Clinical Policy Bulletin: Allergy and Hypersensitivity

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Policy

Aetna considers specific allergy testing and allergy immunotherapy medically necessary for members with clinically significant allergic symptoms. Based on a review of the medical literature and the position statements of scientific organizations in the field of allergy and immunology, Aetna considers the specific allergy testing and treatment described below medically necessary in accordance with the selection criteria noted.

ALLERGY TESTING

Aetna considers the following allergy tests medically necessary:

**Epicutaneous (scratch, prick or puncture)** when IgE-mediated reactions occur to any of the following:

- Foods; or
- Hymenoptera (stinging insects); or
- Inhalants; or
- Specific drugs (penicillins and macromolecular agents).

**Intradermal (Intracutaneous)** when IgE-mediated reactions occur to any of the following:

- Foods; or
- Hymenoptera venom allergy (stinging insects); or
- Inhalants; or
- Specific drugs (penicillins and macromolecular agents).

Number of epicutaneous (percutaneous) and intracutaneous (intradermal) skin tests:

The evaluation of inhalant allergy may require up to 70 percutaneous tests, followed by up to 40 intracutaneous tests (which are usually
performed when percutaneous tests are negative). However, in most cases, fewer tests are required.

**Skin Endpoint Titration (SET)** (also known as intradermal dilutional testing (IDT)) for determining the starting dose for immunotherapy for:

Members highly allergic to hymenoptera venom allergy (stinging insects); or
Members highly allergic to inhalants.

**Number of SET tests:**

It is inappropriate to use SET in place of skin testing; however, when used to determine the starting dose for immunotherapy in highly allergic members, up to 14 titration tests may be necessary. An additional 40 antigens or 80 IDT injections may be medically necessary if any of the initial test results is positive.

**Skin Patch Testing** for diagnosing contact allergic dermatitis.

**Photo Patch Testing** for diagnosing photo-allergy (e.g., photo-allergic contact dermatitis).

**Photo Tests** for evaluating photo-sensitivity disorders.

**Bronchial Challenge Test** for testing with methacholine, histamine or antigens in defining asthma or airway hyperactivity when *either* of the following conditions is met:

Bronchial challenge test is being used to identify new allergens for which skin or blood testing has not been validated; or
Skin testing is unreliable.

**Exercise Challenge Testing** for exercise-induced bronchospasm

**Ingestion (Oral) Challenge Test** for *any* of the following:

Food or other substances (i.e., metabisulfite); or

Drugs when *all* of the following are met:

History of allergy to a particular drug; *and*
There is no effective alternative drug; *and*
Treatment with that drug class is essential.

**In Vitro IgE Antibody Tests** (RAST, MAST, FAST, ELISA, ImmunoCAP) are considered medically necessary for:

Allergic broncho-pulmonary aspergillosis (ABPA) and certain parasitic diseases; or
Food allergy; or
Hymenoptera venom allergy (stinging insects); or
Inhalant allergy; or
Specific drugs.

Number of Tests:

In vitro tests may be medically necessary for the initial allergy screen in lieu of skin testing. An initial allergy screen is 12 tests. Additional tests may be medically necessary if any of the initial test results is positive. If all test results are negative, additional testing beyond the initial allergy screen of 12 tests/allergens is not considered medically necessary.

**Total Serum IgE** for diagnostic evaluation in members with known or suspected ABPA and or hyper IgE syndrome.

Lymphocyte transformation tests (lymphocyte mitogen response test, PHE stimulation test, lymphocyte antigen response assay) are considered medically necessary for evaluating persons with sensitivity to beryllium. Lymphocyte transformation tests are considered experimental and investigational for evaluation of persons with allergies or other hypersensitivities. **Note:** Lymphocyte transformation tests are also considered medically necessary for evaluation of persons suspected of having congenital or acquired immunodeficiency diseases affecting cell-mediated immunity, such as severe combined immunodeficiency, common variable immunodeficiency, X-linked immunodeficiency with hyper IgM, Nijmegen breakage syndrome, reticular dysgenesis, DiGeorge syndrome, Nezelof syndrome, Wiscott-Aldrich syndrome, ataxia telangiectasia, and chronic mucocutaneous candidiasis. Lymphocyte transformation tests are also medically necessary for evaluation of persons with thymoma and to predict allograft compatibility in the transplant setting. For lymphocyte transformation testing for infertility, see [CPB 0327 - Infertility](http://qawww.aetna.com/cpb/medical/data/1_99/0038_draft.html).

Allergy Re-testing: Routine allergy re-testing is not considered medically necessary.

Aetna considers the following tests for allergy testing experimental and investigational as they have not been proven to be effective:

- **ALCAT test** (Antigen Leukocyte Cellular Antibody Test, an automated food allergy test)
- Alpha gal allergy (meat allergy) testing
- Anti-Fc epsilon receptor antibodies testing
- Anti-IgE receptor antibody testing
- Body chemical analysis
- Candidiasis test
- Chlorinated pesticides (serum)
- Chronic Urticaria Index testing
- Clifford materials reactivity testing
- Complement (total or components); (may be appropriate in autoimmune disorders, complement component deficiencies, hereditary angioedema, vasculitis)
Complement Antigen Testing
C-reactive protein (may be appropriate in inflammatory diseases)

**Cytokine and cytokine receptor assay**
Cytotoxic food testing (Bryans Test, ACT)
Electrodermal acupuncture
ELISA/AKT
Eosinophil cationic protein (ECP) test
Food immune complex assays (FICA)
IgG RAST/ELISA testing
Immune complex assay (may be appropriate in autoimmune disorders, systemic lupus erythematosus, vasculitis)

**In-vitro metal allergy testing (as known as lymphocyte transformation tests (LTT))**
Leukocyte antibodies testing
Leukocyte histamine release test
Lymphocytes (B or T subsets); (may be appropriate for collagen vascular disease, immune deficiency syndromes, leukemia, lymphomas)

**Lymphocyte function assay**
Mediator release test (MRT)
Muscle strength testing or measurement (kinesiology) after allergen ingestion
Ophthalmic mucous membrane tests/conjunctival challenge tests
Prausnitz-Kustner or P-K testing -- passive cutaneous transfer test
Provocative nasal test (also known as nasal provocation testing)
Provocation-neutralization testing (Rinkel Test) either subcutaneously or sublingually
Pulse test (pulse response test, reaginic pulse test)
Rebuck skin window test
Serum immunoglobulin A (IgA), immunoglobulin G (IgG) testing for allergy
Sublingual provocative neutralization testing and treatment with hormones
Testing for electromagnetic sensitivity syndrome/disorder (also known as allergy to electricity, electro-sensitivity, electrohypersensitivity, and hypersensitivity to electricity)
Testing for multiple chemical sensitivity syndrome (also known as idiopathic environmental intolerance (IEI), clinical ecological illness, clinical ecology, environmental illness, chemical AIDS, environmental/chemical hypersensitivity disease, total allergy syndrome, cerebral allergy, 20th century disease)
Venom blocking antibodies
Volatile chemical panels (blood testing for chemicals).
Tests listed in section I.A., when performed for indications not listed as medically necessary.

ALLERGY IMMUNOTHERAPY

Aetna considers allergy immunotherapy administered in a medical facility medically necessary for the treatment of the following IgE-mediated allergies:

- Allergic (extrinsic) asthma
- Dust mite atopic dermatitis
- Hymenoptera (bees, hornets, wasps, fire ants) sensitive individuals
- Mold-induced allergic rhinitis
- Perennial rhinitis
- Seasonal allergic rhinitis or conjunctivitis

when all of the following conditions are met:

- Member has symptoms of allergic rhinitis and/or asthma after natural exposure to the allergen; or
- Member has a life-threatening allergy to insect stings (bees, hornets, wasps, and fire ants), and
- Member has skin test and/or serologic evidence of IgE-mediated antibody to a potent extract of the allergen, and
- Avoidance or pharmacologic therapy can not control allergic symptoms or member has unacceptable side effects with pharmacologic therapy.

Note: Also see CPB 0670 - Xolair (Omalizumab).

Aetna considers home administration of allergy immunotherapy experimental and investigational because its safety and effectiveness has not been established.

Aetna considers allergy immunotherapy experimental and investigational for all other indications, including the following because its effectiveness for these indications has not been established:

- Angioedema
- Atopic dermatitis (cover for dust mite atopic dermatitis)
- Chronic urticaria
- Food allergy
- Intrinsic (non-allergic) asthma
- Migraine headaches
- Non-allergic vasomotor rhinitis.

OTHER TREATMENTS
Aetna considers the following treatments medically necessary:

**Rapid desensitization** (a.k.a., rush, cluster or acute desensitization) for members with any of the following conditions:

- Allergy to a particular drug that can not be treated effectively with alternative medications; or
- Insect sting (e.g., wasps, hornets, bees, fire ants) hypersensitivity (hymenoptera); or
- Members with moderate to severe allergic rhinitis who need treatment during or immediately before the season of the affecting allergy.

Rapid desensitization is considered experimental and investigational for other indications because its effectiveness for indications other than the ones listed above has not been established.

**Note:** If a woman is contemplating pregnancy and requires initiation of allergy immunotherapy and/or it is anticipated that she will require allergy medications that may increase risk to her or the fetus, rapid desensitization is an acceptable approach.

**Epinephrine kits** (e.g., Ana-Kit, Epi-Pen auto-injectors) to prevent anaphylactic shock for individuals who have had life-threatening reactions to insect stings, foods, drugs or other allergens or have severe asthma or if needed during immunotherapy. Epinephrine kits are considered experimental and investigational for other indications because their effectiveness for indications other than the ones listed above has not been established.

**Aspirin Desensitization** is considered medically necessary for aspirin sensitive persons who require administration of ASA or ASA-like drugs (aspirin avoidance is not possible) in the setting of:

- chronic rhinosinusitis with nasal polyposis that is refractory to topical glucocorticoids, leukotriene modifying agents, and other therapies; or
- stable cardiovascular disease or cardiovascular risk factors requiring aspirin antiplatelet therapy; or
- the need for NSAIDS to treat chronic inflammatory conditions, such as arthritis; or
- antiphospholipid syndromes during pregnancy; or
- poorly controlled asthma.

Aspirin desensitization is considered experimental and investigational for any other indication.

Aetna considers the following treatments experimental and investigational as they have not been proven to be effective:

- Acupuncture for allergies
- Allergoids (modification of allergens to reduce allergenicity)
Autogenous urine immunization (autogenous urine therapy)
Bacterial immunotherapy
Detoxification for allergies
Ecology units/environmental control units/environmental chemical avoidance for multiple chemical sensitivity syndrome
Enzyme potentiated desensitization (EPD)
Helminth Trichuris suis therapy for allergic rhinitis
Homeopathy for allergies
Neutralization therapy (desensitization neutralization therapy)
Neutralizing therapy of chemical and food extracts
Oral nystatin for the treatment of "candidiasis hypersensitivity syndrome"
Photo-inactivated extracts
Polymerized extracts
Poison ivy/poison oak extracts for immunotherapy in the prevention of toxicodendron (Rhus) dermatitis
Repository emulsion therapy
Rhinophototherapy
Sublingual drops/sublingual immunotherapy other than Oralair, Grastek and Ragwitek. (Oralair and Grastek tablets are considered medically necessary for grass pollen allergies and Ragwitek is considered medically necessary for ragweed pollen allergies.)*
Treatments for electromagnetic sensitivity syndrome/disorder
Ultra low dose enzyme activated immunotherapy (low dose allergens or LDA).

*Note: Some pharmacy benefit plans exclude allergy sera. This exclusion would apply to sublingual immunotherapy. Under plans with this exclusion, coverage of Oralair, Grastek, and Ragwitek may be available under the medical benefit. Please check benefit plan descriptions.

**Background**

Allergy is a hypersensitive reaction that is usually manifested in the clinical form of allergic asthma, hay fever or eczema developing within minutes to a few hours after exposure to an antigen. The most common types of allergies are rhinitis, asthma, food allergy, insect sting allergy, drug allergy and contact dermatitis. Allergy testing is focused on determining what allergens cause a particular reaction and the degree of the reaction and provides justification for recommendations of specific avoidance measures in the home or work environment or the institution of particular medicines or immunotherapy. There are virtually no age limitations for performance of skin tests. However, skin test reactivity may be diminished in infants and the elderly. Types of allergy testing include in vivo, in vitro, provocation testing, and controversial allergy tests.
I. Allergy Testing

A. In-Vivo Diagnostic tests of IgE dependent reactions

Epicutaneous (Scratch, Prick or Puncture) and Intracutaneous In-Vivo Diagnostic Skin Tests

Skin tests for IgE-mediated disease with allergenic extracts have been shown to be effective aids in the assessment of allergic patients. These tests involve the introduction of small quantities of test allergens below the epidermis. Within 15 to 20 mins, a characteristic wheal and flare reaction occurs in patients sensitive to one or more of the test allergens. The majority of allergists use prick or puncture and/or intracutaneous skin tests, since the amount of allergen delivered by these methods is better controlled than by scratch tests. Although skin testing is considered to be a safe procedure, adverse events, such as large local reactions and systemic symptoms may occur in extremely sensitive individuals. Deaths from anaphylaxis after skin testing have been reported. These extremely rare systemic symptoms are less likely to occur with prick or puncture than with intracutaneous tests. Prick or puncture tests are generally considered to be the most convenient, least expensive and most specific screening method for detecting the presence of IgE antibodies in patients with appropriate exposure histories. Prick or puncture tests are generally less sensitive than intracutaneous tests. For inhalant allergens, prick or puncture tests are generally felt to correlate better with the presence of clinical allergy. However, intracutaneous (within the skin) testing may detect relevant sensitivity and should be considered when the prick or puncture test is negative or equivocal to allergens strongly suggested by the patient's history or exposure, or when skin sensitivity may be decreased such as in infants or older patients. Intracutaneous tests permit identification of a larger number of clinically reactive patients, especially those with lower skin test sensitivity.

Skin testing to drugs is generally unreliable, except for the penicillins and macromolecular agents, such as foreign antisera, hormone (e.g., insulin), enzymes (e.g., L-asparaginase, streptokinase, chymopapain), and egg-containing vaccines.

In January 2003, the Board of Directors of the American Academy of Otolaryngic Allergy (AAOA) endorsed strategies for testing for inhalant allergy (Krouse and Mabry, 2003), stating that “[m]embers should practice in ethical and fiscally responsible ways.” The AAOA provided the following guidelines on the necessary number of tests for inhalant allergy (e.g., prick testing, intradermal testing, intradermal dilutional testing (IDT), and in vitro testing):

1. Screening: Screen with no more than 14 relevant antigens plus appropriate controls.
2. Antigen survey: If screening is positive and immunotherapy is contemplated, use no more than 40 antigens. More extensive testing may be justified in special circumstances.

3. Quantification for safe starting point: Use no more than 80 IDT tests routinely. More extensive testing may be justified in special circumstances.

Skin Endpoint Titration (SET)

Skin endpoint titration (SET) (also known as intradermal dilutional testing (IDT)) is intradermal testing of sequential and incremental dilutions of a single antigen. SET involves serial testing with several dilutions of a single treatment allergen or mixture of allergens to identify the lowest dilution that produces a positive skin reaction. In performing the test, wheals of identical size are made in the most superficial layers of the skin and measured for uniformity. The first wheal is made with approximately 0.1 ml of a dilution estimated to be too weak to produce symptoms. Successive wheals are made with serial dilutions, each generally five times stronger than the previous one, until negative responses are replaced by positive responses of increasing size. The "endpoint" is the weakest dilution that produces a positive skin reaction and initiates progressive increase in the diameter of wheals with each stronger dilution. Proponents of SET emphasize that it quantifies skin testing and replaces a single equivocal reaction with a progressive pattern easily identified. When immunotherapy is initiated, starting with too strong an extract may precipitate dangerous allergic reactions, while starting with one too weak may delay treatment results. Skin endpoint titration allows the initiation of immunotherapy with a safe but relatively potent dose, and allows the beginning dosage for each positive responding allergen to be varied depending on its specific "endpoint." Although traditional allergists often rely on single dilution “classical” testing, they have accepted SET over the last decade as effective for quantifying patient sensitivity and for providing a guide for a safe starting dose for immunotherapy noting that studies have not shown it to be an effective guide to a final therapeutic dose. The AAOA also has advised that costly, repetitive endpoint titrations are usually unnecessary because, regardless of what the titration indicates, the dose will be advanced either until the patient can tolerate no more or until a dose is reached that produces satisfactory results. Skin endpoint titration is considered the gold standard of skin testing by the AAOA; the American Medical Association’s Council of Scientific Affairs also is on record that SET is helpful for the delineation of patient-specific sensitivity to various antigens as well as to evaluate a patient's response to various forms of immunotherapy. They note that controlled studies have shown that the intradermal method of SET is effective for quantifying sensitivity to ragweed pollen extract and for identifying patients highly sensitive to ragweed.
While allowing that SET is a valid method for obtaining semi-quantitative information about a person's sensitivity and for determining a safe beginning dose for immunotherapy, the American College of Physicians (ACP) advises that the primary use of SET is to identify hymenoptera venom (yellow jacket, honey bee, hornet, wasp, fire ant) sensitivity and to determine the safe starting dose for venom immunotherapy.

In a guideline, revised in 2003, the AAOA recommends screening prick tests with relevant antigens to determine which to use in subsequent SET (Krouse and Mabry, 2003). The literature on screening supports, and the AAOA recommends, usually screening and billing for no more than 14 antigens (plus the appropriate controls) for an initial allergy evaluation. In most geographic regions, a range of up to 14 allergens is sufficient to check the most prevalent molds, dust components, grasses, trees, animals, and weeds. If screening is positive and immunotherapy is contemplated, the AAOA recommends no more than 40 antigen be tested unless indicated by unusual clinical circumstances. For SET, the AAOA says that up to 80 injections are usually necessary to identify the offending antigen and find a safe starting point for immunotherapy.

Provocation (Challenge) Testing

In provocation or challenge testing, a suspected allergen in a clinically relevant exposure is administered in an attempt to reproduce symptoms. Challenge tests have been broadly applied under research conditions for many years, but there also may be clinical situations in which they can be useful for confirmation of clinical disease. Considerable experience with these methods is required for proper interpretation and analysis.

Patch Testing

Patch testing is an accepted method of differentiating allergic contact dermatitis and irritant contact dermatitis. Twenty to 30 antigens are used in the usual routine screening panel of patch tests. The patches are removed after 48 hours and an initial reading is taken 1 hour later. The final reading is taken a further 48 hours later.

Photo Patch Testing

Some chemicals or medications (e.g., lomefloxacin, ofloxacin, ciprofloxacin and norfloxacin) produce an allergic reaction only when exposed to light (usually ultraviolet type A, UVA). Patients who are over-sensitive to light and those with a rash that appears on parts of the body normally exposed to light but that does not appear in areas shielded from the light should have a photo-patch test. With photo patch testing, 2 identical sets of allergens are placed onto the patient's back on day-1. One of the sets is exposed to UVA light, and the sites are then examined as described above for patch
testing. A positive photo patch test is recorded when an allergic reaction appears only on the light-exposed site.

**Photo Tests**

Photo testing is skin irradiation with a specific range of ultraviolet light. Photo tests are performed for the evaluation of photosensitivity disorders.

**Bronchial Challenge Testing**

Bronchial challenge testing with methacholine, histamine, or allergens is an accepted method of defining asthma or airway hyperactivity when skin testing results are not consistent with the patient's medical history. Results of these tests are ordinarily evaluated by objective measures of pulmonary function and occasionally by characterization of bronchoalveolar lavage samples. Recommended dosage is an incremental increase of pharmacologic dose until a response is produced.

**Exercise Challenge Testing**

Exercise challenge testing is an accepted method of diagnosing exercise induced bronchospasm in asthmatic and non-asthmatic patients.

**Ingestion (Oral) Challenge Testing**

Ingestion (oral) challenge testing is an accepted method of diagnosing allergies to food, drug or other substances (i.e., metabisulfite). Drug challenge testing should not be confused with cutaneous or sublingual provocation and neutralization therapy, which is a non-covered modality.

**Nasal or Conjunctival Provocative or Challenge Tests**

Nasal or conjunctival provocative or challenge tests employed for the diagnosis of either food or inhalant allergies, involve the direct administration of the allergen to the mucosa. The patient is then observed for signs and symptoms and the presence of symptoms is interpreted as a positive indication of allergies. These tests are time consuming, only 1 antigen may be administered per session, a non-standardized quantity of allergen is administered and they have the potential of inducing severe symptoms. There is currently no standard of techniques for nasal or conjunctival challenge tests that can be applied to clinical practice.

**Prausnitz-Kustner or P-K Testing**

Prausnitz-Kustner testing has been used in patients with dermatographia or generalized skin eruptions. A control site on the forearm of a non-allergic recipient is selected. This site is injected intradermally with allergy serum from a patient on whom direct skin tests cannot be done. Allergenic extract is later injected
intradermally into the initial injection site of the recipient and observed for the development of a wheal and flare. Because of the risk of transmitting hepatitis or AIDS, this test is contraindicated.

**Provocation-Neutralization (Rinkel Test)**

Provocation-neutralization is a method of testing for the presence of food, inhalant or environmental chemical allergies by exposing the individual to test doses of these substances intradermally, subcutaneously, or sublingually with the purpose of either producing or preventing subjective symptoms. Provocation-neutralization evolved from the serial end-point titration skin testing procedure (a covered modality), and is based on the concept that extremely small quantities of allergens can cause immediate disappearance (“neutralization”) of ongoing symptoms. Once a test is considered positive (results are interpreted either by subjective symptom provocation or objective skin whealing), a progressive series of lower concentrations are administered under the tongue or skin until a dose is reached at which the patient reports no sensations. This amount of the test substance is considered the “neutralizing dose”, which is then used for future treatment. Sublingual testing has been used mainly in diagnosing food allergy, although extracts of chemicals, inhalant allergens, drugs, and hormones have been administered by the sublingual route. Published literature frequently combines the discussion of testing and treatment as a single entity. Provocation-neutralization is used by those physicians who subscribe to the concept of multiple food and chemical sensitivities (also known as idiopathic environmental intolerance’s (IEI), clinical ecological illness, clinical ecology, environmental illness, chemical AIDS, environmental/chemical hypersensitivity disease, total allergy syndrome, cerebral allergy, 20th century disease) and “delayed food allergy”. When used for the latter, provocative testing may be identified as the intracutaneous progressive dilution food test (IPDFT). Since provocation-neutralization requires the provoking and neutralizing of symptoms to a single item at a time, the patient could be required to undergo hundreds of individual tests requiring weeks or months of full-day testing.

Traditional allergists believe that food hypersensitivities are primarily IgE-mediated and treat with avoidance diet and/or drug therapy. Diagnosis is by history, elimination diets, skin tests, or food challenge. Non IgE-mediated food intolerance is classified as non-immune adverse reactions to food of a pharmacologic (caffeine, histamine, tyramine, serotonin, dopamine, etc.); metabolic (lactose intolerance); or idiosyncratic nature, e.g., food dyes, preservatives (sulfites), flavor enhancers (MSG). The AAOA indicates that provocation-neutralization techniques were developed primarily for these delayed, less obvious, non-IgE-mediated food hypersensitivities and not for confirmation of immediate food allergy obvious by history. Test substances have also included chemicals
such as formaldehyde and alcohol, histamine, tobacco, newsprint and inhalant allergens.

Sublingual provocative neutralization with hormones utilizes the same principles as noted above and involves preliminary extensive blood testing for allergies to hormones and the subsequent administration of small doses of hormones suspected of causing the allergic symptoms. There have been no well-controlled studies that have shown this procedure to be effective in the diagnosis and treatment of symptoms thought to be caused by allergy to hormones.

Both the ACP and the American Academy of Allergy and Immunology (AAAI) consider provocation-neutralization therapy an unproven modality. In a Training Program Directors' Committee Report on Controversial Practices published by the AAAI, provocation-neutralization testing and neutralization therapy are listed as unproven. The AMA's Council on Scientific Affairs, based on the reports in the peer-reviewed scientific literature, stated that there are no well-controlled studies establishing a clear mechanism or cause for multiple chemical sensitivity syndrome. More importantly, there are no well-controlled studies that have demonstrated either diagnostic or therapeutic value for provocation-neutralization therapy.

Provocation-neutralization must not be confused with the recognized forms of target-organ challenge testing (bronchial, ingestion, patch testing), which are covered modalities.

B. In-Vitro Testing

**RAST/MAST/PRIST/RIST/FAST/MRT/VAST/ELISA/ImmunoCAP**

For most allergens, in-vitro allergen - specific immunoassays detect IgE antibody in the serum of most but not all patients who respond clinically to those allergens. The National Asthma Education Program Expert Panel Report (2007) recommends the use of skin testing or in vitro IgE antibody testing to determine the presence of specific IgE antibodies to the allergens to which the patient is exposed. The Expert Panel concluded that allergy skin or in vitro IgE antibody tests are reliable in determining the presence of specific IgE. The Expert Panel Report stated that either skin tests or in vitro IgE antibody tests can be used to assess specific IgE sensitization to *Aspergillus* in persons suspected of having allergic bronchopulmonary aspergillosis.

C. According to the National Asthma Education and Prevention Program *Guidelines for the Diagnosis and Management of Asthma*, advantages of RAST and other in vitro tests over skin tests include the fact that they do not require knowledge of skin testing technique, they do not require availability of allergen extracts, they can be performed on patients who are taking medications that suppress the immediate skin test (e.g., antihistamines, antidepressants), they
carry no risk of systemic reactions, and they can be done on patients with extensive eczema. Despite the advantages, there are 2 major concerns limiting the use of in-vitro tests for allergen-specific IgE in the United States (U.S.). The first limitation is the rather consistent finding that in-vitro tests are not as sensitive as skin tests for detecting allergen-specific IgE. The second limitation is that on a per test basis skin tests have lower time and reagent costs. Other advantages of skin tests are that they are faster (results are available within an hour), and the results are visible to the patient (this may enhance patient compliance).

A variety of modifications have been made to tests related to RAST (such as MAST, PRIST, RIST, FAST, MRT, VAST, ELISA, and ImmunoCAP).

ImmunoCAP (Pharmacia Diagnostics, Clayton, N.C.) is an in vitro-specific immunoglobulin E test that uses a three-dimensional cellulose solid allergen phase; by contrast, the older modified Phadezym-Rast (Pharmacia Diagnostics) uses a 2-dimensional solid phase. The ImmunoCAP provides more rapid results (available in 6 hours) compared to traditional RAST tests (Phadezym-RAST results take 3 days to obtain). With the ImmunoCAP, solid-phase bound allergens are allowed to react with IgE antibodies in the sample; the IgE antibodies are detected by labeled anti-IgE. To minimize handling and increase safety, the system includes instrumentation and computer software that handles the technical manipulations, the measurements and the data management. The assay is calibrated against the WHO standard for IgE and includes 2 sets of calibrators, 1 for specific IgE Ab and low-range total IgE, and the other for wide-range total IgE. Results from published studies report the overall sensitivity and specificity of different allergens compared to expert clinical diagnosis range from 78 to 94 % and 77 to 94 %, respectively.

**Total Serum IgE**

An elevated serum IgE level is one of the diagnostic criteria of allergic bronchopulmonary aspergillosis (ABPA). IgE levels can be used to follow the course of the disease. Serum IgE levels will fall when the disease is successfully treated with corticosteroids; rising IgE levels indicate disease exacerbations.

Total serum level of IgE is correlated with allergic disease in only a general way. Elevated levels are associated with the presence of allergy, while normal levels are not. However there are many individuals with clinical symptoms and allergen-specific IgE who have serum IgE levels within the normal range. Because of this, routine measurement of serum IgE is not a useful screening test for allergy.

**IgG RAST/ELISA Testing**
There is no evidence that IgG antibodies are responsible for delayed allergic symptoms or intolerance to foods. In their Choosing Wisely Campaign, the American Academy of Allergy, Asthma and Immunology recommends against immunoglobulin G (IgG) testing in the evaluation of allergy. The American Academy of Allergy, Asthma & Immunology (AAAAI) states that appropriate diagnosis and treatment of allergies requires specific IgE testing (either skin or blood tests) based on the patient's clinical history.

ALCAT

ALCAT food allergy testing utilizes an indirect method of measuring mediator releases and the effects of other pathogenic mechanisms of allergy and delayed hypersensitivity. It employs semi-automated Coulter Electronics and fully automated computer analysis. This automated testing has not been validated and has not been established as a useful allergy test in clinical practice.

Cytotoxic Testing (Bryans Test)

Cytotoxic testing is based on the theory that the addition of a specific allergen to either whole blood or a serum leukocyte suspension from a suspected allergic patient will result in reduction of the white blood cell count or death of the leukocytes, thereby indicating the presence of an immune response. Controlled studies have failed to substantiate the value of cytotoxic testing for the diagnosis of allergies, whether they are airborne, foods, or chemicals.

ELISA/ACT

ELISA/ACT tests lymphocytes in a laboratory culture for their reaction to up to 300 purified foods, preservatives, chemicals and minerals. The test is offered by Serammune Physicians Laboratory. This test is not FDA approved and is not established as a useful test in clinical practice.

Food Immune Complex Assays (FICA)

FICA are based on the standard solid phase radioimmunoassay methodology. These assays have not yet been subjected to rigorous study of potential false-negative and false-positive results. Clinical studies to date indicate that circulating immune complexes can be found in a normal population of people having no food allergy. The value of the measurement of FICA toward the diagnosis of food allergy remains unproven and does not have a place in current clinical practice.

Rebuck Skin Window Test

Rebuck skin window test is an immunologic test in which the skin is abraded with a scalpel. Laboratory cover slips are placed over the abraded areas for 24 hours. The cover slips are then stained and
analyzed. An immune deficiency may be present if there is an abnormality of monocytes displayed either by their absence or their inability to migrate to intracellular sites of antigen within 12 hours. This test is not useful in documenting allergies since other immunodeficiencies can be found in patients with allergic conditions.

**Leukocyte Histamine Release Test**

The leukocyte histamine release test is a measurement of the amount of histamine released in-vitro. Varying concentrations of an allergen extract are added to the patient's peripheral blood leukocytes. Histamine is normally released as a consequence of the interaction of allergen with cell-bound IgE antibodies. If an individual is atopic to a specific antigen, the leukocytes will not release the histamine in-vitro. Only a limited number of allergens can be tested from a single aliquot of blood and quality control studies have shown considerable variability in the measurement of histamine results.

**Mediator Release Test**

The mediator release test (MRT) (Signet Diagnostic Corporation) has primarily been used to detect intolerance to foods and additives in patients with irritable bowel syndrome. The MRT measures the aggregate release of inflammatory mediators from the patient's immunocytes in vitro after exposure to specific foods and food additives. The results of the mediator release test have been used to design a patient-specific diet to treat IBS by avoiding foods and additives that trigger significant inflammatory mediator release. For the mediator release test, the patient's blood sample is incubated with various extracts of foods and food additives and then analyzed for the presence and aggregate amount of release of inflammatory mediators from the patient's leukocytes. Results are compared to control samples of the patient's blood that have not been exposed to food extracts or additives. The MRT-directed patient-specific diet is one component of the Lifestyle Eating and Performance (LEAP) Disease Management Program (Don Self & Associates, Inc., Whitehouse, TX). The LEAP program is based on the theory that symptoms 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. However, there is no evidence in the peer-reviewed published medical literature to substantiate these claims.

The mediator release test has also been promoted for use in patients with chronic fatigue syndrome, metabolic conditions (e.g., diabetes, obesity), gastrointestinal disorders (e.g., gastroesophageal reflux disease, chronic ulcerative colitis, and Crohn's disease),
neurologic disorders (e.g., migraine headaches, cluster headaches), rheumatologic disorders (inflammatory arthritis, arthralgias, fibromyalgia), otolaryngologic disorders (e.g., perennial rhinitis, chronic sinusitis, chronic otitis media with effusion), dermatologic conditions (e.g., eczema, urticaria, dermatitis), and in patients with behavioral conditions (e.g., attention deficit disorder, hyperactivity, frequent mood swings, inability to concentrate). There are, however, no studies of the mediator release test reported in the peer-reviewed published medical literature that demonstrate improvements in clinical outcomes by incorporating the mediator release test and associated dietary modifications into the clinical management of patients with these conditions. Thus, the mediator release test is considered experimental and investigational.

**Eosinophil Cationic Protein**

Eosinophil cationic protein (ECP) is an eosinophil-specific mediator that can be measured in bodily fluids to estimate the extent of eosinophil activation, although it provides no information about the presence of IgE-mediated allergy. This test requires further characterization before it can be recommended for routine clinical use.

**Anti-IgE and Anti-Fc Epsilon Receptor Antibodies**

Anti-Fc epsilon receptor antibodies are natural antibodies against the alpha chain of the high-affinity receptor for IgE. Guidelines on urticaria from the British Association of Dermatologists (Grattan et al, 2007) stated that the presence of anti-Fc epsilon receptor antibodies indicates an autoimmune urticaria, but make no recommendation for testing for anti-Fc epsilon antibody in the work-up of patients with urticaria. Saini (2010) stated that tests used in investigations of pathogenesis of chronic urticaria include the autologous serum and plasma skin tests, assays for autoantibodies directed against IgE or the FcepsilonRI receptor, and in vitro assessments of basophil function. However, these tests lack specificity and prognostic value for chronic urticaria, are not standardized, and can not be recommended for routine clinical use.

**Clifford Materials Reactivity Testing**

According to Clifford Consulting Research Laboratories, Clifford materials reactivity testing (CMRT) is a laboratory screening process used to help identify sensitivity to various chemicals and compounds used in dental, orthopedic, or surgical implants, in order to select a product to which the patient exhibits the least sensitivity. The laboratory states that they report on more than 11,300 trade-named dental products and 94 chemical groups and families. They state that they have also added an Orthopedic panel reporting on over 4,000 trade-named products for surgical applications. However, there is a lack of peer-reviewed published evidence of the clinical effectiveness of CMRT.
Complement Antigen Test

Complement Antigen Testing (Sage Medical Laboratories) has been used to identify delayed food allergies. However, there is insufficient evidence in the peer-reviewed published medical literature for this approach.

Allergy Immunotherapy

The treatment of allergy is approached 3 ways: (i) avoidance therapy, (ii) pharmacologic therapy, and (iii) immunotherapy. Complete avoidance of the known allergen responsible for inducing the signs and symptoms of the allergy is the most effective treatment for any allergic condition and results in a cure. When avoidance of a specific allergen such as house dust, molds or pollens is impossible, pharmacologic therapy is used (e.g., antihistamines, adrenergic agonists, anticholinergics, beta-adrenergic agonists, corticosteroids, cromolyn sodium and methylxanthines). It has been advocated that the utilization of air cleaners, humidifiers, or dehumidifiers is helpful in reducing allergic irritant substances in the environment; however, research indicates that the use of these mechanical devices was ineffective in reducing clinical symptoms.

Allergy immunotherapy (also known as desensitization, hyposensitization, allergy injection therapy, or "allergy shots"), is indicated in patients whose triggering allergens are not readily avoidable, the allergy is IgE-mediated as documented by skin testing or RAST, the symptoms are not easily controlled with medication, the symptoms encompass more than one season and the patients are likely to cooperate in the program. The severity, duration and frequency of episodes should be explored. Patients with life-threatening allergy (severe anaphylactic reaction) to hymenoptera (venom from bees, hornets, wasps or fire ants) have been shown to respond well to allergy immunotherapy, as well as patients with severe seasonal allergic rhinitis or conjunctivitis, perennial allergic rhinitis, allergic (extrinsic) asthma and mold induced allergic rhinitis. Allergy immunotherapy will help desensitize the patient to the effects of the allergen. The documented allergy should correspond to the allergen planned for immunotherapy. A trial of systemic medications or avoidance of the allergens should be attempted. Two or more medications (antihistamines, steroids, bronchodilators, intranasal cromolyn) if not contraindicated should have been prescribed during the past year or the patient should be currently receiving immunotherapy.

Allergy immunotherapy is defined as the repeated administration of specific allergens to patients with IgE-mediated conditions, for the purpose of providing protection against the allergic symptoms and inflammatory reactions associated with natural exposure to these
allergens. The exact mechanism of action is not known but may involve an increase in allergen-specific IgG antibodies, a decrease in IgE synthesis, and alteration in T-lymphocyte activity. The principal and most effective route of allergen application is by subcutaneous injection. Oral/sublingual application of allergen extracts is discussed controversially in the literature (see provocation-neutralization therapy). There is a great assortment of different allergen extracts available, but only standardized extracts should be used. In the United States, the Food and Drug Administration (FDA) determined that the intracutaneous technique should be used for assigning standardized unitage (i.e., bioequivalency allergy units [BAU]). Patients with allergic rhinitis and/or asthma from tree and grass pollens in the spring, ragweed pollen in the fall and year-round dust-mite sensitivity who have had inadequate response to acceptable symptomatic medication and allergen avoidance are excellent candidates for immunotherapy. Immunotherapy is recommended for patients with allergic asthma unresponsive to allergen avoidance, even when symptomatic relief can be achieved with drug therapy. Treatment plans vary, but generally follow an initial dosing of short intervals (2 to 7 days) and should be increased 1.5 to 2 times with each injection if no reaction occurs. This dosing is followed by a maintenance dosage regimen at 3- or 4-week intervals and is determined by patient tolerance and relief of symptoms. Length of therapy varies from 3 to 5 years. The progress of the patient should be reviewed at regular intervals by the physician. Progressive improvement may be observed over the first 2 to 3 years of treatment. Discontinuation of therapy may be considered any time after a 2 to 3 year trial. The risk of relapse must be weighed against patient preference for continuation of therapy. Examples of potential allergens for which immunotherapy is effective include: animal dander, animal feathers, animal fur, dust, grasses, insects, mites, molds, mushrooms, orris root, plants, pyrethrum, seeds, trees, vegetable gums, weeds, hymenoptera or stinging insects (bees, hornets, wasps, fire ants).

According to guidelines from the American Academy of Asthma, Allergy and Immunotherapy (Cox, et al., 2011), allergen immunotherapy should be administered in a medical facility with trained staff and medical equipment capable of recognizing and treating anaphylaxis. Under rare circumstances, when the benefit of allergen immunotherapy clearly outweighs the risk of withholding immunotherapy (e.g., patients with a history of venom-induced anaphylaxis living in a remote region), at-home administration of allergen immunotherapy can be considered on an individual basis. There are a limited number of studies of home-based allergy immunotherapy. The largest is a prospective study by Hurst, et al. (1999). During a 1-year period, 27 otolaryngic allergy practices recorded all systemic reactions to immunotherapy resulting from
635,600 patient visits and 1,144,000 injections. Sixty percent of injections were given at home. Major systemic reactions were observed after 0.005% of injections. There were no hospitalizations or deaths. Eighty-seven percent of major reactions began within 20 minutes of injection. Frequently observed risk factors for major reactions were buildup phase of immunotherapy, active asthma, and first injection from a treatment vial. The authors reported that home and office injections had similar rates of total systemic reactions, but home-based immunotherapy had far fewer major reactions. A major limitation of the study is that it was limited to otolaryngic allergy practices; the generalizability of the results to primary care practices is uncertain.

There is no evidence that immunotherapy is beneficial for food allergy, migraine headaches, vasomotor rhinitis, intrinsic (non-allergic) asthma, or chronic urticaria. In addition, there is little evidence that immunotherapy benefits atopic dermatitis and angioedema. 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.

A structured evidence-based assessment of sublingual immunotherapy for adults conducted by the BlueCross BlueShield Association Technology Evaluation Center (2003) concluded that “[w]ether [sublingual immunotherapy] improves health outcomes when compared with injection [allergen-specific immunotherapy] has not yet been demonstrated in the investigational setting. It is uncertain whether FDA-licensed allergen preparations manufactured for allergy testing and injection [allergen-specific immunotherapy] are suitable for sublingual administration. Based on the above, use of sublingual immunotherapy for patients with allergies does not meet the TEC criteria.”

Cox and colleagues (2006) stated that sublingual immunotherapy (SLIT) has been utilized with increasing frequency in Europe and is viewed with increasing interest by allergists in the United States. To address this interest, a Joint Task Force of the American College of Allergy, Asthma and Immunology and the American Academy of Allergy, Asthma and Immunology's Immunotherapy and Allergy Diagnostic Committees evaluated the evidence on the effectiveness of SLIT. The task force concluded that despite clear evidence that SLIT is an effective treatment, there are still many unanswered questions, including effective dosage, treatment schedules, and overall duration of treatment. Until these questions have been answered, an assessment of the cost/benefit ratio of the treatment cannot be made. Sublingual immunotherapy does seem to be associated with few severe side effects, but it has not been used in high-risk asthmatic patients, nor in the studies reviewed has it been
used as a mixture of non-cross-reacting allergens. Furthermore, there is currently no allergy extract approved for this use in the United States, nor is there a Current Procedural Terminology code for billing purposes. All of these factors should be considered before contemplating initiation of SLIT treatment for allergic patients.

Nelson (2009) reviewed the literature on allergen immunotherapy for studies simultaneously using 2 or more distinct allergen extracts in either subcutaneous or sublingual immunotherapy. A total of 13 studies were identified, subcutaneous injections (n = 11), sublingual administration (n = 1), and both (n = 1). In studies with adequate information, administration of 2 extracts by means of either subcutaneous immunotherapy or sublingual immunotherapy was effective. In studies using multiple allergens, 3 studies showed clear efficacy, whereas in the other 2 studies, lack of efficacy might have been due to inadequate doses of extract or omission of clinically relevant allergens in the treatment regimen. The author concluded that simultaneous administration of more than 1 allergen extract is clinically effective. However, more studies are needed, particularly with more than 2 allergen extracts and with sublingual administration.

Hoeks et al (2008) examined the evidence of the safety and effectiveness of SLIT as a curative therapy for allergies in children. All randomized, double-blind and placebo-controlled studies (DBRPCT’s) on SLIT in asthma or rhinoconjunctivitis in children were selected from Medline, Embase and Cochrane Central Register of Controlled Trials. Also references of the found articles were used. The selected studies were assessed for quality and the different outcomes were evaluated. A total of 13 DBRPCT’s on SLIT in children were selected, 5 studies on children with house dust mite allergy and 8 studies on children with grass pollen allergy. There was considerable heterogeneity among the different studies with respect to the choice and definition of outcome criteria. The quality of the included studies was moderate. After treatment with SLIT, especially reported symptoms decreased without improvement of objective parameters. Positive results originated especially from significant differences within the intervention group before and after treatment. These investigators concluded that it was impossible to substantiate the claim of authors of the studies regarding the favorable effects of SLIT in children with asthma or rhinoconjunctivitis, since all studies had serious methodological flaws. However, the studies showed that SLIT seems to be safe in children in the doses applied. This is in agreement with the findings of Roder et al (2008) who reported that there is currently insufficient evidence that immunotherapy in any administration form has a positive effect on symptoms and/or medication use in children and adolescents with allergic rhinoconjunctivitis.

In a randomized, double-blind, placebo-controlled study, Severino et
al (2008) evaluated if SLIT might potentially be beneficial in hymenoptera (honeybee) allergy. The sting challenge in large local reactions (LLRs) was used to test this hypothesis. After the baseline sting challenge, subjects were randomized to either SLIT or placebo for 6 months. The treatment involved a 6-week build-up period, followed by maintenance with 525 microg of venom monthly. The sting challenge was repeated after 6 months. A total of 30 patients (18 males; mean age of 44.5 years) were enrolled, and 26 completed the study, with 1 dropout in the active group and 3 dropouts in the placebo group. In the active group the median of the peak maximal diameter of the LLRs decreased from 20.5 to 8.5 cm (p = 0.014), whereas no change was seen in the placebo group (23.0 versus 20.5 cm, p = not significant). The diameter was reduced more than 50 % in 57 % of patients. One case of generalized urticaria occurred in a placebo-treated patient at sting challenge. No adverse event caused by SLIT was reported. The authors concluded that honeybee SLIT significantly reduced the extent of LLRs, and its safety profile was good. Although LLRs are not an indication for immunotherapy, this proof-of-concept study suggested that SLIT in hymenoptera allergy deserves further investigation. Trials involving systemic reactions and dose-ranging studies are needed.

Skoner and colleagues (2010) examined the maintenance dose range of sublingual standardized glycerinated short ragweed pollen extract in adults with ragweed-induced rhinoconjunctivitis. A total of 115 patients with ragweed-induced rhino-conjunctivitis were randomly allocated to placebo (n = 40), medium-dose extract (4.8 microg Amb a 1/d; n = 39), or high-dose extract (48 microg Amb a 1/d; n = 36). In a 1-day (rush) dose-escalation regimen, ragweed pollen extract was administered sublingually in incremental doses until maximum tolerable or scheduled dose was reached and then maintained during the ragweed pollen season. Patient diaries were used to monitor nasal and ocular symptoms and medication. The primary endpoint was symptom score. Both active treatment groups achieved a 15 % reduction in total rhino-conjunctivitis symptom scores compared with placebo during the entire ragweed pollen season, but the difference was not statistically significant (p > 0.10). However, in an analysis of co-variance correcting for pre-seasonal symptoms, both mean daily symptom scores (0.19 +/- 1.16 versus 1.00 +/- 2.30) and medication scores (0.0003 +/- 0.63 +/- 1.06) for the entire pollen season were significantly reduced in the high-dose versus placebo groups, respectively (p < or = 0.05). Ragweed-specific IgG, IgG(4), and IgA antibodies were increased after treatment in the medium- and high-dose groups and not the placebo group. Frequency of adverse events was similar between the placebo and treatment groups, but oral-mucosal adverse events occurred more often with treatment. The authors concluded that standardized glycerinated short ragweed pollen extract administered sublingually at maintenance doses of 4.8 to 48 microg Amb a 1/d
was safe and can induce favorable clinical and immunologic changes in ragweed-sensitive subjects. However, the authors noted that additional trials are needed to establish efficacy.

Sieber et al (2010) compared the effectiveness of perennial and co-seasonal high-dose SLIT treatments as well as ultra-rush and classical titrations in a real-world setting for pollen allergens. An individual patient data (IPD) meta-analysis was performed of 3 open, prospective observational studies on high-dose SLIT using IR-standardized allergen extracts in patients with allergic rhinitis with and without asthma. A total of 1,052 patients aged 24.9 years (mean) were treated with SLIT and included in this IPD meta-analysis. Individual studies and total data pool analyses revealed consistent improvements in rhino-conjunctivitis symptom scores. Stratified analyses revealed consistent improvements in symptomatic score and medication score regardless of the type of sensitization and type of treatment. Ultra-rush titration resulted in considerably more pronounced improvement in symptom scores than classical titration, possibly due to better compliance of patients receiving that supervised titration. Adverse events occurred in 24% of patients during titration and in 18% of patients during maintenance treatment. The vast majority of events (89% and 87%) were mild-to-moderate, predominantly local symptoms in the oral cavity. There were no differences detected between the study titration or treatment schedules. No serious adverse reactions were reported. Nearly all patients (88%) decided to continue SLIT after completion of the studies. High-dose SLIT with seasonal allergens given as co-seasonal or perennial treatment appears to be effective and well-tolerated in daily medical practice. Improved compliance under ultra-rush titration and seasonal SLIT treatment may further enhance effectiveness. The authors stated that randomized controlled trials are needed for the further evaluation of these findings.

Lin and colleagues (2013) systematically reviewed the safety and effectiveness of aqueous sublingual immunotherapy for allergic rhino-conjunctivitis and asthma. The databases of MEDLINE, EMBASE, LILACS, and the Cochrane Central Register of Controlled Trials were searched through December 22, 2012. English-language RCTs were included if they compared sublingual immunotherapy with placebo, pharmacotherapy, or other sublingual immunotherapy regimens and reported clinical outcomes. Studies of sublingual immunotherapy that are unavailable in the U.S. and for which a related immunotherapy is unavailable in the U.S. were excluded. Paired reviewers selected articles and extracted the data. The strength of the evidence for each comparison and outcome was graded based on the risk of bias (scored on allocation, concealment of intervention, incomplete data, sponsor company involvement, and other bias), consistency, magnitude of effect, and the directness of the evidence. A total of 63 studies with 5,131 participants met the
inclusion criteria. Participants’ ages ranged from 4 to 74 years; 20 studies \( (n = 1,814 \text{ patients}) \) enrolled only children. The risk of bias was medium in 43 studies (68 %). Strong evidence supports that sublingual immunotherapy improves asthma symptoms, with 8 of 13 studies reporting greater than 40 % improvement versus the comparator. Moderate evidence supports that sublingual immunotherapy use decreases rhinitis or rhino-conjunctivitis symptoms, with 9 of 36 studies demonstrating greater than 40 % improvement versus the comparator. Medication use for asthma and allergies decreased by more than 40 % in 16 of 41 studies of sublingual immunotherapy with moderate grade evidence. Moderate evidence supports that sublingual immunotherapy improves conjunctivitis symptoms (13 studies), combined symptom and medication scores (20 studies), and disease-specific quality of life (8 studies). Local reactions were frequent, but anaphylaxis was not reported. The authors concluded that the overall evidence provided a moderate grade level of evidence to support the effectiveness of sublingual immunotherapy for the treatment of allergic rhinitis and asthma, but high-quality studies are still needed to answer questions regarding optimal dosing strategies. There were limitations in the standardization of adverse events reporting, but no life-threatening adverse events were noted in this review.

In an editorial that accompanied the afore-mentioned study, Nelson (2013) stated that “[A]lthough patients may prefer a therapy that is relatively safe and can be administered at home, FDA approval has not been granted yet, and many unanswered questions remain about the use of sublingual immunotherapy”.

D. The National Institute of Allergy and Infectious Diseases’ guidelines for the diagnosis and management of food allergy (Boyce et al, 2010) stated that (i) the expert panel does not recommend using allergen-specific immunotherapy to treat IgE-mediated food allergy (Rationale: Allergen-specific immunotherapy improves clinical symptoms of FA while on treatment. However, it is currently difficult to draw conclusions on the safety of such an approach and whether clinical tolerance [i.e., improvement in clinical symptoms that persists even after allergen-specific immunotherapy is discontinued] will develop with long-term treatment). Allergen-specific immunotherapy can improve clinical symptoms of food allergy for some patients. However, additional safety and efficacy data are needed before such treatment can be recommended. Because of the risk of severe reactions, the approach should only be used in highly controlled settings, and (ii) the expert panel does not recommend immunotherapy with cross-reactive allergens for treating IgE-mediated food allergy (Rationale: Although some evidence exists to suggest that specific immunotherapy with cross-reactive allergens is beneficial in treating food allergy, additional safety and efficacy data are needed before such treatment can be recommended). It has been hypothesized that immunotherapy with cross-reactive antigens could benefit patients with food allergy, yet the safety of this
approach has been evaluated in a highly controlled setting in only 1 study to date. Replication of these findings with additional safety and efficacy data in clinical practice settings is needed.

de Bot et al (2011) evaluated the quality of systematic reviews and meta-analyses of SLIT for allergic rhinitis in children, published since 2000. Eligible reviews were identified by searching Medline/PubMed, Embase, and the Cochrane Library, from 2000 through 2008. Methodological quality was assessed using the assessment of multiple systematic reviews instrument. A total of 10 systematic reviews were included, 1 of which was published in the Cochrane Library. Eight reviews gave some details about the search strategy. None of the reviews included measures to avoid selection bias. In 60 % of the reviews, the methodological quality of the included studies was (partly) assessed. Four reviews pooled the results of individual studies, neglecting clinical heterogeneity. Three of the 10 reviews provided information about sources of funding or grants from industry. Of the 10 reviews, the 6 reviews with the highest overall score scored 5 to 8 points, indicating moderate quality. The authors concluded that systematic reviews are useful to evaluate the efficacy of SLIT in children. Although more reviews have become available, the methodological quality could be improved.

They stated that SLIT for children could be promising, but methodological flaws in the reviews and individual studies are too serious to draw definite conclusions.

In a Cochrane review, Calderon et al (2011) evaluated the effectiveness of SLIT compared with placebo for reductions in ocular symptoms, topical ocular medication requirements and conjunctival immediate allergen sensitivity. These investigators searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (The Cochrane Library 2011, Issue 1), MEDLINE (January 1950 to January 2011), EMBASE (January 1980 to January 2011), Latin American and Caribbean Literature on Health Sciences (LILACS) (January 1982 to January 2011), Web of Science (January 1970 to January 2011), Biosis Previevs, (January 1979 to January 2011), the metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com) (January 2011), ClinicalTrials.gov (www.clinicaltrials.gov) (January 2011), the Australian New Zealand Clinical Trials Registry (ANZCTR) (www.actr.org.au) (July 2010), SCOPUS (November 2008) and the UK Clinical Trials Gateway (January 2010). There were no language or date restrictions in the search for trials. All electronic databases except for SCOPUS, the UK Clinical Trials Gateway and ANZCTR were last searched on 19 January 2011. Randomized controlled trials (RCTs), double-masked and placebo controlled, which evaluated the efficacy of SLIT in patients with symptoms of allergic rhino-conjunctivitis (ARC) or allergic conjunctivitis (AC) were included in this analysis. The primary outcome was the total ocular symptom scores. Secondary
endpoints included individual ocular symptom scores (such as itchy eyes, red eyes, watery eyes, swollen eyes), ocular medication scores (eye drops) and conjunctival immediate allergen sensitivity (CIAS). Data were analyzed and reported as standardized mean differences (SMDs) using Review Manager software. A total of 42 trials (n = 3,958 total participants; n = 2,011 SLIT and n = 1,947 placebo) had available data to evaluate the efficacy of SLIT on AC and were included in the meta-analyses. Heterogeneity among studies (I(2) statistic) was around 50 % or below for all endpoints. Sublingual immunotherapy induced a significant reduction in both total ocular symptom scores (SMD -0.41; 95 % confidence interval [CI]: -0.53 to -0.28; p < 0.00001; I(2) = 59%) and individual ocular symptom scores for red eyes (SMD -0.33; 95 % CI: -0.45 to -0.22; p < 0.00001; I(2) = 27 %), itchy eyes (SMD -0.31; 95 % CI: -0.42 to -0.20; p < 0.00001; I(2) = 46 %) and watery eyes (SMD -0.23; 95 % CI: -0.34 to -0.11; p < 0.0001; I(2) = 42 %) compared to placebo. Those participants having active treatment showed an increase in the threshold dose for the conjunctival allergen provocation test (SMD 0.35; 95 % CI: 0.00 to 0.69; p = 0.05; I(2) = 43 %). No significant reduction was observed in ocular eye drops use (SMD -0.10; 95 % CI: -0.22 to 0.03; p = 0.13; I(2) = 34 %). The authors concluded that overall, SLIT is moderately effective in reducing total and individual ocular symptom scores in participants with ARC and AC. There were however some concerns about the overall quality of the evidence-base, this relating to inadequate descriptions of allocation concealment in some studies, statistical heterogeneity and the possibility of publication bias. They stated that there is a need for further large rigorously designed studies that examine long-term effectiveness after discontinuation of treatment and establish the cost-effectiveness of SLIT.

Allergoids

Allergoids are formalin treated allergens which have been shown to be as effective as conventional aqueous extracts and superior to placebo in terms of reduction of symptom medication scores, production of an increase in ragweed IgG levels, and a decrease in seasonal rise in ragweed IgE levels. Allergoids are licensed and manufactured for general distribution in Europe, but not yet in the United States.

Enzyme Potentiated Desensitization (EPD)

Enzyme potentiated desensitization is patented in Europe under the brand name of Epidyme. This immunotherapy consists of a mixture of allergens to molds, grass, weeds, trees, dust mites, dog and cat dander, and house dust. These allergens are administered in the doctor’s office. While this is common practice in Europe, it is not on the United States market or regulated/approved by the U.S. FDA. The FDA has banned importation of EPD. There is a lack of clinical
trials supporting the efficacy of this product.

A variant of enzyme potentiated desensitization is ultra low dose enzyme activated immunotherapy (also known as low dose allergens or LDA), which has been described as a method of immunotherapy enhanced by a minute dose of the enzyme, beta glucuronidase. According to proponents, the beta glucuronidase activates extremely miniscule doses of various allergens and stimulates the production of T-suppressor cells. The T-suppressor cells, in turn, down regulate the T-helper cells that are causing allergic symptoms by misidentifying normal substances in the body as allergens. LDA uses the same active components as EPD, but utilizes more more pollens, foods and other allergens.

**Photo-Inactivation**

Photo-inactivation of an antigen with ultraviolet may allow larger doses of antigen to be administered with fewer adverse effects. Currently, these preparations are used for research purposes only and not in clinical practice.

**Polymerized Ragweed Extract**

Polymerized ragweed extract has been employed for treatment of ragweed hay fever in placebo-controlled trials and has been shown to produce a significant decrease in symptoms and medication scores. However, polymerized ragweed extracts have not yet been licensed or manufactured for general distribution in the United States.

**Rhinophototherapy**

Phototherapy has a profound immunosuppressive effect and is able to inhibit hypersensitive reactions in the skin. Leimgruber (2006) stated that phototherapy applied inside the nose (rhinophototherapy) is among new therapeutic options being developed for allergic rhinitis to counteract its impact on quality of life and health costs. The author noted that the immunosuppressive effect of phototherapy has been tested in nasal mucosa. This application has shown anti-inflammatory results in nasal cleaning fluid and, consequently, may reduce allergic rhinitis. The author noted that long-term studies involving large cohorts of patients are needed if rhinophototherapy is going to be prescribed without restrictions.

In a randomized, double-blind study (n = 49), Koreck et al (2005) examined if phototherapy using a combination of UVB (5 %), UVA (25 %), and visible light (70 %), referred to as mUV/VIS (rhinophototherapy), is effective in treating allergic rhinitis. The study was carried out during the ragweed season. Each intra-nasal cavity was illuminated 3 times a week for 3 weeks with mUV/VIS or
with low-intensity visible light (control group). Symptom scores, inflammatory cells, and their mediators were assessed in nasal lavages. In vitro effects of mUV/VIS irradiation on T-cell and eosinophil apoptosis, and its inhibitory effect on mediator release from basophils were examined. Rhinophototherapy was well-tolerated, and resulted in a significant improvement of clinical symptoms for sneezing (p < 0.016), rhinorrhea (p < 0.007), nasal itching (p < 0.014), and total nasal score (p < 0.004). None of the scores improved significantly in the control group. The investigators reported that scores for nasal obstruction slightly improved after rhinophototherapy and significantly increased in the control group (p < 0.017). In the nasal lavage, rhinophototherapy significantly reduced the number of eosinophils and the level of eosinophil cationic protein and IL-5. In vitro irradiation of T-cells and eosinophils with rhinophototherapy dose-dependently induced apoptosis. In addition, rhinophototherapy inhibited the mediator release from RBL-2H3 basophils. These promising results would need to be replicated in a larger clinical trial with longer-term follow-up.

The Helminth Trichuris Suis Therapy

In a double-blind, placebo-controlled, parallel group study, Bager et al (2010) ascertained the effectiveness of helminth Trichuris suis therapy for the treatment of allergic rhinitis. A total of 100 subjects aged 18 to 65 years with grass pollen-induced allergic rhinitis were randomly assigned to ingest a total of 8 doses with 2,500 live Trichuris suis ova or placebo with an interval of 21 days. The primary outcome was a change in mean daily total symptom score for runny, itchy, sneezing nose (maximum change, 9.0) or in percentage of well days during the grass pollen season. Treatment with Trichuris suis ova (n = 49) compared with placebo (n = 47) caused transient diarrhea peaking at day 41 in 33 % of participants (placebo, 2 %), and increased eosinophil counts (p < 0.001) and Trichuris suis-specific IgE (p < 0.05), IgG (p < 0.001), IgG(4) (p < 0.003), and IgA (p < 0.001), whereas there was no significant change in symptom scores (0.0; 95 % confidence interval [CI]: -0.5 to 0.4; p = 0.87), well days (3 %; 95 % CI: -9 % to 14 %; p = 0.63), total histamine (p = 0.44), grass-specific IgE (p = 0.76), or diameter of wheal reaction on skin prick testing with grass (p = 0.85) or 9 other allergens. The authors concluded that repeated treatment with the helminth Trichuris suis induced a substantial clinical and immunologic response as evidence of infection, but had no therapeutic effect on allergic rhinitis.

II. Urine Auto-Injection

The practice of injection of an extract of the patient's own urine for diagnosis and treatment of allergy is clearly unacceptable and must be discouraged. It is not based on rational theory, and there have been no
scientific investigations of efficacy and safety. There is a potential danger for autoimmune nephritis with this procedure.

III. Multiple Chemical Sensitivity Syndrome

Multiple chemical sensitivity (MCS) (also known as idiopathic environmental intolerance (IEI), clinical ecological illness, clinical ecology, environmental illness, chemical AIDS, environmental/chemical hypersensitivity disease, total allergy syndrome, cerebral allergy, 20th century disease) has been used to describe a condition whereby an individual becomes chronically ill from exposure to chemicals in foods and the environment at doses far below the levels normally considered safe. Resulting “allergies” to these chemicals have been postulated to cause a number of troubling symptoms (e.g., fatigue, irritability, behavior problems, depression, confusion, and nervous tension in children) in the absence of objective physical findings. The existence of such a syndrome has been based on anecdotal reports and uncontrolled studies. Several well-designed investigations suggest that most people diagnosed with MCS have a medical or psychosomatic disorder that they can not accept, preferring instead to interpret their symptoms as environmental sensitivities. If this is true, the diagnosis of MCS may delay proper medical and psychiatric care.

The theories and practices involving environmental allergies of this type have been severely criticized by the American Medical Association, the American College of Physicians, the Canadian Psychiatric Association, the International Society of Regulatory Toxicology and Pharmacology, the American Academy of Allergy, Asthma and Immunology (AAAAI), and several scientific panels that have investigated them. Based on the reports in the peer-reviewed scientific literature, the American Medical Association's Council on Scientific Affairs stated that “there are no well controlled studies establishing a clear mechanism or cause for multiple chemical sensitivity syndrome.” Recently (January 1999), the AAAAI reviewed the evidence again and concluded, “Rigorously controlled studies to verify the patient's reported subjective sensitivity to specific environmental chemicals have yet to be done. Moreover, there is no evidence that these patients have any immunologic or neurologic abnormalities. In addition, no form of therapy has yet been shown to alter the patient's illness in a favorable way.”

Confinement in an environmental control unit or facility (ecology unit), which has been used as a treatment for environmental illnesses and hypersensitivities, has not been established as an effective or appropriate treatment.

IV. Electromagnetic Sensitivity Syndrome

A number of people who suffer from non-specific health symptoms (e.g., allergies, headache, fatigue, skin symptoms, anginal-like complaints, difficulties in concentrating, mood and sleep disturbances) have claimed that they are sensitive to electromagnetic waves and electromagnetic pollution from antennas, cell phones, computers, electrical appliances,
video display units, and overhead power lines, etc. The term "electromagnetic sensitivity (also known as allergy to electricity, electro-sensitivity, electrohypo-sensitivity, and hypersensitivity to electricity) has been used to describe these individuals. However, it is not an established disease. There is no reliable clinical data to support the theory that low level electromagnetic waves cause these symptoms. There are no accepted diagnostic criteria or procedures for the diagnosis and treatment of electromagnetic sensitivity. Furthermore, no direct cause-effect relationship between electromagnetic sensitivity symptoms and electromagnetic fields has been proven.

A number of controlled studies have found no effect of exposure to electromagnetic fields on symptoms or signs. Lonne-Rahm et al (2000) studied the effects of provocation with stress and electricity of patients with "sensitivity to electricity". A total of 24 patients with self-reported "sensitivity to electricity" were divided into 2 groups and tested in a double-blind provocation study. These patients, who reported increased skin symptoms when exposed to electromagnetic fields, were compared with 12 age- and sex-matched controls. Both groups were exposed to 30-min periods of high or low stress situations, with and without simultaneous exposure to electromagnetic fields from a visual display unit. The matched controls were tested twice and given the same exposure as the patients, but had the fields turned on every time. Stress was induced by requiring the participants to act in accordance with a random sequence of flashing lights while simultaneously solving complicated mathematical problems. Blood samples were analyzed for levels of the stress-related hormones melatonin, prolactin, adrenocorticotropic hormone, neuropeptide Y, and growth hormone, and the expression of different peptides, cellular markers, and cytokines (CD1, factor XIIIa, somatostatin, and tumor necrosis factor-alpha). Skin biopsies were also analyzed for the occurrence of mast cells. Stress provocation resulted in feelings of more intense mental stress and elevated heart rate. The patients reported increased skin symptoms when they knew or believed that the electromagnetic field was turned on. With the blind conditions, there were no differences between "on" or "off". Inflammatory mediators and mast cells in the skin were not affected by the stress exposure or by exposure to electromagnetic fields. The authors concluded that the patients did not react to the fields.

Flodin et al (2000) performed a provocation study in the homes or workplaces of patients with electric hypersensitivity; they also studied the symptoms and on-off answer 24 hours after the exposure. A total of 15 subjects selected as having fast and distinct reactions from electric equipment were provoked on 4 occasions: mainly 2 true and 2 sham provocations. The intervals between exposure were a few or more days in order to provide the subjects with an opportunity to recover before the next provocation. A control group of healthy subjects with normal hearing and vision verified that the provocations were performed in a blind manner. Patients suffering from "electric hypersensitivity" were no better than the control group in deciding whether or not they were exposed to electric and magnetic fields. The authors concluded that exposure to electric and
magnetic fields per se does not seem to be a sufficient cause of the symptoms experienced by this patient group.

Lyskov et al (2001) examined possible neurophysiological effects of intermittent 15 sec on/off cycle, 60 Hz, 10 microT magnetic field exposure on patients with perceived "electromagnetic hypersensitivity" (EHS), and control subjects during rest and performance of a mental arithmetic task. A total of 20 participants (15 females, 5 males, 31 to 60 years old, mean of 45.8 +/- 0.7 years) were invited from the group of EHS patients. Twenty volunteers (15 females, 5 males, 31 to 59 years old, mean of 45.0 +/- 0.7 years) served as a control group. The test protocol consisted of a set of examinations: EEG, visual evoked potentials, electrodermal activity, ECG, and blood pressure. The total duration of the test was 40 mins, divided into 2 10-min rest periods and 2 10-min periods of mathematical performance. Magnetic field and sham exposures were presented randomly during these periods, resulting in 4 different conditions: (i) Field-Rest, (ii) Sham-Rest, (iii) Field-Math, and (iv) Sham-Math. The data showed significant main effects of the group factor (EHS versus control subjects) on heart rate (F(1,80) = 20.6; p < 0.01), heart rate spectrum ratio (F(1,80) = 9.5; p = 0.02), and electrodermal activity (F(1,76) = 4.2; p = 0.04), whereas EEG characteristics did not differ between groups. The Condition factor (mathematical task versus relaxed) showed main effects for heart rate (F(1,80) = 14.8; p < 0.01), heart rate spectrum ratio (F(1,80) = 7.8; p = 0.06), electrodermal activity (F(1,76) = 56.8; p < 0.01), and alpha and theta spectral bands of EEG. Magnetic field exposure did not affect autonomous system or electroencephalographic variables of either group. These data do not indicate that EHS patients or control are affected by low-level 60 Hz magnetic field exposure. However, persons reporting EHS differed from the control subjects in baseline values of investigated physiological characteristics. Perhaps EHS patients have a rather distinctive physiological predisposition to sensitivity to physical and psychosocial environmental stressors.

In a double-blind, randomized, within participants provocation study, Rubin et al (2006) examined if people who report being sensitive to mobile phone signals have more symptoms when exposed to a pulsing mobile signal than when exposed to a sham signal or a non-pulsing signal. A total of 60 "sensitive" people who reported often getting headache-like symptoms within 20 minutes of using a global system for mobile communication (GSM) mobile phone and 60 "control" subjects who did not report any such symptoms were included in this study. Subjects were exposed to 3 conditions: (i) a 900 MHz GSM mobile phone signal, (ii) a non-pulsing carrier wave signal, and (iii) a sham condition with no signal present. Each exposure lasted for 50 mins. The principal outcome measure was headache severity assessed with a 0 to 100 visual analog scale (VAS). Other outcomes included 6 other subjective symptoms and subjects' ability to judge whether a signal was present. Headache severity increased during exposure and decreased immediately afterwards. However, no strong evidence was found of any difference between the conditions in terms of symptom severity. Nor did evidence of any differential effect of condition between the 2 groups exist. The proportion of sensitive subjects
who believed a signal was present during GSM exposure (60%) was similar to the proportion who believed one was present during sham exposure (63%). The authors concluded that no evidence was found to indicate that people with self-reported sensitivity to mobile phone signals are able to detect such signals or that they react to them with increased symptom severity. As sham exposure was sufficient to trigger severe symptoms in some participants, psychological factors may have an important role in causing this condition.

Wallace et al (2010) conducted a randomized, double-blind, provocation study to establish whether short-term exposure to a radio system used by United Kingdom police (TETRA) base station signal has an impact on the health and well-being of individuals with self-reported “electrosensitivity” and of participants who served as controls. A total of 51 individuals with self-reported electrosensitivity and 132 age- and sex-matched controls participated in an open provocation test; 48 sensitive and 132 control participants went on to complete double-blind tests in a fully screened semi-anechoic chamber. Heart rate, skin conductance, and blood pressure readings provided objective indices of short-term physiological response; VAS and symptom scales provided subjective indices of well-being. These investigators found no differences on any measure between TETRA and sham (no signal) under double-blind conditions for either controls or electrosensitive participants, and neither group could detect the presence of a TETRA signal at rates greater than chance (50%). When conditions were not double-blind, however, the self-reported electrosensitive individuals did report feeling worse and experienced more severe symptoms during TETRA compared with sham.

Nieto-Hernandez et al (2011) noted that concerns have been raised about possible health effects from radiofrequency fields pulsing at around 16 Hz. The TETRA employs signals that pulse at 17.6 Hz. These investigators examined if exposure to a continuous wave signal at 385.25 MHz or a TETRA-like signal resulted in symptoms among users reporting sensitivity to TETRA compared to users not reporting sensitivity to TETRA. A total of 60 sensitive and 60 non-sensitive users were exposed to 3 50-min conditions: (i) a signal with a 16 Hz component, (ii) a continuous wave condition and (iii) a sham condition. The mean radiated power for the 16 Hz and continuous wave conditions was 250 mW. The order of conditions was randomized and testing was conducted double-blind. Participants reported the severity of 8 symptoms during and after each exposure, their mood state at the end of each exposure, and whether they could tell which sessions involved active signals. Exposure to the continuous wave signal increased ratings of headache in all participants, fatigue in non-sensitive participants and difficulty concentrating in sensitive participants. Paradoxically, it reduced sensations of itching in sensitive participants. These effects were not observed in the condition with 16 Hz pulsing, except for those relating to concentration. Adjusting for multiple comparisons removed most significant effects, but not those relating to itch. The authors conclude that these findings suggested that exposure to TETRA signals is not responsible for symptoms reported by some users, although exposure to a continuous wave signal may affect symptoms.
V. Oral Nystatin for the Treatment of "Candidiasis Hypersensitivity Syndrome"

Dismukes et al (1990) stated that candida albicans infection has been proposed to cause a chronic hypersensitivity syndrome characterized by fatigue, pre-menstrual tension, gastro-intestinal symptoms, and depression. Long-term antifungal therapy has been advocated as treatment for the syndrome, which is most often diagnosed in women with persistent or recurrent candida vaginitis. These investigators determined the effectiveness of nystatin therapy for presumed candidiasis hypersensitivity syndrome. They conducted a 32-week randomized, double-blind, cross-over study using 4 different combinations of nystatin or placebo given orally or vaginally in 42 pre-menopausal women who met present criteria for the syndrome and had a history of candida vaginitis. The outcomes studied were the changes from base line in scores for vaginal, systemic, and overall symptoms and in the results of standardized psychological tests. The 3 active-treatment regimens (oral and vaginal nystatin, oral nystatin and vaginal placebo, and oral placebo and vaginal nystatin) and the all-placebo regimen significantly reduced both vaginal and systemic symptoms \( p < 0.001 \), but nystatin did not reduce the systemic symptoms significantly more than placebo. On average, the scores for systemic symptoms improved 25% with the 3 active-treatment regimens and 23% with the all-placebo regimen, a difference of only 2% (95% CI: -3 to 7%). As expected, the 3 active-treatment regimens were more effective than placebo in relieving vaginal symptoms \( p < 0.001 \). All 4 regimens reduced psychological symptoms and global indexes of distress; there were no significant differences among the treatment regimens. The authors concluded that in women with presumed candidiasis hypersensitivity syndrome, nystatin does not reduce systemic or psychological symptoms significantly more than placebo. Consequently, the empirical recommendation of long-term nystatin therapy for such women appears to be unwarranted.

VI. Alpha Gal Allergy (Meat Allergy) Testing

Alpha-gal, a sugar carbohydrate found in beef, lamb, and pork is thought to be associated with a rare meat allergy, which produces a hive-like rash; and, in some people, a dangerous anaphylactic reaction roughly 4 hours after consuming the meat. This rare meat allergy is believed to be caused by antibodies to the alpha-gal sugar that are produced in humans after they are bitten by common Lone Star ticks. However, the relationship between tick bites, sensitization to red meat, and alpha-gal remains uncertain; and a valid diagnostic test for this allergy has not been established.

Mullins et al (2012) described a prospective evaluation of the clinical significance of gelatin sensitization, the predictive value of a positive test result, and an examination of the relationship between allergic reactions to red meat and sensitization to gelatin and galactose-\(\alpha\)-1,3-galactose (alpha-Gal). Adult patients evaluated in the 1997 to 2011 period for suspected allergy/anaphylaxis to medication, insect venom, or food were skin tested with gelatin colloid were included in this study. In-vitro (ImmunoCAP) testing was undertaken where possible. Positive gelatin test results were
observed in 40 of 1,335 subjects: 30 of 40 patients with red meat allergy (12 also clinically allergic to gelatin), 2 of 2 patients with gelatin colloid-induced anaphylaxis, 4 of 172 patients with idioopathic anaphylaxis (all responded to intravenous gelatin challenge of 0.02 to 0.4 g), and 4 of 368 patients with drug allergy. Test results were negative in all patients with venom allergy (n = 241), non-meat food allergy (n = 222), and miscellaneous disorders (n = 290). ImmunoCAP results were positive to alpha-Gal in 20 of 24 patients with meat allergy and in 20 of 22 patients with positive gelatin skin test results. The results of gelatin skin testing and anti-alpha-Gal IgE measurements were strongly correlated (r = 0.46, p < 0.01). Alpha-Gal was detected in bovine gelatin colloids at concentrations of approximately 0.44 to 0.52 μg/g gelatin by means of inhibition RIA. The authors concluded that most patients allergic to red meat were sensitized to gelatin, and a subset was clinically allergic to both. The detection of alpha-Gal in gelatin and correlation between the results of alpha-Gal and gelatin testing raise the possibility that alpha-Gal IgE might be the target of reactivity to gelatin. The authors concluded that the pathogenic relationship between tick bites and sensitization to red meat, alpha-Gal, and gelatin (with or without clinical reactivity) remains uncertain.

Saleh et al (2012) noted that while most allergic responses to food are directed against protein epitopes and occur within 30 mins of ingesting the allergen, recent studies suggested that delayed reactions may occur, sometimes mediated by IgE antibodies directed against carbohydrate moieties. These investigators summarized the clinical features and management of delayed hypersensitivity reactions to mammalian meat mediated by IgE antibodies to galactose-alpha 1,3-galactose (alpha-gal), an oligosaccharide. A PubMed search was conducted with MeSH terms: galactosyl-(1,3) galactose, oligosaccharides, cetuximab, allergy/hypersensitivity, and anaphylaxis. Reported cases with alpha-gal-mediated reactions were reviewed. A total of 32 cases of adults presenting with red-meat induced allergy thought to be related to oligosaccharides have been reported in the literature so far, making this a rare and evolving syndrome. Most of these patients demonstrated delayed reactions to beef, as was seen in the case reported by the authors in this manuscript. IgE specific to alpha-gal was identified in most patients with variable response to skin testing with beef and pork. Inhibition studies in some cases showed that the IgE antibodies to beef were directed towards alpha-gal in the meat rather than the protein. The patients often reported history of tick bites, the significance of which is unclear at present. Reactions to cetuximab, a monoclonal antibody, were mediated by a similar mechanism, with IgE antibodies directed against an alpha-gal moiety incorporated in the drug structure. The authors concluded that alpha-gal is an oligosaccharide recently incriminated in delayed anaphylactic reactions to mammalian meats such as to beef, pork, and lamb. It appears that anaphylactic reactions to the anti-cancer biological agent, cetuximab, may be linked mechanistically to the same process. They stated that more studies are needed to understand the underlying molecular basis for these delayed reactions in specific, and their broader implications for host defense in general.
Jape (2012) stated that the association between the carbohydrate galactose-\[alpha\]-1,3-galactose (alpha-Gal) and anaphylaxis was first documented after severe hypersensitivity reactions to cetuximab, a chimeric mouse-human IgG1 monoclonal antibody approved for targeted therapy of carcinomas of colon, as well as of the head and neck region. Alpha-Gal is a ubiquitous glycan moiety expressed on cells and tissue of non-primate mammals. Since this epitope is not expressed in humans, it is very immunogenic for them. Alpha-Gal is located on the Fab portion of cetuximab and thus on the murine part of the chimera. The anaphylactic reactions to the antibody were mediated by IgE specific for alpha-Gal. Anti-alpha-Gal-IgE were first detected in sera of patients from the southeastern U.S. and reacted with a wide range of mammalian allergens. The geographic distribution prompted investigations of sensitization routes apart from the ingestion of red meat, such as tick bites and parasitic infections. Anti-alpha-Gal-IgE seems to be of clinical relevance for allergy to red meat and for the pork-cat syndrome. It is also associated with a novel form of delayed anaphylaxis, which appears more than 3 hours following the ingestion of red meat (beef, pork and lamb), a phenomenon which is still to be elucidated. For most of these patients conventional skin prick tests with commercial reagents proved insufficient for diagnosis.

Ebo et al (2013) stated that recent observations have disclosed that the galactose-alpha (1,3)-galactose (alpha-gal) moiety of non-primate glycoproteins can constitute a target for meat allergy. These researchers described adults with allergic reactions to mammalian meat, dairy products and gelatin. They examined if patients could demonstrate sensitization to activated recombinant human coagulation factor VII ectapog alpha that is produced in baby hamster kidney cells. A total of 10 adults with mammalian meat, dairy products and gelatin allergies were examined using quantification of specific IgE and/or skin prick test for red meat, milk, milk components, gelatin, cetuximab and eptacog alpha. Most patients demonstrated quite typical clinical histories and serological profiles, with anti-alpha-gal titers varying from less than 1 % to over 25 % of total serum IgE. All patients demonstrated negative sIgE for gelatin, except the patient with a genuine gelatin allergy. All patients also demonstrated a negative sIgE to recombinant milk components casein, lactalbumin and lactoglobulin. Specific IgE to eptacog was positive in 5 out of the 9 patients sensitized to alpha-gal and none of the 10 control individuals. The authors concluded that the findings of this series confirmed the importance of the alpha-gal carbohydrate moiety as a potential target for allergy to mammalian meat, dairy products and gelatin (oral, topical or parenteral) in a Flemish population of meat allergic adults. It also confirmed in-vitro tests to mammalian meat generally to be more reliable than mammalian meat skin tests, but that diagnosis can benefit from skin testing with cetuximab. Specific IgE to gelatin is far too insensitive to diagnose alpha-gal related gelatin allergy. IgE binding studies indicate a potential risk of alpha-gal-containing human recombinant proteins produced in mammals.

Also, an UpToDate review on “Allergy to meats” (Commins, 2013) states that “The utility of IgE-determinations, either by skin testing or
immunoassay, is less certain for the diagnosis of meat allergy than for many other food allergies .... Because of the issues discussed above, the best approach to diagnosis of meat allergy is not known .... The diagnosis of meat allergy involves history, objective testing, and possibly food challenge. However, the sensitivity and specificity of tests for meat-specific IgE are relatively poor. The use of fresh meat for skin testing may improve sensitivity".

VII. **Body Chemical Analysis**

Body chemical analysis is usually seen in the diagnosis of a condition known as "idiopathic environmental intolerances" or "multiple food and chemical sensitivities". Samples of whole blood, serum, red blood cells, urine, fat and hair are tested for the presence of environmental chemicals. The most common chemicals measured are organic solvents, other hydrocarbons, pesticides and metals. Some proponents of this testing also recommend measurements of the quantity of vitamins, minerals and amino acids in blood and urine in a search for "environmental sensitivities". However, the concept of multiple food and chemical sensitivities manifested by numerous symptoms in the absence of objective physical findings lacks scientific foundation. There is no evidence to suggest that these patients suffer from an immunological abnormality. The existence of such an illness is based on anecdotal reports with no verification using well-designed clinical trials. Moreover, there is no scientific evidence to support the value of diagnostic testing associated with idiopathic environmental intolerances or multiple food and chemical sensitivities, including body chemical analysis.

VIII. **Chronic Urticaria Index Testing**

Viswanathan et al (2012) stated that the clinical implications of autoimmune testing in chronic idiopathic urticaria (CIU) are not well-established. These investigators identified the association of autoimmune biomarkers in CIU with disease severity. They retrospectively evaluated 195 patients with a diagnosis of CIU for the presence of anti-nuclear antibody (ANA), anti-thyroglobulin antibody (ATG), anti-thyroperoxidase antibody (ATPO), and chronic urticaria (CU) index. The patients were categorized into controlled and refractory subgroups based on their response to antihistamines with or without a leukotriene receptor antagonist. The percentage of patients with a positive test for ANA (titer > 1:160), ATG, ATPO, and CU Index were 29 %, 6 %, 26 %, and 38 %, respectively. Among those tested, the percentage of patients categorized as refractory was significantly higher in those with a positive CU index (80 % versus 46 %; p = 0.01) or a positive ANA titer (50 % versus 30 %; p = 0.04) than those with negative test results; however, a similar relationship was not observed for ATPO or ATG antibodies. Odds ratios of individual or combinations of autoimmune biomarkers in CIU were examined for associations with refractoriness to anti-histamines with or without a leukotriene receptor antagonist. The CU Index alone has an odds ratio of 4.5 (p = 0.005), whereas the combination of ANA, ATG, and ATPO has an odds ratio of 3.1 (p = 0.01) and ANA alone has an odds ratio of 2.3 (p = 0.04) for correlating with a refractory outcome.
The authors concluded that their findings indicated the CU Index independently has the strongest correlation with disease severity followed by the combination of ANA, ATG, and ATPO and the ANA alone. This was a retrospective study; its findings need to be validated by well-designed studies.

Cho et al (2013) compared the prevalence of basophil-activating autoantibodies (elevated CU Index) in patients with CU, rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE). Clinical characteristics and laboratory studies were examined for an association with the CU Index. Adult patients, 27 with CU, 27 with RA, and 26 with SLE, and 20 healthy controls were compared on the basis of the CU Index panel, anti-IgE, and anti-thyroid antibodies. The CU Index values were significantly higher in the CU group when compared with the RA group but not when compared with the SLE group. 33 % of CU, 23 % of SLE, 3.7 % of RA, and 15 % of controls had a positive CU Index. Elevated anti-thyroid antibody levels did not correlate with a positive CU Index in any of the groups. An elevated CU Index in the SLE group was not associated with age, sex, ethnicity, disease severity, or history of atopy. The authors concluded that the CU Index values were elevated in patients with CU and SLE. The presence of these autoantibodies did not correlate with disease activity or presence of thyroid antibodies. They stated that functional autoantibodies may not be specific for CIU, and their role in non-urticarial systemic autoimmune diseases requires further investigation.

Also, an UpToDate review on “Chronic urticaria: Clinical manifestations, diagnosis, pathogenesis, and natural history” (Saini, 2013) states that “The presence of IgG autoantibodies to the IgE receptor or the Fc region of IgE can be demonstrated in as many as 30 to 50 percent of children and adults with CU. These autoantibodies can trigger histamine release when incubated with normal basophils and can activate mast cells, possibly through a mechanism involving complement. Assays are commercially available for detecting anti-FcεRI-alpha antibodies (e.g., the Chronic Urticaria Index), although the clinical utility of this test is not well established ... Similar to the ASST, the autoantibodies described above are not specific to CU. Anti-FcεRI-alpha antibodies have been identified in healthy subjects and in people with other autoimmune diseases, including pemphigus vulgaris, systemic lupus erythematosus, dermatomyositis, and pemphigoid, suggesting that they may represent an epiphenomenon. In addition, the levels of autoantibodies in CU do not appear to change with the clinical activity of the disease, and the presence of these autoantibodies does not appear to predict more difficult to manage disease. Also problematic is the fact that commercial assays for anti-FcεRI-alpha antibodies are based upon basophil-activation tests, for which there are no widely accepted standards across laboratories”.

IX. Immunoglobulin G (IgG) Testing

One of the AAAAI’s “Five Things Physicians and Patients Should Question” (2012) noted that “Appropriate diagnosis and treatment of allergies requires specific IgE testing (either skin or blood tests) based on
the patient's clinical history. The use of other tests or methods to diagnose allergies is unproven and can lead to inappropriate diagnosis and treatment”. The AAAAI stated that “Don't perform unproven diagnostic tests, such as immunoglobulin G (IgG) testing or an indiscriminate battery of immunoglobulin E (IgE) tests, in the evaluation of allergy". http://www.choosingwisely.org/wp-content/uploads/2012/12/5things_12_factsheet_AAAAI1.pdf.

X. Miscellaneous Tests for Allergy

Otani et al (2014) stated that food allergy (FA) negatively affects quality of life in caregivers of food-allergic children, imposing a psychosocial and economic burden. Oral immunotherapy (OIT) is a promising investigational therapy for FA. However, OIT can be a source of anxiety as it carries risk for allergic reactions. The effect of OIT with multiple food allergens (mOIT) on FA-specific health-related quality of life (HRQL) has never been studied in participants with multiple, severe food allergies. This study was the first to investigate the effects of mOIT on FA-related HRQL in caregivers of pediatric subjects. Caregiver HRQL was assessed using a validated Food Allergy Quality of Life - Parental Burden (FAQL-PB). Parents of participants in 2 single-center phase I clinical trials receiving mOIT (n = 29) or rush mOIT with anti-IgE (omalizumab) pre-treatment (n = 11) completed the FAQL-PB prior to study intervention and at 2 follow-up time-points (6 months and 18 months). Parents of subjects not receiving OIT (control group, n = 10) completed the FAQL-PB for the same time-points. Health-related quality of life improved with clinical (change less than -0.5) and statistical (p < 0.05) significance in the mOIT group (baseline mean 3.9, 95 % CI: 3.4 to 4.4; 6-month follow-up mean 2.5, 95 % CI: 2.0 to 3.0; 18-month follow-up mean 1.8, 95 % CI: 1.4 to 2.1) and rush mOIT group (baseline mean 3.9, 95 % CI: 3.1 to 4.7; 6-month follow-up mean 1.7, 95 % CI: 0.9 to 2.6; 18-month follow-up mean 1.3, 95 % CI: 0.3 to 2.4). Health-related quality of life scores did not significantly change in the control group (n = 10). The authors concluded that multi-allergen OIT with or without omalizumab leads to improvement in caregiver HRQL, suggesting that mOIT can help relieve the psychosocial and economic burden FA imposes on caregivers of food-allergic children.

These investigators stated that one drawback of this study was that all subjects were recruited from volunteers. Although this potentially introduced selection bias toward more severely affected families, this bias reflected the patient population that would seek out additional therapy such as oral immunotherapy. Also, these were phase I studies. Although the control group was not placebo-controlled, it would not have been possible to test the full psychosocial effect of the intervention if subjects were blinded and did not know they were protected. Despite the control group being comparable and selected using the same criteria, it is possible that the intense follow-up with bi-weekly visits to see food allergy specialists during OIT escalation phase positively affected the treatment group caregiver quality of life. However, previous studies looking at allergist interventions such as DBPCFC (positive outcome) and self-regulation telephone intervention did not show significant impact on overall HRQL.
scores. The authors stated that these findings suggested that mOIT, with or without omalizumab, can lead to significant improvements in caregiver HRQL that persist with ongoing treatment. They noted that these findings support OIT as a promising therapy for food allergy and suggest that OIT can help relieve the psychosocial burden food allergy imposes on caregivers of food-allergic children; they stated that validated measures of quality of life should be included in future phase II clinical trials.

Cytokine and cytokine receptor assays have not been demonstrated to be effective in the management of any allergic disease.

Lymphocyte function assays are not abnormal in patients with allergy.

In-vitro metal allergy tests, known as lymphocyte transformation tests (LTT) have been used to test for allergies to metals in jewelry and dental implants and could potentially be used to test individuals who have or are considering metal orthopedic implants. However, there is insufficient evidence that in-vitro metal allergy testing improves patient management decisions or health outcomes for total joint replacement patients. No national organizations have issued recommendations regarding in-vitro metal allergy testing and orthopedic implants.

Thyssen et al (2011) stated that allergic complications following insertion of metallic orthopedic implants include allergic dermatitis reactions but also extra-cutaneous complications. As metal-allergic patients and/or surgeons may ask dermatologists and allergologists for advice prior to orthopedic implant surgery, and as surgeons may refer patients with complications following total joint arthroplasty for diagnostic work-up, there is a continuous need for updated guidelines. This review presented published evidence for patch testing prior to surgery and proposed tentative diagnostic criteria that clinicians can rely on in the work-up of patients with putative allergic complications following surgery. Few studies have investigated whether subjects with metal contact allergy have increased risk of developing complications following orthopedic implant insertion. Metal allergy might in a minority increase the risk of complications caused by a delayed-type hypersensitivity reaction. These researchers noted that they did not know how to identify the subgroups of metal contact allergic patients with a potentially increased risk of complications following insertion of a metal implant. They recommended that clinicians should refrain from routine patch testing prior to surgery unless the patient has already had implant surgery with complications suspected to be allergic or has a history of clinical metal intolerance of sufficient magnitude to be of concern to the patient or a health provider. The authors concluded that clinical work-up of a patient suspected of having an allergic reaction to a metal implant should include patch testing and possibly in-vitro testing.

Schalock et al (2012) noted that cutaneous and systemic hypersensitivity reactions to implanted metals are challenging to evaluate and treat. Although they are uncommon, they do exist, and require appropriate and complete evaluation. This review summarized the evidence regarding evaluation tools, especially patch testing and LTT, for hypersensitivity reactions to implanted metal devices. Patch testing is the gold standard for
metal hypersensitivity, although the results may be subjective. Regarding pre-implant testing, those patients with a reported history of metal dermatitis should be evaluated by patch testing. Those without a history of dermatitis should not be tested unless considerable concern exists. Regarding post-implant testing, a subset of patients with metal hypersensitivity may develop cutaneous or systemic reactions to implanted metals following implant. For symptomatic patients, a diagnostic algorithm to guide the selection of screening allergen series for patch testing was provided. This review did not mention the use of in-vitro metal allergy testing/lymphocyte transformation tests.

Granchi et al (2012) reported a systematic review and meta-analysis of the peer-reviewed literature focusing on metal sensitivity testing in patients undergoing total joint replacement (TJR). These investigators evaluated the risk of developing metal hypersensitivity post-operatively and its relationship with outcome and investigated the advantages of performing hypersensitivity testing. They undertook a comprehensive search of the citations quoted in PubMed and EMBASE: 22 articles (comprising 3,634 patients) met the inclusion criteria. The frequency of positive tests increased after TJR, especially in patients with implant failure or a metal-on-metal coupling. The probability of developing a metal allergy was higher post-operatively (odds ratio (OR) 1.52 (95 % CI: 1.06 to 2.31)), and the risk was further increased when failed implants were compared with stable TJRs (OR 2.76 (95 % CI: 1.14 to 6.70)). The authors concluded that hypersensitivity testing was not able to discriminate between stable and failed TJRs, as its predictive value was not statistically proven.

Pinson et al (2014) reviewed the clinical manifestations, testing methods, and treatment options for hypersensitivity reactions to total joint arthroplasty procedures. Studies were identified using MEDLINE and reference lists of key articles. Randomized controlled trials were selected when available. Systematic reviews and meta-analyses of peer-reviewed literature were included, as were case series and observational studies of clinical interest. Total joint arthroplasty procedures are increasing, as are the hypersensitivity reactions to these implants. Evidence is not conclusive as to whether metal joint implants increase metal sensitivity or whether metal sensitivity leads to prosthesis failure. Currently, patch testing is still the most widely used method for determining metal hypersensitivity; however, there are no standardized commercial panels specific for total joint replacements available currently. In-vitro testing has shown comparable results in some studies, but its use in the clinical setting may be limited by the cost and need for specialized laboratories. Hypersensitivity testing is generally recommended before surgery for patients with a reported history of metal sensitivity. In cases of metal hypersensitivity-related joint failure, surgical revision ultimately may be required. Knowledge about joint replacement hypersensitivity reactions becomes vital because the approach to the evaluation depends on appropriate testing to guide recommendations for future arthroplasty procedures. The authors concluded that evaluation of hypersensitivity reactions after total joint arthroplasty requires a systematic approach, including a careful history, targeted evaluation with skin testing, and in-vitro studies.
In a systematic review with meta-analysis, Cuervo-Perez et al (2014) evaluated the validity, performance, safety and diagnostic efficiency of in-vitro immunological techniques for allergies. These investigators applied a search strategy studies in PubMed, Sciencedirect and Wiley, with search terms activation basophil test, lymphocyte transformation test, specific IgE immunoassay. They determined the reproducibility of the selection, extraction and quality assessment of articles; and calculated sensitivity, specificity, likelihood ratios, predictive values, proportion of false, accuracy, odds ratio, Youden index J and ROC curve in Meta-DiSc(es) and Epidat 3.0. soft-ware. These researchers included 18 studies with 3,520 individuals, 58 % patients and 42 % healthy. Activation of basophils showed sensitivity of 78 % (95 % CI: 74 to 81), specificity 95 % (95 % CI: 83 to 100), positive likelihood ratio 9.9 (95 % CI: 6.8 to 14.4) and negative of 0.20 (95 % CI: 0.13 to 0.30) a diagnostic OR 70.8 (IC95: 40.2 to 124.8) and area under the curve of 0.97. In particular, immunoglobulin E sensitivity was 72 % (95 % CI: 69 to 75), specificity 90 % (95 % CI: 88 to 92), positive likelihood ratio 12.9 (95 % CI: 4.0 to 41.6) negative likelihood ratio 0.32 (95 % CI: 0.23 to 0.43), diagnostic OR 41.6 (95 % CI: 11.6 to 148.9) and area under the curve 0.87. The authors concluded that activation of basophils and specific IgE are useful tests for diagnosing allergies.

Furthermore, an UpToDate review on “Overview of in vitro allergy tests” (Nolte et al, 2014) does not mention the use of lymphocyte testing for metals.

Appendix

Documentation Requirements

The member’s medical record must contain documentation that fully supports the medical necessity for services included within this CPB. This documentation includes, but is not limited to, relevant medical history, physical examination, and results of pertinent diagnostic tests or procedures.

Include in the record the following information: Medical history, examination, and results of diagnostic testing (including allergy testing) upon which the need for the treatment is based.

A plan of treatment and dosage regimen must be documented in the member’s medical record. The record should be prepared so that the data regarding injection and responses can be appreciated in a logical and sequential sense.

When an evaluation and management service is billed on the same day as allergen immunotherapy (by the same physician) a separately identifiable service must be documented in the medical record.

Documentation must support the use of the code (e.g., number of venoms, number of vials).

Documentation must be available to Aetna upon request.
CPT Codes / ICD-9 Codes / HCPCS Codes

Allergy testing:

Epicutaneous (scratch, prick, or puncture):

CPT codes covered if selection criteria are met:

- 95004  Percutaneous tests (scratch, puncture, prick) with allergenic extracts, immediate type reaction, including test interpretation and report by a physician, specify number of tests
- 95017  Allergy testing, any combination of percutaneous (scratch, puncture, prick) and intracutaneous (intradermal), sequential and incremental, with venoms, immediate type reaction, including test interpretation and report, specify number of tests
- 95018  Allergy testing, any combination of percutaneous (scratch, puncture, prick) and intracutaneous (intradermal), sequential and incremental, with drugs or biologicals, immediate type reaction, including test interpretation and report, specify number of tests

ICD-9 codes covered if selection criteria are met:

- 477.0 - 477.9  Allergic rhinitis
- 691.8  Other atopic dermatitis and related conditions
- 692.5  Contact dermatitis and other eczema due to food in contact with skin
- 693.1  Dermatitis due to food taken internally
- 708.0  Allergic urticaria
- 989.5  Toxic effect of venom
- 995.27  Other drug allergy
- 995.60 - 995.69  Anaphylactic shock due to adverse food reaction
- 995.7  Other adverse food reactions, not elsewhere classified

Other ICD-9 codes related to the CPB:

- 995.0  Other anaphylactic shock
- 995.1  Angioneurotic edema
- 995.3  Allergy, unspecified
Venomous spiders, scorpion, hornets, wasps, and bees, centipede and venomous millipede (tropical) or other venomous arthropods as the cause of poisoning and toxic reactions.

Drugs, medicinals and biological substances causing adverse effects in therapeutic use.

Personal history of allergy to medicinal agents.

Personal history of allergy, other than to medicinal agents.

**Intradermal (Intracutaneous) when IgE-mediated reactions occur:**

**CPT codes covered if selection criteria are met:**

- **95018**  Allergy testing, any combination of percutaneous (scratch, puncture, prick) and intracutaneous (intradermal), sequential and incremental, with drugs or biologicals, immediate type reaction, including test interpretation and report, specify number of tests.

- **95024**  Intracutaneous (intradermal) tests with allergenic extracts, immediate type reaction, including test interpretation and report by a physician, specify number of tests.

- **95027**  Intracutaneous (intradermal) tests, sequential and incremental, with allergenic extracts for airborne allergens, immediate type reaction, including test interpretation and report by a physician, specify number of tests.

- **95028**  Intracutaneous (intradermal) tests with allergenic extracts, delayed type reaction, including reading, specify number of tests.

**ICD-9 codes covered if selection criteria are met:**

- **477.0 - 477.9**  Allergic rhinitis

- **691.8**  Other atopic dermatitis and related conditions

- **692.5**  Contact dermatitis and other eczema due to food in contact with skin

- **693.1**  Dermatitis due to food taken internally

- **708.0**  Allergic urticaria

- **989.5**  Toxic effect of venom

- **995.27**  Other drug allergy
Anaphylactic shock due to adverse food reaction

Other ICD-9 codes related to the CPB:

995.0  Other anaphylactic shock
995.1  Angioneurotic edema
995.3  Allergy, unspecified
E905.1  Venomous spiders, scorpion, hornets, wasps, and bees,
E905.5  centipede and venomous millipede (tropical) or other
        venomous arthropods as the cause of poisoning and toxic
        reactions
E930.0  Drugs, medicinals and biological substances causing adverse
E949.9  effects in therapeutic use
V14.0  Personal history of allergy to medicinal agents
V15.01  Personal history of allergy, other than to medicinal agents
V15.09  

Skin Endpoint Titration (SET):

CPT codes covered if selection criteria are met:

95027  Intracutaneous (intradermal) tests, sequential and incremental,
        with allergenic extracts for airborne allergens, immediate type
        reaction, including test interpretation and report by a physician,
        specify number of tests

ICD-9 codes covered if selection criteria are met:

477.0 - 477.9  Allergic rhinitis
989.5  Toxic effect of venom
V15.06  Allergy to insects

Other ICD-9 codes related to the CPB:

E905.1  Venomous spiders, scorpion, hornets, wasps, and bees,
E905.5  centipede and venomous millipede (tropical) or other
        venomous arthropods as the cause of poisoning and toxic
        reactions

Skin Patch Testing:

CPT codes covered if selection criteria are met:

95044  Patch or application tests(s) (specify number of tests)
ICD-9 codes covered if selection criteria are met:

- 691.8 Other atopic dermatitis and related conditions
- 692.0 Contact dermatitis due to detergents
- 692.1 Contact dermatitis due to oils and greases
- 692.2 Contact dermatitis due to solvents
- 692.3 Contact dermatitis due to drugs and medicinals in contact with skin
- 692.4 Contact dermatitis due to other chemical products
- 692.5 Contact dermatitis due to food in contact with skin
- 692.6 Contact dermatitis due to plants [except food]
- 692.81 Contact dermatitis due to cosmetics
- 692.83 Contact dermatitis due to metals
- 692.84 Contact dermatitis due to animal (cat) (dog) dander
- 708.0 Allergic urticaria

Photo Patch Test:

CPT codes covered if selection criteria are met:

- 95052 Photo patch test(s) (specify number of tests)

ICD-9 codes covered if selection criteria are met:

- 692.72 Acute dermatitis due to solar radiation

Photo Tests:

CPT codes covered if selection criteria are met:

- 95056 Photo tests

ICD-9 codes covered if selection criteria are met:

- 692.72 Acute dermatitis due to solar radiation

Bronchial Challenge Test:

CPT codes covered if selection criteria are met:

- 95070 Inhalation bronchial challenge testing (not including necessary pulmonary function tests); with histamine, methacholine, or similar compounds
- 95071 with antigens or gases, specify
### Other CPT codes related to the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>94150</td>
<td>Vital capacity, total (separate procedure)</td>
</tr>
<tr>
<td>94200</td>
<td>Maximum breathing capacity, maximum voluntary ventilation</td>
</tr>
<tr>
<td>94621</td>
<td>Pulmonary stress testing; complex (including measurements of CO₂ production, O₂ uptake, and electrocardiographic recordings)</td>
</tr>
<tr>
<td>94680</td>
<td>Oxygen uptake, expired gas analysis; rest and exercise, direct, simple</td>
</tr>
<tr>
<td>94681</td>
<td>Including CO₂ output, percentage oxygen extracted</td>
</tr>
<tr>
<td>94690</td>
<td>Rest, indirect (separate procedure)</td>
</tr>
<tr>
<td>94726</td>
<td>Plethysmography for determination of lung volumes and, when performed, airway resistance</td>
</tr>
<tr>
<td>94729</td>
<td>Diffusing capacity (e.g., carbon monoxide, membrane) (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>94770</td>
<td>Carbon dioxide, expired gas determination by infrared analyzer</td>
</tr>
</tbody>
</table>

### HCPCS codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J7674</td>
<td>Methacholine chloride administered as inhalation solution through a nebulizer, per 1mg</td>
</tr>
</tbody>
</table>

### ICD-9 codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>493.00</td>
<td>Extrinsic asthma</td>
</tr>
<tr>
<td>493.02</td>
<td></td>
</tr>
<tr>
<td>493.90</td>
<td></td>
</tr>
<tr>
<td>493.92</td>
<td></td>
</tr>
<tr>
<td>495.0</td>
<td>Extrinsic allergic alveolitis</td>
</tr>
<tr>
<td>495.9</td>
<td></td>
</tr>
<tr>
<td>518.3</td>
<td>Pulmonary eosinophilia</td>
</tr>
</tbody>
</table>

**Exercise Challenge Testing:**

### CPT codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>94010</td>
<td>Spirometry, including graphic record, total and timed vital capacity, expiratory flow rate measurement(s), with or without maximal voluntary ventilation</td>
</tr>
<tr>
<td>94060</td>
<td>Bronchodilation responsiveness, spirometry as in 94010, pre- and post-bronchodilator administration</td>
</tr>
<tr>
<td>94070</td>
<td>Bronchospasm provocation evaluation, multiple spirometric determinations as in 94010, with administered agents (e.g., antigen(s), cold air, methacholine)</td>
</tr>
</tbody>
</table>
94150  Vital capacity, total (separate procedure)
94200  Maximum breathing capacity, maximum voluntary ventilation
94240  Functional residual capacity or residual volume; helium method, nitrogen open circuit method, or other method
94350  Determination of maldistribution of inspired gas; multiple breath nitrogen washout curve including alveolar nitrogen or helium equilibration time
94360  Determination of resistance to airflow, oscillatory or plethysmographic methods
94375  Respiratory flow volume loop
94620  Pulmonary stress testing, simple (e.g., 6-minute walk test, prolonged exercise test for bronchospasm with pre- and post-spirometry and oximetry)
94621  Pulmonary stress testing; complex (including measurements of CO₂ production, O₂ uptake, and electrocardiographic recordings)
94680  Oxygen uptake, expired gas analysis; rest and exercise, direct, simple
94681  including CO₂ output, percentage oxygen extracted
94690  rest, indirect (separate procedure)
94720  Carbon monoxide diffusing capacity (e.g., single breath, steady state)
94770  Carbon dioxide, expired gas determination by infrared analyzer

**HCPCS codes covered if selection criteria are met:**

J7674  Methacholine chloride administered as inhalation solution through a nebulizer, per 1 mg

**ICD-9 codes covered if selection criteria are met:**

493.81  Exercise induced bronchospasm

**Ingestion (Oral) Challenge Test:**

**CPT codes covered if selection criteria are met:**

95076  Ingestion challenge test (sequential and incremental ingestion of test items, eg, food, drug or other substance); initial 120 minutes of testing
95079  Ingestion challenge test (sequential and incremental ingestion of test items, eg, food, drug or other substance); each
additional 60 minutes of testing (List separately in addition to code for primary procedure)

**ICD-9 codes covered if selection criteria are met:**

693.1  Dermatitis due to food taken internally

995.27  Other drug allergy

995.60 - 995.69  Anaphylactic shock due to adverse food reaction

995.7  Other adverse food reactions, not elsewhere classified

V14.0 - V14.9  Personal history of allergy to medicinal agents

**RAST, MAST, FAST, ELISA, ImmunoCAP when percutaneous testing of IgE-mediated allergies cannot be done:**

**CPT codes covered if selection criteria are met:**

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

83518  single step method (e.g., reagent strip)

83519  Immunoassay, analyte quantitative; by radiopharmaceutical technique (e.g., RIA)

83520  not otherwise specified

86003  Allergen specific IgE; quantitative or semi-quantitative, each allergen

86005  qualitative, multi-allergen screen (dipstick, paddle or disk)

**ICD-9 codes covered if selection criteria are met:**

477.0 - 477.9  Allergic rhinitis

518.6  Allergic bronchopulmonary aspergillosis

691.8  Other atopic dermatitis and related conditions

692.3  Contact dermatitis and other eczema due to drugs and medicines in contact with skin

692.5  Contact dermatitis and other eczema due to food in contact with skin

693.1  Dermatitis due to food taken internally

708.0  Allergic urticaria

989.5  Toxic effect of venom
995.27 Other drug allergy
995.60 - Anaphylactic shock due to adverse food reaction
995.69
995.7 Other adverse food reactions, not elsewhere classified [except Alpha gal allergy testing for meat allergy]

Other ICD-9 codes related to the CPB:
995.0 Other anaphylactic shock
995.1 Angioneurotic edema
995.3 Allergy, unspecified

Total Serum IgE:

CPT codes covered if selection criteria are met:
82785 Gammaglobulin; IgE

ICD-9 codes covered if selection criteria are met:
518.6 Allergic bronchopulmonary aspergillosis

Lymphocyte transformation tests:

CPT codes covered if selection criteria are met:
86353 Lymphocyte transformation, mitogen (phytomitogen) or antigen induced blastogenesis

ICD-9 codes covered if selection criteria are met:
112.0 Candidiasis of mouth
164.0 Malignant neoplasm of thymus
212.6 Benign neoplasm of thymus
279.06 Common variable immunodeficiency
279.11 DiGeorge's syndrome
279.12 Wiskott-Alrich syndrome
279.13 Nezelof's syndrome
279.2 Combined immunity deficiency
985.3 Toxic effects of beryllium and its compounds

Other ICD-9 codes related to the CPB:
279.49 Autoimmune disease, not elsewhere classified
289.89  Other specified diseases of blood and blood-forming organs
334.8  Other spinocerebellar diseases
606.0 - 606.9  Infertility, male
628.0 - 628.9  Infertility, female
E866.4  Accidental poisoning by other metals and their compounds and fumes
V42.0 - V42.9  Organ or tissue replaced by transplant
V72.7  Diagnostic skin and sensitization tests

Tests considered experimental and investigational for routine allergy testing:

CPT codes not covered for indications listed in the CPB:

83520  Immunoassay, analyte quantitative; not otherwise specified [anti-IgE receptor antibody testing]
84600  Volatiles (e.g., acetic anhydride, carbon tetrachloride, dichloroethane, dichloromethane, diethylether, isopropyl alcohol, methanol)
86001  Allergen specific IgG quantitative or semi-quantitative, each allergen
86021  Antibody identification; leukocyte antibodies
86140  C-reactive protein
86160  Complement; antigen, each component
86161  functional activity, each component
86162  total hemolytic (CH50)
86243  Fc receptor
86332  Immune complex assay
86343  Leukocyte histamine release test (LHR)
86352  Cellular function assay involving stimulation (eg, mitogen or antigen) and detection of biomarker (EG, ATP) [anti-IgE receptor antibody testing]
86485  Skin test; candida
86628  Antibody; candida
88184 Flow cytometry, cell surface, cytoplasmic, or nuclear marker, technical component only; first marker [anti-IgE receptor antibody testing]

88185 each additional marker (List separately in addition to code for first marker) [anti-IgE receptor antibody testing]

88342 Immunohistochemistry (including tissue immunoperoxidase), each antibody

88343 each additional separately identifiable antibody per slide (List separately in addition to code for primary procedure)

88346 Immunofluorescent study, each antibody; direct method

95060 Ophthalmic mucous membrane tests

95065 Direct nasal mucous membrane test

95831 Muscle testing, manual (separate procedure) with report; extremity (excluding hand) or trunk

95832 hand, with or without comparison with normal side

95833 total evaluation of body, excluding hands

95834 total evaluation of body, including hands

G0461 Immunohistochemistry or immunocytochemistry, per specimen; first single or multiplex antibody stain

G0462 each additional single or multiplex antibody stain (list separately in addition to code for primary procedure)

Mediator Release Test and Cytotoxic food testing (Bryans Test, ACT):

CPT codes not covered for indications listed in the CPB:

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

83518 single step method (e.g., reagent strip)

83519 Immunoassay, analyte quantitative; by radiopharmaceutical technique (e.g., RIA)

83520 not otherwise specified

86807 Serum screening for cytotoxic percent reactive antibody (PRA); standard method

86808 quick method

ICD-9 codes not covered for indications listed in the CPB:
307.81  Tension headache
314.00 - Hyperkinetic syndrome of childhood
314.9
339.00 - Other headache syndromes
339.89
346.00 - Migraine
346.93
472.0 - 472.2  Chronic pharyngitis and nasopharyngitis
473.0 - 473.9  Chronic sinusitis
477.0 - 477.9  Allergic rhinitis
530.81  Esophageal reflux
555.0 - 555.9  Regional enteritis
556.0 - 556.9  Ulcerative colitis
564.1  Irritable bowel syndrome
627.2  Symptomatic menopausal or female climacteric states
690.10 - Erythemosquamous dermatosis, atopic dermatitis and
693.9  related conditions, contact dermatitis and other eczema and
dermatitis due to substances taken orally
708.0 - 708.9  Urticaria
714.0 - 714.9  Rheumatoid arthritis and other inflammatory polyarthropathies
729.0 - Other and unspecified disorders of soft tissue
729.99
780.71 - Malaise and fatigue
780.79
784.0 - Symptoms involving the head and neck
784.99

There is no specific code for Cliffords Material Reactivity Testing:

Allergy immunotherapy:

CPT codes covered if selection criteria are met:

95115 - Professional services for allergen immunotherapy (for rapid
95170, 95199  desensitization see below) [except home administration]

CPT codes not covered for indications listed in the CPB:
97810 - Acupuncture
97814

**HCPC codes covered if selection criteria are met:**

J0171 Injection, adrenalin, epinephrine, 0.1 mg

**Other HCPCS codes related to the CPB:**

J2357 Injection, omalizumab, 5 mg

**ICD-9 codes covered if selection criteria are met:**

372.05 Acute atopic conjunctivitis
372.14 Other chronic allergic conjunctivitis
477.0 - 477.9 Allergic rhinitis [except non-allergic vasomotor]
493.00 - Extrinsic asthma
493.02
493.90 -
493.92
691.8 Other atopic dermatitis and related conditions [dust mite]
989.5 Toxic effect of venom

**ICD-9 codes not covered for indications listed in the CPB:**

346.00 - Migraine
346.93
493.10 - Intrinsic and chronic obstructive asthma [non-allergic]
493.82
692.5 Contact dermatitis and other eczema due to food in contact with skin
693.1 Dermatitis due to food taken internally
708.8 Other specified urticaria [chronic]
995.1 Angioneurotic edema

**Other Treatments:**

**Rapid desensitization:**

**CPT codes covered if selection criteria are met:**

95180 Rapid desensitization procedure, each hour (e.g., insulin, penicillin, equine serum)

**ICD-9 codes covered if selection criteria are met:**
477.0 - 477.9  Allergic rhinitis
989.5  Toxic effect of venom
995.27  Other drug allergy
V15.06  Allergy to insects

Other ICD-9 codes related to the CPB:
E905.1  Venomous spiders, scorpion, hornets, wasps, and bees,
E905.5  centipede and venomous millipede (tropical) or other
  venomous arthropods as the cause of poisoning and toxic
  reactions
V07.1  Need for desensitization to allergens
V07.2  Prophylactic immunotherapy

Aspirin Desensitization:
No specific code

Other ICD-9 codes related to the CPB:
714.0 - 714.9  Rheumatoid arthritis and other inflammatory polyarthropathies
V07.1  Need for desensitization to allergens
V14.8  Personal history of allergy to other specified medicinal agents
  [aspirin sensitivity]

Oralair, Grastek and Ragwitek:
No specific code

ICD-9 codes covered if selection criteria are met:
477.0  Allergic rhinitis due to pollen

The above policy is based on the following references:


30. American Academy of Allergy, Asthma and Immunology/American College of Allergy, Asthma and Immunology/Joint Council of Allergy, Asthma and Immunology. Practice parameters for the diagnosis and treatment of asthma. J Allergy Clin Immunol. 1995;96(5 Pt 2):707-870.


80. Corbillion E, Rame J-M. Indications for the specific-IgE test for the diagnosis and monitoring of allergies [summary]. Saint-Denis La Plaine, France: Haute Autorite de sante/French National Authority for Health (HAS); 2006.


98. Joint Task Force on Practice Parameters, American Academy of Allergy, Asthma and Immunology, American College of Allergy, Asthma and Immunology, Joint Council of Allergy, Asthma and Immunology. Allergen immunotherapy: A practice parameter second update. J Allergy Clin Immunol 2007;120(3 Suppl):S25-S85.


127. Commins SP. Allergy to meats. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed November 2013.


130. Saini S. Chronic urticaria: Clinical manifestations, diagnosis, pathogenesis, and natural history. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed October 2013.


