BlueCross BlueShield of Alabama

Name of Policy:
Antigen Leukocyte Cellular Antibody Test (ALCAT)

Policy #: 165
Category: Laboratory

Latest Review Date: February 2014
Policy Grade: C

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:

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.

Environmental illness refers to a physiologic reaction that is triggered by an exogenous agent, which can be ingested, inhaled, or exposed 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 (GI) tract disorders such as irritable bowel syndrome, eczema, chronic fatigue, and migraine headache.

Food allergy is the most well-defined type of environmental illness and is estimated to affect 8% of children. In most cases, true food allergy is characterized by a classic immunologic response, i.e., an IgE 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 Diseases.

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. It is hypothesized that physiologic reactions to food may manifest as a range of nonspecific symptoms, such as GI 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 nonimmunologic reaction that can lead to a constellation of GI 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 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 allergic in nature, identification of the inciting agent(s) can be difficult because the symptoms are chronic in nature. 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 of time and symptoms observed. Following the elimination period, a rechallenge can be performed to ascertain whether symptoms return. Elimination diets often need to be done sequentially with a large number of items, so that the process can be lengthy and cumbersome.

The ALCAT test is intended to identify foods and other environmental agents for which an individual may have intolerance. It is not intended to diagnose food allergy. 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 is targeted to 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 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.

Policy:

Antigen Leukocyte Cellular Antibody Test (ALCAT) does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is **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:

Assessment of a diagnostic technology typically focuses on three categories of evidence: (1) technical performance (test-retest reliability or interrater reliability); (2) diagnostic accuracy (sensitivity, specificity, and positive and negative predictive value) in relevant populations of patients; and (3) demonstration that the diagnostic information can be used to improve patient outcomes. In addition, subsequent use of a technology outside of the investigational setting may also be evaluated. These categories of evidence, although not always evaluated in sequence, can be considered similar to the 4 phases of therapeutic studies.

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

Technical Performance

The technical performance of the test refers to the ability of the test to accurately identify changes in the number and size of leukocytes and platelets. The technology uses the "Coulter Counter" technique that is in widespread use in clinical medicine, and thus is expected to have an accuracy that is similar to standard technology for counting and measuring cells.

The reproducibility of the test is uncertain. There were no publications identified that evaluated test-test reproducibility over time.

Diagnostic Accuracy
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. There were no published studies identified that reported on the sensitivity and specificity of the ALCAT test, in comparison with a double-blind food challenge. One study from 1995 compared ALCAT and cytotoxic testing, which is not a test routinely used in clinical care at present, in 56 children between the ages of 0.5 and 16 years. This study reported that results of the two tests were consistent in two thirds of the patients.

Impact on Health Outcomes
One randomized controlled trial was identified that evaluated the use of the ALCAT test in facilitating weight loss, changes in body composition, and health symptoms. 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 versus 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 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.

There was a greater reduction in weight in the ALCAT group compared with the control group (-1.04kg vs +0.32kg, $p<0.001$), 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 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. Also, the validity of the results are reduced by limitations in patient selection, lack of blinding, and provision of dietary guidance to the ALCAT group but not the control group.

A small number of case series have been published, reporting outcomes following ALCAT testing and treatment based on ALCAT results. These studies are not sufficient to establish efficacy because they cannot control for the natural history of the disorder or for nonspecific factors such as the placebo effect. An example of one such study is by Solomon. 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 three to six months after treatment. Outcomes were measured at one to two years post treatment 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%-82% was reported, and for immunotherapy a range of improvement of 9%-75% was reported.

Another uncontrolled study that used the ALCAT test as the basis for an elimination diet was published by Mylek in 1995. This study enrolled 72 patients with a range of symptoms that were 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%).

Summary
The ALCAT test is a blood test that is intended to diagnose intolerance to foods and other environmental agents. 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. A few low-quality studies report improvement in outcomes following use of the ALCAT test, but it is not possible to determine whether these changes occur as a result of test itself, versus bias, variation in the natural history of the condition, and/or the placebo effect. Guidelines for the diagnosis of food allergy from the National Institute of Allergy and Infectious Disease (NIAID) do not discuss use of the ALCAT test. Due to the limitations of the evidence base, and lack of acceptance of the test as a component of standard care by experts in this area, the ALCAT test is considered not medically necessary for all indications.

Practice Guidelines and Position Statements
There were no clinical practice guidelines identified for the diagnosis and management of food intolerance.

NIAID published guidelines on the diagnosis and management of food allergy in 2010. These guidelines define and distinguish food intolerance from food allergy, but do not provide recommendations for diagnosis and management of intolerance. For the diagnosis of food allergy, the guidelines state 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."

Key Words:
Antigen leukocyte cellular antibody test, ALCAT; Life Eating and Performance (LEAP); Mediator Release Testing (MRT); IgE concentration food allergy testing; IgG Food and Environmental testing, Enzyme-Linked; Immunosorbent Assay

Approved by Governing Bodies:
The ALCAT test is a laboratory-developed test that is not subject to U.S. Food and Drug Administration approval. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act.

The ALCAT website (Cell Sciences Systems, Deerfield Beach, FL) 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 range from 70-320.

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 contracts: FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Current Coding:

CPT code:

83516	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; qualitative or semiquantitative, multiple step method
86849	Unlisted immunology procedure

References:

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Policy History:

Medical Policy Group, February 1999
Medical Policy Group, May 2004 **(2)**
Medical Policy Administration Committee, May 2004
Available for comment June 28-August 11, 2004
Medical Policy Group, May 2005 **(1)**
Medical Policy Group, May 2006 **(1)**
Medical Policy Group, May 2007 **(1)**
Medical Policy Group, May 2009 **(1)**
Medical Policy Group, May 2010
Medical Policy Group, May 2011 **(3)**
Medical Policy Group, September 2011 **(1):** Added CPT code 83516 to policy; no change in policy statement
Medical Policy Administration Committee, September 2011
Available for comment September 22 through November 7, 2011
Medical Policy Group, January 2013 **(3):** Updated Key Words; no change in policy statement
Medical Policy Panel, February 2014
Medical Policy Group, February 2014 **(1):** Update to Description, Key Points and References; no change to policy statement

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