Healthy Blue

Medical Policy

Subject:	Selected Blood, Serum and Cellular Allergy and Toxicity Tests		
Document#:	LAB.00027	**Publish Date:**	08/29/2018
Status:	Reviewed	**Last Review Date:**	07/26/2018

Description/Scope

This document addresses selected unproven blood, serum and cellular allergy and toxicity tests. Allergy testing is used to determine if a symptom could be the result of an allergic reaction (involving antibodies and histamine release). The document does not address generally accepted diagnostic tools such as percutaneous (scratch, prick, or puncture) tests, the allergen-specific serum IgE test, food elimination diets and oral food challenges (double-blind, placebo-controlled food challenge).

For additional information, please see:

- MED.00059 Idiopathic Environmental Illness (IEI)

Position Statement

Investigational and Not Medically Necessary:

The following blood, serum and cellular allergy or toxicity tests are considered **investigational and not medically necessary:**

- Antigen leukocyte cellular antibody test (ALCAT); **or**
- Cytotoxic test; **or**
- HEMOCODE Food Tolerance System; **or**
- IgG food sensitivity test; **or**
- Immuno Blood Print test; **or**
- Leukocyte histamine release test (LHRT).

Rationale

ALCAT

The antigen leukocyte cellular antibody test (ALCAT) measures whole blood leukocyte activity to identify allergens which cause an increase in the leukocyte activity. The ALCAT has been promoted as a diagnostic test for food allergy or intolerance (chemical sensitivity) and as a tool to establish elimination diets.

Mylek and colleagues (1995) explored the use of the ALCAT results as the base for elimination diet treatment in several conditions considered to be the result of food allergy (intolerance). A total of 72 participants (45 children and 27 adults), suffering from various symptoms of unproven etiologies and who had undergone a variety of

treatments without improvement, were enrolled in the study. An ALCAT with 50 foods, skin prick test with 11 common inhalants and 28 foods and a detailed history were performed. Clinicians assessed whether the diet tailored on the basis of the ALCAT results achieved an improvement in symptoms after 1 month of an individual elimination diet. Emotional disturbances were assessed after the participants had been on the elimination diet for 4 months. The best results (83% improvement) were seen in symptoms related to arthritis. A 75% improvement was reported in urticaria, bronchitis and gastroenteritis. Less favorable results (32% improvement) were reported in childhood hyperactivity. The researchers concluded that "using the ALCAT Test in the course of allergologic diagnosis helps to describe less common foods that may cause reactions similar to that of apple, beetroots, lettuce, leek, pears, millet, oat or rice, etc." Some of the limitations of the Mylek study include a lack of a definition of "emotional disturbances", and the fact that detailed study methods and results were not published. The authors indicate that the study participants were assessed for symptom improvement after 1 month on the elimination diet and for improvement in emotional disturbances after 4 months on the elimination diet. However, the authors failed to report exactly what was evaluated during the clinical assessment, how the severity of symptoms were measured and failed to provide a breakdown of the results at the 1- and 4-month intervals.

Several review articles have addressed unproven tests for allergy diagnosis (Hammond, 2018; Wuthrick 2005) and have concluded that the ALCAT test results are not reproducible and do not correlate with clinical symptoms.

The evidence based allergy testing guidelines from the American Academy of Allergy, Asthma and Immunology (AAAAI) and the National Institute of Allergy and Infectious Diseases do not mention ALCAT as one of the recognized tests for the evaluation of potential allergy (Boyce 2010; Sampson, 2014).

Currently, there is insufficient evidence in the peer-reviewed, published, scientific literature to support the use of this testing in the diagnosis or management of chemical or food allergies.

Cytotoxic Testing
Cytotoxic testing for food allergies or food intolerances is an in vitro technique purported to be useful for diagnosing food allergies. The premise of cytotoxic testing is based on the theory that mixing an individual's white blood cells with an antigen to which that individual is allergic results in injury to the cells. Cytotoxic testing has been identified by a variety of names, including but not limited to, Bryan's Test, the leukocytotoxicity test, the leukocytic food allergy test, the cytotoxic leukocyte test and the CYTOTOXIC test.

The Health Care Financing Administration (HCFA) and the Federal Trade Commission (FTC) requested that the United States Food and Drug Administration (FDA) assess the validity, accuracy, and effectiveness of "in vitro" cytotoxic testing as a diagnostic tool. The FDA concluded that the cytotoxic test is "An unproven diagnostic procedure unsupported by the scientific literature or well-controlled studies and clinical trials" (FDA, 1985).

The peer-reviewed scientific published literature on cytotoxic testing consists primarily of review articles, small case studies and uncontrolled, non-randomized studies.

Several national and international organizations and scientific groups have reviewed the literature related to cytotoxic testing and have concluded that the test is unproven. The Centers for Medicare and Medicaid Services

(CMS) issued a National Coverage Determination which states "cytotoxic leukocyte tests for food allergies are excluded from Medicare coverage because available evidence does not show that these tests are safe and effective" (CMS, 1985). A position statement by the American Academy of Allergy, Asthma, and Immunology (AAAAI) concluded cytotoxic testing is either disproved or unproven and therefore is not recommended for the diagnosis of food allergy (Samson, 2014). A joint report of the Royal College of Physicians and the British Nutrition Foundation (1984) concluded that the results of cytotoxic testing are of no diagnostic value. NIAID does not recommend nonstandardized tests (cytotoxic testing) for the routine evaluation of IgE-mediated food allergies (Boyce, 2010).

IgG-Mediated Food Sensitivity Testing
Measurement of IgG and specifically IgG4 antibodies is frequently carried out in the research settings as diagnostic and prognostic tests to determine response to allergy treatments. Specific IgG/IgG4 results do not correlate with oral food challenges and are not recommended for diagnosing food allergies. The guidelines published by the AAAAI state that "measurement of food-specific IgG and IgG4 antibodies in serum are not recommended for the diagnosis of non–IgE-mediated food-related allergic disorders" (Sampson, 2014).

A 2018 review article by Hammond and Lieberman identified several studies evaluating food-specific serum IgG, but none of the studies were well-designed trials and many of them lacked controls.

The European Academy of Allergy and Clinical Immunology (EAACI) notes that testing for blood IgG4 against different foods is being more frequently performed with large-scale screening for hundreds of food items by ELISA-type and radioallergosorbent-type tests. However, many serum samples show positive IgG4 results in the absence of corresponding clinical symptoms. These findings, in conjunction with the lack of convincing evidence for the histamine-releasing properties of IgG4 in humans, and lack of any controlled studies on the diagnostic value of IgG4 testing in food allergy, do not provide any basis for the hypothesis that food-specific IgG4 results in food hypersensitivity. To the contrary, elevated IgG4 levels may indicate that an individual has been repeatedly exposed to food components, recognized as foreign proteins by the immune system. Its presence should not be considered as a factor which causes hypersensitivity, but rather as an indicator for immunological tolerance, linked to the activity of regulatory T cells. Food-specific IgG4 does not indicate (imminent) food allergy or intolerance, but rather a physiological response of the immune system after exposure to food components. Therefore, "Testing of IgG4 to foods is considered as irrelevant for the laboratory work-up of food allergy or intolerance and should not be performed in case of food-related complaints" (Stapel, 2008).

IgG antibody testing for food intolerance is generally offered by CLIA (Clinical Laboratory Improvement Amendments) approved laboratories. The BloodPrint™ test (Immuno Laboratories, Fort Lauderdale, FL) is an example of a laboratory test that measures IgG response. There are several types of BloodPrint tests which vary by number. The numbers (154, 115, 88, 108 and 104) are indicative of how many different foods are being tested. Samples for the BloodPrint test can be drawn at a local laboratory or a physician's office and sent to Immuo Laboratories for processing at a CLIA certified facility. A search of the peer-reviewed, scientific literature did not reveal any published studies for the BloodPrint test.

The HEMOCODE™ Food Tolerance System (Gemoscan, Ontario, Canada) is marketed as more than an IgG test. In addition to the test, it includes a "comprehensive program", supervised by Doctors of Naturopathic Medicine. The system includes a preliminary face-to-face consultation and follow-up review of the test results with a health professional. The HEMOCODE Food Tolerance System is not available online but can be purchased through participating retailers. A search of the peer-reviewed, scientific literature did not reveal any publications related to the HEMOCODE test.

The US BioTek Laboratories (Shoreline, WA) IgG antibody assays (IgA and IgG) measure all 4 subclasses (IgG1 through IgG4) and are reported as a total IgG value on a semi-quantitative scale for each antigen. Information on the US BioTek Laboratories web site indicates that the panel is not available online but can be requested via a healthcare practitioner. A search of the peer-reviewed, scientific literature did not reveal any publications related to the US BioTek Laboratories antibody assessment panel.

The Complement Antigen Test (Sage Medical Laboratories, Ormond Beach, FL) measures IgG and components of complement to identify delayed food allergies. However, a search of the peer-reviewed, scientific literature did not reveal any publications related to the Complement Antigen Test. The Complement Antigen Test should not be confused with a complement assay or complement testing which measures the activity of the complement system. Unlike the Complement Antigen Test which measures circulating immune complexes (antibody-complement) response to delayed food allergies, complement testing is routinely carried out to diagnose and monitor certain autoimmune disorders, such as rheumatoid arthritis and systemic lupus erythematosus.

Leukocyte histamine release test
In the leukocyte histamine release test, leukocytes from the serum of an allergic individual are observed for the release of histamine in the presence of an antigen.

The peer-reviewed scientific published literature on LHRT consists primarily of small case studies and uncontrolled, non-randomized studies.

The AAAAI guidelines for allergy diagnostic testing indicate that the LHRT is a valuable research tool for in vitro investigations of allergy (Bernstein, 2008). The guidelines published by the NIAID indicate that although the basophil histamine release/activation test is not a routine diagnostic test for IgE-mediated food allergies, it is commonly used in the research setting (Boyce, 2010).

Background/Overview

According to the National Institute of Allergy and Infectious Diseases (NIAID), food allergies should be suspected in the following: (1) individuals presenting with anaphylaxis or select symptoms that occur within minutes to hours of ingesting food, especially in young children and/or if symptoms have followed the ingestion of a specific food on more than one occasion; (2) infants, young children and selected older children diagnosed with conditions such as moderate to severe atopic dermatitis (AD), eosinophilic esophagitis (EoE), enterocolitis, enteropathy, and allergic proctocolitis; and (3) adults diagnosed with EoE (Boyce, 2010).

The standard of care in the medical community for diagnosing food allergies includes a medical history, a physical examination and diagnostic tools, such as the percutaneous (scratch, prick, or puncture) tests, the allergen-specific serum IgE test, food elimination diets and oral food challenges (double-blind, placebo-controlled food challenge).

Unproven blood, serum and cellular allergy and toxicity tests, addressed in this document, are described below.

ALCAT
ALCAT measures whole blood leukocyte activity to identify allergens which cause an increase in leukocyte activity. An electronic counter measures the change in number and size of leukocytes which have been incubated with purified food or mold extracts. A histogram is produced which reflects the cell count and cell size. The test samples are then compared with a "Master Control" graph. The ALCAT has been promoted as a diagnostic test for food allergy or intolerance (chemical sensitivities) in conditions such as, but not limited to arthritis, urticaria, bronchitis, gastroenteritis, childhood hyperreactivity, rhinitis, and atopic dermatitis. Typically, the results are used to establish elimination diets for these diseases. The ALCAT is manufactured by Cell Science Systems, Corp. (CSS), located in Deerfield Beach, Florida. All specimens submitted for ALCAT testing are processed at the CSS CLIA certified lab.

Cytotoxic testing
Cytotoxic testing for food allergies is purported to be useful for diagnosing food allergies and food intolerances. The premise of cytotoxic testing is based on the theory that mixing an individual's white blood cells with an antigen to which that individual is allergic, results in injury to the cells. This test involves the exposure of leukocytes to the presence of food extracts to which the individual is allergic. A technician then observes the unstained cells for changes in the size, shape, appearance or integrity. Swelling, vacuolation or other cytotoxic changes in cell morphology are taken as evidence of an allergic reaction to food.

IgG-Mediated Food Sensitivity Testing
IgG antibody testing for food intolerance is based on the premise that elevated levels of IgG antibodies are an indicator of food intolerances. Immunoglobulin G (IgG) is frequently divided into four subclasses. Selective deficiencies in one or more of the four IgG groups may be seen in some individuals with repeated infections. IgG and IgG subclasses can be measured in a manner similar to those for allergen specific IgE. Controversy exists regarding whether increases of IgG4 are valid indicators of either diagnosis of a food allergy or clinical efficacy after immunotherapy.

Leukocyte histamine release test
The leukocyte histamine release test (LHRT, basophil histamine release test) measures the amount of histamine released in the presence of an antigen. Varying concentrations of an allergen extract are added to the peripheral blood leukocytes of the individual being tested. Histamine is normally released as a result of the interaction of allergen with cell-bound IgE antibodies. If the individual is allergic to a specific antigen, the leukocytes should release histamine in-vitro upon stimulation of said antigen, unless the individual has recently been exposed and his/her cells are in a refractory state. A limited number of allergens can be tested using a single aliquot of blood.

Definitions

Allergen: Any substance that can cause an allergic reaction.

Allergy: An acquired potential for developing adverse reactions that are mediated by the immune system (via IgE antibodies).

Antibody: A type of protein produced by the immune system in response to substances called antigens.

Antigen: Any substance that, when introduced into the body, evokes an immune response and stimulates the production of antibodies.

Atopic dermatitis: A skin disease characterized by areas of severe itching, redness, and scaling.

CLIA: Clinical Laboratory Improvement Amendments. Passed by the U. S. Congress in 1988, CLIA established quality standards for all non-research laboratory testing conducted on specimens obtained from humans for the purpose of providing information for the diagnosis, prevention, treatment of disease, or impairment of, or assessment of health.

Complement assay (test): A test which measures the activity of a group of 9 proteins (numbered C1-C9) that travel via the bloodstream, work with the immune system and play a role in the development of inflammation.

Gastroenteritis: Inflammation of the stomach and intestines.

Leukocytes: White blood cells.

Rhinitis: Inflammation and irritation of some internal areas of the nose; also referred to as a runny nose.

Urticaria: Red, raised areas of skin that are usually a sign of an allergic reaction; also referred to as hives.

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

83516	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; qualitative or semiquantitative, multiple step method [when specified as ALCAT]
86343	Leukocyte histamine release test (LHR)
86849	Unlisted immunology procedure [when specified as Complement Antigen Test for delayed food allergy]
95199	Unlisted allergy/clinical immunologic service or procedure [when specified as cytotoxic testing for allergies]

ICD-10 Diagnosis

All diagnoses

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

CPT

82787	Gammaglobulin (immunoglobulin); immunoglobulin subclasses (eg, IgG1, 2, 3, or 4), each
86001	Allergen specific IgG quantitative or semiquantitative, each allergen

ICD-10 Diagnosis

E73.0-E73.9	Lactose intolerance
K30	Functional dyspepsia
K52.21-K52.29	Allergic and dietetic gastroenteritis and colitis
K58.0-K58.9	Irritable bowel syndrome
K90.0	Celiac disease
K90.41-K90.49	Other malabsorption due to intolerance
L27.2	Dermatitis due to ingested food
R10.0-R10.9	Abdominal and pelvic pain
R11.0-R11.2	Nausea and vomiting
R53.81-R53.83	Other malaise and fatigue
R63.0-R63.8	Symptoms and signs concerning food and fluid intake
T78.00XA-T78.09XS	Anaphylactic reaction due to food
T78.1XXA-T78.1XXS	Other adverse food reactions, not elsewhere classified
Z91.010-Z91.018	Food allergy status

References

Peer Reviewed Publications:

1. Antico A, Pagani M, Vescovi PP, et al. Food-specific IgG4 lack diagnostic value in adult patients with chronic urticaria and other suspected allergy skin symptoms. Int Arch Allergy Immunol. 2011; 155(1):52-56.

2. Beyer K, Teuber SS. Food allergy diagnostics: scientific and unproven procedures. Curr Opin Allergy Clin Immunol. 2005; 5(3):261-266.
3. Hammond C, Lieberman JA. Unproved diagnostic tests for food allergy. Imunol Allergy Clin N Am. 2018; 38: 153-163.
4. Lieberman P, Crawford L, Bjelland J. Controlled study of the cytotoxic food test. JAMA. 1975; 231(7):728-730.
5. Myłek 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):625-629.
6. Niggemann B, Gruber C. Unproven diagnostic procedures in IgE-mediated allergic diseases. Allergy. 2004; 59(8):806-808.
7. Noh G, Ahn HS, Cho NY, et al. The clinical significance of food specific IgE/IgG4 in food specific atopic dermatitis. Pediatr Allergy Immunol. 2007; 18(1):63-70.
8. Wuthrich B. Unproven techniques in allergy diagnosis. J Investig Allergol Clin Immunol. 2005; 15(2):86-90.

Government Agency, Medical Society, and Other Authoritative Publications:

1. Bernstein IL, Li JT, Bernstein DI, et al. American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI). Allergy diagnostic testing: an updated practice parameter. Ann Allergy Asthma Immunol. 2008; 100(3 Suppl 3):S1-S148.
2. Boyce JA, Assa'ad A, Burks AW, et al. National Institute of Allergy and Infectious Diseases (NIAID). Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. J Allergy Clin Immunol. 2010; 126(6 Suppl):S1-S58.
3. Centers for Medicare and Medicaid Services. National Coverage Determination for Cytotoxic Food Tests. NCD #110.13. Effective August 5, 1985. Available at: http://www.cms.gov/. Accessed on May 24, 2018.
4. Sampson HA, Aceves S, Bock SA, et al. American Academy of Allergy, Asthma & Immunology (AAAAI); the American College of Allergy, Asthma & Immunology (ACAAI); and the Joint Council of Allergy, Asthma & Immunology (JCAAI) Joint Task Force on practice parameters. Food allergy: a practice parameter update–2014. J Allergy Clin Immunol. 2014; 134(5):1016-1025.
5. Stapel SO, Asero R, Ballmer-Weber BK, et al. European Academy of Allergy and Clinical Immunology (EAACI). Testing for IgG4 against foods is not recommended as a diagnostic tool: EAACI Task Force Report. Allergy. 2008; 63(7):793-796.
6. U.S. Food and Drug Administration. Inspections, Compliance, Enforcement, and Criminal Investigations. CPG Sec. 370.100 Cytotoxic Testing for Allergic Diseases. Revised 3/95. Page updated 03/20/2015. Available at: http://www.fda.gov/iceci/compliancemanuals/compliancepolicyguidancemanual/ucm123806.htm. 4. Accessed on May 24, 2018.

Websites for Additional Information

1. American Academy of Allergy, Asthma, and Immunology (AAAAI). Available at: http://www.aaaai.org/home.aspx. Accessed on May 24, 2018.
2. Department of Health and Human Services. Centers for Medicare and Medicaid Services. CLIA, Clinical Laboratories Improvements Amendments (CLIA). ICN # 006270 July 2014. Available at:

https://www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNProducts/Downloads/CLIABrochure.pdf. Accessed on May 24, 2018.
3. U. S. Food and Drug Administration. Regulatory Information. Guidance. Complementary and Alternative Medicine Products and their Regulation by the Food and Drug Administration. Page last updated 08/05/2014. Available at: http://www.fda.gov/RegulatoryInformation/Guidances/ucm144657.htm. Accessed on May 24, 2018.

Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Reviewed	07/26/2018	Medical Policy & Technology Assessment Committee (MPTAC) review. The document header wording updated from "Current Effective Date" to "Publish Date". Description, Rationale and References sections updated. Updated Coding section to include additional diagnosis codes.
Reviewed	08/03/2017	MPTAC review. Updated the Rationale and References sections.
Reviewed	08/04/2016	MPTAC review. Updated the Rationale, Definitions, References and Index sections. Updated Coding section and removed ICD-9 codes.
Reviewed	08/06/2015	MPTAC review. Updated review date, References and History sections. Expanded the Rationale and Index section to address US Bio Tek Laboratories Antibody Assessment Panel and the Complement Antigen Test.
Reviewed	08/14/2014	MPTAC review. Updated Description, Rationale, References and History sections.
Revised	02/13/2014	MPTAC review. Scope of document revised to address selected blood, serum and cellular allergy and toxicity tests. Revised the position statement to indicate the ALCAT, cytotoxic test; HEMOCODE Food Tolerance System, IgG food

		sensitivity, BloodPrint and leukocyte histamine release test are all considered investigational and not medically necessary. Updated the Rationale, Coding, References, Definitions and History sections.
Reviewed	08/08/2013	MPTAC review. Updated review date, references and history sections.
New	08/09/2012	MPTAC review. Initial document development.