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Allergy Management

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Related Policies (if applicable)
RX501.058: Omalizumab
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MED206.005: Antigen Leukocyte Antibody Test (ALCAT)

Disclaimer

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Coverage

This medical policy has become inactive as of the end date above. There is no current active version and this policy is not to be used for current claims adjudication or business purposes.

The following methods of allergy testing and allergy therapy **may be considered medically necessary** in those individuals with a history of allergic disease:

Allergy Testing
Direct Skin Testing
1. Percutaneous (scratch, prick, or puncture);
2. Intracutaneous (intradermal);
3. Skin patch testing (application);
4. Photo Patch.

Serum Allergy Testing (IgE)

Serum allergy testing (e.g., Radioallergosorbent (RAST), Multiple Radioallergosorbent [MAST], Florescent Allergosorbent [FAST], Enzyme-linked Immunosorbent Assay [ELISA] or Paper Radioimmunosorbent Test [PRIST]) for allergen testing for e.g., food, inhalant, insect venom, or drug **may be considered medically necessary** when any of the following criteria are met:

- Skin testing is not possible due to one of the following:
    - Widespread skin disease; or
    - Receiving skin test suppressive therapy that cannot be discontinued; or
    - Uncooperative patients; or
    - History suggests an unusually greater risk of anaphylaxis from skin testing; **OR**
- As an adjunctive laboratory test when testing for allergens such as insect venom, inhalants, food (see **NOTE 1**), or specific drugs.

NOTE 1: Evaluation for IgE antibody-associated food allergies: Specific IgE tests (skin prick tests, serum tests, or both) when used as diagnostic tools for evaluation of food allergies may be used when suspicion of specific food allergens is high. These tests are not effective for indiscriminate screening (e.g., using panels of tests without consideration of likely causes) and therefore generally should not be used for that purpose.

Total Serum IgE Concentration **may be considered medically necessary** in those individuals suspected of having:

1. Allergic bronchopulmonary aspergillosis;
2. Immune deficiency disease (i.e., Wiskott-Aldrich syndrome, hyper-IgE staphylococcal abscess syndrome);
3. IgE myeloma;
4. Pemphigoid.

NOTE 2: See medical policy RX501.058 Xolair (omalizumab) for further information regarding Xolair and serum total IgE levels.

Serial endpoint testing (SET) (also known as intradermal dilutional testing [IDT]) **may be considered medically necessary** for the determination of a safe starting dose for testing or immunotherapy when there is potential for the specific allergen in question to produce a severe systemic allergic reaction or anaphylaxis.

Nasal cytograms **may be considered medically necessary** when performed for the purpose of identifying exudative evidence of nasal allergy or infection.

Inhalational bronchial challenge testing (e.g., methacholine or histamine) **may be considered medically necessary** for those individuals suspected of having asthma or hyper-responsive airways.

Medically supervised oral challenge/provocation testing **may be considered medically necessary** for those individuals with a suspected food allergy when the history and testing (e.g., skin-prick testing) may not clearly confirm the diagnosis.

Medically supervised oral challenge/provocation testing **may be considered medically necessary** for those individuals with a history of allergy to a specific drug; when no alternative drug is available, and the medication is essential.

The following methods of allergy testing **are considered experimental, investigational and/or unproven:**

1. Provocation tests (i.e., intradermal) for food or food additive allergies;
2. Provocation-Neutralization testing;
3. Nasal Challenge tests;
4. Conjunctival challenge test (ophthalmic mucous membrane test);
5. Cytotoxic food tests (Bryan's Test);
6. Leukocyte histamine release test (LHRT);
7. Rebuck skin window test;
8. Passive transfer or Prausnitz-Kustner test;
9. Sublingual provocation food testing;
10. IgG food and environmental testing;
11. Applied kinesiology (allergy testing by testing muscle strength or weakness);
12. Electrodermal testing (Vega).

Allergy Therapy

Allergy immunotherapy **may be considered medically necessary** in individuals with demonstrated hypersensitivity that cannot be managed by medications and avoidance.

Rapid desensitization/Rush Immunotherapy **may be considered medically necessary** for individuals with the following indications:

- Allergy to a specific drug that cannot be treated effectively with alternative medications; or
- Hymenoptera stings (e.g., wasps, hornets, bees, fire ants) hypersensitivity.

The following methods of allergy immunotherapy **are considered experimental, investigational and/or unproven** for the treatment of food, molds, chemicals, pollens, and other allergies including the preparation of and administration of immunotherapy:

1. Provocation and neutralization therapy; using intradermal and subcutaneous routes; AND
2. Intranasal immunotherapy; AND
3. Urine auto-injections (autogenous urine immunization); freshly collected urine, having been sterilized and filtrated, injected to the donating patient; AND
4. Repository emulsion therapy; solutions of vegetable and mineral oils containing additional allergens, to produce slow releases of the allergens at the injection site; AND
5. Allergoids (modification of allergens to reduce allergenicity).

Subcutaneous allergen immunotherapy for the following indications **is considered experimental, investigational and/or unproven:**

- Chronic urticaria;
- Angioedema;

- Food hypersensitivity.

Allergen-proof supplies (mattresses, mattress casings, pillows, or pillow casings) **are considered not medically necessary** as they are considered personal convenience items.

NOTE 3: For information on Idiopathic Environmental Intolerance or Illness (IEI) Management, (also contains information on Lifestyle Eating and Performance [LEAP] program, and the Mediator Release Test [MRT]) see MED206.003; Sublingual Immunotherapy as a Technique of Allergen-Specific Therapy see MED206.006; Antigen Leukocyte Antibody Test (ALCAT) see MED206.005 and for Xolair (Omalizumab) see RX501.058.

Policy Guidelines

Payment for allergy serum is limited to the amount actually provided to the patient on a given date of service but no more than 60 units per two (2) months. This statement does not apply to rapid desensitization.

Description

An allergy is an abnormal reaction to an ordinarily harmless substance called an allergen. When an allergen (such as pollen) is absorbed into the body of an allergic individual that individual's immune system views the allergen as an invader and a chain reaction is initiated. White blood cells of the immune system produce IgE antibodies. These antibodies attach themselves to special mast cells causing a release of potent chemicals such as histamine. These chemicals cause generalized symptoms as well as localized reactions in any organ system of the body. The reactions may be acute, subacute, chronic, immediate or delayed, and may be caused by numerous offending agents, such as pollen, molds, dust, mites, animal dander, stinging insect venoms, foods, and drugs.

For instance, food allergy is the most well-defined type of environmental illness and is estimated to affect 8% of children. (1) 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 National Institute of Allergy and Infectious Disease (NIAID). (2)

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 (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.

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, 1 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 the process can be lengthy and cumbersome.

Allergy Testing:
The optimum management of the allergic patient should include a careful history and physical examination and confirmation of the cause of the allergic reaction obtained from some of the testing methods.

Direct Skin Testing - Several types of skin tests are used in allergy diagnostics (4):

- Skin Prick Test (SPT): This represents the first level of approach for the diagnosis of type I, immediate, IgE-mediated allergy. It is safe, has high sensitivity and good specificity when performed and interpreted correctly; a specific variant of type I skin tests is prick-to-prick testing (PPT) with native allergens.
- Intradermal Test (IDT): This can be used to evaluate both immediate IgE-mediated allergy and delayed-type hypersensitivity, according to the time of read-out. It has increased sensitivity and decreased specificity compared to SPT.
- Patch test: This is used for delayed type, cell mediated, hypersensitivity reactions. It has no relevance for IgE-mediated allergy.

Photopatch Testing- This test is used to detect photoallergic reactions to various antigens such as sunscreens and drugs. (5)

Serum Allergy Testing - IgE-mediated allergic diseases is useful in the identification of the causative allergen(s) and usually involves different laboratory procedures. In particular:

- The total IgE assay which is nonspecific and provides only gross information.
- Serum specific IgE assays against allergen sources/molecules are the most commonly used in vitro diagnostic approach. They can be performed by a singleplexed or multiplexed strategy.

Anostegui et al. (2020) notes that serum IgE testing entails no risk to the patient other than a blood draw and is preferable if the patient has an unstable or uncontrolled medical condition, is at high risk of anaphylaxis, is taking essential medication that interferes with testing, is very young such that the procedure would be unduly stressful, or has a skin condition that limits available skin for testing. (4)

Serial Endpoint Testing (SET): This type of testing 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"). This is typically done for venom and drug allergy. In addition, SET has been used to guide the initiation of immunotherapy, by using the endpoint dilution as the starting antigen dose. The Rinkel method differs from SET. Barton et al. (1983) noted that Rinkel was acquainted with the concept of minute optimal dose therapy, refined the original technique and developed the method of endpoint skin testing. (6) Barton et al. notes that controlled studies have failed to support the skin titration (Rinkel method) used to establish an optimal dose for the relief of hay fever symptoms.

Nasal Cytogram: This microscopic study of nasal secretions used to determine whether a patient has an allergy to inhalants or food, or if an acute or chronic viral infection is present, resulting in rhinitis or otitis.

Bronchial Challenge Test: Histamine or methacholine may be used to perform this test when it is necessary to determine if the patient has hyper-responsive airways. Airway hyper-responsiveness is defined as the predisposition of the airways of patients to narrow excessively in response to stimuli that would produce little or no effect in healthy subjects. Airway hyper-responsiveness is considered a hallmark of asthma and may be used as a tool in the diagnosis, classification of severity and management of asthma. (7) For patients with typical intermittent asthma symptoms and normal baseline spirometry, a distinct clinical response to empiric therapy may be adequate diagnostically. However, bronchial challenge testing using methacholine may be needed if the diagnosis of asthma is in question.

Methacholine inhalation challenge is a type of pharmacologic bronchial challenge. The test starts with a baseline breathing test (spirometry) including a forced expiratory volume (FEV1). Patients breathe progressively stronger doses of inhaled methacholine given by a nebulizer, according to a protocol. Spirometry would then be performed before and after each dose of inhaled methacholine to evaluate the amount of airway narrowing. The test stops once the lung function (FEV1) drops by 20% or more from baseline or the maximum dose of methacholine is reached. Certain medications may need to be stopped prior to a methacholine inhalation challenge to obtain accurate results. (8)

Oral Food Challenges

Types of Oral Food Challenges (OFC) include open (unmasked), single-blind with or without placebo, and double-blind, placebo-controlled challenges which are described as follows: (9)

- Open or unmasked OFC: An unblinded, unmasked feeding of the food in its natural form.
- Single blind OFC: With this test, the physician/medical provider is aware when the challenge food is being ingested but the patient is not.
- 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."

Because food challenges carry risk of anaphylaxis, food challenges should be performed in a setting which is most appropriate and safest for the patient as determined by the physician. Double blind food challenge testing should not be performed at home.

Sampson et al. (2014) notes the decision to conduct OFCs in the clinical versus hospital setting should be determined based on the severity of the patient's prior reaction to the food, epidemiologic risks associated with the food being challenged, availability of necessary tools in the event of a severe reaction, and expertise of the supervising clinician. (9)

Sublingual Provocation-Neutralization Food Testing: The test consists of placing a concentration of an allergenic extract under a patient's tongue and waiting 10 minutes for any symptoms to appear. When the physician is satisfied he has determined the cause of the symptoms, he administers a "neutralizing" dose, which is usually a diluted solution of the same allergenic extract. The symptoms are then expected to disappear in the same sequence in which they appeared. Advocates claim that if the neutralizing dose is given before a challenge test (for instance, eating a meal containing the offending food), the person will not have symptoms.

Nasal Challenge Test (also called nasal mucous membrane test; nasal challenge/provocation test): This test has been proposed as a tool in the diagnosis of allergic rhinitis. It is performed to duplicate the patient's main symptoms or signs by controlled exposure to a suspected antigen and is delivered by direct application to the nasal mucous membranes. Evaluation of the patient's response to the allergen is recorded.

Conjunctival Challenge Testing (ophthalmic mucous membrane test): Allergenic extract is placed into the conjunctival sac of the eye, followed by observation for redness, itchiness, tearing of the eye, and other similar symptoms.

Cytotoxic Food Testing (Leukocytotoxic Test): This test involves the response of specially collected white blood cells to the presence of food extracts to which the patient may be allergic.

Leukocyte Histamine Release Test (LHRT): Measures the amount of histamine released from the white blood cells in response to exposure to an allergen.

Rebuck Skin Window Test: A test of the inflammatory process in which the skin is abraded, and a cover slip is applied to the abraded area. The cover slips are removed and replaced at intervals and examined for the presence of cells involved in the immune response.

Passive Transfer or Prausnitz-Kustner Test: Performed by injecting serum intradermally from a suspect allergic patient into a nonallergic patient and later challenging the injection site with antigens. Due to the dangers of transmitting blood-borne infections this test is no longer used.

IgG Food and Environmental Testing/IgG4 Antigen Levels: These tests are a subclass of immunoglobulin G. Selective deficiencies in one or more of the four IgG subclasses are seen in

some patients with repeated infections. Measurements of IgG4 antibodies have been used in research settings to determine response to allergy treatments.

Kinesiology: The patient holds a vial with a specific food in one hand, while the examiner tests the muscular strength of the opposite arm by applying a light pressure. Food allergy/intolerance is indicated by a decreased muscular contraction when the suspected substance is held. (4)

Electrodermal testing: The patient is placed in a circuit where a galvanometer measures skin conductance. Vials with food extract are sequentially inserted into the circuit. A positive response consists of a drop in conductance. (4)

Allergy Therapy:
Once the offending agent has been identified, treatment is managed by avoidance, medication, or immunotherapy, which are described as follows:

Avoidance: Preferred treatment to eliminate the allergen, requiring a change of diet, occupation, or residence; discontinuance of a drug; or removal of a household pet. However, complete avoidance may be impossible.

Medication: Provide symptomatic relief for the patient but does not address the cause of the problem. Medications may include steroids, antihistamines, or decongestants.

Immunity: Freedom from or protection against certain diseases. Conventional or traditional immunotherapy, desensitization or allergy shots, may be recommended for patients with moderate to severe symptoms throughout most of the year who do not respond adequately to medications, and whose symptoms are triggered by an allergen that is not easily avoided (such as pollens or house dust mites). Immunotherapy involves the repeated injections of allergenic extracts (tiny amounts of allergen) that are given over a period of time. Immunotherapy treatment can be categorized into the build-up and maintenance phases. The immunotherapy build-up schedule gradually increases the amount of extract. “The frequency of allergen immunotherapy administration during a conventional build-up phase is generally 1 to 3 injections per week.” (10).

Rush Immunotherapy: Rush or rapid immunotherapy is an accelerated schedule of immunotherapy that involves shortening the length of the build-up phase. Drug or venom rush or rapid immunotherapy is done if sensitivity has been established by history, anaphylactic shock, positive challenge testing, and/or positive skin testing. In cases where drug administration for treatment is essential and no alternative exists, rapid desensitization may be done. In some situations, the patient is hospitalized to provide supportive and resuscitation equipment to promptly treat the patient for any life-threatening reaction; and the allergen doses are increased over a one- to three-day period. Drug desensitization should be performed in an appropriate setting, and supervised by a physician familiar with the procedure, with continual monitoring of the patient and readiness to treat reactions, including anaphylaxis. (11)

Premedication of antihistamines and steroids may be given before rush immunotherapy. Baseline spirometry may be performed in asthmatic patients. An example of rush immunotherapy is when penicillin desensitization is used as an emergent need to prepare an allergic patient for treatment of bacterial endocarditis.

Provocation and Neutralization Therapy: This method has been purported as a test for allergies, foods, and environmental chemicals. Patients are exposed to test doses of substances and observed for the presence of symptoms. Then a diluted version of the offending substance is given to relieve symptoms.

Intranasal Immunotherapy: Intranasal administration of allergen extracts to improve symptoms of allergic rhinitis both to pollens and house dust mites.

Urine Auto-Injections (Autogenous Urine Immunization): In this treatment, a patient's urine is collected and sterilized. It is injected into the donating patient and presumed to provide relief from allergy symptoms.

Repository Emulsion Therapy: This technique uses mineral oil and antigenic material. The water in oil emulsion provides a slower release of these materials purported to provide protection for a prolonged period of time.

Allergoids: Allergoids are modified allergen extracts purported to reduce the extract's allergenicity while still evoking an immune response.

Rationale

This policy was originally created in 1990; and has been updated with searches of the PubMed database through April 2022. Following is a summary of the key literature to date.

Allergy Testing

An allergy is a hypersensitive reaction of the body's immune system to an allergen. Allergens can include substances such as pollen, dust, mold, food, medications, and insect stings. The body's immune reaction produces immunoglobulins antibodies. Allergy testing is done to identify the allergen(s) that produced the immunoglobulin E (IgE) mediated hypersensitivities.

Current allergy management uses specific tests to identify and confirm the causative agent (the "allergen"), and skin tests are the most convenient. These tests should be selected and based on the information provided by the patient's history. It is common practice to do prick skin testing first. This is usually sufficient for detecting sensitivity to most allergens. More sensitive intradermal testing can be used to test suspected allergens that have previously produced negative or equivocal prick tests. For foods, prick tests alone are diagnostic. Food intradermal tests are likely to produce positive reactions of no clinical significance and are potentially

dangerous. (12) On the other hand, when a prick/puncture skin test has negative results, for evaluation of drug and insect sting sensitivity, intradermal testing may be done. (4, 11, 13)

Birch et al. (2022) notes that the results from the skin and intradermal tests alone cannot be used to make a diagnosis; the patient history must correlate. Some patients may have high IgE or positive skin prick or intradermal tests and do not react in the real world. In contrast, patients can have a negative skin prick test and have a history of a reaction to that allergen. (14)

Serial Endpoint Testing (SET)

In a 2011 article Boyles reported on the experience of conducting allergy testing in 52 patients with a history of allergic rhinitis. (15) Patients underwent SET testing, as well as in vitro and prick testing. All 52 patients were positive for one or more allergens on SET testing. Twenty-two of the 52 (42%) patients had no reaction to either of the other 2 types of testing. Of the remaining patients, 11 of 52 (21%) had positive reactions to in vitro testing, 5 (10%) had positive reactions to prick testing, and 14 (27%) patients had positive reactions to both in vitro and prick testing. The author did not report treatment outcomes in the group of 52 patients. However, he stated that all of 230 patients in his practice who were given immunotherapy based on their response to SET testing said that they had either complete or significant relief of symptoms after treatment. The study was not designed prospectively to evaluate the accuracy or clinical utility of SET.

Nasal cytograms

Myszkowska et al. (2022) reported on a retrospective analysis to evaluate to what extent the cytological picture of the nasal mucosa coincides with the diagnosis of a given disease, taking into account the content of eosinophils. (16) Cytograms performed in 842 patients were included. Significant relationship between the Epith:Infl ratio and the four groups of diseases ($Chi^2 = 9.6488$; $p = .014$) was confirmed. The more intensive inflammation was found, the higher percentage of patients had manifested the increased level of eosinophils (> 1% in the inflammatory cells). The value of 20% of eosinophils in all counted cells corresponds to around 45% of eosinophils in the inflammatory cells in patients with the evident inflammatory picture. Allergic rhinitis presents a different cytological picture regarding the eosinophilic reaction against the background of the inflammation process: the higher degree of inflammation observed, the lower amount of eosinophils detected, with the exception of allergic rhinitis provoked by pollen allergens.

Ciofalo et al. (2019) noted that allergic rhinitis (AR) affects half of the adult population, while in children prevalence of AR vs. non-allergic rhinitis (NAR) of 3-4:1 is reported. (17) The study sought to define the distribution of chronic rhinopathy in adult and pediatric populations, to classify "cellular" NAR into subgroups based on cytological features, and to identify overlapped rhinitis (OR). A retrospective study was conducted on 907 patients, divided into two groups: 135 children --69 females and 66 males, average age 9.8 years (range 4-17) and 772 adults --392 females and 380 males, average age 45.28 years (range 18-90). All patients with a suspicion of rhinopathy were submitted to nasal endoscopy, skin prick test (SPT), dosage of serum specific

IgE, CT scan of nasal, and sinusal structures when chronic rhinosinusitis was suspected. The findings revealed that in the adult population of the study, 61% presented a diagnosis of chronic rhinitis: 213 patients (45.2%) had AR, 31 (6.6%) OR, and 227 (48.2%) NAR (77.5% of these patients presented a pattern of "cellular" NAR). In the pediatric population, 83% patients presented a rhinopathy: 61 (54.5%) with AR, 38 (34%) with NAR, and 13 (11.5%) with OR. Within the NAR group, 71% had a "cellular" pattern. The authors concluded that nasal cytology is a tool that provides a more precise differential diagnosis of chronic rhinitis through the study the of nasal mucosa and the identification of "cellular" NAR and OR, even in the pediatric population.

Bronchial Challenge Testing:

Brigham and West (2015) note spirometry with bronchodilator reversibility testing remains the mainstay of asthma diagnostic testing for children and adults. (18) Repetition of the test over several time points may be necessary to confirm airway obstruction and variability thereof. Repeated peak flow measurement is relatively simple to implement in a clinical and home setting. Bronchial challenge testing is reserved for patients in whom the aforementioned testing has been unrevealing but clinical suspicion remains, though is associated with low specificity.

UpToDate notes the accurate identification of a specific inhaled allergen by antigenic challenge is largely a research tool for investigation of mechanisms of asthma, the efficacy of new therapeutic agents, and suspected occupational allergens. Allergen inhalation challenge is a specialized procedure and should not be undertaken by individuals unfamiliar with the technique. Bronchoprovocation tests with specific occupational agents should only be performed in specialized centers. (19)

Oral food challenge

Bernstein et al. (1982) evaluated the role of double-blind food challenge (DBFC) in suspected food sensitivity in the adult as compared with established tests of food allergy, including the skin test, RAST, and leukocyte histamine release (LHR) to specific food antigens. (20) Twenty-two subjects (ages 18 to 67) with histories of reactions to foods were challenged with freeze-dried food or placebo in opaque dye-free capsules, in increasing doses over a 90 min span to a total of 13 to 15 gm. This was repeated twice at weekly intervals by similar DBFC. DBFC was preceded by skin testing and venipuncture for RAST and LHR studies. Patients were kept under observation for 2 hours, after which each was asked to maintain a detailed diary of related symptoms and food ingested over the following week. Of 46 DBFCs, 13 (21%) were positive. The correlation with positive skin tests and positive DBFC was 4/13 (30%). The correlation with positive LHR and positive DBFC was lower at 2/13 (15%), and 1/13 (7.6%) with RAST. The authors concluded that DBFC is an effective test of adult food sensitivity compared with tests usually performed and should be used when the diagnosis is in doubt.

Mankad et al. (2008) reported on a practical alternative to double-blind, placebo-controlled food challenge. The authors evaluated open food challenges administered in an office setting. (21) The authors noted a total of 109 patients (69% male) underwent 150 open food challenges,

most of which were to milk (n = 39), peanut (n = 37), and egg (n = 29). There were 40 positive challenges (27% of all challenges) in 33 patients. Reactions were mild to moderate in 92% of positive challenges. Cutaneous reactions occurred in 68% of positive challenges, followed by gastrointestinal tract reactions (45%) and upper respiratory tract reactions (38%), excluding laryngeal symptoms. No patient had cardiovascular involvement. Food specific IgE values did not correlate with reaction severity. Interventions included observation or antihistamine only in 92% of positive challenges. For negative challenges to milk, peanut, and egg, median prechallenge food specific IgE approached previously published negative predictive values for these foods. Negative challenges in patients allowed the introduction of 19 different foods into the diet of 88 patients. The authors concluded that Open food challenges are a safe procedure in the office setting for patients selected based on history and food specific IgE approaching negative predictive values.

Perry et al. (2004) also addressed the risk of oral food challenges through a retrospective chart review on children who underwent food challenges. (22) Results included 584 challenges completed, 253 (43%) resulted in an allergic reaction. There were 90 milk, 56 egg, 71 peanut, 21 soy, and 15 wheat failed challenges. Of patients who failed, there were 197 (78%) cutaneous, 108 (43%) gastrointestinal, 66 (26%) oral, 67 (26%) lower respiratory, and 62 (25%) upper respiratory reactions. No patients had cardiovascular symptoms. There was no difference between foods in the severity of failed challenges or the type of treatment required to reverse symptoms. All reactions were reversible with short-acting antihistamines +/- epinephrine, beta-agonists, and/or corticosteroids. No children required hospitalization, and there were no deaths. The authors concluded that there are risks associated with food challenges, and the risks are similar for each of the foods studied. Given the benefits that result from a negative challenge, these risks are reasonable when challenges are performed under the guidance of an experienced practitioner in a properly equipped setting.

<u>Controversial/Unproven Allergy Testing Methods</u>

Provocation and Neutralization Testing

This method is used to both diagnose and treat allergic diseases. Barton et al. (1983) notes that support for this technique is essentially anecdotal. (6) In 2008, Bernstein et al. (12) listed Provocation-Neutralization under the “Unproven Test” section in that practice parameter. In 1990, Jewett et al. assessed in a double-blind study the validity of symptom provocation. (23) Symptoms evaluated in 18 patients included nasal stuffiness, dry mouth, nausea, fatigue, headache, and feelings of disorientation or depression. Results noted by the authors included responses of the patients to the active and control injections were indistinguishable, as was the incidence of positive responses. The authors concluded that when the provocation of symptoms to identify food sensitivities is evaluated under double-blind conditions, this type of testing, as well as the treatments based on “neutralizing” such reactions, appears to lack scientific validity.

Nasal Challenge tests

In 2002, Litvyakova and Baraniuk reviewed literature and noted that the nasal provocation test has not been standardized and noted a wide variety of techniques and approaches to dosing

and concentration of allergen extracts and delivery systems. The authors also noted a lack of a unified outcomes-evaluation system in different countries. (24)

Conjunctival Challenge Testing

Both Mortemousque et al. (2006) and Schroder and Mosges (2018) addressed ambiguities regarding conjunctival provocation testing. (25, 26) Mortemousque et al. noted that there was no validated consensus regarding the criteria for positivity of the conjunctival provocation test (CPT) in routine practice; the group's endeavor was to establish major guidelines for conducting the test, to standardize approaches and identify areas of uncertainty. Schroder and Mosges noted that there was no consensus about its predictive value; the intent of their article was to evaluate under which conditions the CPT can predict the symptom severity during the allergy season after previous allergen immunotherapy (AIT). The authors noted in their literature review that 3 out of 4 randomized controlled trials (RCTs) showed a correlation between CPT reactivity and symptoms occurring under natural allergen exposure after previous AIT. The authors' concluded: CPT has a predictive value and can consequently be used to assess the efficacy of an administered AIT if performed according to a standardized challenge protocol with high-quality allergen extracts. A variety of positive criteria, as a response to CPT, have been noted to include itching, composite scores, and digital photos to analyze allergic hyperemia. (27, 28)

Cytotoxic Testing

Both Barton et al. (1983) and Bernstein et al. (2008) note studies have shown that results do not correlate with clinical evidence of food allergy. (6, 12) Barton et al. also addresses that the efficacy of cytotoxic testing as a diagnostic tool for inhalant allergies has also not been validated.

In 1976, Benson and Arkins evaluated a test conducted in a double-blind manner to determine the validity of cytotoxic food testing. (29) Nine atopic patients with or without a history of food allergy were studied along with 5 nonatopic patients. The authors noted there were 46 positive tests without correlation and 2 negative tests with positive histories. Conclusions reached by the authors included reproducibility of the tests to only 3 foods, but no apparent correlation with clinical symptoms and currently, cytotoxic tests offer no reliable help in establishing the diagnosis of food allergy.

Leukocyte Histamine Release Test (LHRT)

In 2004, Brown et al. noted the objective of a double-blind randomized placebo-controlled crossover trial was to assess the utility of a number of in vitro tests to diagnose venom allergy and to monitor immunotherapy. (30) Histamine release test (HRT) was one of the tests performed at enrollment and at completion of treatment prior to a diagnostic sting challenge. The results noted by the authors included: only intradermal venom skin testing and histamine release test identified those at risk of sting anaphylaxis in the placebo group. The authors concluded that HRT warrants further assessment for diagnosis of venom allergy. None of the tests evaluated appear to be reliable markers of successful venom immunotherapy.

Sato et al., in 2011, noted that due to the possibility of serious symptoms that could occur during an oral food challenge (OFC) test, whether to perform an OFC should be carefully considered. The authors also noted that the utility of the HRT in the diagnosis of childhood food allergy has not been fully examined. (31) Sixty-four subjects with suspected food allergies were evaluated. The histamine release threshold was defined as the minimum concentration of food antigen to induce a 10% net histamine release, was analyzed in association with food allergy diagnosis. The authors noted that they were able to determine the cutoff value for the HRT threshold in relation to outcomes of oral food challenges. Efficiency was 70.3% for heated egg allergy, 78.0% for raw egg allergy, 77.6% for cow's milk allergy and 70.7% for wheat allergy. Conclusions noted by the authors' included that the HRT threshold measurement for egg white, milk, and wheat antigen is related to outcomes of oral food challenge tests and is useful in determining when oral food challenge tests should be performed.

Rebuck Skin Window Test

Zimmerli and Gallin (1987) compared the Rebuck skin window technique with the skin blister chamber technique to study the dynamics of the inflammation in vivo. (32) The authors noted that the type of inflammation is basically different in each of these methods. Whereas the former technique provokes a late monocytic response, the latter technique provokes virtually no monocyte accumulation. The authors observed cell accumulation under different conditions, i.e., in the presence and in the absence of a foreign body (coverslip). The authors noted that controlled experiments showed that the continuous presence of the coverslip in the skin window is the critical element provoking accumulation of monocytes. A different degree of neutrophil degranulation in presence and absence, respectively, of a foreign body may be responsible for the different types of inflammatory response.

Sublingual Provocation Food Testing

In 1980, Lehman noted in a double-blind study of 15 subjects with chronic allergic conditions that edema and swelling of the nasal mucosa were observed as frequently when a placebo was given as when sublingual food drops containing corn, egg, milk, or yeast were given. (33) He noted that this method of testing does not differentiate between placebo and food drops.

Allergy Therapy

Avoidance/environmental controls are the most important component of therapy. In many cases, if a patient can eliminate their exposure to an allergen their symptoms will decrease markedly and there is no need for further forms of treatment, however, this is not always possible.

The second mode of therapy is medication. Medication is an important form of therapy and in some patients such as asthmatics, it is essential. In recent years, newer and better medications (e.g., antihistamines, corticosteroids, bronchodilators) make complete control of the allergic patient possible. In most situations, medication relieves or alleviates the symptoms but does not address the cause. In many patients, medication and avoidance are enough to relieve the patient adequately so that no further treatment is necessary.

Immunotherapy (e.g., desensitization, hyposensitization, allergy injection therapy or “allergy shots”) is used to treat patients who are sensitive to inhaled allergens, such as pollens, molds, dander, and house dust. Studies have found immunotherapy to be extremely effective for stinging insect allergy. Immunotherapy for food allergies is not recommended because of the chance of a severe allergic reaction to the injection and because avoidance can often be achieved.

Conventional/Traditional Immunotherapy or rush immunotherapy is not a cure, only a treatment modality. Ideally, immunotherapy should provide the allergic patient with maximal clinical benefit with minimal risk. The concerns with rush immunotherapy as compared to traditional immunotherapy, has been the higher rate of systemic reactions. The major risk factor of allergy immunotherapy is anaphylaxis. Immunotherapy should be administered under the supervision of an appropriately trained physician who can recognize early signs and symptoms of anaphylaxis and administer emergency medications if needed.

Alvarez-Cuesta et al. (2022) noted in a World Allergy Organization committee statement addressing intravenous rapid drug desensitization (RDD) that RDD is a technique to temporarily modify a patient’s immune response to a drug in a few hours. (34) Rapid drug desensitization is usually considered only when there is no alternative drug, but it is widely accepted that it should also be considered when the culprit drug is more effective or is associated with fewer side effects. Rapid drug desensitization is helpful in patients who have experienced confirmed drug hypersensitivity reactions (DHRs) that are amenable to desensitization, including anaphylaxis. This consensus document noted that DHRs are usually divided according to the timing of their onset into immediate (I-DHR) and non-immediate (NI-DHR). The document notes typical occurrence times following exposure for severe immediate reactions and that most classifications consider that I-DHRs can happen for some drugs as late as within 6 hours of exposure (or 4 hours for vaccines). The authors go on to note that a type I Gell and Coombs category features immediate IgE-mediated DHRs leading to mast cell/basophil degranulation with symptoms from mild urticaria to anaphylaxis. They also note that some authors argue that type I DHRs should also include non-IgE mediated activation of mast cells/basophils. RDD has been mainly studied for use on type I-DHRs (acute onset reactions involving the release of preformed mediators of mast cells and basophils). The authors mention that delabeling and desensitization are high-risk and high-complexity allergy-specific techniques. As such, they need specific resources and specific spaces led and managed by experts in drug allergy.

<u>Controversial/Unproven Allergy Therapy</u>

Provocative and Neutralization therapy

Teuber and Vogt (1999) noted a case report describing the risks associated with use of an unproven technique, provocation/neutralization, in diagnosis and treatment of a reported food allergy in a patient with systemic mastocytosis. (35) The physician that practiced provocative /neutralization placed the patient on "neutralizing" injections of milk and wheat. The authors’ note that the patient experienced flushing, palpitations, and lightheadedness with syncope upon injections into her thigh. The authors’ concluded: The patient's previous history of urticaria pigmentosa, documented in medical records, and visible on physical examination, was

discounted by a practitioner. This patient subsequently had potentially life-threatening reactions to "provocative" skin testing and "neutralizing" injections. Patients with systemic mastocytosis are at risk for significant mast cell mediator release during immunotherapy, conventional or alternative.

Intranasal Immunotherapy
In 1995 Passalacqua et al. noted that previous studies had demonstrated local nasal immunotherapy (LNIT) to be an effective treatment for rhinitis due to pollens and mites. Passalacqua et al. investigated the effect of LNIT on the local inflammatory phenomena, employing the model of nasal allergenic challenge. (36) The study involved 20 adults involved in a double-blind, placebo-controlled trial of preseasonal immunotherapy with Parietaria. A significant reduction of symptoms, inflammatory infiltration, and intercellular adhesion molecule-1 (ICAM-1) expression on epithelial cells after nasal challenge was evidence as long-lasting effect. No changes in serum allergen-specific IgE, IgG, and soluble eosinophil cationic protein were detected, whereas an unexpected increase of soluble ICAM-1 was found in the placebo group only. The authors noted that treatment was well tolerated and a significant clinical improvement under natural allergenic exposure was observed in the active group. The present study provides, for the first time, evidence that LNIT is able to modulate the nasal allergic inflammation.

Cox et al. (2011) noted that randomized placebo-controlled studies demonstrate that intranasal administration of allergen extracts improves symptoms of allergic rhinitis both to pollens and house dust mites. … With intranasal and intrabronchial allergen administration, local symptoms were decreased by use of pretreatment with sodium cromoglycate. Despite reported clinical successes, both approaches have been largely abandoned. (10)

Urine Auto-Injection (Autogenous Urine Immunization)
In 1983, Barton et al. noted that autogenous-urine immunization was introduced in the 1940's. by Plesch who cited anecdotal evidence of relief from symptoms such as asthma, constipation, urticaria, food allergy and depression. (6) Barton et al. also notes that the use of autogenous-urine immunization has no proven efficacy and can predispose the patient to potential harmful effects.

Repository emulsion therapy
Eger and Harris (1965) noted in a series of cases in which emulsion repository desensitization therapy for allergic disease was carried out, the amount of emulsion injected was, for a time, one milliliter. Then, for a second period, the volume was reduced to 0.5 milliliter, and minor refinements of technique were introduced. Many of the patients treated in the first period were also treated in the second. The incidence of untoward reaction, ranging from mild soreness to the development of draining cysts at the site of injection into the arm, was greatly reduced between the first and second periods. (37) The authors noted that the prompt resolution of almost all of these reactions and the sterile nature of the fluid aspirated from those that had to be treated this way, would indicate an irritation or foreign body reaction. The possibility of local skin hypersensitivity cannot be excluded.

Allergoids

Cox et al. (2011) notes allergoids are chemically modified extracts that reduce IgE binding capacity. Furthermore, the authors go on to note allergoids are used, on average, in 20% of subcutaneous immunotherapy (SCIT) treatments prescribed in Europe, but the use varies in different countries. There are no FDA-approved allergoids in the United States. (10)

Practice Guidelines and Position Statements

The World Allergy Organization (WAO)

In 2020, Ansotegui et al. in a WAO position paper addressing IgE allergy diagnostics and other relevant tests in allergy noted that 6-8% of children and 2-3% of adults are affected by food allergy. They state however, that the public perception of food allergy/intolerance is higher, as one out of three people believes they are allergic or intolerant to one or more foods. The authors noted that this perception is at least in part based on the results of unproven diagnostic approaches. The WAO listed the following unproven diagnostic approaches: Specific IgG antibodies, Cytotoxic test, hair analysis, iridology, kinesiology and electrodermal testing. (4)

The American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI)

In 2008, Bernstein et al. (12) noted in an updated Practice Parameter for Allergy Diagnostic Testing:

Specific organ challenge tests may facilitate or confirm clinical diagnosis under certain circumstances:

1. Investigation of potential “new” allergens,
2. Confirmation of clinical diagnosis when the history is suggestive but skin and/or in vitro test results are negative,
3. Confirming food allergy,
4. Monitoring of therapy, and
5. Substantiating occupational sensitivity.

The practice parameter further notes “In general, specific bronchial challenge testing is most often performed for research or when there is diagnostic uncertainty or dispute.” Summary Statement 49 notes: Specific (allergic) bronchial challenge provides a measure of lower airway clinical sensitivity when there is uncertainty or dispute. (B)

In addition, the practice parameter contains additional information addressing bronchial challenge related to occupational challenge testing.

The following unproven tests are addressed in a Summary Statement 154. Procedures for which there is no evidence of diagnostic validity include cytotoxic tests, provocation-neutralization, electrodermal testing, applied kinesiology, iridology, hair analysis, or food specific IgG, IgG4, and IgG/IgG4 antibody tests (B).

In 2011, Cox et al. (10) in the Allergen immunotherapy: A practice parameter third update noted the following:
Conditions for which immunotherapy is investigational:

- Food hypersensitivity. Summary Statement 12: Clinical trials do not support the use of subcutaneous immunotherapy for food hypersensitivity. [Strength of recommendation: A- Directly based on category I evidence].

Conditions for which immunotherapy is not indicated:

- Urticaria and angioedema. Summary Statement 14: Clinical studies do not support the use of allergen immunotherapy for chronic urticaria, angioedema, or both. Therefore, allergen immunotherapy for patients with chronic urticaria, angioedema, or both is not recommended. [Strength of recommendation: D- Directly based on category IV evidence or extrapolated from category I, II, or III evidence].

In a 2014 Food Allergy Practice Parameter Update, Sampson et al. (9) included the following summary statement:

- Summary Statement 34: Unproved tests, including allergen specific IgG measurement, cytotoxicity assays, applied kinesiology, provocation neutralization, and hair analysis, should not be used for the evaluation of food allergy. [Strength of recommendation: Strong; C Evidence].

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	82785, 83516, 86001, 86003, 86005, 86008, 86160, 86343, 86486, 89190, 95004, 95017, 95018, 95024, 95027, 95028, 95044, 95052, 95056, 95060, 95065, 95070, 95076, 95079, 95117, 95120, 95125, 95130, 95131, 95132, 95133, 95134, 95144, 95145, 95146, 95147, 95148, 95149, 95165, 95170, 95180, 95199
HCPCS Codes	J3490, J7665, J7674, J8499

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been changed since this medical policy document was written. See Medicare's National Coverage at <http://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
12/31/2025	Document became inactive.
06/15/2024	Reviewed. No changes.
11/01/2023	Document updated with literature review. The following changes were made to Coverage: 1) Clarified double blind food challenge testing to oral challenge/provocation testing and added criteria to the oral challenge/provocation testing; 2) Clarified rush or rapid immunotherapy to rapid desensitization/rush immunotherapy and added criteria to the rapid desensitization/rush Immunotherapy statement; 3) Clarified nomenclature for serial endpoint testing (SET); 4) Added: applied kinesiology (allergy testing by testing muscle strength or weakness); and electrodermal testing (Vega) to the list of methods of allergy testing that are considered experimental, investigational and/or unproven. The following references were added: 1, 4-5, 14-16, and 34; other references were updated, and some removed.
08/15/2022	Reviewed. No changes.
01/01/2022	Document updated with literature review. The following changes were made to Coverage: 1) Added criteria to bronchial challenge testing; 2) Made language clarifications to the allergy testing section; 3) Made language clarification to the allergy therapy section; 4) Added “Allergoids (modification of allergens to reduce allergenicity)” to experimental, investigational and/or unproven list in the allergy therapy section; 5) Added “Subcutaneous allergen immunotherapy for the following indications is considered experimental, investigational and/or unproven: chronic urticaria, angioedema and food hypersensitivity.” The following references were added: 10-15, 25, 28-32.
01/15/2021	Reviewed. No changes.
08/01/2019	Document updated with literature review. Coverage has changed: 1) Criteria added for Serum Allergy Testing (IgE) which may be considered medically necessary when criteria are met; 2) Removed Specific IgE in vitro testing/IgE

	concentration food-specific allergy testing from allergy testing considered experimental, investigational and/or unproven list; 3)Added NOTE 1: Evaluation for IgE antibody-associated food allergies: Specific IgE tests (skin prick tests, serum tests, or both) when used as diagnostic tools for evaluation of food allergies may be used when suspicion of specific food allergens is high. These tests are not effective for indiscriminate screening (e.g., using panels of tests without consideration of likely causes) and therefore generally should not be used for that purpose. 4) Added NOTE 2: See medical policy RX501.058 Xolair (omalizumab) for further information regarding Xolair and serum total IgE levels. 5) Moved Coverage for Antigen Leukocyte Antibody Test (ALCAT) to MED206.005; 6) Moved Coverage for Sublingual Immunotherapy as a Technique of Allergen-Specific Therapy to MED206.006; 7) Removed Coverage addressing Lifestyle Eating and Performance (LEAP) program, including the Mediator Release Test (MRT) used to identify "delayed food allergies" and treatments, but Coverage still remains on medical policy MED206.003 Idiopathic Environmental Intolerance or Illness (IEI) Management. References added 6-7, 9-23. Some references removed.
09/15/2017	Document updated with literature review. The following change was made to Coverage: "rhinoconjunctivitis" was added to the medical necessity statement for sublingual immunotherapy.
10/01/2016	Reviewed. No changes.
01/01/2015	Document updated with literature review. The following coverage changes have been made: Addition/clarification: The following example (i.e. intradermal) was added to the following statement: The following methods of allergy testing are considered experimental, investigational and/or unproven for the following tests: Provocative tests (i.e. intradermal) for food or food additive allergies. The following changes have been added to the coverage section: Sublingual immunotherapy using Oralair®, Grastek®, or Ragwitek® may be considered medically necessary, when used according to FDA-labeling, for the treatment of pollen-induced allergic rhinitis when criteria are met. Sublingual immunotherapy as a technique of allergy immunotherapy is considered experimental, investigational and/or unproven for all other uses. The following addition/clarification: Non-FDA approved was added to the following statement: The following methods of allergy immunotherapy are considered experimental, investigational and/or unproven for the treatment of food, molds, chemicals, pollens, and other allergies including the preparation of and administration of immunotherapy: Non-FDA approved sublingual immunotherapy (SLIT); oral application of natural or enzymatically altered antigens.
09/15/2013	Document updated with literature review. Coverage unchanged. CPT/HCPCS code(s) updated.

06/01/2012	Policy partially updated, serial endpoint testing (SET) is now considered conditionally medically necessary, literature reviewed.
03/01/2010	Policy updated with literature review. Coverage was clarified: sublingual therapy is considered experimental, investigational and unproven including the preparation and administration of immunotherapy.
07/15/2008	Coverage change.
02/15/2008	Coverage change.
01/01/2008	Codes Revised/Added/Deleted
05/01/2007	Codes Revised/Added/Deleted
10/15/2004	Revised/Updated Entire Document
12/01/2003	Revised/Updated Entire Document
04/01/2002	Revised/Updated Entire Document
05/01/1996	Revised/Updated Entire Document
07/01/1993	Revised/Updated Entire Document
01/01/1993	Revised/Updated Entire Document
05/01/1990	New Medical Document.