Allergy Testing

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DESCRIPTION

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.

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

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

The Board of Directors of the American Academy of Otolaryngic Allergy (AAOA) endorsed strategies for testing for inhalant allergy, 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):

- Screening: Screen with no more than 14 relevant antigens plus appropriate controls.
- 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.
- 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, honeybee, hornet, wasp, fire ant) sensitivity and to determine the safe starting dose for venom immunotherapy.

In a guideline, the AAOA recommends screening prick tests with relevant antigens to determine which to use in subsequent SET. 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 antigens 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.

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.

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.

Ingestion (Oral) Challenge Testing
Ingestion (oral) challenge testing is an accepted method of diagnosing allergies to food, drug or other substances (i.e., metabisulfite).

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.

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 proven modalities.

Bead-Based Epitope Assay (BBEA)
A bead-based epitope assay (BBEA) has been proposed to diagnose and monitor patients with food allergies. The test breaks down allergenic proteins into smaller components, called epitopes. It then measures the reactivity of a patient's IgE/IgG4 levels to each epitope to generate a detailed reactivity profile that can be used by clinicians to manage the allergy. There are several IgE epitope mapping methods based on the binding of IgE molecules to peptides that are derived from the allergen, thereby allowing for the identification of epitopes.

AllerGenis™ has developed technology using data-driven machine learning and multiplex immunoassay technology that is proposed to more precisely diagnose and monitor patients with food allergies. According to the manufacturer's website, the diagnostic technology subdivides allergenic proteins into smaller peptides, called epitopes, and measures the reactivity of a patient's IgE to these epitopes. The platform uses a high-throughput, Luminex bead-based epitope assay (BBEA) to analyze IgE reactivity to discrete food allergen epitopes (e.g., VeriMAP™ Peanut Dx, VeriMAP™ Peanut Sensitivity). The VeriMAP Peanut Dx is a peanut allergen-specific IgE and quantitative assessment of 64 epitopes using enzyme-linked immunosorbent assay (ELISA) combined with Luminex's bead-based xMAP® Technology to measure the reactivity of a patient's antibodies to each epitope in order to generate a detailed reactivity profile.

The evidence in the published peer-reviewed medical literature evaluating the effectiveness of BBEA primarily consists of cohort studies and comparative case control studies with prospective and retrospective designs with relatively small sample sizes. Further studies are needed to establish that the bead-based epitope assay improves outcomes compared to alternative treatment modalities.

In-Vitro Testing=
RAST/MAST/PRIST/RIST/FAST/MRT/VAST/ELISA/ImmunoCAP
For most allergens, in-vitro allergen - specific immunoassays detect IgE antibody in the serum of most but not all patients who respond clinically to those allergens. The National Asthma Education Program Expert Panel Report 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.

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).

The role of IgE in mediating a protective anti-helminth immune response remains controversial. A parasitic (helminthic) intestinal infection caused by Ascaris lumbricoides, hookworm, Trichuris trichiura and Strongyloides stercoralis which are the most prevalent helminth parasitic infections in humans.

The management of serve allergic or eosinophilic asthma includes biologic therapy: omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab. In addition to these approved therapies there are also several new biologics currently under investigation for severe asthma treatment. The available biologic therapy can be clustered into three categories, those that target immunoglobulin E (IgE) (omalizumab), interleukin-5 (IL-5) (reslizumab, benralizumb, and mepolizumab), and interleukin-4 and 13 (IL-4)/ (IL-13) (dupilumab). Biologic therapy has also been included in the most recent Global Initiative for Asthma (GINA) 2019 guidelines. Like all medications, biologic therapies have side effects and adverse events that health-care providers and patients must be aware of when using these therapies. A rare, and under-studied adverse event that can occur with biologic therapy use is the acquisition of a parasite, more specifically a helminthic infection. IgE and eosinophils play an important role in a host's defense against parasites. Therefore, therapies that target IgE, or cytokines involved in the allergen response pathway, can theoretically lead to an increased risk of acquiring or

not being able to clear parasites. However, there is a lack of enough human trials on biologic therapy and its relationship to parasitic infection to create a conclusion on its long-term effect. Further studies are needed to look for a relationship between parasites (the idea that reduction of IgE could play a role in improving the expulsion of parasites) and these medications.

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.

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 (e.g., 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. This test is not FDA approved and is not established as a useful test in clinical practice.

Food Immune Complex Assays FICA
Food Immune Complex Assays **(**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.

Body Chemical Analysis
Body chemical analysis is typically seen in the diagnosis of a condition known as "idiopathic environmental intolerances" (IEIs) or "multiple food and chemical sensitivities." Samples of whole blood, serum, erythrocytes, 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." 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. There is no scientific evidence to support the value of diagnostic testing associated with IEIs or multiple food and chemical sensitivities, including body chemical analysis. Body chemical analysis is therefore considered unproven.

Mediator Release Test (MRT)
The mediator release test (MRT) has primarily been used to detect intolerance to foods and additives in patients with irritable bowel syndrome. The MRT measures the aggregate release of inflammatory mediators from the patient's immunocytes in vitro after exposure to specific foods and food additives. The results of the mediator release test have been used to design a patient-specific diet to treat IBS by avoiding foods and additives that trigger significant inflammatory mediator release. For the mediator release test, the patient's blood sample is incubated with various extracts of foods and food additives and then analyzed for the presence and aggregate amount of release of inflammatory mediators from the patient's leukocytes. Results are compared to control samples of the patient's blood that have not been exposed to food extracts or additives. The MRT-directed patient-specific diet is one component of the Lifestyle Eating and Performance (LEAP) Disease Management Program (Don Self & Associates, Inc., Whitehouse, TX). The LEAP program is based on the theory that symptoms irritable bowel syndrome and other certain conditions are caused by the physiological effects of non-IgE mediated immune reactions in response to sensitivities to specific foods and food additives. The LEAP program also includes patient selection tools, a self-directed stress reduction program, and outcomes assessment tools. According to the manufacturer, the LEAP program has been successful in reducing or eliminating symptoms in 84 % of patients with irritable bowel syndrome, functional diarrhea, and

related conditions. However, there is no evidence in the peer-reviewed published medical literature to substantiate these claims.

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

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. Current society guidelines make no recommendation for testing for anti-Fc epsilon antibody in the work-up of patients with urticaria. A study investigated of pathogenesis of chronic urticaria include the autologous serum and plasma skin tests, assays for autoantibodies directed against IgE or the FcepsilonRI receptor, and in vitro assessments of basophil function. However, these tests lack specificity and prognostic value for chronic urticaria, are not standardized, and cannot be recommended for routine clinical use.

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

The American Board of Internal Medicine's (ABIM) Foundation Choosing Wisely® Initiative (2014): The Choosing Wisely initiative includes the following recommendations:

American Academy of Asthma, Allergy, and Immunology: regarding allergy testing:

- 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.
- Don't routinely do diagnostic testing in patients with chronic urticaria.
- Don't perform food IgE testing without a history consistent with potential IgE-mediated food allergy.

American Academy of Pediatrics: Don't perform screening panels for food allergies without previous consideration of medical history.

American Academy of Dermatology: Don't use skin prick tests or blood tests such as the radioallergosobent test (RAST) of the routine evaluation of eczema.

Practice Guidelines and Position Statements

American Academy of Allergy, Asthma and Immunology (AAAAI)
In 2008, the American Academy of Allergy, Asthma and Immunology (AAAAI) updated their 1999 guideline regarding allergy diagnostic testing: Allergy Diagnostic Testing: An Updated Practice Parameter. This updated practice parameter includes the following recommendations:

- Prick/puncture tests or intracutaneous tests are the preferred techniques for IgE-mediated hypersensitivity.
- Specific organ challenge tests may facilitate or confirm a clinical diagnosis under certain circumstances:
    - Investigation of potential new allergen(s)
    - Confirmation of clinical diagnosis when the history is suggestive but skin and/or invitro test results are negative
    - Confirming food allergy
    - Monitoring of therapy
    - Substantiating occupational sensitivity.
- Specific (allergic) bronchial challenge provides a measure of lower airway clinical sensitivity when there is uncertainty or dispute.

Unproven Tests

- Procedures for which there is no evidence of diagnostic validity include cytotoxic tests, provocation-neutralization, electrodermal testing, applied kinesiology, iridology, hair analysis, or food specific IgG, IgG4, and IgG/IgG4 antibody tests. (B)

In 2012, the American Academy of Allergy, Asthma and Immunology (AAAAI), issued the following: "Five Things Physicians and Patients Should Question"

- "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".

- "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".

American Academy of Allergy, Asthma & Immunology (AAAI), American College of Allergy, Asthma & Immunology (ACAAI), the Joint Council of Allergy, Asthma and Immunology (JCAAI), and the American Gastroenterological Association (AGA)
Measurement of allergen-specific IgG or IgG4 antibodies in the evaluation of food allergy is considered a test of unproven or no value**.**

The American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI)
In 2012, the American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) updated their practice parameter which stated the following:

- **Summary Statement 127**. IgG and IgG subclass antibody tests for food allergy do not have clinical relevance, are not validated, lack sufficient quality control, and should not be performed.

PRIOR APPROVAL

Not applicable.

POLICY

See Related Medical Policy

- 02.01.01 Allergy Immunotherapy

Allergy testing using the following types of tests may be considered **medically necessary** for individuals with clinically significant allergic history of symptoms (i.e., the symptoms are not adequately controlled by empiric conservative therapy):

Note: *Testing must correlate specifically to the individual's history, risk of exposure and physical findings.*

- **Epicutaneous (scratch, prick or puncture)** testing may be considered **medically necessary** when immunoglobulin E (IgE)-mediated reactions occur (*see Policy Guidelines*) to any of the following:
  - Foods; **or**
  - Hymenoptera (stinging insects); **or**
  - Inhalants; **or**

- Specific drugs (penicillins and macromolecular agents).

- **Intradermal (Intracutaneous)** testing may be considered **medically necessary** when immunoglobulin E (IgE)- mediated reactions occur (*see Policy Guidelines*) to any of the following:
  - Foods; **or**
  - Hymenoptera (stinging insects); **or**
  - Inhalants; **or**
  - Specific drugs (penicillins and macromolecular agents).

Note: *The number of max units for epicutaneous (percutaneous) and intracutaneous (intradermal) skin tests will be the following when medical necessity criteria are met:*

- *95004 70 max units*
- *95024 40 max units*
- *95028 40 max units*

- **Skin Endpoint Titration (SET)** testing (also known as intradermal dilutional testing (IDT) for determining the starting dose for immunotherapy) may be considered **medically necessary** for any of the following:
  - Individual is highly allergic to hymenoptera venom allergy (stinging insects); **or**
  - Individual is highly allergic to inhalants.

Note*: The number of max units for skin endpoint titration (SET) tests will be the following when medical necessity criteria are met:*

- *95017 27 max units*
- *95018 19 max units*
- *95027 80 max units*

- **Skin Patch Testing** may be considered **medically necessary** for diagnosing contact allergic dermatitis.

Note: *The number of max units for skin patch testing will be the following when medical necessity criteria are met:*

- *95044 42 max units*

- **Photo Patch Testing** (95052, 95056) may be considered **medically necessary** for diagnosing photo-allergy (e.g., photo-allergic contact dermatitis).

- **Photo Tests** (95044) may be considered **medically necessary** for evaluating photo-sensitivity disorders.

Note: *The number of max units for phot patch testing and photo tests will be the following when medical necessity criteria are met:*

- 95052 20 max units

- 95056 20 max units
- 95044 42 max units

- **In-Vitro IgE Antibody Tests (RAST, MAST, FAST, PRIST, RIST, MRT (modified RAST), VAST, ELISA, or ImmunoCAP)** testing may be considered **medically necessary** for any of the following indications:
  - Individual is receiving skin test suppressive medical therapy that cannot be temporarily discontinued (e.g., beta blockers).
  - Presence of widespread skin disease (e.g., dermatographism, ichthyosis, intensive dermatitis or generalized eczema).
  - Evaluating cross-reactivity between insect venoms.
  - As an adjunctive laboratory test for disease activity of allergic bronchopulmonary aspergillosis (ABPA); **AND**

  The testing is being performed for any of the following indications:
  - Allergic broncho-pulmonary aspergillosis (ABPA)**; or**
  - Food allergy; **or**
  - Hymenoptera venom allergy (stinging insects); **or**
  - Inhalant allergy; **or**
  - Specific drugs.

Note: *The number of max units for In- Virto IgE Antibody Tests (RAST, MAST, FAST, PRIST, RIST, MRT (modified RAST), VAST, ELISA, ImmunoCAP) will be the following when medical necessity criteria are met:*

- *86003 36 max units*
- *86005 4 max units*
- *86008 48 max units*
- *83516 40 max units*

- **Alpha-Gal Allergy (Meat Allergy) Testing** (86003) may be considered **medically necessary** for individuals who present with documentation of either of the following after ingestion of mammalian meat, typically within 3 to 6 hours:
  - Urticaria, angioedema or anaphylaxis; **or**
  - Gastro-intestinal symptoms (e.g., abdominal pain, diarrhea and/or vomiting) accompanied by pre-syncope or syncope.

Note: *The number of max units for Alpha-Gal Allergy (Meat Allergy) Testing will be the following when medical necessity criteria are met:*

- *86003 36 max units*

Allergy testing will be considered **not medically necessary** for the following indications:

- When the criteria above are not met
- Individual is being treated successfully for allergies
- Individual with mild symptoms

- Individual who has had a negative skin testing for allergy in question

Allergy Retesting
Routine annual allergy re-testing utilizing the above allergy testing without a definite clinical indication is considered **not medically necessary.**

Note: *With the exception of venom skin tests, which may require a repeat test at three-to-six-month intervals when the initial test is negative and would be considered* ***medically necessary.***

Allergy testing including but not limited to the following is considered **investigational** because the evidence is insufficient in determining this testing results in improved net health outcomes:

- ALCAT test (Antigen Leukocyte Cellular Antibody Test, an automated food allergy test)
- Anti-Fc epsilon receptor antibodies testing
- Anti-IgE receptor antibody testing
- Basophil Activation Testing (BAT)
- Body chemical analysis (testing for idiopathic environmental intolerances" (IEIs) or multiple food and chemical sensitivities)
- Complement Antigen Testing when utilized for the diagnosis of delayed food allergies
- Cytotoxic food testing (Bryans Test)
- ELISA/ACT
- Eosinophil cationic proteic (ECP) test
- Food Allergen Epitope Analysis or Bead Based Epitope Assay (BBEA) (0165U and 0178U) (e.g., VeriMAP Peanut DX)
- Food immune complex assays (FICA)
- Food specific IgG antibodies
- Leukocyte antibodies testing (86343)
- Mediating a protective anti-helminth (parasitic) immune response
- Mediator release test (MRT)
- Ophthalmic mucous membrane tests/ conjunctival challenge test
- Panel testing for food sensitivities or food allergies including SAGE testing for food delayed sensitivity and Biotek food allergy panel
- Passive cutaneous transfer test - Prausnitz-Kustner or P-K testing
- Provocation testing (e.g., Rinkel test) either subcutaneously or sublingually
- Provocative nasal test (also known as nasal provocation testing)
- Precision diagnostics for food allergy with non-personalized large panel testing
- Pulse test (pulse response test, reaginic pulse test)
- Rebuck Skin Window test
- Sublingual allergy desensitization to aeroallergens
- Testing for other immunoglobulin (e.g., IgG, IgG4, IgA, IgM, IgD) or subclasses to determine allergies

Policy Guidelines

- The most common signs and symptoms of a Type 1 IgE mediated (allergic) reaction includes the development of hives, pruritis, angioedema, flushing, wheezing, rhinitis and abdominal cramping.
- A severe reaction of a Type 1 IgE mediated (allergic) reaction causes anaphylaxis which may cause loss of consciousness, nausea, vomiting, tachycardia and hypotension.
- Skin testing is the gold standard and preferred method for detecting IgE mediated sensitization because the response reflects onto the biology of the individual:
    - Skin testing introduces a small amount of allergen under the skin within 15-20 minutes a wheal (swelling) and flare (redness) skin response may occur if positive.
    - The primary factor affecting probability of a relevant food allergy is the patient history suggesting a highly suspect food causing an allergic response. The clinical history is the most pertinent factor to determine the likelihood of clinical allergy that is then corroborated with posttest probability of a positive IgE mediated test.
    - Specific IgE testing has been used to diagnose food allergy using an automated system for a large number if samples in a standardized way. A cut off of 0.35 kU/ L has a high sensitivity but low specificity for certain allergens therefor using a 95% positive predictive value (PPV) cutoff the specificity of IgE testing increases. It is important to note that diagnostic cutoffs with 95% PPV and NPV 50% values can vary depending on the food being studied. The rationale is that conventional IgE in vitro testing uses natural extracts with a complex mixture of proteins. The allergen tests for IgE binds (in vitro testing) to a single allergen and the list of allergenic molecules may not be complete in commercial laboratories. Limitations of multiple in vitro panel assays introduces a concern that they reveal sensitization to protein molecules with potentially no clinical relevance since they are being tested without a linkage to relevant antigens from the patient history. This is why skin testing is the preferred method for detecting IgE sensitization since it is a biologic response to the patient's own immunologic state.
- Testing that measure IgE in Vitro (in the test tube) may be challenging to interpret since results are based on a laboratory allergen and antibody reaction that is calibrated.

Limitations of Skin Testing:

- Age
    - Generally, not preferred less than 6 months of age due to potential for less accuracy since infant skin can be less reactive.
    - Patient cooperation in small children may be limited.
- Antihistamines either prescription (Hydroxyzine [Vistaril]) or over the counter (Claritin, Zyrtec, Allegra, or Benadryl) should be stopped for at least 5 days.

- Beta blockers (relative contraindication) should be stopped for at least 72 hours (if possible) since they interfere with treatment to the event of an allergic reaction.
- Tricyclic antidepressants may interfere with skin testing.
- Prednisone > 10 mg for more than 2 weeks may interfere with skin testing.

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 82784 Gammaglobulin (immunoglobulin); IgA, IgD, IgG, IgM, each
- 82785 Gammaglobulin (immunoglobulin); IgE
- 82787 Gammaglobulin (immunoglobulin); immunoglobulin subclasses (e.g., IgG1, 2, 3, or 4), each
- 83516 Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; qualitative or semiquantitative, multiple step method (may be utilized RAST, MAST, FAST, PRIST, RIST, MRT (modified RAST), VAST, ELISA, or ImmunoCAP)
- 86001 Allergen specific IgG quantitative or semiquantitative, each allergen
- 86003 Allergen specific IgE; quantitative or semiquantitative, each allergen (may be utilized RAST, MAST, FAST, PRIST, RIST, MRT (modified RAST), VAST, ELISA, or ImmunoCAP) (may also be utilized for Alpha-gal allergy (meat allergy) testing)
- 86005 Allergen specific IgE; qualitative, multiallergen screen (e.g., disk, sponge, card) (RAST, MAST, FAST, PRIST, RIST, MRT (modified RAST), VAST, ELISA, or ImmunoCAP)
- 86008 Allergen specific IgE, quantitative or semiquantitative, recombinant or purified component (RAST, MAST, FAST, PRIST, RIST, MRT (modified RAST), VAST, ELISA, or ImmunoCAP)
- 86343 Leukocyte histamine release test (LHR)
- 86849 Unlisted immunology procedure
- 95004 Percutaneous tests (scratch, puncture, prick) with allergenic extracts, immediate type reaction, including test interpretation and report, specify number of tests (Epicutaneous (scratch, prick or puncture)
- 95017 Allergy testing, any combination of percutaneous (scratch, puncture, prick) and intracutaneous (intradermal), sequential and incremental, with venoms, immediate type reaction, including test interpretation and report, specify number of tests (Epicutaneous (scratch, prick or puncture)
- 95018 Allergy testing, any combination of percutaneous (scratch, puncture, prick) and intracutaneous (intradermal), sequential and incremental, with drugs or biologicals, immediate type reaction, including test interpretation and report, specify number of tests (Epicutaneous (scratch, prick or puncture)

- 95024 Intracutaneous (intradermal) tests with allergenic extracts, immediate type reaction, including test interpretation and report, specify number of tests
- 95027 Intracutaneous (intradermal) tests, sequential and incremental, with allergenic extracts for airborne allergens, immediate type reaction, including test interpretation and report, specify number of tests (Skin Endpoint Titration [SET]
- 95028 Intracutaneous (intradermal) tests with allergenic extracts, delayed type reaction, including reading, specify number of tests
- 95044 Patch or application test(s) (specify number of tests)
- 95052 Photo patch test(s) (specify number of tests)
- 95056 Photo tests
- 95060 Ophthalmic mucous membrane tests
- 95065 Direct nasal mucous membrane test
- 95199 Unlisted allergy/clinical immunologic service or procedure
- 0165U Peanut allergy-specific quantitative assessment of multiple epitopes using enzyme-linked immunoabsorbant assay (ELISA), blood, individual epitope results and probability of peanut allergy (VeriMAP Peanut DX)
- 0178U Peanut allergen-specific quantitative assessment of multiple epitopes using enzyme-linked immunosorbent assay (ELISA), blood, report of minimum eliciting exposure for a clinical reaction (VeriMAP Peanut DX)

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POLICY HISTORY

Date	Reason	Action
February 2022	Annual Review	Policy Revised
November 2021	Interim Review	Policy Revised
February 2021	Annual Review	Policy Revised
February 2020	Annual Review	Policy Revised
February 2019	Annual Review	Policy Revised
February 2018	Annual Review	Policy Revised
February 2017	Annual Review	Policy Revised
April 2016	Annual Review	Policy Revised
May 2015	Annual Review	Policy Revised
June 2014	Annual Review	Policy Revised
August 2013	Annual Review	Policy Revised
September 2012	Annual Review	Policy Revised
September 2011	Annual Review	Policy Renewed

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

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