Allergy Testing and Allergy Immunotherapy

Policy Number: 2.01.501  Last Review: 6/2020

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for allergy testing and immunotherapy when it is determined to be medically necessary because the criteria shown below are met.

Please see Related Policy: APEA-G2031

See MCG A-0147 (patch testing), A-0148 (skin testing), A-0149 (IgE in vitro testing), A-0429 (subcutaneous immunotherapy) A-0430 (sublingual immunotherapy)

When Policy Topic is covered

Allergy Testing
The following allergy tests may be considered medically necessary in the diagnosis of the allergic patient:
- Total Serum IgE Concentration (Blood Test)
- Certain bronchial challenge tests (See medical review guidelines under Policy Considerations)
- Double Blind Food Challenge Test

When Policy Topic is not covered

Allergy tests considered investigational in the diagnosis of the allergic patient include, but are not limited to:
- Anti-Fc epsilon receptor antibodies testing
- Anti-IgE receptor antibody testing
- Applied Kinesiology testing (muscle strength testing) after allergen ingestion
- Body Chemical Analysis for Multiple Chemical Sensitivities (MCS)
- Candida Hypersensitivity Syndrome Testing
- Chlorinated pesticides (serum)
- Clifford materials reactivity testing
- Complement (total or components); (may be appropriate in autoimmune disorders, complement component deficiencies, hereditary angioedema, vasculitis)
- Conjunctival challenge test (ophthalmic mucous membrane test)
- Cytokine or Cytokine Receptor assays for MCS
- Cytotoxic food tests
- Electrodermal Acupuncture for foods and other substances
- ELISA/ACT test (not the same as the enzyme-linked immunosorbent assay (ELISA) test)
- Eosinophil cationic protein (ECP) test
- EPD (Enzyme Potentiated Desensitization)
- Food Immune Complex Assay (FICA)
- Hair analysis
- In vitro particle size measurement for the purpose of screening hypersensitivity reactions to foods and chemicals.
- Leukocyte antibodies testing
- Leukocyte histamine release testing
- Lymphocyte Function assays for environmental or chemical allergens
- Lymphocyte subsets
- Mediator release testing
- Nasal challenge test
- Passive transfer or P-K (Prausnitz-Kustner) test (obsolete—replaced by Radioallergosorbent Tests)
- Prausnitz-Kustner or P-K testing -- passive cutaneous transfer test
- Provocative food and inhalant (intradermal, subcutaneous, or sublingual). This testing is also identified as neutralizing dose immunotherapy or (NDIT) or Provocative-Neutralization
- Pulse Test (pulse response test, reaginic pulse test)
- Rebuck skin window test
- Serum IgG levels (when done as part of an allergy evaluation)
- Testing for electromagnetic sensitivity syndrome/disorder (also known as allergy to electricity, electro-sensitivity, electrohypersensitivity, and hypersensitivity to electricity)
- Venom blocking antibodies
- Volatile chemical panels (blood testing for chemicals)

Allergy Immunotherapy is considered **investigational** for the following indications:
- Provocative and neutralization therapy for food allergies, by sublingual, intradermal, and subcutaneous routes. Provocative and neutralization therapy involves administering neutralizing doses rather than standard doses of allergens either under the tongue or into the skin;
- Urine autoinjections (autogenous urine immunization) - (a substance from the urine is injected into the skin;
- Repository emulsion therapy;
- Rinkel, also known as serial dilution endpoint titration therapy for ragweed pollen hay

Testing and immunotherapy not meeting medical necessity criteria are considered **investigational**.
Considerations
The following guidelines should be considered when reviewing claims for specific medically necessary testing modalities:

- **Total Serum IgE Concentration** - This testing modality is not indicated in most allergic patients, but may be indicated for those patients suspected of having allergic bronchopulmonary aspergillosis, immune deficiency disease characterized by increased IgE levels (e.g., Wiskott-Aldrich syndrome, hyper-IgE staphylococcal abscess syndrome), IgE myeloma, or pemphigoid.

- **Bronchial Challenge Test** - Histamine or methacholine is used to perform this test when it is necessary to determine if the patient has hyper-responsive airways. Volatile chemicals are used to perform the test when the allergy is encountered in an occupational setting. This test may also be performed if there is no skin test, or, if a non-allergic reactions must be confirmed. If dust, ragweed, or other common allergens are the suspected cause of the problem, this test is not medically necessary, since skin tests can be used in these situations.

- **Double Blind Food Challenge Test** - With this test, the patient ingests the food to which sensitivity is suspected. Both the patient and the physician are “blinded.” In the latter case, this is considered to be part of the office visit and no additional benefits are provided.

Description of Procedure or Service
Allergic or hypersensitivity disorders may be manifested by generalized systemic reactions as well as localized reactions in any organ system of the body. The reactions may be acute, subacute or chronic, immediate or delayed, and may be caused by numerous offending agents, e.g., pollen, molds, dust, mites, animal dander, stinging insect venom, foods, and drugs.

Allergy testing can be broadly subdivided into in vivo and in vitro methodologies. In vivo methodologies include skin allergy testing (i.e., skin prick testing, skin scratch testing, intradermal testing, skin patch testing, and skin endpoint titration (SET), bronchial provocation tests, and food challenges. In vitro allergy tests include various techniques to test the blood for the presence of specific IgE antibodies to a particular antigen (i.e., RAST and ELISA tests), and leukocyte histamine release test (LHRT). LHRT may also be referred to as basophil histamine release test. Skin prick testing and in vitro analyses of IgE are the most commonly performed allergy tests.

In vitro particle size measurement for screening hypersensitivity reactions (e.g., Mediator Release Test® or MRT®) involves the measurement of the aggregate release of inflammatory mediators from an individual's immunocytes after exposure to various food extracts and chemicals (e.g., food additives). A determination is made of the difference in volume of circulating immunocytes and plasma before and after an in vitro antigen challenge. For the Mediator Release
Test®, portions of an individual’s blood sample are incubated with various food extracts and food additives (typically 150 different substances). The degree of reactivity is determined by the degree of mediator release from the cells. A response, change in cellular and plasma volume, is thought to indicate a hypersensitivity reaction and results are used as a basis for modifying an individual’s diet. The MRT® is one component of the Lifestyle Eating and Performance (LEAP®) Program of oligoantigenic dieting. This type of testing has been promoted for individuals with, among other conditions, irritable bowel syndrome, chronic fatigue syndrome, migraine headaches, and dermatologic conditions (e.g., eczema, dermatitis).

The optimum management of the allergic patient should include a careful history and physical examination and may include confirming the cause of allergic reaction by information from some of the testing methods outlined above.

Immunotherapy involves regular injections of extracts prepared from the allergen(s) to which a patient is sensitized. The goal of immunotherapy is to reduce symptoms and use of rescue medications. It begins with low doses to prevent untoward reactions, with gradually increasing doses injected as immunity to the antigen develops. After the maintenance dose is achieved, immunotherapy usually is continued for several years. Clinical benefits from multiple years of subcutaneous injections for allergen-specific immunotherapy may persist for several years after treatment is discontinued.

**MRT (Mediator Release Testing)**

Commercially available mediator release testing (MRT, Signet Diagnostic Corporation, [http://www.nowleap.com](http://www.nowleap.com)) is based on measuring the reaction of various immune mediator chemicals released into the blood in response to a food or chemical to which an individual has become sensitive or intolerant. The result is that when exposed to such foods or chemicals blood cells release various chemicals that cause an alteration of the ratio of solids (cells) to liquid (serum) in blood that can be measured. The white blood cells and platelets shrink and the volume of the liquid increases. The degree of change can be measured and reported as mild or moderate to severe corresponding with the degree of sensitivity to that particular food, additive or chemical.

Once the MRT determines the reactivity to the sensitivity and intolerance the patient’s blood cells, the LEAP program formulates a dietary program for the patient to follow. The LEAP program is based on the theory that symptoms of irritable bowel syndrome and other certain conditions are caused by the physiological effects of non-IgE mediated immune reactions in response to sensitivities to specific foods and food additives. The LEAP program also includes patient selection tools, a self-directed stress reduction program, and outcomes assessment tools. According to the manufacturer, the LEAP program has been successful in reducing or eliminating symptoms in 84 % of patients with irritable bowel syndrome, functional diarrhea, and related conditions.
Signet markets the testing for several conditions based on limited published research combined with clinical experience and patient testimonials. They claim success with reducing or eliminating a myriad of symptoms or conditions. These include migraines, headaches, autistic behavior, anxiety, depression, ADD, sinus and ear, nose and throat problems, irritable bowel syndrome, vomiting syndromes, Celiac, chronic stomachaches, bladder problems, fibromyalgia, arthritis, eczema, hives, and chronic fatigue syndrome.

Rationale – Allergy Testing
This policy is based on a 2002 TEC Assessment (1) that offered the following observations and conclusions:

- Serial endpoint titration (SET) is a form of intradermal skin testing that uses increasing doses of antigen to determine the concentration at which the reaction changes from negative to positive (i.e., the endpoint). The test has been used for diagnosing allergic disorders, and is a potential alternative to other diagnostic tests such as skin prick testing or in vitro testing for this purpose. Also, SET has been used to guide the initiation of immunotherapy, by using the endpoint dilution as the starting antigen dose.

- The available literature on SET has many limitations. Many of the studies are from the late 1970s and early 1980s, and are of poor methodologic quality when judged by current quality assessment techniques. The studies that evaluate SET as a diagnostic test do not enroll representative patients samples, only report on the correlation and/or concordance of SET with alternative tests, and do not provide sufficient information to derive sensitivity or specificity. The interpretation of SET and the alternative tests are not performed in a blinded manner. Thus these studies are potentially prone to spectrum bias, referral bias, ascertainment bias, and are not sufficient to permit conclusions on the diagnostic accuracy of SET.

- The majority of trials that evaluate SET-guided immunotherapy do not report improved outcomes with SET as compared to placebo or alternative delivery methods. However, the conclusions that can be derived from these data are also limited. The trials are small, do not report power calculations, or define the level of improvement in symptoms that is clinically meaningful. The studies do not used standardized outcomes measures, do not include pre- and post-measurements, and do not report the degree of improvement over the course of the study. In many studies, subjective improvement is the main outcome measure used. Furthermore, the same physicians providing the treatment assess patient outcomes, and no trial uses blinded outcome assessment.

Additional Information
SET has been a particular interest of the American Academy of Otolaryngic Allergy (AAOA). In 1996, the AAOA published a clinical practice guideline focused on allergic rhinitis. (2) This practice guideline offered the following recommendation:

- “Intradermal dilution testing provides an accurate, rapid diagnostic test for allergy that correlated well with in vitro determinations. Advantages over skin prick testing include the ability to identify a correct starting dose for immunotherapy and to avoid being misled by a flash or single unusual allergy
response. It is a safe technique when properly used. Criticisms of the method relate primarily to the fact that it takes more injections and carries the potential to escalate the expense of allergy testing. A critical appraisal of allergy immunotherapy comparing immunotherapy treatment based on intradermal testing versus skin prick testing demonstrated similar results, with a trend to less adverse reactions with intradermal testing...the use of intradermal testing, in conjunction with history and clinical judgment, is acceptable allergy practice.”

In spite of this recommendation, the practice guideline offers no specific references, limiting scientific review of the above conclusions. While a list of general references is provided at the end of the guideline, key studies forming the basis of the above conclusion are not provided.

In 1987, the American Medical Association’s Council on Scientific Affairs Allergy Panel published a report on in vivo diagnostic testing and immunotherapy for allergy. (3) Skin endpoint titration was addressed in this report, and the following conclusion was offered: "Skin endpoint titration provides a safe and effective measure of patient sensitivity. Controlled studies have shown that the intradermal method of skin end-point titration is effective in quantifying sensitivity to ragweed extract and for identifying patients highly susceptible to ragweed. The method provides reliability comparable to that of in vitro leukocyte histamine release and radioallergosorbent test. Controlled studies have shown that the prick test methods of skin end-point titration can be used as a measure of response to immunotherapy of cat extract.”

The references included in the above paragraph were either considered by the 2002 TEC Assessment, or did not meet the specific study selection criteria. As noted in the TEC Assessment, “the available literature has many methodologic limitations. Many of the studies are from the late 1970s and 1980s, are of poor methodologic quality when judged by current quality assessment techniques.”

2003 Update
This policy is updated in 2003 with a focused review of the leukocyte histamine release test (LHRT), listed as an investigational allergy test. A review of the literature from 1995 to present did not identify published peer-reviewed articles that would prompt reconsideration of this interpretation, and thus the policy statement is unchanged. LHRT is a technique to evaluate the in vitro release of histamine from leukocytes (i.e., basophils) in response to exposure to an allergen, and thus is designed to provide an in vitro correlate to an in vivo allergic response (i.e., skin prick testing). In contrast, the RAST test attempts to correlate the presence of allergy to serum levels of antigen-specific IgE as an index of allergic reactivity. Initially, measurements of histamine release required isolation of leukocytes from whole blood followed by the isolation of the released histamine; the laboratory techniques were difficult and time consuming and thus LHRT was primarily used as a research tool only. Recently, a special type of glass fiber has been developed that binds histamine with high affinity and selectivity. These glass fibers can be used as a “solid phase” to absorb the histamine that is released
directly into the blood. The recent commercial availability of simplified and automated methods of laboratory analysis (i.e., both ELISA and radioimmunoassays) have renewed interest in the clinical applications of LHRT in the evaluation of food, inhalant, and drug allergies. (4-6) Technologies related to histamine release assays include assays for the release of sulphidoleukotriene or the flow cytometric detection of CD36 expression on the stimulated basophils. Both of these tests are similar to LHRT in that they detect the activation of basophils as a direct reflection of the immune response.

The published literature regarding LHRT is reviewed using the same criteria as used in the TEC Assessment of SET. For example, quality indicators for studies of diagnostic trials include:

- Prospective enrollment
- Representative patient population enrolled
  - Appropriate spectrum of patients
  - Unbiased enrollment (no referral bias)
  - Few patients not enrolled that are eligible
  - Appropriate accounting for all eligible patients
- All eligible patients receive both tests
- LHRT interpreted independently of alternative test (i.e., skin prick, RAST, or bronchial provocation test)
- Alternative tests interpreted independently of LHRT.

In assessing the diagnostic accuracy, the comparative reproducibility, sensitivity, and specificity of LHRT are the primary outcomes to be considered. In the absence of an accepted gold standard for the diagnosis of allergy, it is difficult to ascertain the comparative performance characteristics of available diagnostic tests. For this reason, the concordance, or correlation of results from different tests is typically reported for LHRT. The published literature regarding the commercially available LHRTs suffers from the same limitations as the literature regarding serial endpoint titration (see above). Specifically the interpretation of LHRT and the alternative tests were not performed in a blinded manner, or the study did not indicate whether or not there were blinded interpretations of the tests. (7-8) Some studies included patients with known allergies, and thus these highly selective populations do not represent the same population with equivocal allergy histories that would undergo testing. (6, 9-11) In some situations, results were compared with bronchial provocation testing, considered the gold standard for inhalant allergies. However, bronchial provocation may only be performed on a subset of patients with a limited number of allergens. For example, bronchial provocation may only be performed when there are discordant results between RAST and skin prick testing. (10) Thus overall, these studies are potentially prone to spectrum bias, referral bias, ascertainment bias, and are not sufficient to permit conclusions on the diagnostic accuracy of LHRT. It has been suggested that LHRT may be a valuable test in those patients with discordant results of skin prick testing and RAST testing, but studies focusing on this subgroup of patients were not identified in a literature search.

**In Vitro Particle Size Measurement**
At present, very few studies have been published involving the use of this test in screening for hypersensitivity reactions to foods (e.g., sensitivity to cow’s milk) and chemicals. Randomized controlled trials are needed to determine the efficacy of this test and to substantiate any potential health benefits associated with its use in diet modification. (13-17)

References:

Rationale – Allergy Immunotherapy
This policy is updated in 2003 with a focused review of two of the immunotherapy procedures addressed in this policy, sublingual immunotherapy (SLIT) and serial
endpoint testing (SET)-guided immunotherapy. This update is based on TEC Assessments that offered the following observations and conclusions:

**Sublingual Immunotherapy (1)**
Studies of sublingual immunotherapy (SLIT) or subcutaneous injection of allergen-specific immunotherapy (ASIT) commonly measure allergic symptoms and use of rescue medications using quantitative scales. Double-blind, placebo-controlled randomized trials have reported attenuated allergic symptoms and reduced medication use after injection ASIT for various allergens. In addition, evidence shows that clinical benefits from multiple years of ASIT persist for several years after injections are discontinued. The TEC Assessment reviews trials of SLIT if they are placebo-controlled or they directly compare SLIT with ASIT.

Twenty-one placebo-controlled clinical trials met selection criteria. Patient sample size was small in most of them. The predominance of evidence suggested that, when prepared in potencies similar to the available studies and compared with placebo, SLIT decreased one or more symptoms for patients with pollen or dust mite allergies. Systemic side effects occurred in only one study, and these were not life threatening. Evidence on whether SLIT may also reduce use of rescue medications was conflicting and inconclusive.

The established alternative to SLIT has been injection ASIT. Whether SLIT improves health outcomes when compared with injection ASIT could not be determined from the available evidence. The results of 2 trials that directly compared SLIT with injection ASIT were insufficient to permit conclusions. Patient groups in each trial were small (10-15 patients per arm), and each was of short duration. Neither trial followed up patients after immunotherapy was terminated, and thus neither trial speaks to the persistence of possible therapeutic effects.

**Serial Endpoint Testing-Guided Immunotherapy (2)**
Serial endpoint testing (SET) is a form of intradermal skin testing that uses increasing doses of antigen to determine the concentration at which the reaction changes from negative to positive (the endpoint). SET has also been used to guide the initiation of immunotherapy by using endpoint dilution as a starting antigen dose.

The majority of trials that evaluate SET-guided immunotherapy do not report improved outcomes with SET, as compared to placebo or alternative delivery method. However, the conclusions that can be derived from these data are also limited. The trials are small, do not report power calculations, and do not define the level of improvement of symptoms that is clinically significant. The studies do not use standardized outcome measures and do not report the degree of improvement over the course of study. In many studies, subjective improvement is the main outcome measure used. Furthermore, the same physicians providing treatment assess patient outcome, and no trial uses blinded outcome assessment.

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References:
Billing Coding/Physician Documentation Information

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Additional Policy Key Words
N/A

Policy Implementation/Update Information

7/1/00 New policy.
7/1/01 Policy statement revised to include the following as investigational:
Applied Kinesiology testing (muscle strength testing),
Body Chemical Analysis for Multiple Chemical Sensitivities (MCS),
Candida Hypersensitivity Syndrome Testing, Cytokine or Cytokine Receptor assays for MCS, Electrodermal Acupuncture for foods and other substances, Food Immune Complex Assay (FICA), Hair analysis, Lymphocyte Function assays for environmental or chemical allergens, Lymphocyte subsets, Pulse Test, Serum IgG levels (when done as part of an allergy evaluation), Rhinomanometry, Acoustic Rhinomanometry
1/1/02 No policy statement changes.
1/1/03 No policy statement changes.
1/1/04 Policy statement revised to include the following as investigational:
Antigen leukocyte cellular antibody test (ALCAT), ELISA/ACT test (not the same as the enzyme-linked immunosorbent assay (ELISA) test), EPD (Enzyme Potentiated Desensitization)
11/1/04 Claims processing guidelines updated to remove the following from Specific IgE In Vitro tests (RAST, MAST, FAST, and ELISA):
Up to 20 tests may be approved on an initial claim. If claims for additional tests done within a 24 month period are received, medical records should be reviewed to determine medical necessity.
1/1/05 No policy statement changes.
7/1/06 Policy statement revised to be combined with Allergy Immunotherapy.
Topics of Clinical Ecology, Sublingual Immunotherapy and Serial Endpoint Testing are now covered under separate policies.
7/1/07 No policy statement changes.
7/1/08 Policy statement updated to include In Vitro particle size measurement as investigational.
7/1/09  No policy statement changes.
7/1/10  No policy statement changes.
7/1/11  No policy statement changes.
7/1/12  Policy archived.
5/1/14  Policy removed from archives. ALCAT removed from this policy and is now addressed in a separate policy.
7/1/15  No policy statement changes.
7/1/16  No policy statement changes.
2/1/17  Medically necessary policy statement for “Rapid Desensitization” updated to include members with moderate to severe allergic rhinitis who need treatment during or immediately before the season of the affecting allergy. Considerations section updated.
7/1/17  No policy statement changes.
7/1/18  No policy statement changes.
7/1/19  No policy statement changes.
6/1/20  Removed many policy statements for Medical Necessary and Investigational. Added note at the top: See MCG A-0147 (patch testing), A-0148 (skin testing), A-0149 (IgE in vitro testing), A-0429 (subcutaneous immunotherapy) A-0430 (sublingual immunotherapy). Removed most codes from table.

State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.