A separate copy of this form must accompany each policy submitted for review. Policies submitted without this form will not be considered for review.

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<th>Plan: Aetna Better Health</th>
<th>Submission Date: 04/01/2019</th>
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<tr>
<td>Policy Number: 0038</td>
<td>Effective Date:</td>
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<td>Policy Name: Allergy and Hypersensitivity</td>
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Type of Submission – Check all that apply:
- [ ] New Policy
- [ ] Revised Policy
- [x] Annual Review – No Revisions*

*All revisions to the policy must be highlighted using track changes throughout the document. Please provide any clarifying information for the policy below:

**CPB 0038 Allergy and Hypersensitivity**

Clinical content was last revised on 03/12/2018. No additional non-clinical updates were made by Corporate since the last PARP submission.

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<th>Name of Authorized Individual (Please type or print):</th>
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<tr>
<td>Dr. Bernard Lewin, M.D.</td>
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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 specific allergy testing medically necessary for members with clinically significant allergic history of symptoms when all of the following criteria are met: 1) symptoms are not adequately controlled by empiric conservative therapy; and 2) testing must correlate specifically to the member’s history, risk of exposure and physical findings; and 3) test technique and/or allergens tested must have proven efficacy demonstrated through scientifically valid medical studies published in the peer-reviewed literature.

- Aetna considers the following allergy tests medically necessary:
  
  Epicutaneous (scratch, prick or puncture) when immunoglobulin E (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 (up to 80 units are considered medically necessary).

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 1) patients receiving skin test suppressive medication therapy that cannot be temporarily discontinued (e.g., antihistamines or beta blockers); 2) presence of widespread skin disease (e.g., dermatographism, ichthyosis, intensive dermatitis or generalized eczema); 3) uncooperative patients (e.g., small children, individuals with mental or physical impairments); 4) when clinical history suggests an unusually greater risk of anaphylaxis from skin testing; 5) evaluating cross-reactivity between insect venoms; or 6) as an adjunctive laboratory test for disease activity of allergic bronchopulmonary aspergillosis or
certain parasitic diseases; and testing is performed for any of the following indications:

- 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 40 tests for inhalant allergies and 12 tests for food and other allergies. 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 tests/allergens is not considered medically necessary.

Total Serum IgE (paper radioimmunosorbent test [PRIST], radioimmunosorbent test [RIST]) 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 (../300_399/0327.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)
  - Allergen specific IgG (RAST/ELISA) testing
  - Allergy testing and desensitization for poison ivy, oak and sumac
  - Alpha gal allergy (meat allergy) testing
  - Anti-Fc epsilon receptor antibodies testing
  - Anti-IgE receptor antibody testing
  - Atopy patch testing for the diagnosis of food protein-induced enterocolitis syndrome (FPIES)
  - Basophil activation test (BAT)
  - 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/ACT
  - Eosinophil cationic protein (ECP) test
- Food immune complex assays (FICA)
- Food specific IgG antibodies

☐

Genetic testing for food allergy

- 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))
- In vitro histamine release testing such as the leukocyte histamine release (LHR) test
- In vitro lymphocyte proliferation test
- Leukocyte antibodies testing
- 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 food-specific IgE to identify food triggers of FPIES
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 the following conditions are met:

- Member has severe, seasonal or perennial IgE-dependent symptoms of allergic rhinoconjunctivitis or asthma after natural exposure to the allergen and both of the following criteria are met:
  - Member has skin test and/or serologic evidence of IgE-mediated antibody to a potent extract of the allergen, and
  - Avoidance or pharmacologic therapy cannot control allergic symptoms or member has unacceptable side effects with pharmacologic therapy; or
• Member has a life-threatening IgE mediated allergy to insect stings (bees, hornets, wasps, and fire ants); or

• Hypersensitivity to allergens that cannot be managed by medication or avoidance.

**Note:** Also see CPB 0670 - Xolair (Omalizumab) (../600_699/0670.html).

• 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 cannot 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.

Allergens should be individually prepared for the individual and the allergen content should be based on appropriate skin testing or appropriate in vitro testing. 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 polyps 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

- Intradermal grass pollen immunotherapy for the treatment of allergic rhinitis
- Neutralization therapy (desensitization neutralization therapy)
- Neutralizing therapy of chemical and food extracts

- Oral immunotherapy (OIT) for the treatment of food allergy
- Oral leukotriene receptor antagonists for allergic rhinitis
- 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
- Probiotics for food allergy prevention or treatment
- 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.)
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 immunoglobulin E (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
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. 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**

Total serum IgE concentrations (paper radioimmunosorbent test [PRIST], radioimmunosorbent test [RIST]) – This type of testing is less useful in assessing the risk of allergic disease, but may be indicated for those patients suspected of having allergic bronchopulmonary aspergillosis, eczema, hyper-IgE syndrome, certain stages of human immunodeficiency virus (HIV), IgE myeloma, graft versus host disease or immune deficiency diseases characterized by increased IgE levels (eg, Wiskott-Aldrich syndrome).

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., migraines, 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 Fc epsilonRI receptor, and in vitro assessments of basophil function. However, these tests lack specificity and prognostic value for chronic urticaria, are not standardized, and cannot 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 (eg, 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 "whether [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 rhinoconjunctivitis 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 rhinoconjunctivitis 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 +/- 1.64 versus 0.63 +/- 1.06) for the entire pollen season were significantly reduced in the high-dose versus placebo groups, respectively (p < 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 randomized controlled trials (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 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 Previews, (January 1979 to January 2011), the metaRegister of Controlled Trials (mRCT) (January 2011), ClinicalTrials.gov (January 2011), the Australian New Zealand Clinical Trials Registry (ANZCTR) (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 (I² 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; I² = 59%) and individual ocular symptom scores for red eyes (SMD -0.33; 95 % CI: -0.45 to -0.22; p < 0.00001; I² = 27 %), itchy eyes (SMD -0.31; 95 % CI: -0.42 to -0.20; p < 0.00001; I² = 46 %) and watery eyes (SMD -0.23; 95 % CI: -0.34 to -0.11; p < 0.0001; I² = 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; I² = 43 %). No significant reduction was observed in ocular eye drops use (SMD -0.10; 95 % CI: -0.22 to 0.03; p = 0.13; I² = 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 cannot 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
hypotheses, 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, electrohypersensitivity, 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-α-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 idiopathic 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 patient’s 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-thyroidperoxidase 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-FceRI-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-FceRI-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”.

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
hypothesis 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, Sciedirect 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-DiSe(es) and Epidat 3.0 software. 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.

XI. Allergy Immunotherapy for the Treatment of Allergic Rhino-Conjunctivitis

The European Academy of Allergy and Clinical Immunology (EAACI)’s Position paper on “Allergen immunotherapy trials for allergic rhino-conjunctivitis” (Pfaar et al, 2014) stated that a standardized and globally harmonized method for analyzing the clinical effectiveness of allergen immunotherapy (AIT) products in RCTs is needed. The EAACI Task Force highlighted the combined symptom and medication score (CSMS) as the primary end-point for future RCTs in AIT for allergic rhino-conjunctivitis.

XII. Oral Food Desensitization

Meglio and colleagues (2015) noted that attempts aimed at inducing food tolerance through oral food desensitization (OFD) for the treatment of IgE-mediated food allergies are increasing. In Italy, a number of allergy centers offer this procedure. These researchers collected information on how these centers are organized, how patients are selected, methods used to administer OFD and how adverse reactions are managed. A questionnaire was e-mailed to all the Italian allergy centers offering OFD. The survey showed a high degree of variability between centers. A correct diagnosis of food allergy is crucial for selecting patients for OFD. In the Italian allergy centers, oral food challenges are mostly open label (84%), but in 16% of cases they are single-blind (8%) or double-blind (8%). A high proportion of allergy centers (83%) offer OFD to
children presenting forms of anaphylaxis triggered by traces -- or very low doses -- of food allergen. The majority of allergy centers (76 %) enrolled patients over 3 years of age, with 44 % enrolling patients above the age of 5. Not-controlled asthma, unreliability of parents in the management of OFD and/or risk of adverse events were the main reasons for exclusion from the procedure. The authors concluded that although OFD may sometimes be successful and may be considered a valid alternative to an elimination diet, further RCTs are needed, in order to clarify some controversial points, such as the characteristics of the child undergoing OFD, and the methods of food preparation and administration. Moreover, further studies should further investigate OFD safety, efficacy and costs.

XIII. Oral Leukotriene Receptor Antagonists for Allergic Rhinitis

The American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNSF)’s clinical practice guideline on “Allergic rhinitis” (Seidman et al, 2015) recommended against clinicians offering oral leukotriene receptor antagonists as primary therapy for patients with allergic rhinitis.

XIV. Probiotics for Allergy Prevention or Treatment

In an update on “Current care guideline: Food allergy (children)”, Makela et al (2015) states that elimination diets are not recommended for breast-feeding mothers; probiotics are not recommended for allergy prevention or treatment; food challenges are the basis of the diagnosis, but it can be improved by IgE component diagnostics. The treatment for severe symptoms is specific food avoidance, mildly symptomatic children should continue with versatile diet. Specific oral tolerance induction is a safe and effective treatment in most of the pediatric patients.

XV. Epinephrine

The major therapeutic effects of systemic epinephrine include bronchial smooth muscle relaxation, cardiac stimulation, vasodilation in skeletal muscle, and stimulation of glycogenolysis in the liver and other calorigenic mechanisms. Auvi7Q (epinephrine injection) is a non-selective alpha and beta-adrenergic receptor agonist. Auvi7Q (epinephrine injection) is indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis. Auvi7Q (epinephrine injection) is available as a 0.3 mg/0.3 mL and 0.15 mg/0.15 mL epinephrine injection in a pre-filled auto-injector. In conjunction with use, seek immediate medical or hospital care. Do not inject
intravenously, into buttock, or into digits, hands, or feet. The presence of a sulfite in this product should not deter use. Administer with caution in patients with heart disease; may aggravate angina pectoris or produce ventricular arrhythmias.

XVI. Sublingual Immunotherapy

When grass pollen allergen extract is allowed to dissolve sublingually, allergens bind to epithelial cells and cross the oral mucosa, where they are taken up by tolerogenic antigen-presenting cells (i.e., Langerhans cells and myeloid dendritic cells). The allergens are then processed into small immunogenic peptides, and the antigen-presenting cells migrate into local regional lymph nodes (submaxillary, cervical, internal jugular). There, allergen peptide fragments are presented to naive CD4+ T cells. This interaction stimulates suppressive T helper (Th) 1 and regulatory T cells and inhibits the activation and proliferation of Th2 cells. Subsequently, T cells encourage B cells to produce protective antibody responses, including secretion of allergen-specific IgG4 and IgA and, later, inhibition of IgE. Regulatory T cells may also suppress other inflammatory cells (e.g., eosinophils, mast cells, basophils) either by cytokine secretion or direct cell-to-cell contact. CD4+ T cells eventually migrate into the blood and tissues, resulting in allergen tolerance.

Sublingual Grass Pollen Allergen Extract is indicated for the treatment of grass pollen-induced allergic rhinitis with or without conjunctivitis confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies for any of the grass species contained in the products.

Oralair (Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass Mixed Pollens Extract) is a sublingual immunotherapy containing dried extracts from 5 different species. Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass Mixed Pollens Extract is available as Oralair in 100 IR and 300 IR sublingual tablets. For adults 18 through 65 years of age, the dose is 300 IR (index of reactivity) daily. For children and adolescents 10 through 17 years of age, the dose is increased over the first three days from 100 IR on the first day, 100 IR twice on the second day, and 300 IR on the third and subsequent days.

Grastek (Timothy Grass Pollen Allergen Extract) is a sublingual immunotherapy containing dried extract from timothy grass. Timothy Grass Pollen Allergen Extract is available as Grastek in 2800 BAU sublingual tablets. The dose of Grastek is one tablet sublingually daily.
Ragwitek (Short Ragweed Pollen Allergen Extract) is a sublingual immunotherapy containing dried extract from short ragweed. Short Ragweed Pollen Allergen Extract is available as Ragwitek in 12 Amb sublingual tablets. Ragwitek therapy must be initiated 12 weeks before the expected onset of ragweed pollen season and continue treatment throughout the season. The dose of Ragwitek is one tablet sublingually daily.

Sublingual Grass Pollen Allergen Extract therapy is not indicated in eosinophilic esophagitis; severe, unstable or uncontrolled asthma; persons with a history of severe systemic allergic reactions; or persons with a history of severe local reactions to sublingual allergen immunotherapy.

Warnings and Precautions: Sublingual Grass Pollen Allergen Extract can cause life-threatening allergic reactions such as anaphylaxis and severe laryngopharyngeal edema. Do not administer Sublingual Grass Pollen Allergen Extract to patients with severe, unstable or uncontrolled asthma. Observe patients in the office for at least 30 minutes following the initial dose. Prescribe autoinjectable epinephrine, instruct and train patients on its appropriate use, and instruct patients to seek immediate medical care upon its use. Sublingual Grass Pollen Allergen Extract may not be suitable for patients with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction. Sublingual Grass Pollen Allergen Extract may not be suitable for patients who may be unresponsive to epinephrine or inhaled bronchodilators, such as those taking beta-blockers. In case of oral inflammation or wounds, stop treatment with Sublingual Grass Pollen Allergen Extract to allow complete healing of the oral cavity.

In a double-blind, randomized, placebo-controlled trial, Virchow and colleagues (2016) evaluated the effectiveness and adverse events (AEs) of the house dust mite (HDM) SLIT tablet versus placebo for asthma exacerbations during an inhaled corticosteroid (ICS) reduction period. The trial included 834 adults with HDM allergy-related asthma not well controlled by ICS or combination products, and with HDM allergy-related rhinitis. Key exclusion criteria were forced expiratory volume in 1 second (FEV1) less than 70 % of predicted value or hospitalization due to asthma within 3 months before randomization. Effectiveness was assessed during the last 6 months of the trial when ICS was reduced by 50 % for 3 months and then completely withdrawn for 3 months. Subjects were randomized in 1:1:1 manner to once-daily treatment with placebo (n = 277) or HDM SLIT tablet (dosage groups: 6 SQ-HDM [n = 275] or 12 SQ-HDM [n = 282]) in addition to ICS and the short-acting β2-agonist salbutamol. Primary outcome was time to first moderate or severe asthma exacerbation during the ICS reduction period. Secondary outcomes were deterioration in asthma symptoms, change in
allergen-specific immunoglobulin G4 (IgG4), change in asthma control or asthma quality-of-life questionnaires, and adverse events. Among 834 randomized patients (mean age of 33 years [range of 17 to 83]; women, 48 %), 693 completed the study. The 6 SQ-HDM and 12 SQ-HDM doses both significantly reduced the risk of a moderate or severe asthma exacerbation compared with placebo (hazard ratio [HR]: 0.72 [95 % CI: 0.52 to 0.99] for the 6 SQ-HDM group, p = 0.045, and 0.69 [95 % CI: 0.50 to 0.96] for the 12 SQ-HDM group, p = 0.03). The absolute risk differences based on the observed data (full analysis set) in the active groups versus the placebo group were 0.09 (95 % CI: 0.01 to 0.15) for the 6 SQ-HDM group and 0.10 (95 % CI: 0.02 to 0.16) for the 12 SQ-HDM group. There was no significant difference between the 2 active groups. Compared with placebo, there was a reduced risk of an exacerbation with deterioration in asthma symptoms (HR, 0.72 [95 % CI: 0.49 to 1.02] for the 6 SQ-HDM group, p = 0.11, and 0.64 [95 % CI: 0.42 to 0.96] for the 12 SQ-HDM group, p = 0.03) and a significant increase in allergen-specific IgG4. However, there was no significant difference for change in asthma control questionnaire or asthma quality-of-life questionnaire for either dose. There were no reports of severe systemic allergic reactions. The most frequent adverse events were mild-to-moderate oral pruritus (13 % for the 6 SQ-HDM group, 20 % for the 12 SQ-HDM group, and 3 % for the placebo group), mouth edema, and throat irritation. The authors concluded that among adults with HDM allergy-related asthma not well controlled by ICS, the addition of HDM SLIT to maintenance medications improved time to first moderate or severe asthma exacerbation during ICS reduction, with an estimated absolute reduction at 6 months of 9 to 10 percentage points; the reduction was primarily due to an effect on moderate exacerbations. They stated that treatment-related adverse events were common at both active doses; further studies are needed to assess long-term safety and effectiveness.

XVII. Sublingual Immunotherapy for Asthmatic Children Sensitized to House Dust Mite

Liao and colleagues (2015) stated that the house dust mite is one of the most common allergens worldwide. While there is evidence that house dust mite subcutaneous immunotherapy is effective and has long-term benefit in children, the evidence of the benefit of house dust mite SLIT is less convincing. The purpose of this meta-analysis was to evaluate that safety and effectiveness of dust mite SLIT in children with asthma. Medical Literature Analysis and Retrieval System Online, ISI Web of Knowledge, and Cochrane Central Register of Controlled Trials databases until February 2014 were searched. The primary outcome was mean change in asthma symptom score. Secondary outcomes included mean change in serum immunoglobulin G4 (sIgG4),
specific Dermatophagoides pteronyssinus, IgE levels, and medication score. Safety was also assessed. These researchers found that SLIT significantly decreased asthma symptom score ($p = 0.007$) and increased sIgG4 levels ($p = 0.011$) greater than control in children (less than 18 years of age) with asthma. There was no difference between SLIT and control groups in specific D pteronyssinus IgE levels ($p = 0.076$) and medication score ($p = 0.408$). The safety profile was similar between groups. The authors concluded that the findings of this study indicated that dust mite SLIT therapy was effective in reducing asthma symptoms and in increasing sIgG4; but did not significantly reduce medication scores or specific D pteronyssinus IgE levels. They stated that these findings are not enough to support the use of dust mite SLIT in children with asthma.

**XVIII. Basophil Activation Testing**

Mangodt et al (2015) noted that diagnosis of immediate drug hypersensitivity reactions (IDHRs) is based upon history-taking, skin prick or intradermal tests and quantification of specific IgE antibodies. Unfortunately, this is often insufficient to correctly identify patients with IgE-mediated IDHRs and is impossible in the case of non-IgE-mediated IDHRs. Drug provocation tests (DPT) are considered the “gold standard” diagnostic but are not always possible, for ethical and practical reasons. Therefore, the validation of new cellular tests such as basophil activation testing (BAT) was necessary. This review focused on the applications of BAT in IDHRs. A literature search was conducted, using the words basophil, flow cytometry, immediate drug allergy and drugs; this was complemented by the authors' own expertise. BAT/HistaFlow is a useful diagnostic tool in IDHRs, mainly used to diagnose allergy to neuromuscular blocking agents (NMBAs), antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs) and iodinated radio-contrast media. Its sensitivity varies between 50 % and 60 %, and specificity attains 80 %, except for with quinolones and NSAIDs. The authors concluded that diagnostic utility of BAT (and to lesser extent HistaFlow) has been demonstrated and is mostly applied in IDHRs. However, they stated that larger-scale collaborative studies are needed to optimize test protocols and validate the entry of BAT as a diagnostic instrument in drug allergy.

Steiner et al (2016) stated that DHRs resemble typical IgE-mediated symptoms. Clinical manifestations range from local skin reactions, gastro-intestinal and/or respiratory symptoms to severe systemic involvement with potentially fatal outcome. Depending on the substance group of the eliciting drug the correct diagnosis is a major challenge. Skin testing and in-vitro diagnostics are often unreliable and not
reproducible. The involvement of drug-specific IgE is questionable in many cases. The culprit substance (parent drug or metabolite) and potential cross-reacting compounds are difficult to identify, patient history and DPT often remain the only means for diagnosis. Hence, several groups proposed BAT for the diagnosis of immediate DHRs as basophils are well-known effector cells in allergic reactions. However, the usefulness of BAT in immediate DHRs is highly variable and dependent on the drug itself plus its capacity to spontaneously conjugate to serum proteins. Stimulation with pure solutions of the parent drug or metabolites thereof versus drug-protein conjugates may influence sensitivity and specificity of the test. These investigators reviewed the available literature about the use of BAT for diagnosing immediate DHRs against drug classes (e.g., antibiotics, biologicals, NSAIDs, NMBAs, and radio-contrast media). Influencing factors like the selection of stimulants or of the identification and activation markers, the stimulation protocol, gating strategies, and cut-off definition were addressed in this overview on BAT performance. The overall aim was to evaluate the suitability of BAT as biomarker for the diagnosis of IDHRs.

Furthermore, an UpToDate review on “Overview of in vitro allergy tests” (Nolte et al, 2016) states that “The basophil histamine release test measures the release of histamine from human peripheral blood basophils incubated with allergen. When well-characterized allergens are used, this test is similar to skin testing in accuracy. The test relies on living cells and thus requires that blood samples are submitted and tested within 24 hours. Only a few laboratories perform the test. Basophil histamine release is not standardized and is considered an investigative tool for drug, food, and environmental allergens. Other tests of basophil function following incubation with allergen include release of leukotriene C4 (LTC4) and measurement of the level of activation via expression of surface proteins (such as CD63 or CD203c) by flow cytometry. Although promising, these tests are not as useful as skin testing and are not approved for diagnostic use in the United States”.

XIX. Measurement of Serum Food-Antigen-Specific IgE for Predicting Food Allergy Development

Spergel and colleagues (2015) noted that children with atopic dermatitis (AD) have a higher risk for development of food allergies. These researchers examined the incidence of food allergy development in infants with AD and the predictive value of serum food-antigen-specific IgE (sIgE) measurements. This trial examined the long-term safety and effectiveness of pimecrolimus cream 1% in more than 1,000 infants (3 to 18 months) with mild-to-severe AD without a history of food allergy. Food allergy
development was followed throughout a 36-month randomized double-blind phase followed by an open-label (OL) phase up to 33 months. Furthermore, sIgE for cow’s milk, egg white, peanut, wheat, seafood mix, and soybean were measured by ImmunoCAP at baseline, end of the double-blind phase, and end of OL phase. By the end of the OL phase, 15.9% of infants with AD developed at least 1 food allergy; allergy to peanut was most common (6.6%), followed by cow’s milk (4.3%) and egg white (3.9%). Seafood, soybean, and wheat allergies were rare. Levels of sIgE for milk, egg, and peanut increased with severity of AD, as determined by Investigator’s Global Assessment score. These investigators assigned sIgE decision points for the 6 foods and tested their ability to predict definite food allergy in this population. Positive predictive values (PPVs) for published and newly developed sIgE decision points were low (less than 0.6 for all values tested). The authors concluded that in a large cohort of infants at risk for development of food allergy, sIgE levels were not clinically useful for predicting food allergy development.

XX. Patch Testing with Metal Alloy Discs

Thomas and associates (2015) noted that intolerance reactions to metal implants may be caused by metal allergy. However, prior to implantation, “prophetic”/prophylactic patch testing should not be performed. Pre-implant patch testing should only be done to verify or exclude metal allergy in patients with a corresponding history. In case of implant-related complications -- in particular following replacement arthroplasty -- such as pain, effusion, skin lesions, reduced range of motion or implant loosening, orthopedic causes should be ruled out first. Work-up of suspected metal implant allergy should then be done using the Deutsche Keramische Gesellschaft (DKG) standard series, which includes nickel, cobalt, and chromium preparations. Various studies assessing the usefulness of metal alloy discs for patch testing have shown this particular approach to be ineffective with respect to providing reliable information on metal allergy. Any positive reaction in such tests cannot be assigned to a specific metal contained within the alloy. Furthermore, there is a risk of broad and indiscriminate use of these readily available discs. Accordingly, given the lack of additional benefit compared to patch testing with standardized metal salt preparations, the authors, on behalf of the DKG, did not recommend patch testing with metal alloy discs.

XXI. Sublingual Immunotherapy for Seasonal Allergic Rhinitis

In a randomized, double-blind, placebo-controlled, 3-parallel-group study, Scadding and colleagues (2017) examined if 2 years of treatment with grass pollen sublingual
immunotherapy, compared with placebo, provides improved nasal response to allergen challenge at 3-year follow-up. This trial was performed in a single academic center in adult patients with moderate-to-severe seasonal allergic rhinitis (interfering with usual daily activities or sleep). First enrollment was March 2011, last follow-up was February 2015. A total of 36 participants received 2 years of sublingual immunotherapy (daily tablets containing 15 µg of major allergen Phleum p 5 and monthly placebo injections), 36 received subcutaneous immunotherapy (monthly injections containing 20 µg of Phleum p 5 and daily placebo tablets) and 34 received matched double-placebo. Nasal allergen challenge was performed before treatment, at 1 and 2 years of treatment, and at 3 years (1 year after treatment discontinuation). Total nasal symptom scores (TNSS; range of 0 [best] to 12 [worst]) were recorded between 0 and 10 hours after challenge. The minimum clinically important difference for change in TNSS within an individual is 1.08. The primary outcome was TNSS comparing sublingual immunotherapy versus placebo at year 3. Subcutaneous immunotherapy was included as a positive control. The study was not powered to compare sublingual immunotherapy with subcutaneous immunotherapy. Among 106 randomized participants (mean age of 33.5 years; 34 women [32.1 %]), 92 completed the study at 3 years. In the intent-to-treat population, mean TNSS score for the sublingual immunotherapy group was 6.36 (95 % CI: 5.76 to 6.96) at pre-treatment and 4.73 (95 % CI: 3.97 to 5.48) at 3 years, and for the placebo group, the score was 6.06 (95 % CI: 5.23 to 6.88) at pre-treatment and 4.81 (95 % CI: 3.97 to 5.65) at 3 years. The between-group difference (adjusted for baseline) was -0.18 (95 % CI: -1.25 to 0.90; [p = 0.75]). The authors concluded that among patients with moderate-to-severe seasonal allergic rhinitis, 2 years of sublingual grass pollen immunotherapy was not significantly different from placebo in improving the nasal response to allergen challenge at 3-year follow-up.

XXII. Food Protein-Induced Enterocolitis Syndrome

Nowak-Węgrzyn and colleagues (2017a) stated that food protein-induced enterocolitis syndrome (FPIES) is a non-IgE-, cell-mediated food allergy of unknown prevalence and pathophysiology. Onset is typically during the 1st year of life; seafood-induced FPIES may start in adulthood. Acute FPIES manifests within 1 to 4 hours after ingestion with repetitive emesis, pallor, and lethargy progressing to dehydration and hypovolemic shock in 15 % of cases. Chronic FPIES manifests with intermittent emesis, watery diarrhea, and poor growth progressing to dehydration and hypovolemic shock over a period of days to weeks. Chronic FPIES has been only reported in infants aged less than 3 months fed with cow milk (CM) or soy formula. The most
common triggers are CM, soy, rice, and oat. Diagnosis of FPIES relies on recognition of a pattern of clinical symptoms and may be missed owing to the absence of typical allergic symptoms (e.g., urticaria, wheezing) and delayed onset in relation to food ingestion. Physician-supervised food challenge is recommended if diagnosis or the trigger food is not clear and to evaluate for resolution. Testing for food-specific IgE (sIgE) is usually negative, although a subset of patients, usually with CM-induced FPIES may develop sensitization to foods. Such atypical FPIES tends to have a more prolonged course. Despite the potential severity of the reactions, no fatalities have been reported, and FPIES has a favorable prognosis. In most cases, FPIES resolves by age 3 to 5 years, although persistence of CM-induced FPIES and soy FPIES into adulthood has been reported. The 1st international consensus guidelines on diagnosis and management of FPIES were published in 2017. Given that the pathophysiology of FPIES is poorly understood, there are no diagnostic biomarkers and no therapies to accelerate resolution. These unmet needs warrant future investigations to improve the care of patients with FPIES.

The International consensus guidelines for the diagnosis and management of food protein-induced enterocolitis syndrome (Nowak-Węgrzyn et al, 2017b) does not recommend routine testing for food sIgE to identify food triggers of FPIES because FPIES is not an IgE-mediated process [Strength of recommendation: Moderate; Evidence strength: III; Evidence grade: C].

An UpToDate review on “Food protein-induced enterocolitis syndrome (FPIES)” (Nowak-Węgrzyn, 2017c) states that “Allergy testing -- Overall, the majority of patients have negative skin prick tests and undetectable serum food-specific IgE at diagnosis. Approximately 21 % of patients with solid-food FPIES and 18 to 30 % with cow’s milk or soy FPIES have detectable food-specific IgE to the same food, and up to 39 % of children with FPIES have sensitization (positive IgE test) to different foods. Atopy patch testing (APT) was evaluated in 19 infants aged 5 to 30 months with challenge-confirmed FPIES. APT correctly predicted 28 of 33 outcomes of OFCs. All positive OFCs had a positive APT, although 5 patients with positive APT did not react upon OFC. These results have not been confirmed by other studies. Thus, further evaluation is required to determine the role of APT in the diagnosis of FPIES”.
XXIII. Genetic Testing for Food Allergy

Li and colleagues (2016) stated that food allergy is common among children and adults worldwide. Recent studies have improved our understanding of the genetic mechanism of food allergy and further studies may result in clinical application through genetic testing. Genetic factors are important in the development of food allergy. An increasing number of genes have been associated with food allergy in recent years. These include mutations and genetic variants in the filaggrin gene, the association of human leukocyte antigen (HLA)-DR and HLA-DQ regions with food allergy, copy number variation impacting CTNNA3 and RBFOX1, DNA methylation that partially mediates single nucleotide polymorphism (SNP) association at the HLA-DR and HLA-DQ loci, as well as other genes. Several studies have implicated differences in gut microbiota composition in food allergy. The authors concluded that with the advance of high-throughput genotyping and sequencing techniques together with improved analytical methods, the contributions of genetic and environmental factors in development of food allergy are being clarified. Yet much remains to be explored and more studies with larger sample sizes, better phenotyping, and improved quality control genomics methods are needed. These researchers stated that a reliable genetic test should provide reliable and relevant information regarding development of the disease in question. They noted that although underlying genetic mechanism for food allergy are starting to unravel, a panel of reliable markers for genetic testing in food allergy is still lacking. The future possibilities of such testing lie in further research dissecting the complex interplay between genetic components and diverse environmental factors, including the microbiota, in the pathogenesis and expression of food allergy. In the near future, these investigators anticipate to establish a panel of biomarkers to identify high-risk populations where preventive measures can reduce severe food allergy emergencies, facilitate accurate identification of allergen sources and to predict effective treatment options and thus improve overall patient care.

Yang and associates (2017) noted that refractory esophageal stricture (RES) may be attributed to food allergy. Its etiology and pathogenesis are not fully understood. Identification of novel genetic variants associated with this disease by exome sequencing (exome-seq) may provide new mechanistic insights and new therapeutic targets. These researchers identified new and novel disease-associating variants, whole-
exome sequencing (WES) was performed on an Illumina NGS platform in 3 children with RES as well as food allergy. A total of 91,024 variants were identified. By filtering out “normal variants” against those of the 1,000 Genomes Project, these investigators identified 12,741 remaining variants, which are potentially associated with RES plus food allergy. Among these variants, there are 11,539 SNPs, 627 deletions, 551 insertions and 24 mixture variants. These variants are located in 1,370 genes. They are enriched in biological processes or pathways such as cell adhesion, digestion, receptor metabolic process, bile acid transport and the neurological system. By the PubMatrix analysis, 50 out of the top 100 genes, which contain most variants, have not been previously associated with any of the 17 allergy-associated diseases. These 50 genes represent newly identified allergy-associated genes. Those variants of 627 deletions and 551 insertions have also not been reported before in RES with food allergy. The authors concluded that exome-seq is potentially a powerful tool to identify potential new biomarkers for RES with food allergy. This study has identified a number of novel genetic variants, opening new avenues of research in RES plus food allergy. Moreover, they stated that additional validation in larger and different patient populations and further exploration of the underlying molecular mechanisms are needed. These researchers noted that this study was limited to only 3 patients, and thus no solid conclusion could be drawn without a proper control and a large sample size. Replication of these findings in larger and different populations, in addition to experimental delineation of the underlying molecular mechanisms, is needed to validate the candidate variants identified here as true genetic biomarkers and to develop them into potential therapeutic targets in refractory esophageal stricture presenting with food allergy.

**XXIV. Intradermal Grass Pollen Immunotherapy for the Treatment of Allergic Rhinitis**

Slovick and colleagues (2017) noted that repeated low-dose grass pollen intradermal allergen injection suppresses allergen-induced cutaneous late-phase responses comparably with conventional subcutaneous and sublingual immunotherapy. These researchers evaluated the safety and effectiveness of grass pollen intradermal immunotherapy in the treatment of allergic rhinitis. These researchers randomly assigned 93 adults with grass pollen-induced allergic rhinitis to receive 7 pre-seasonal intradermal allergen injections (containing 7 ng of Phl p 5 major allergen) or a histamine control. The primary end-point was daily combined symptom-medication scores during the 2013 pollen season (area under the curve). Analysis was by intention-to-treat. Skin biopsy specimens were collected after intradermal allergen challenges, and late-phase
responses were measured 4 and 7, 10, or 13 months after treatment. There was no significant difference in the primary end-point between treatment arms (active, n = 46; control, n = 47; MD, 14; 95 % CI: -172.5 to 215.1; p = 0.80). Among secondary end-points, nasal symptoms were worse in the intradermal treatment group, as measured based on daily (MD, 35; 95 % CI: 4.0 to 67.5; p = 0.03) and VAS (MD, 53; 95 % CI: -11.6 to 125.2; p = 0.05) scores. In a per-protocol analysis intradermal immunotherapy was further associated with worse asthma symptoms and fewer symptom-free days. Intradermal immunotherapy increased serum Phleum pratense-specific IgE levels (p = 0.001) compared with those in the control arm. T-cells cultured from biopsy specimens of subjects undergoing intradermal immunotherapy had higher expression of the TH2 surface marker CRTH2 (p = 0.04) and lower expression of the TH1 marker CXCR3 (p = 0.01), respectively. Late-phase responses remained inhibited 7 months after treatment (p = 0.03). The authors concluded that this was the 1st RCT to directly evaluate the effectiveness of intradermal grass pollen immunotherapy, and the results suggested that this approach is not clinically effective, despite local suppression of skin late-phase responses. Moreover, the data suggested that this resulted in immunologic priming and worsening of allergic rhinitis symptoms, providing direct evidence that dermal allergen exposure has the potential to exacerbate rather than ameliorate allergic disease.

XXV. Intramuscular Steroids for the Treatment of Allergic Rhinitis:

In a review entitled “Seasonal allergic rhinitis: Limited effectiveness of treatments” (No authors listed, 2008), the article noted that seasonal allergic rhinitis, otherwise known as hay fever, is a harmless condition, although it can cause major discomfort and interfere with activities of daily living. The authors conducted a review of the literature, based on their in-house methodology, to determine the risk-benefits of treatments used in this setting. Placebo-controlled trials showed that sodium cromoglicate relieved symptoms, especially if it is used before symptoms appear. Adverse effects were rare with sodium cromoglicate nasal solutions and eye drops. Nasal steroids have well-documented efficacy; beclometasone is the best choice. Adverse effects include epistaxis, nasal irritation and, occasionally, systemic disorders. Oral anti-histamines are less effective than nasal steroids. They also provoke adverse effects, especially drowsiness. Nasal azelastine appeared to have a similar efficacy as oral anti-histamines. The adverse effects of systemic steroids must not be over-looked, especially with long-term use. Oral administration is an alternative for severe symptoms that do not respond to other treatments, although this is rarely the case. Long-
acting intramuscular steroids carry an increased risk of adverse effects. Despite evaluation in several RCTs, there is no firm evidence that homeopathic preparations have any specific efficacy in allergic rhinitis. Vasoconstrictors, ipratropium and montelukast, have negative risk-benefit balances in hay fever. When a single allergen is responsible (grasses, ragweed, birch), clinical trials suggested that specific desensitization can provide a modest improvement. However, this treatment carries a risk of local adverse effects, as well as a risk of rare but severe anaphylactic reactions, especially in patients who also have unstable severe asthma. Sublingual desensitization appeared to be even less effective than subcutaneous desensitization in adults. Follow-up is too short to know whether there is a risk of severe anaphylactic reactions. The results of pediatric studies were even less convincing. In practice, when drug therapy is needed to relieve symptoms of seasonal allergic rhinitis, sodium cromoglicate is the 1st-line treatment. If a nasal steroid solution is chosen, it should be used for the shortest possible period.

The Global Allergy and Asthma European Network’s “Allergic rhinitis and its impact on asthma (ARIA) guidelines” (Brozek et al, 2010) recommended that clinicians do not administer intramuscular glucocorticosteroids (strong recommendation / low-quality evidence). Possible side effects of intramuscular glucocorticosteroids may be far more serious than the condition they are supposed to treat (i.e., allergic rhinitis).

Agency for Healthcare Research and Quality (AHRQ)'s Effective Health Care Program on “Treatments for seasonal allergic rhinitis” (2012) stated that “although FDA approved for SAR, intramuscular corticosteroid injections are not recommended for the treatment of SAR and will not be reviewed in this report”.

Aasbjerg et al (2013) noted that in Denmark, 23 % of the adult population have allergic rhinitis. These researchers have previously demonstrated that a majority of hay fever patients are treated with depot-steroid injections in violation of the guidelines. It has been hypothesized that 1 to 2 annual depot-steroid injections are not harmful to the patient. These investigators examined if the depot-steroid treatment of allergic rhinitis instead of immunotherapy increases risk of steroid-related diseases. They carried out a retrospective study based on Danish National Registries 1995 to 2011 covering diagnoses, medications, as well as clinical outcomes. The main analysis was time-dependent Poisson regression models with results presented as rate ratios (RR), and
incidence per 1,000 patient years. Steroid use was defined as minimum 1 injection during April to July for at least 3 consecutive years. Treatment with specific immunotherapy against grass, birch or both was used as non-steroid control group. Relative risk of adverse outcomes such as osteoporosis, infections, diabetes and/or tendon rupture was investigated. These researchers identified 47,382 individuals with rhinitis; 55.8 % treated with steroids, 37.6 % with immunotherapy, and 6.7 % with both. No significant differences in infections or tendon rupture were observed. For steroid treatment RR of diabetes was 1.5 (95 % CI: 1.3 to 1.8; p < 0.001), incidence 3.9 (95 % CI: 3.5 to 4.3), and RR of osteoporosis was 1.2 (95 % CI: 1.0 to 1.5; p = 0.023), incidence 2.8 (95 % CI: 2.5 to 3.1). Risk of diabetes culminated within the first 2 years of treatment start. The authors concluded that compared to immunotherapy regular use of depot-steroid injections to treat allergic rhinitis is associated with increased risk of being diagnosed with diabetes and osteoporosis. They stated that treating seasonal allergic rhinitis with depot-steroid injections should be abandoned and replaced with immunotherapy, as annual depot-steroid treatment is associated with increased risk of diabetes and osteoporosis.

Furthermore, UpToDate reviews on “Pharmacotherapy of allergic rhinitis” (deShazo and Kemp, 2017) and “Allergic conjunctivitis: Management” (Hamrah and Dana, 2017) do not mention intramuscular steroid as a therapeutic option.

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 / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>95004</td>
<td>Percutaneous tests (scratch, puncture, prick) with allergenic extracts, immediate type reaction, including test interpretation and report by a physician, specify number of tests</td>
</tr>
<tr>
<td>95017</td>
<td>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</td>
</tr>
<tr>
<td>95018</td>
<td>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</td>
</tr>
</tbody>
</table>

ICD-10 codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J30.1 - J30.9</td>
<td>Allergic rhinitis</td>
</tr>
<tr>
<td>L20.84</td>
<td>Intrinsic (allergic) eczema</td>
</tr>
<tr>
<td>L25.4</td>
<td>Unspecified contact dermatitis due to food in contact with skin</td>
</tr>
<tr>
<td>L27.2</td>
<td>Dermatitis due to ingested food</td>
</tr>
<tr>
<td>L50.0</td>
<td>Allergic urticaria</td>
</tr>
<tr>
<td>T50.995+</td>
<td>Adverse effect of other drugs, medicaments and biological substances</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>T63.001+ -</td>
<td>Toxic effect of contact with venomous animals and plants</td>
</tr>
<tr>
<td>T63.94x+</td>
<td></td>
</tr>
<tr>
<td>T78.00+ -</td>
<td>Anaphylactic shock due to adverse food reaction</td>
</tr>
<tr>
<td>T78.09+</td>
<td></td>
</tr>
<tr>
<td>T78.1+</td>
<td>Other adverse food reactions, not elsewhere classified</td>
</tr>
</tbody>
</table>

Intradermal (Intracutaneous) when IgE-mediated reactions occur:

CPT codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>95024</td>
<td>Intracutaneous (intradermal) tests with allergenic extracts, immediate type reaction, including test interpretation and report by a physician, specify number of tests</td>
</tr>
<tr>
<td>95027</td>
<td>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</td>
</tr>
<tr>
<td>95028</td>
<td>Intracutaneous (intradermal) tests with allergenic extracts, delayed type reaction, including reading, specify number of tests</td>
</tr>
</tbody>
</table>

ICD-10 codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J30.1  - J30.9</td>
<td>Allergic rhinitis</td>
</tr>
<tr>
<td>L20.84</td>
<td>Intrinsic (allergic) eczema</td>
</tr>
<tr>
<td>L25.4</td>
<td>Unspecified contact dermatitis due to food in contact with skin</td>
</tr>
<tr>
<td>L27.2</td>
<td>Dermatitis due to ingested food</td>
</tr>
<tr>
<td>L50.0</td>
<td>Allergic urticaria</td>
</tr>
<tr>
<td>T50.995+</td>
<td>Adverse effect of other drugs, medicaments and biological substances</td>
</tr>
<tr>
<td>T63.001+ -</td>
<td>Toxic effect of contact with venomous animals and plants</td>
</tr>
<tr>
<td>T63.94x+</td>
<td></td>
</tr>
<tr>
<td>T78.00+ -</td>
<td>Anaphylactic shock due to adverse food reaction</td>
</tr>
<tr>
<td>T78.09+</td>
<td></td>
</tr>
<tr>
<td>T78.1+</td>
<td>Other adverse food reactions, not elsewhere classified</td>
</tr>
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</table>

Skin Endpoint Titration (SET):

CPT codes covered if selection criteria are met:
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>95027</td>
<td>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</td>
</tr>
</tbody>
</table>

ICD-10 codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J30.1 - J30.9</td>
<td>Allergic rhinitis</td>
</tr>
<tr>
<td>T63.001+ - T63.94x+</td>
<td>Toxic effect of contact with venomous animals and plants</td>
</tr>
<tr>
<td>Z91.030 - Z91.038</td>
<td>Insect allergy status</td>
</tr>
</tbody>
</table>

Skin Patch Testing:

CPT codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>95044</td>
<td>Patch or application tests(s) (specify number of tests)</td>
</tr>
</tbody>
</table>

ICD-10 codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>L20.84</td>
<td>Intrinsic (allergic) eczema L23.0</td>
</tr>
<tr>
<td>- L23.9</td>
<td>Allergic contact dermatitis</td>
</tr>
<tr>
<td>L50.0</td>
<td>Allergic urticaria</td>
</tr>
</tbody>
</table>

ICD-10 codes not covered for indications listed in the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>K52.21</td>
<td>Food protein-induced enterocolitis syndrome</td>
</tr>
</tbody>
</table>

Photo Patch Test:

CPT codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>95052</td>
<td>Photo patch test(s) (specify number of tests)</td>
</tr>
</tbody>
</table>

ICD-10 codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>L56.1</td>
<td>Drug photoallergic response</td>
</tr>
<tr>
<td>L56.2</td>
<td>Photocontact dermatitis [berloque dermatitis]</td>
</tr>
<tr>
<td>L56.3</td>
<td>Solar urticaria</td>
</tr>
</tbody>
</table>

Photo Tests:

CPT codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>95056</td>
<td>Photo tests</td>
</tr>
</tbody>
</table>

ICD-10 codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>L56.1</td>
<td>Drug photoallergic response</td>
</tr>
<tr>
<td>L56.2</td>
<td>Photocontact dermatitis [berloque dermatitis]</td>
</tr>
<tr>
<td>L56.3</td>
<td>Solar urticaria</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>--------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td><strong>Bronchial Challenge Test:</strong></td>
</tr>
<tr>
<td></td>
<td>CPT codes covered if selection criteria are met:</td>
</tr>
<tr>
<td>95070</td>
<td>Inhalation bronchial challenge testing (not including necessary pulmonary tests); with histamine, methacholine, or similar compounds</td>
</tr>
<tr>
<td>95071</td>
<td>with antigens or gases, specify</td>
</tr>
<tr>
<td></td>
<td><strong>Other CPT codes related to the CPB:</strong></td>
</tr>
<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 (eg, 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>
<tr>
<td></td>
<td><strong>HCPCS codes covered if selection criteria are met:</strong></td>
</tr>
<tr>
<td>J7674</td>
<td>Methacholine chloride administered as inhalation solution through a nebulizer, per 1mg</td>
</tr>
<tr>
<td></td>
<td><strong>ICD-10 codes covered if selection criteria are met:</strong></td>
</tr>
<tr>
<td>J45.20 - J45.998</td>
<td>Asthma</td>
</tr>
<tr>
<td>J67.0 - J67.9</td>
<td>Hypersensitivity pneumonitis due to organic dust</td>
</tr>
<tr>
<td>J82</td>
<td>Pulmonary eosinophilia, not elsewhere classified</td>
</tr>
<tr>
<td></td>
<td><strong>Exercise Challenge Testing:</strong></td>
</tr>
<tr>
<td></td>
<td>CPT codes covered if selection criteria are met:</td>
</tr>
<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>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>--------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------</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>
<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>94240</td>
<td>Functional residual capacity or residual volume; helium method, nitrogen open circuit method, or other method</td>
</tr>
<tr>
<td>94350</td>
<td>Determination of maldistribution of inspired gas; multiple breath nitrogen washout curve including alveolar nitrogen or helium equilibration time</td>
</tr>
<tr>
<td>94360</td>
<td>Determination of resistance to airflow, oscillatory or plethysmographic methods</td>
</tr>
<tr>
<td>94375</td>
<td>Respiratory flow volume loop</td>
</tr>
<tr>
<td>94617</td>
<td>Exercise test for bronchospasm, including pre- and post-spirometry, electrocardiographic recording(s), and pulse oximetry</td>
</tr>
<tr>
<td>94618</td>
<td>Pulmonary stress testing (eg, 6-minute walk test), including measurement of heart rate, oximetry, and oxygen titration, when performed</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>94720</td>
<td>Carbon monoxide diffusing capacity (e.g., single breath, steady state)</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 1 mg</td>
</tr>
</tbody>
</table>

ICD-10 codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J45.990</td>
<td>Exercise induced bronchospasm</td>
</tr>
</tbody>
</table>

Ingestion (Oral) Challenge Test:                                                                                                                                                                                                 |

CPT codes covered if selection criteria are met:
ICD-10 codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>L27.2</td>
<td>Dermatitis due to ingested food</td>
</tr>
<tr>
<td>T50.995+</td>
<td>Adverse effect of other drugs, medicaments and biological substances</td>
</tr>
<tr>
<td>T78.00+ - T78.1+</td>
<td>Anaphylactic shock due to adverse food reaction</td>
</tr>
<tr>
<td>T78.1+</td>
<td>Other adverse food reactions, not elsewhere classified</td>
</tr>
<tr>
<td>Z88.0 - Z88.9</td>
<td>Allergy status to drugs, medicaments and biological substances</td>
</tr>
</tbody>
</table>

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

CPT codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>83516</td>
<td>Immunoassay for analyte other than infectious agent antibody or infectious agent antigen, qualitative or semiquantitative; multiple step method</td>
</tr>
<tr>
<td>83518</td>
<td>single step method (e.g., reagent strip)</td>
</tr>
<tr>
<td>83519</td>
<td>Immunoassay, analyte quantitative; by radiopharmaceutical technique (e.g., RIA)</td>
</tr>
<tr>
<td>83520</td>
<td>not otherwise specified</td>
</tr>
<tr>
<td>86003</td>
<td>Allergen specific IgE; quantitative or semi-quantitative, each allergen [covered for up to 40 in vitro IgE antibody tests for inhalant allergies and 12 tests for food and other allergies]</td>
</tr>
<tr>
<td>86005</td>
<td>qualitative, multi-allergen screen (dipstick, paddle or disk) [covered for up to 40 in vitro IgE antibody tests for inhalant allergies and 12 tests for food and other allergies]</td>
</tr>
</tbody>
</table>

ICD-10 codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>B44.81</td>
<td>Allergic bronchopulmonary aspergillosis</td>
</tr>
<tr>
<td>B65.0 - B83.9</td>
<td>Helminthiases [parasitic diseases]</td>
</tr>
<tr>
<td>B85.0 - B89</td>
<td>Pediculosis, acariasis and other infestations [parasitic diseases]</td>
</tr>
<tr>
<td>F43.0</td>
<td>Acute stress reaction [uncooperative patients]</td>
</tr>
<tr>
<td>F70 - F79</td>
<td>Intellectual disabilities [uncooperative patients]</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>------------</td>
<td>-----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>F84.0 - F84.9</td>
<td>Pervasive developmental disorders [uncooperative patients]</td>
</tr>
<tr>
<td>F90.0 - F90.9</td>
<td>Attention-deficit hyperactivity disorders [uncooperative patients]</td>
</tr>
<tr>
<td>F91.0 - F91.9</td>
<td>Conduct disorders [uncooperative patients]</td>
</tr>
<tr>
<td>J30.1 - J30.9</td>
<td>Allergic rhinitis</td>
</tr>
<tr>
<td>L20.0 - L30.9</td>
<td>Dermatitis and eczema</td>
</tr>
<tr>
<td>L50.0</td>
<td>Allergic urticaria</td>
</tr>
<tr>
<td>L50.3</td>
<td>Dermatographic urticarial [dermatographism]</td>
</tr>
<tr>
<td>L85.0</td>
<td>Acquired ichthyosis</td>
</tr>
<tr>
<td>Q80.0 - Q80.9</td>
<td>Congenital ichthyosis</td>
</tr>
<tr>
<td>T50.995+</td>
<td>Adverse effect of other drugs, medicaments and biological substances</td>
</tr>
<tr>
<td>T63.001+ - T63.94x+</td>
<td>Toxic effect of contact with venomous animals and plants</td>
</tr>
<tr>
<td>T78.00+ - T78.09+</td>
<td>Anaphylactic shock due to adverse food reaction</td>
</tr>
<tr>
<td>T78.1+</td>
<td>Other adverse food reactions, not elsewhere classified [except Alpha gal allergy testing for meat allergy]</td>
</tr>
<tr>
<td>T88.6xx+</td>
<td>Anaphylactic reaction due to adverse effect of correct drug or medicament properly administered [risk of anaphylaxis from skin testing]</td>
</tr>
</tbody>
</table>

Total Serum IgE:  
CPT codes covered if selection criteria are met:  
82785 Gammaglobulin; IgE  
ICD-10 codes covered if selection criteria are met:  
B44.81 Allergic bronchopulmonary aspergillosis  
Lymphocyte transformation tests:  
CPT codes covered if selection criteria are met:  
86353 Lymphocyte transformation, mitogen (phytomitogen) or antigen induced blastogenesis [not covered for in-vitro metal allergy testing]  
ICD-10 codes covered if selection criteria are met:  
B37.0 Candidal stomatitis  
B37.83 Candidal cheilitis  
C37.0 Malignant neoplasm of thymus  
D15.0 Benign neoplasm of thymus
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>D81.0 - D81.9</td>
<td>Combined immunodeficiencies</td>
</tr>
<tr>
<td>D82.0</td>
<td>Wiskott-Aldrich syndrome</td>
</tr>
<tr>
<td>D82.1</td>
<td>DiGeorge's syndrome</td>
</tr>
<tr>
<td>D83.0 - D83.9</td>
<td>Common variable immunodeficiency</td>
</tr>
<tr>
<td>T56.7+</td>
<td>Toxic effects of beryllium and its compounds</td>
</tr>
</tbody>
</table>

Tests considered experimental and investigational for routine allergy testing:

CPT codes not covered for indications listed in the CPB:

Basophil activation test (BAT), Genetic testing for food allergy - no specific code:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>82784</td>
<td>Gammaglobulin (immunoglobulin) IgA, IgD, IgG, IgM, each</td>
</tr>
<tr>
<td>84238</td>
<td>Receptor assay; non-endocrine (specify receptor) [cytokine and cytokine assay]</td>
</tr>
<tr>
<td>84600</td>
<td>Volatiles (eg, acetic anhydride, diethylether)</td>
</tr>
<tr>
<td>86001</td>
<td>Allergen specific IgG quantitative or semi-quantitative, each allergen</td>
</tr>
<tr>
<td>86003</td>
<td>Allergen specific IgE; quantitative or semiquantitative, crude allergen extract, each. [testing for food-specific IgE to identify food triggers of FPIES]</td>
</tr>
<tr>
<td>86021</td>
<td>Antibody identification; leukocyte antibodies</td>
</tr>
<tr>
<td>86140</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>86160</td>
<td>Complement; antigen, each component</td>
</tr>
<tr>
<td>86161</td>
<td>functional activity, each component</td>
</tr>
<tr>
<td>86162</td>
<td>total hemolytic (CH50)</td>
</tr>
<tr>
<td>86243</td>
<td>Fc receptor</td>
</tr>
<tr>
<td>86332</td>
<td>Immune complex assay</td>
</tr>
<tr>
<td>86343</td>
<td>Leukocyte histamine release test (LHR)</td>
</tr>
<tr>
<td>86352</td>
<td>Cellular function assay involving stimulation (eg, mitogen or antigen) and detection of biomarker (EG, ATP) [anti-IgE receptor antibody testing]</td>
</tr>
<tr>
<td>86485</td>
<td>Skin test; candida</td>
</tr>
<tr>
<td>86628</td>
<td>Antibody; candida</td>
</tr>
<tr>
<td>88184</td>
<td>Flow cytometry, cell surface, cytoplasmic, or nuclear marker, technical component only; first marker [anti-IgE receptor antibody testing]</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>---------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>88185</td>
<td>each additional marker (List separately in addition to code for first marker) [anti-IgE receptor antibody testing]</td>
</tr>
<tr>
<td>88341</td>
<td>Immunohistochemistry or immunocytochemistry, per specimen; each additional single antibody stain procedure (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>88342</td>
<td>Immunohistochemistry or immunocytochemistry, per specimen; initial single antibody stain procedure</td>
</tr>
<tr>
<td>88344</td>
<td>Immunohistochemistry or immunocytochemistry, per specimen; each multiplex antibody stain procedure</td>
</tr>
<tr>
<td>88346</td>
<td>Immunofluorescence, per specimen; initial single antibody stain procedure</td>
</tr>
<tr>
<td>95060</td>
<td>Ophthalmic mucous membrane tests</td>
</tr>
<tr>
<td>95065</td>
<td>Direct nasal mucous membrane test</td>
</tr>
<tr>
<td>95831</td>
<td>Muscle testing, manual (separate procedure) with report; extremity (excluding hand) or trunk</td>
</tr>
<tr>
<td>95832</td>
<td>hand, with or without comparison with normal side</td>
</tr>
<tr>
<td>95833</td>
<td>total evaluation of body, excluding hands</td>
</tr>
<tr>
<td>95834</td>
<td>total evaluation of body, including hands</td>
</tr>
<tr>
<td>G0461</td>
<td>Immunohistochemistry or immunocytochemistry, per specimen; first single or multiplex antibody stain</td>
</tr>
<tr>
<td>G0462</td>
<td>each additional single or multiplex antibody stain (list separately in addition to code for primary procedure)</td>
</tr>
</tbody>
</table>

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

CPT codes not covered for indications listed in the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>83516</td>
<td>Immunoassay for analyte other than infectious agent antibody or infectious agent antigen, qualitative or semiquantitative; multiple step method</td>
</tr>
<tr>
<td>83518</td>
<td>single step method (e.g., reagent strip)</td>
</tr>
<tr>
<td>83519</td>
<td>Immunoassay, analyte quantitative; by radiopharmaceutical technique (e.g., RIA)</td>
</tr>
<tr>
<td>83520</td>
<td>not otherwise specified</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>----------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>86807</td>
<td>Serum screening for cytotoxic percent reactive antibody (PRA); standard method</td>
</tr>
<tr>
<td>86808</td>
<td>quick method</td>
</tr>
</tbody>
</table>

ICD-10 codes not covered for indications listed in the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>F90.0 - F90.9</td>
<td>Attention-deficit hyperactivity disorders</td>
</tr>
<tr>
<td>G43.001 - G43.919</td>
<td>Migraine</td>
</tr>
<tr>
<td>G44.001 - G44.89</td>
<td>Other headache syndromes</td>
</tr>
<tr>
<td>J30.1 - J30.9</td>
<td>Allergic rhinitis</td>
</tr>
<tr>
<td>J31.0 - J31.2</td>
<td>Chronic rhinitis, nasopharyngitis and pharyngitis</td>
</tr>
<tr>
<td>J32.0 - J32.9</td>
<td>Chronic sinusitis</td>
</tr>
<tr>
<td>K21.0 - K21.9</td>
<td>Gastro-esophageal reflux disease</td>
</tr>
<tr>
<td>K50.00 - K50.919</td>
<td>Crohn's disease [regional enteritis]</td>
</tr>
<tr>
<td>K51.00 - K51.919</td>
<td>Ulcerative colitis</td>
</tr>
<tr>
<td>K52.21</td>
<td>Food protein-induced enterocolitis syndrome</td>
</tr>
<tr>
<td>K58.0 - K58.9</td>
<td>Irritable bowel syndrome</td>
</tr>
<tr>
<td>L20.0 - L30.9</td>
<td>Dermatitis and eczema</td>
</tr>
<tr>
<td>L50.0 - L50.9</td>
<td>Urticaria</td>
</tr>
<tr>
<td>M05.00 - M14.89</td>
<td>Inflammatory polyarthropathies</td>
</tr>
<tr>
<td>M79.0 - M79.5</td>
<td>Other and unspecified soft tissue disorders, not elsewhere classified</td>
</tr>
<tr>
<td>N95.1</td>
<td>Menopausal and female climacteric states</td>
</tr>
<tr>
<td>R53.0 - R53.83</td>
<td>Malaise and fatigue</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>-----------------</td>
<td>------------------------------------------------------------</td>
</tr>
<tr>
<td>R04.0 - R04.1,</td>
<td>Symptoms and signs involving the head and neck</td>
</tr>
<tr>
<td>R06.5 - R06.7,</td>
<td></td>
</tr>
<tr>
<td>R06.89, R07.0,</td>
<td></td>
</tr>
<tr>
<td>R09.81 - R09.89,</td>
<td></td>
</tr>
<tr>
<td>R19.6, R22.0 -</td>
<td></td>
</tr>
<tr>
<td>R22.1, R47.01 -</td>
<td></td>
</tr>
<tr>
<td>R47.9, R48.0 -</td>
<td></td>
</tr>
<tr>
<td>R48.9, R49.0 -</td>
<td></td>
</tr>
<tr>
<td>R49.9, R51, R68.84</td>
<td></td>
</tr>
<tr>
<td>T78.1xxA - T78.1xxS</td>
<td>Other adverse food reactions, not elsewhere classified</td>
</tr>
</tbody>
</table>

There is no specific code for Cliffords Material Reactivity Testing:

Allergy immunotherapy:

CPT codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>95115 - 95170,</td>
<td>Professional services for allergen immunotherapy (for rapid desensitization see</td>
</tr>
<tr>
<td>95199</td>
<td>below) [except home administration] [not covered for intradermal grass pollen health]</td>
</tr>
</tbody>
</table>

CPT codes not covered for indications listed in the CPB:

Oral immunotherapy - no specific code:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>97810 - 97814</td>
<td>Acupuncture</td>
</tr>
</tbody>
</table>

HCPCS codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J0171</td>
<td>Injection, adrenalin, epinephrine, 0.1 mg</td>
</tr>
</tbody>
</table>

Other HCPCS codes related to the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J2357</td>
<td>Injection, omalizumab, 5mg</td>
</tr>
</tbody>
</table>

ICD-10 codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>H10.10 - H10.13</td>
<td>Acute atopic conjunctivitis</td>
</tr>
<tr>
<td>H10.44</td>
<td>Vernal conjunctivitis</td>
</tr>
<tr>
<td>H10.45</td>
<td>Other chronic allergic conjunctivitis</td>
</tr>
<tr>
<td>J30.1 - J30.9</td>
<td>Allergic rhinitis</td>
</tr>
<tr>
<td>J45.20 - J45.998</td>
<td>Asthma [covered for allergic (extrinsic)] [not covered for intrinsic (non-allergic)]</td>
</tr>
<tr>
<td>L20.89</td>
<td>Other atopic dermatitis [dust mite]</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>T63.001+</td>
<td>Toxic effect of contact with venomous animals and plants</td>
</tr>
<tr>
<td>T63.94x+</td>
<td></td>
</tr>
<tr>
<td>Z91.030</td>
<td>Insect allergy status [bees, hornets, wasps, and fire ants]</td>
</tr>
<tr>
<td>Z91.038</td>
<td></td>
</tr>
</tbody>
</table>

ICD-10 codes not covered for indications listed in the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>G43.001</td>
<td>Migraine</td>
</tr>
<tr>
<td>G43.919</td>
<td></td>
</tr>
<tr>
<td>L25.4</td>
<td>Unspecified contact dermatitis due to food in contact with skin</td>
</tr>
<tr>
<td>L27.2</td>
<td>Dermatitis due to ingested food</td>
</tr>
<tr>
<td>L50.8</td>
<td>Other urticaria [chronic]</td>
</tr>
<tr>
<td>T78.3+</td>
<td>Angioneurotic edema</td>
</tr>
</tbody>
</table>

Other Treatments:

Rapid desensitization:

CPT codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>95180</td>
<td>Rapid desensitization procedure, each hour (e.g., insulin, penicillin, equine serum)</td>
</tr>
</tbody>
</table>

ICD-10 codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J30.0 - J30.9</td>
<td>Allergic rhinitis</td>
</tr>
<tr>
<td>T50.995+</td>
<td>Adverse effect of other drugs, medicaments and biological substances</td>
</tr>
<tr>
<td>T63.001+</td>
<td>Toxic effect of contact with venomous animals and plants</td>
</tr>
<tr>
<td>T63.94x+</td>
<td></td>
</tr>
<tr>
<td>Z91.030</td>
<td>Allergy to insects</td>
</tr>
<tr>
<td>Z91.038</td>
<td></td>
</tr>
</tbody>
</table>

Aspirin Desensitization:

No specific code

Oralair, Grastek and Ragwitek:

ICD-10 codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J30.1</td>
<td>Allergic rhinitis due to pollen</td>
</tr>
</tbody>
</table>

The above policy is based on the following references:

http://www.aetna.com/cpb/medical/data/1_99/0038.html


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.

http://www.aetna.com/cpb/medical/data/1_99/0038.html


80. Corbillon 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.


recommendations of the German Contact Dermatitis Research Group
for seasonal allergic rhinitis. Cochrane Database Syst Rev. 2007;
(1):CD001936.
88. Altunç U, Pittler MH, Ernst E. Homeopathy for childhood and adolescence
89. National Asthma Education and Prevention Program (NAEPP). Expert panel
report 3: Guidelines for the diagnosis and management of asthma.
90. Calabria CW, Hagan L. The role of intradermal skin testing in inhalant
91. Hoeks SB, de Groot H, Hoekstra MO. Sublingual immunotherapy in
children with asthma or rhinoconjunctivitis: Not enough evidence because
of poor quality of the studies; a systematic review of literature. Ned
92. Röder E, Berger MY, de Groot H, van Wijk RG. Immunotherapy in children
and adolescents with allergic rhinoconjunctivitis: A systematic review.
for large local reactions caused by honeybee sting: A double-blind,
94. Koh GC, Shek LP, Goh DY, Van Bever H, Koh DS. Eosinophil cationic protein:
705.
95. Nelson HS. Multiallergen immunotherapy for allergic rhinitis and asthma. J
96. Cochard MM, Eigenmann PA. Sublingual immunotherapy is not always a
antibodies against gliadin and human tissue transglutaminase in stool to
screen for coeliac disease in children: Validation study. BMJ. 2006;332
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.


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173. deShazo RD, Kemp SF. Pharmacotherapy of allergic rhinitis. UpToDate Inc., Waltham, MA. Last reviewed October 2017.

The Pennsylvania Medical Assistance Programs considers oral leukotriene receptor antagonists to be medically necessary for allergic rhinitis.