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Antigen Leukocyte Antibody Test		
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Policy Statement

The Antigen Leukocyte Antibody Test (ALCAT) is considered **not medically necessary** for all indications.

Policy Guidelines

There are various sizes of Antigen Leukocyte Antibody Test (ALCAT) panels, and they are likely reported with multiple units of CPT code:

 83516: Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; qualitative or semiquantitative, multiple step method (e.g., the Antigen Leukocyte Antibody Test Platinum Comprehensive Panel might be reported with 320 units of code 83516)

Description

The Antigen Leukocyte Antibody Test (ALCAT) is intended to diagnose intolerance to foods and other environmental agents. It is a blood test that assesses the response of leukocytes and platelets to a panel of foods and/or other environmental agents by measuring the change in size and number of cells following exposure to a specific agent.

Related Policies

• N/A

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. 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.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

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. 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.

Rationale

Background

Antigen Leukocyte Antibody Test

The 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.^{1,} 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 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 to 357.^{1,}

Literature Review

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

There is a lack of full-length, peer-reviewed publications evaluating the utility of the ALCAT. Many citations from the manufacturer's website and other Internet sources are abstracts presented at scientific meetings or articles published in non-peer-reviewed journals that are not indexed in MEDLINE. This evidence review summarizes the most relevant publications identified through MEDLINE and supplemental searches.

Clinical Context and Test Purpose

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.²,

Food allergy is the most well-defined type of environmental illness and is estimated to affect 8% of children.^{3,} In most cases, true food allergy is characterized by a classic immunologic response (i.e., 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.^{4,}

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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.^{3,} 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, patients 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 patients 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, one 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.

The purpose of the ALCAT in patients 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 question addressed in this evidence review is: Does the use of ALCAT improve the net health outcome in individuals with suspected intolerance of environmental agents or food?

The following PICOs were used to select literature to inform this review.

Patients

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

Interventions

The test being considered is ALCAT, which is performed in an outpatient primary care or allergy specialist setting.

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, which are performed in an outpatient primary care or allergy specialist setting.

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 four weeks to evaluate test results to one to two years to evaluate reductions in morbid events and medication use.

Study Selection Criteria

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

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- 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)
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires a review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

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).

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 the results of the two 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

An 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 two 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 instructed to pursue a diet of their choosing. The ALCAT group received dietary guidance on dietary changes that were recommended based on ALCAT results. Outcomes were measured after four weeks of the intervention and included changes in weight, body composition, and symptoms on the DSI. Eight participants were lost to follow-up, seven in the control group and one in the ALCAT group.

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There was a greater reduction in weight in the ALCAT group than in the control group (-1.04 kg vs +0.32 kg; *P*<0.001), as well as a greater reduction in the percent body fat (-1.2% vs +0.7%, *P*<0.001). 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 trial have limited clinical relevance because the outcomes reported (weight loss, body composition) are not applicable to the main clinical use of the test or relevant to the population assessed in this review. Additionally, the validity of the results was reduced due to limitations in patient selection, lack of blinding, and the 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).^{2,} 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 endpoint titration at three to six months after treatment. Outcomes were measured at one to two 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 ALCAT as the basis for an elimination diet is that by Mylek (1995).^{7,} This study enrolled 72 patients with a range of symptoms considered to be the result of food intolerance. The largest percentage 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%).

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 foods who receive the ALCAT, the evidence includes an RCT and case series. The relevant outcomes are morbid events and medication use. 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. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Practice Guidelines and Position Statements

No clinical practice guidelines were identified in the diagnosis and management of food intolerance.

The National Institute of Allergy and Infectious Disease (2010) published guidelines on the diagnosis and management of food allergy.^{4,} These guidelines defined and distinguished food intolerance from food allergy but did not provide recommendations for the 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."

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U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in August 2019 did not identify any ongoing or unpublished trials that would likely influence this review.

References

- 1. Solomon BA. The ALCAT Test A guide and barometer in the therapy of environmental and food sensitivities. *Environ Med.* 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):512-526. PMID 23639501
- 3. NIAID-Sponsored Expert Panel, 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/alcattest/. Accessed August 3, 2018.
- 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.* Jan 1995;40(3):452-456. 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.* Jan 1995;40(3):625-629. PMID 8775317
- 8. Blue Cross Blue Shield Association. Medical Policy Reference Manual, No. 2.01.93 (October 2019).

Documentation for Clinical Review

Please provide the following documentation (if/when requested):

- History and physical and/or consultation notes from referring provider including:
- Previous diagnostic testing(s) and response(s) including duration
- o Reason for request of procedure

Coding

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This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

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The following services may be considered not medically necessary.

Туре	Code	Description	
CPT®	83516	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; qualitative or semiquantitative, multiple step method	

Туре	Code	Description
HCPCS	None	
ICD-10	Nono	
Procedure	NUTE	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action	Reason
05/29/2015	BCBSA Medical Policy adoption	Medical Policy Committee
05/01/2017	Policy revision without position change	Medical Policy Committee
12/01/2017	Policy revision without position change	Medical Policy Committee
12/01/2018	Policy revision without position change	Medical Policy Committee
12/01/2019	Policy revision without position change	Medical Policy Committee

Definitions of Decision Determinations

Medically Necessary: A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. 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 covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.