this study have limited clinical relevance because the outcomes reported (weight loss and body composition) are not applicable to the main clinical use of the test or relevance to the population assessed in this review. Additionally, the validity of the results was reduced by limitations in patient selection, lack of blinding, and provision of dietary guidance to the ALCAT group but not the control group.

Case Series

A small number of case series have reported on outcomes following an ALCAT evaluation and treatment based on ALCAT results. These studies are not sufficient to establish efficacy because case series do not control for the natural history of the disorder or for nonspecific factors such as the placebo effect. An example of such a study is Solomon (1992).[1] In this publication, 172 patients with a range of symptoms were tested with ALCAT. Treatment was a food elimination diet, and/or allergy immunotherapy, based on ALCAT results. Follow-up allergy testing was performed with serial end point titration at 3 to 6 months after treatment. Outcomes were measured at 1 to 2 years posttreatment by an independent reviewer who asked subjects to rate the effectiveness of treatment on a 1- to 10- scale. For elimination diets, a range of improvement in individual symptoms of 20% to 82% was reported, and for immunotherapy, a range of improvement of 9% to 75% was reported.

Another uncontrolled study that used the ALCAT as the basis for an elimination diet is that by Mylek (1995).[7] This study enrolled 72 individuals with a range of symptoms considered to be the result of food intolerance. The largest percent improvement in symptoms was reported for arthritis (83%), urticaria (75%), bronchitis (70%), and gastroenteritis (70%). A smaller degree of improvement was reported for the symptoms of hyperreactivity (32%), rhinitis (47%), and atopic dermatitis (49%).

Section Summary: Individuals with Suspected Intolerance of Environmental Agents or Food

There is a lack of published research on the diagnostic accuracy of ALCAT; therefore, it is not possible to determine the sensitivity, specificity, and/or predictive value of the test compared with alternatives. A few low-quality studies have reported improvements in outcomes following the use of ALCAT, but it is not possible to determine whether these changes occurred as a result of the test itself, bias, variation in the natural history of the condition, and/or the placebo effect. Because the clinical validity of ALCAT has not been established, a chain of evidence supporting the clinical utility of the test cannot be constructed.

SUMMARY OF EVIDENCE

For individuals who have a suspected intolerance of environmental agents or food who receive the Antigen Leukocyte Antibody Test (ALCAT), the evidence includes a randomized controlled trial and case series. Relevant outcomes are morbid events and medication use. There is a lack of published research on the diagnostic accuracy of the ALCAT test; therefore it is not possible to determine the sensitivity, specificity, and/or predictive value of the test compared with alternatives. A few low-quality studies report improvements in outcomes following use of ALCAT, but it is not possible to determine whether these changes occurred as a result of test itself, bias, variation in the natural history of the condition, and/or the placebo effect. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

National Institute of Allergy and Infectious Disease

In 2010, the National Institute of Allergy and Infectious Disease published guidelines on the diagnosis and management of food allergy.[3] These guidelines defined and distinguished food intolerance from food allergy, but did not provide recommendations for diagnosis and management of intolerance. For the diagnosis of food allergy, the guidelines stated that "tests selected to evaluate food allergy should be based on the patient's medical history and not comprise large general panels of food allergens."

U.S. Preventive Services Task Force Recommendations
Not applicable.

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov did not identify any ongoing or unpublished trials that would likely influence this review.

Government Regulations
National:
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Local:
Wisconsin Physicians Service Insurance Corporation
Local Coverage Determination (LCD): Allergy Testing (L36402)
Original Effective Date: For services performed on or after 03/18/2016
Revision Effective Date: For services performed on or after 09/26/2024

The following tests are considered experimental and investigational for allergy testing as these have not been proven to be effective or appropriate for the evaluation and/or management of IgE-mediated allergic reactions.

- Antigen leukocyte cellular antibody (ALCAT) automated food allergy testing

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Allergy Testing and Immunotherapy
- Diagnosis and Management of Idiopathic Environmental Intolerance (i.e., Multiple Chemical Sensitivities) (Retired)
- Sublingual Immunotherapy as a Technique of Allergen-Specific Therapy (Retired)
- Xolair® (Omalizumab/ruhMab-E25) (Retired)

References

1. Solomon B.A. The ALCAT Test – A guide and barometer in the therapy of environmental and food sensitivities. Environmental Medicine 1992; 9(2):1-6.
2. Gupta RS, Dyer AA, Jain N et al. Childhood food allergies: current diagnosis, treatment, and management strategies. Mayo Clin Proc. May 2013; 88(5):512-26. PMID 23639501
3. Boyce JA, Assa'ad A et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. J Allergy Clin Immunol. Dec 2010; 126(6 Suppl):S1-58. PMID 21134576
4. Cell Sciences Systems. ALCAT test. N.d.; https://cellsciencesystems.com/patients/alcat-test/ Accessed 2/1/23.
5. Buczylko K, Obarzanowski T, Rosiak K et al. Prevalence of food allergy and intolerance in children based on MAST CLA and ALCAT tests. Rocz Akad Med Bialymst. 1995; 40(3):452-6. PMID 8775289
6. Kaats GR, Pullin D, Parker LK. The short term efficacy of the ALCAT test of food sensitivities to facilitate changes in body composition and self-reported disease symptoms: a randomized controlled study. Bariatrician. 1996; Spring:18-23.
7. Mylek D. ALCAT Test results in the treatment of respiratory and gastrointestinal symptoms, arthritis, skin and central nervous system. Rocz Akad Med Bialymst. 1995; 40(3):625-9. PMID 8775317

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 2/7/25, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
9/1/14	6/17/14	6/23/14	Joint policy established
7/1/16	4/19/16	4/19/16	Routine maintenance
7/1/17	4/18/17	4/18/17	Routine maintenance
7/1/18	4/17/18	4/17/18	Routine maintenance
7/1/19	4/16/19		Routine maintenance
7/1/20	4/14/20		Routine maintenance
7/1/21	4/20/21		Routine maintenance
7/1/22	4/19/22		Routine maintenance
7/1/23	4/18/23		Routine maintenance (jf) Vendor Managed: NA
7/1/24	4/16/24		Routine maintenance (jf) Vendor Managed: NA
7/1/25	4/15/25		Routine maintenance (jf) Vendor Managed: 2023 Avalon G2031 Allergen Testing

Next Review Date: 2nd Qtr, 2026

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: ANTIGEN LEUKOCYTE ANTIBODY TEST

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered
BCNA (Medicare Advantage)	See Government Regulations section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.