Medical Coverage Policy

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Allergy Testing and Non-Pharmacologic Treatment

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Overview

This Coverage Policy addresses testing and non-pharmacologic treatment for allergy. Allergy testing may be in vivo (i.e., testing on or near the patient and monitoring the patient's physiological response(s)) or in vitro procedures (i.e., analyzing the individual's serum). Non-pharmacologic immunotherapy may be allergen immunotherapy by subcutaneous injection and sublingual antigen extract drop immunotherapy preparations.

Coverage Policy

Testing:

Medically Necessary

The following in vivo allergy tests are considered medically necessary:

- prick/puncture allergy testing to diagnose suspected immunoglobulin E (IgE)-mediated hypersensitivity to inhalants, foods, hymenoptera (e.g., bee venom), drugs and/or chemicals

- intradermal allergy testing to diagnose suspected immunoglobulin E (IgE)-mediated hypersensitivity to inhalants, hymenoptera (e.g., bee venom), drugs and/or chemicals
- skin patch testing to diagnose suspected contact allergic dermatitis
- photo patch testing to diagnose suspected contact photosensitization (e.g., photoallergic contact dermatitis)
- skin patch testing performed prior to joint replacement surgery for **EITHER** of the following:
    - previous surgery involving an implant with complications suspected to be caused by metal allergy
    - history of severe localized (i.e., blistering, hives, and/or extensive rash) or systemic cutaneous reaction to metals
- skin patch testing performed following joint replacement surgery when **BOTH** of the following criteria are met:
    - presence of symptoms attributable to metal allergy/hypersensitivity (e.g., pain, swelling, cutaneous rash, loss of function)
    - etiology other than metal allergy/hypersensitivity (e.g., infection, mechanical failure) have been ruled out
- food/food additive ingestion double-blind challenge/provocation to diagnose suspected IgE-mediated hypersensitivity if skin testing is negative or equivocal, despite a history and physical findings suggestive of hypersensitivity
- drug provocation/bronchial challenge test to diagnose suspected IgE-mediated hypersensitivity when there is a confirmed history of allergy to a drug, and the individual requires the particular drug for treatment of a diagnosed condition, and there is no effective alternative drug available
- skin serial endpoint titration (SET) for determination of a safe starting dose for testing or immunotherapy when there is potential for the specific allergen in question to produce a severe systemic reaction or anaphylaxis (such as with bee venom)

When in vivo allergy testing is considered medically necessary as noted in the criteria above, the following frequency limits apply (rolling 12 months):

- percutaneous (scratch, puncture, prick) testing (CPT code 95004): 80 units
- intracutaneous (intradermal) testing (CPT code 95024): 40 units

In vitro allergy testing (blood serum analysis, e.g., ImmunoCAP®, radioallergosorbent test [RAST], multiple radioallergosorbent test [MAST], fluorescent allergosorbent test [FAST], paper radioimmunosorbent test [PRIST], radioimmunosorbent test [RIST], enzyme-linked immunosorbent assay [ELISA], MRT [modified RAST], and VAST) is considered medically necessary when ANY of the following criteria is met:

- for the diagnosis of suspected IgE-mediated food or inhalant allergies for one of the following indications:
    - individual with severe dermatographism, ichthyosis or generalized eczema
    - individual who cannot be safely withdrawn from medications that interfere with skin testing (such as long-acting antihistamines, tricyclic antidepressants)
    - individual who has a history of a previous systemic reaction to skin testing
    - individual in whom skin testing was equivocal/inconclusive and in vitro testing is required as a confirmatory test
- as an alternative to skin testing for the evaluation of cross-reactivity between insect venoms
- when specific IgE immunoassays are used as adjunctive testing for disease activity of allergic bronchopulmonary aspergillosis and certain parasitic diseases

When in vitro allergy testing is considered medically necessary as noted in the criteria above, the following frequency limit applies (rolling 12 months):

- allergen specific IgE; quantitative or semiquantitative testing (CPT code 86003): 80 units

In vitro metal lymphocyte transformation testing (LTT) performed prior to joint replacement surgery is considered medically necessary when ALL of the following criteria are met:

- previous surgery involving an implant, with complications suspected to be caused by metal allergy
- history of severe localized (i.e., blistering, hives, and/or extensive rash) or systemic cutaneous reaction to metals
- skin patch testing is contraindicated or results are equivocal

In vitro metal lymphocyte transformation testing (LTT) performed following joint replacement surgery is considered medically necessary when ALL of the following criteria are met:

- presence of symptoms attributable to metal allergy/hypersensitivity (e.g., pain, swelling, cutaneous rash, loss of function)
- etiology other than metal allergy/hypersensitivity (e.g., infection, mechanical failure) have been ruled out
- skin patch testing (detailed above) is contraindicated or results are equivocal

Not Medically Necessary

In vitro allergy testing is considered not medically necessary for ANY of the following:

- individual with no contraindications to skin testing
- individual being treated successfully for allergies
- individual with mild symptoms
- individual who has had negative skin testing for the allergy in question

In vivo or in vitro allergy testing is considered experimental, investigational or unproven for any other indication.

The following in vivo and in vitro allergy tests for the diagnosis or management of allergic disease are considered experimental/investigational or unproven:

- nasal challenge/provocation
- conjunctival challenge/provocation
- bronchial provocation/challenge testing for common allergens (e.g., dust, ragweed)
- provocation-neutralization testing (subcutaneous, sublingual or intradermal) or Rinkel test
- electrodermal testing or electro-acupuncture
- applied kinesiology or muscle strength testing of allergies
- reaginic pulse testing or pulse testing for allergies
- total serum IgE (except as noted in the General Background section of this coverage policy
- total serum immunoglobulin G (IgG), immunoglobulin A (IgA) and immunoglobulin M (IgM)
- testing of specific IgG antibody (e.g., by RAST or ELISA testing)
- cytotoxic testing, leukocytotoxic testing or Bryan's test
- lymphocyte subset counts
- lymphocyte function assay
- cytokine and cytokine receptor assay
- food immune complex assay (FICA)
- leukocyte histamine release testing
- body chemical analysis
- antigen leukocyte cellular antibody (ALCAT) automated food allergy testing
- complement antigen testing*
- bead-based epitope assay (BBEA)

*Note: Complement antigen testing may be indicated for the diagnosis and management of inflammatory conditions (e.g., rheumatoid arthritis, systemic lupus erythematosus).

Treatment:

Medically Necessary

Subcutaneous allergen immunotherapy is considered medically necessary for the treatment of allergic asthma and allergic rhinitis (with or without allergic conjunctivitis) when ALL of the following criteria are met:

- presence of specific immunoglobulin E (IgE) to the allergen in question demonstrated by skin testing or serum/in-vitro testing
- hypersensitivity cannot be managed by medications or allergen avoidance
- professional services for the supervision of preparation and provision of antigens for allergen immunotherapy, single or multiple antigens (CPT® code 95165) up to a maximum of 150 doses per year (i.e., rolling 12 months).

Subcutaneous allergen immunotherapy is considered medically necessary for the treatment of Hymenoptera (e.g., hornet, wasp, bee, fire ant) venom allergy when ALL of the following criteria are met:

- history of systemic reaction to a Hymenoptera sting
- presence of Hymenoptera-specific IgE demonstrated by skin testing or serum/in-vitro testing
- professional services for the supervision of preparation and provision of antigens for allergen immunotherapy, single or multiple antigens (CPT codes 95145-95149, 95170)

Not Medically Necessary

Subcutaneous allergen immunotherapy is considered experimental, investigational or unproven for any other indication, including but not limited to the following:

- angioedema
- atopic dermatitis
- chronic urticaria
- food hypersensitivity

Each of the following is considered experimental, investigational or unproven for the treatment of allergy (this list may not be all-inclusive):

- acupuncture for allergies
- allergoids
- autogenous urine injections
- detoxification for allergies
- environmental chemical avoidance for idiopathic environmental intolerances
- epicutaneous immunotherapy
- helminth trichuris suis therapy
- homeopathic remedies for allergies
- injection of food extracts
- intranasal immunotherapy
- low-dose immunotherapy
- oral immunotherapy (OIT) for food hypersensitivity (unless the use is approved by the Food and Drug Administration [FDA])
- peptide therapy
- provocation-neutralization therapy
- rhinophototherapy
- rotational and multiple food elimination diets (e.g., rotary diversified diet)

- ultra-low dose enzyme activated immunotherapy/low-dose allergens (LDA)

Sublingual antigen extract drop immunotherapy preparations are considered experimental, investigational or unproven.**

** There is no accepted CPT code for sublingual antigen extract drop immunotherapy preparations

Note: Please refer to Drug and Biologic Coverage Policies 1902: Sublingual Allergen Immunotherapy and 2004: Peanut (arachis hypogaea) allergen powder-dnfp for information regarding FDA-approved non-subcutaneous allergen immunotherapy.

General Background

Allergies result from an overreaction of the immune system to foreign substances (e.g., pollen, dust, mold, animal fur or dander, stinging insect venom, food). An allergy develops when the body is exposed to a substance that prompts the initiation of an immune response. This response involves the production of antibodies, called immunoglobulins (Igs), which are directed against proteins of the foreign substance, called allergens or antigens. While there are five classes of immunoglobulins, it is IgE that is typically involved in allergic reactions. When an allergy-prone individual is exposed to a specific antigen, B-cells produce an IgE that recognizes only that antigen. This antigen-specific IgE then binds to receptors on specific cells that reside in tissue (mast cells) or circulate in the blood (basophils). Upon re-exposure to the same antigen, the antigen-specific IgE binds to membrane receptors on tissue mast cells and blood basophils and then releases a series of chemicals (histamine, leukotrienes, cytokines and proteases) that regulate the allergic reaction. While the allergic reaction begins immediately, signs and symptoms of the reaction may occur within seconds or minutes (immediate hypersensitivity), may be delayed for several hours (delayed hypersensitivity), or may involve both early-and late-phase reactions.

Testing

Allergy tests are performed to verify or exclude the presence of IgE-mediated hypersensitivity and to identify the causative allergen(s). Testing may involve in vivo procedures, which determine the presence of specific IgE by administering an IgE-specific allergen into, on or near the patient and monitoring the patient's physiological response(s). Allergy tests may also be in vitro procedures that determine the presence of specific IgE or elevated total IgE by analyzing patient serum.

The allergy testing methods and recommendations detailed below are based primarily on practice parameters and recommendations from the American Academy of Allergy, Asthma, and Immunology (AAAAI) and the American Academy of Otolaryngic Allergy (AAOA).

In Vivo Allergy Testing

The number/frequency of tests needed to diagnose an individual with allergies is varied. Up to 80 percutaneous skin tests may be necessary to diagnose food allergies (scratch, puncture, prick, CPT code 95004). Up to 40 intracutaneous (intradermal) tests with allergenic extracts (CPT code 95024) is considered appropriate. If allergy skin tests cannot be performed due to a skin condition, etc., up to 40 allergen-specific IgE tests may be considered appropriate (CPT code 86003). Frequency is based on a rolling 12 months basis.

In vivo allergy tests fall into two general categories: skin tests and organ challenge (or provocation) tests. Both are designed to confirm hypersensitivity and identify the antigen(s) responsible for the allergic reaction. The most common in vivo allergy tests are outlined below. The efficacy of some in vivo allergy tests has not been firmly established, due to the limited numbers of well-designed clinical trials. Few prospective studies are available, and evidence is primarily in the form of expert opinion.

Skin testing can be utilized to detect immediate hypersensitivity (IgE-dependent reactions) and delayed hypersensitivity (cell-mediated immune reactions). The two major methods of skin testing for IgE-mediated disease include the prick-puncture test and the intradermal test. A positive response to skin testing is typically

indicated by the presence of a wheal and/or flare at the test site. Scratch testing is no longer a recommended allergy testing procedure, due to reproducibility issues and the high incidence of false-positive reactions.

Skin testing is contraindicated in patients with severe dermatographism (allergy in which a pale, raised wheal is produced when skin is scratched), ichthyosis (condition in which skin is dry and scaly, resembling fish skin) or generalized eczema; in patients who cannot be withdrawn from medications that interfere with skin testing (such as long-acting antihistamines and tricyclic antidepressants); and in patients who have a history of a previous systemic reaction to skin testing.

Prick/puncture tests are used for confirmation of clinical immediate hypersensitivity induced by inhalant and food allergens. Skin prick/puncture tests are generally considered the most specific screening method for detecting the presence of IgE antibodies in patients with appropriate exposure histories. These tests may also be used in the diagnosis of drug and chemical hypersensitivity reactions. Prick/puncture tests are generally less sensitive than intradermal testing. For inhalant allergies, prick/puncture tests have been shown to correlate better with the presence of clinical allergy. Skin testing is considered the gold standard for the diagnosis of IgE-mediated allergic disease. The Joint Task Force of Allergy, Asthma, and Immunology recommends skin prick/puncture tests as the primary test for the diagnosis of IgE-mediated allergic diseases.

Intradermal or intracutaneous tests are generally used when increased sensitivity is the main goal of testing (i.e., when prick/puncture tests are negative despite a compatible history of exposure). Intradermal tests are more sensitive but less specific than prick/puncture tests for most allergens but are superior to other skin tests for assessing hypersensitivity to hymenoptera (stinging insects) and penicillin or allergens of lower potency. Intradermal testing for food allergies is not recommended because of the high rate of false positive test results and the potential for anaphylaxis.

Repeat skin testing with multiple antigens is not indicated on a regular basis (e.g., yearly). Indications for repeat testing include changing symptoms, new exposures, or 3–5 years of venom immunotherapy.

Patch testing is used to determine the presence or cause of delayed hypersensitivity reactions originating on the skin. It is primarily used to assess allergic contact dermatitis, an eczema-type, immunologically-mediated skin reaction which is largely cell-mediated but may contain an IgE-mediated component. The clinical utility of patch testing to identify allergic reactions other than those originating on the skin (such as inhalants or food allergens) has not been determined. It is estimated that 20–30 antigens used in the panel of patch tests will identify between 50% and 70% of the clinically relevant causes of contact dermatitis.

Certain substances may elicit an allergic reaction only when exposed to light. In photo patch testing, the suspected chemical or medication is applied in two separate areas. One of the areas is exposed to a range of ultraviolet type A light and then examined for the presence of a reaction. Testing is considered positive if only the area that has been exposed to the ultraviolet light demonstrates an allergic reaction.

Oral challenge may be used to confirm or diagnose IgE-mediated hypersensitivity to specific foods, food additives and preservatives, or drugs. Food challenge is time-consuming and associated with the potential for anaphylaxis. Simpler measures, such as skin tests and elimination of suspected foods from the diet, are typically tried first. If skin tests are negative or equivocal and inconsistent with a history suggestive of food allergy, and symptoms abate after elimination of suspected foods, one food at a time is added back into the diet (open food challenge) until symptoms recur. Blinded, controlled food challenge (by ingestion) may be undertaken when skin tests are negative or inconsistent with a history that suggests food allergy. Sublingual food allergy testing, in which the food in question is placed under the tongue and not ingested, is an unproven testing method (see "provocation-neutralization," below). Double-blind food challenges are typically reserved for a select subset of patients.

Drug provocation/bronchial challenge testing is typically undertaken only if the need to confirm or exclude hypersensitivity outweighs the risk of severe reaction. This may occur in patients who have a history of allergy to a particular drug for which there is no effective alternative but who need that drug for treatment. Bronchial challenge testing is used in the diagnosis and management of asthma to quantify allergic airway responsiveness to pharmacological agents, such as methacholine or histamine. Bronchial provocation/challenge testing with

extracts of common aeroallergens such as dust or ragweed, however, has no established clinical value and offers no additional clinical information beyond that obtained by a well-taken clinical history and a carefully performed skin test.

Serial endpoint titration (SET) is a variation of intradermal skin testing in which increasing doses of antigen are used to determine the concentration at which the reaction changes from negative to positive (i.e., the endpoint). SET has been used as an alternative to skin prick testing or in vitro testing and has also been used to guide initiation of immunotherapy, with the endpoint dilution used as the starting dose. Although not considered a replacement for skin testing, SET may be indicated for determination of a safe starting dose for testing or immunotherapy when there is potential for the specific allergen in question to produce a severe systemic reaction or anaphylaxis (such as with bee venom).

Additional In Vivo Diagnostic Procedures
Nasal challenge/provocation testing has been proposed as a tool in the diagnosis of allergic rhinitis. It is used in studies of allergic rhinitis, but its utility in clinical practice has not been established. Evidence available regarding the value of this testing is primarily in the form of expert opinion rather than studies assessing the technique. A review of the current published, peer-reviewed scientific literature indicates that the role of nasal challenge testing in the diagnosis and management of allergic diseases has not been established.

Conjunctival challenge testing also has been used in the diagnosis of allergic rhinitis as well as of allergic conjunctivitis. Few data are available regarding the value of conjunctival challenge. The role of conjunctival challenge testing in the diagnosis and management of allergic diseases has not been established, based on a review of the published, peer-reviewed scientific literature.

Provocation-neutralization, sometimes referred to as the Rinkel test, is a procedure that evolved from serial endpoint titration. This method has been proposed as a test for allergies to foods, inhalants and environmental chemicals. It exposes the patient to test doses of substances intradermally, subcutaneously or sublingually, with the goal of either producing or preventing symptoms. There are no standardized protocols, and its safety and efficacy have not been established. The American Academy of Allergy and Immunology consider this testing method unproven. Provocation-neutralization is a method often used by physicians who subscribe to the concept of multiple food and chemical sensitivities, also referred to as idiopathic environmental intolerances (IEIs). Based on a review of the current published, peer-reviewed scientific literature, provocation-neutralization is an unproven testing method.

Electrodermal testing, also referred to as "electro-acupuncture," has been proposed as a method to identify substances, especially foods, to which the patient is allergic and to provide information about optimal dilution of treatment extracts in immunotherapy. It is performed with a device that uses a galvanometer to measure electrical activity of the skin at designated acupuncture points. There is no scientific or clinical evidence available that demonstrates that electrodermal testing can diagnose allergies. This technique is considered unproven.

Applied kinesiology involves testing for specific allergies by measuring the patient’s muscle strength. Allergens are placed in containers that the patient holds in one hand while a technician estimates muscle strength in the opposite arm. Based on a review of the published, peer-reviewed scientific literature, this technique is unproven.

Reaginic pulse testing involves measuring a change in pulse rate after the ingestion, injection or sublingual application of an allergen. There is no basis for its role in the diagnosis of allergic disease. A review of the literature indicates that this is an unproven test for the diagnosis of allergies.

In Vitro Allergy Testing
The discovery of the role of IgE in clinical allergy testing resulted in the development of in vitro diagnostic assays to test for allergen sensitivity. The first immunoassays were developed to quantify the serum concentration of total IgE. In normal individuals, IgE is usually present at low levels; 130 ng/ml represents the upper limit of the normal range. However, a significant number of asymptomatic normal individuals, such as those with parasitic diseases or with depressed cell-mediated immunity, exceed this level. Also, some allergic patients may exhibit normal total IgE levels in the presence of elevated levels of specific IgE. Methods were therefore developed to assay allergen-specific IgE. The radioallergosorbent test (RAST) system was developed for in vitro

measurement of specific IgE in a patient's serum. Other in vitro tests for specific IgE have been developed and employ the same principles as the RAST but use an enzymatic (MAST) or fluorogenic (FAST) detection system in place of a radioactive label.

In vitro tests that screen for multiple allergens in a single assay (Phadiatop®, Pharmacia Diagnostics) or that can be used in an automated system (ImmunoCAP®, Pharmacia Diagnostics) have been developed. The ImmunoCAP is designed as a "sandwich" immunoassay. The sensitivity and specificity of the ImmunoCAP compares favorably with those of the modified PhadezymRAST® system. Results from studies have indicated that, when compared to skin prick testing as the gold standard, the ImmunoCAP system has been shown to have a greater sensitivity (80–95%) than RAST and to have similar specificity (85%). Other modified versions of the RAST test include the PRIST, RIST, MRT (modified RAST) and ELISA IgE tests.

The overall sensitivity of in vitro immunoassays compared with prick/puncture skin tests has been reported to range from 50–90%, with an average of about 70–75% from most studies. Skin testing, therefore, continues to be the preferred method for the diagnosis of IgE-mediated sensitivity. According to practice parameters issuedby the AAAI, selective use of in vitro tests may be justified for patients in whom skin testing is inappropriate. Situations in which specific IgE immunoassays may be appropriate include:

- testing of patients with severe dermatographism, ichthyosis or generalized eczema
- testing in patients who cannot be withdrawn from medications that interfere with skin testing (patients receiving long-acting antihistamines or tricyclic antidepressants)
- testing in patients who have a clinical history suggesting an unusually greater risk for anaphylaxis or who have had a previous systemic reaction to skin testing
- testing of patients with mental or physical impairments

It should be noted that specific IgE immunoassays do not have sufficient sensitivity for absolute positive prediction of anaphylactic sensitization to venoms, penicillin and other drugs. This method of testing should not be used to provide definitive diagnoses, due to the potential for serious consequences resulting from a false-negative outcome. Allergen-specific IgE immunoassays provide neither diagnostic nor prognostic information when measured in the cord blood of newborn infants.

In vitro allergy testing is not indicated when there are no contraindications to skin testing or in patients who are successfully being treated for allergies, have mild symptoms and a short allergy season, or have had negative skin testing for the allergy in question.

Total serum IgE testing in patients with allergic disease has no established clinical role. Substantial proportions of individuals with IgE-mediated allergic disease have normal serum IgE levels, and many nonallergic diseases are associated with elevated serum IgE. Measurement of serum IgE may be indicated in adults with conditions such as suspected allergic bronchopulmonary aspergillosis and hyper-IgE syndromes (dermatitis and recurrent pyogenic infections), certain stages of HIV infection, IgE myeloma, drug-induced interstitial nephritis, graft-versus-host disease, several parasitic diseases and specific immune deficiency diseases. In children, serum concentrations of IgE increase slowly with development, with highest levels typically found in late adolescence. High concentrations of serum IgE measured in the first year of life have been shown to correlate with future development of atopic disease. However, in clinical situations when presenting signs of allergic disease are evident, total IgE levels do not provide additional diagnostic information. Furthermore, normal IgE levels do not exclude the diagnosis of allergic disease in infants or children.

Total serum IgG, IgA and IgM testing is not typically clinically useful, since their levels are not altered by allergic diseases. Based on a review of the literature, the role of routine quantitative measurement of serum IgG, IgA and IgM in the diagnosis and management of allergic disease has not been established.

Serum IgG antibodies are not involved in the pathogenesis of atopic disease. Although it has been suggested that IgG antibodies may be responsible for delayed symptoms or vague intolerance to foods, there is no evidence available that validates this contention. RAST and similar technologies are capable of detecting minute quantities of such antibodies, and it is known that low-level IgG antibodies to foods circulate normally but have no known pathogenic significance. The measurement of specific IgG antibodies is of no diagnostic value in the

management of patients with atopic (allergic) disease. There is insufficient evidence in the published, peer-reviewed scientific literature to support the use of specific IgG antibody testing by RAST or ELISA in the diagnosis or treatment of allergic disease without suspected immunodeficiency.

The cytotoxic test, also known as the "leukocytotoxic test" or Bryan's Test, has been proposed for food allergies but has no scientific support as a procedure for the diagnosis of food allergies or inhalant allergies. The rationale for this test is based on a claim that morphological changes in peripheral-blood leukocytes in contact with allergens in vitro indicate that the patient is allergic to the particular allergen. There is insufficient evidence in the published, peer-reviewed scientific literature to support the use of this testing in the diagnosis or management of allergic disease. The role of this testing in the diagnosis or management of allergic disease has not been established.

Lymphocyte subset counts may be useful in the diagnosis of lymphocyte cellular immunodeficiencies and lymphocytic leukemias. Quantifying lymphocyte subsets, however, has not been proven to be of any value in the diagnosis or management of allergic disease.

Lymphocyte function assays may be appropriate in the diagnosis of some immunodeficiency diseases; however, they are not abnormal in allergic diseases. The use of this testing in the diagnosis or management of allergic disease is unproven.

Cytokine and cytokine receptor assays have not been shown to be useful in the diagnosis or management of any allergic disease and are therefore considered unproven.

The food immune complex assay (FICA) is based on the solid-phase radioimmunoassay methodology. It has not been shown in well-designed clinical trials that any well-defined clinical disease involves pathogenic circulating immune complexes to foods. Furthermore, it has not been shown that the assay for such complexes is diagnostic of any disease. The clinical value of food immune complex assays in the diagnosis and management of allergic disease has not been established. The technique is therefore considered unproven.

Leukocyte histamine release testing is an in vitro test that evaluates the presence of specific IgE antibodies. The test has been proposed for the diagnosis of various allergic conditions, including atopic disorders and stinging insect allergies. Leukocyte histamine release testing detects the release of histamine from basophils in a sample of whole blood exposed to allergens in vitro. It is a cumbersome test typically conducted in research laboratories, and has not been studied fully for its predictive value in determining specificity and sensitivity. Its role in the diagnosis and management of allergic disease outside of the investigative setting has not been established.

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.

Antigen leukocyte cellular antibody testing (ALCAT) is an automated method of testing for food allergies that is purported to identify food sensitivity by using a modified Coulter counter linked to a computer program to measure the change in white blood cells incubated with purified food and mold extract. There is insufficient evidence in the published peer-reviewed scientific literature to support the use of this testing in the diagnosis or management of allergic disease.

Complement antigen testing has been proposed for the diagnosis of delayed food allergies. Complement activation is a multi-component immune system response commonly present in inflammatory conditions (e.g.,

rheumatoid arthritis, arthritis, systemic lupus erythematosus). The degree of complement activation may be used to indicate the intensity of the inflammatory process. The role of complement antigen testing in the diagnosis of allergy has not been established.

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. The epitope mapping technology of such peptide arrays, by means of immobilized peptides on a surface, have been subjected to substantial development over the last decades. Typically, overlapping peptides of 10–20 amino acid residues are synthetized in parallel, for example, on a glass slide or a nitrocellulose membrane. A few years ago standard peptide synthesis could only synthetize a few hundred peptides, but with the recent technological advances, synthesis of up to 2,100,000 peptides is now a possibility. These advances in peptide arrays have recently allowed for the identification of epitopes on the amino acid level this being able to identify the amino acids within an epitope contributing to the binding to IgE of peanut allergic patients (Broekman, et al., 2015).

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 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 (Suprun, et al., 2019; Suárez-Fariñas, et al., 2019; Flinterman, et al., 2008; Shreffler, et al., 2005; Beyer, et al., 2003). More rigorous studies are needed to establish that the bead-based epitope assay improves outcomes compared to alternative treatment modalities.

Arthroplasty Implants: Testing for Metal Allergy/Hypersensitivity
Metal implants are widely used in orthopedic surgery for joint arthroplasty and fracture fixation. Metallic implants are frequently composed of stainless steel, Vitallium, titanium, Zirconium, and cobalt-chromium-molybdenum alloys. These alloys are typically composed of metals including aluminum, chromium, cobalt, nickel, molybdenum, vanadium, titanium and iron. Intolerance reactions to metal implants include dermatitis, impaired wound healing, effusion, pain, or loosening. It is important to distinguish between cutaneous contact sensitivity and sensitivity to implanted devices. Local reactions at the time of contact (e.g., rash, urticarial, swelling) are seen with hypersensitivity related to cutaneous contact with metallic objects such as jewelry Metal contact allergy/hypersensitivity is quite common, and there is insufficient evidence to demonstrate that this places patients at increased risk of developing complications following orthopedic implant procedures. Routine testing for metal allergy prior to joint implantation therefore has not been established. There may be a role such testing, however, in patients with a history of severe localized (e.g., hives, blistering, extensive rash) or systemic cutaneous reactions, or in those with a history of complications suspected to be caused by metal allergy with a prior implant.

Evidence evaluating the relationship between metal allergy/sensitivity and implant outcomes is limited. In reviewing the approach to the clinical work-up of patients with putative allergic disease to metallic orthopedic implants, Thyssen et al. (2011) stated that the overall risk of developing extracutaneous allergic reactions following total hip arthroplasty is comparable in metal patch test positive and negative subjects. It has been proposed that up to 5% of total joint arthroplasty failure within seven years of surgery may be caused by debris-induced immune reactivity, including delayed-type hypersensitivity reactions to metals. The authors recommend that clinicians should not perform 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. In this case it would be advisable to avoid an implant containing metal(s) that the patient reacted to during allergy testing. The authors propose that the clinical work-up of a patient suspected of having an allergic reaction to a metal implant would include patch testing and possibly in vitro testing. The

toxicity of some metals may hamper in vitro testing, and patch testing may allow screening for more metals. In vitro testing may be useful, however, in doubtful cases and offer quantitative estimates.

Granchi et al. (2012) published results of a systematic review and meta-analysis of metal sensitivity testing in patients undergoing total joint arthroplasty, to assess the risk of developing metal hypersensitivity postoperatively and the impact on outcomes, and also to investigate the advantages of performing hypersensitivity testing. A total of 22 studies (3654 patients) met the inclusion criteria. Fourteen studies were eligible for calculating the risk of metal allergy in patients undergoing joint replacement. The frequency of positive tests increased following joint replacement, particularly in patients with implant failure or a metal-on-metal coupling. The probability of developing a metal allergy was higher postoperatively (odds ratio [OR] 1.52 (95% confidence interval [CI] 1.06-2.31, p=0.02). Ten studies were eligible to calculate the risk of metal allergy according to the status of the replacement. The probability of having a metal allergy was more than double in patients who had a failed replacement than in those with a stable replacement (OR 2.76 [95% CI 1.14-6.70, p=0.02) There was significant heterogeneity between studies, however, and no predictive value regarding the status of the replacement could be attributed to the testing results for metal sensitization. The meta-analysis confirmed that the probability of developing a metal allergy is higher post-operatively, and the risk is even greater when failed replacements are compared with stable replacements.

In terms of defining the advantage of hypersensitivity testing, the findings demonstrated that pre-or post-operative screening has no predictive value. The authors noted, however, that most papers concluded that hypersensitivity testing should be performed preoperatively in patients with a history of metal allergy, and should be performed in those with a failed replacement when hypersensitivity is suspected, after excluding infection and mechanical failure. The authors stated that the question of which test is best is debatable, since both in vitro and in vivo testing have advantages and disadvantages. Limitations of large-scale application of in vitro testing include the cost and need for specialized laboratories. The patch test is considered the reference method for diagnosing contact allergy, but the use of patch testing in detecting hypersensitivity to implant materials is controversial. The frequency of positive patch tests increases, however, when more haptens are tested.

Metal alloys are also used in other procedures; including dental implants, cardiovascular stents, and gastrointestinal wire mesh stents. There is insufficient evidence evaluate the clinical utility of metal allergy testing for these indications.

Treatment

Evidence-based clinical practice guidelines support the use of subcutaneous allergen immunotherapy for the management of allergic asthma, allergic rhinitis (with or without conjunctivitis), and stinging insect venom hypersensitivity. Clinical studies do not support the use of allergen immunotherapy for treatment of angioedema, atopic dermatitis, chronic urticaria, and food hypersensitivity. Numerous allergy treatment methods have been proposed as alternatives to subcutaneous allergen immunotherapy, as detailed above. There is insufficient evidence in the published medical literature to demonstrate the safely and efficacy of these alternative treatments.

The allergy treatment recommendations in this Coverage Policy are based primarily on practice parameters developed by a joint task force representing the American Academy of Allergy, Asthma, and Immunology (AAAAI) and the American College of Allergy, Asthma & Immunology (ACAAI) (Cox, et al., 2011).

Subcutaneous Allergen Immunotherapy

Subcutaneous immunotherapy (SCIT) consists of gradual administration of increasing amounts of allergen to which the individual is sensitive, in order to temper the immune response and alleviate allergic symptoms. Subcutaneous injection immunotherapy is an established form of treatment and may be considered for individuals with symptoms of allergic rhinitis, allergic conjunctivitis, or allergic asthma with natural exposure to allergens and who demonstrate specific IgE antibodies to the relevant allergen(s). SCIT is usually only recommended for the treatment of allergic respiratory disease following a period of pharmacologic management and observation. Factors to be considered in determining treatment include the severity/duration of symptoms, patient preference/acceptability, adherence, medication requirements, response to avoidance measures, and the adverse effects of medications. The expected response to immunotherapy is antigen specific and depends on the accurate identification and selection of component allergens based on the individual's history, exposure and

diagnostic test results (skin testing or serum/in-vitro testing). There is insufficient evidence to support the use of allergen immunotherapy for atopic dermatitis, food hypersensitivity, chronic urticarial, or angioedema.

The allergy immunotherapy recommendations in this Coverage Policy are based primarily on practice parameters developed by a joint task force representing the American Academy of Allergy, Asthma, and Immunology (AAAAI) and the American College of Allergy, Asthma & Immunology (ACAAI) (Cox, et al., 2011)

Injection Schedules: There are two phases of allergy immunotherapy administration; the initial build-up phase and the maintenance phase. In the build- up phase, the dose and concentration of allergen immunotherapy extract are increased, and in the maintenance phase, the patient receives an effective therapeutic dose over a period of time. With the most common build-up phase schedule, injections are administered one to three times per week. With this schedule, patients usually reach a maintenance dose in three to six months, depending on the starting dilution and occurrence of reactions. If a systemic reaction occurs, immunotherapy may be discontinued, or if continued, the dose is reduced. Immunotherapy schedules may need to be adjusted for a variety of reasons, including missed visits, high pollen or mold seasons, addition of a new allergen, or systemic reaction.

Once a patient reaches the maintenance phase, the interval between injections can be progressively increased as tolerated, to an interval of up to four weeks for inhalant allergens and up to eight weeks for venom. The effective therapeutic dose or maintenance dose is the dose that provides therapeutic efficacy without significant adverse local or systemic reactions. Three to five years of maintenance therapy is generally considered optimal for maximum clinical benefit.

Accelerated Immunotherapy Schedules
Accelerated immunotherapy schedules include cluster immunotherapy and rush immunotherapy. Accelerated immunotherapy schedules may permit an individual to reach a maintenance dose sooner, but are associated with a higher risk of systemic reactions for inhalant allergens, especially with high-risk patients (e.g., those with markedly positive prick/puncture or in vitro IgE test responses).

Cluster immunotherapy: With cluster immunotherapy, several injections (usually two or three) are administered during each visit in order to achieve a maintenance dose more rapidly than conventional schedules. In cluster immunotherapy, several injections at increasing doses (generally 2–3 per visit) are administered sequentially in a single day of treatment on nonconsecutive days. The maintenance dose is usually achieved more rapidly that with a conventional (single injection per session) schedule. Cluster schedules usually include fewer total injections than are used with conventional schedules, and permit a patient to reach a maintenance dose sooner, usually in one to four weeks.

Rush Immunotherapy: With rush immunotherapy, incremental doses of allergen are administered at varying intervals between 15 and 60 minutes over one to three days until the target therapeutic dose is achieved. Rush immunotherapy for inhalant allergies may be associated with a significant risk of systemic reactions. Rush schedules for stinging Hymenoptera venom immunotherapy are not associated with an increased incidence of systemic reactions, however.

Alternative Allergy Treatment Methods
Numerous alternative allergy treatment methods have been identified in the professional society guidelines and textbook literature. These allergy treatment methods remain unproven at this time due to a lack of supporting evidence published in the peer-reviewed scientific literature. The role of these techniques in the management of allergic disease has not yet been established. Some of the alternative allergy treatment methods utilize extracts that are not U.S. Food and Drug Administration (FDA)-approved.

Acupuncture: Acupuncture has been used by allergic patients for the relief of allergic rhinitis, asthma, allergic dermatoses and by patients who have other symptoms or medical problems that they consider to be allergic. Despite the report by some patients of temporary benefit, this is an unproven form of allergy therapy due to lack of published scientific literature.

Allergoids: Allergoids are allergenic proteins that are treated with formaldehyde to produce larger molecules with decreased ability to react with IgE antibodies. Allergoids are licensed and manufactured for general distribution in Europe, but are not available in the United States.

Autogenous urine injection: Autogenous urine injection revolves around the theory that urine produced by the patient contains unspecified chemicals during an allergic reaction and that injection of these chemicals inhibits or neutralizes future allergic reactions. There is a lack of scientific evidence to support autogenous urine injections. Repeated injections of these antigens could induce autoimmune nephritis.

Detoxification: Detoxification is a method used by individuals who believe that an allergic state can be induced by toxic damage to the immune system from exposure to environmental chemicals. It is believed that certain lipid-soluble chemicals may be stored in body fat for long periods. Detoxification consists of sauna and exercise. The individual ingests high-dose niacin to induce erythema. Body fluids are replenished with water and electrolytes and certain essential oils are consumed, presumably to help replace fat-soluble chemical contaminants. This procedure takes approximately five hours and is repeated daily for 20–30 days. This form of therapy has not been well-studied and is unproven.

Environmental chemical avoidance: Individuals with idiopathic environmental intolerance (formerly referred to as multiple chemical sensitivity), have been described as failing to adapt to synthetic chemicals. The 1999 American Academy of Allergy, Asthma and Immunotherapy (AAAAI) position statement on idiopathic environmental intolerance states that a causal connection between environmental chemicals, foods, and/or drugs and the patient's symptoms continues to be speculative and cannot be based on the results of currently published scientific studies.

Epicutaneous immunotherapy: Epicutaneous immunotherapy involves the use of patches as a dosage form for allergen specific immunotherapy. An adverse effect of this therapy is patch-induced eczema at the patch site. This allergy treatment method remains unproven due to a lack of supporting evidence published in the peer-reviewed scientific literature.

Fleischer et al. (2019) assessed the efficacy and adverse events of epicutaneous immunotherapy using a peanut patch among peanut-allergic children. The phase 3, randomized, double-blind, placebo-controlled trial included peanut-allergic children aged 4–11 years (n=356). Children did not have a history of a severe anaphylactic reaction, however developed objective symptoms during a double-blind, placebo-controlled food challenge at an eliciting dose of 300 mg or less of peanut protein. Patients were randomized to receive daily treatment with a peanut patch containing either 250 µg of peanut protein (n=238) or placebo (n=118) for 12 months. The primary outcome measured the percentage difference in responders between the peanut patch and the placebo patch based on eliciting dose (highest dose at which objective signs/symptoms of an immediate hypersensitivity reaction developed) which was determined by food challenges at baseline and at month 12. Participants with baseline eliciting dose of 10 mg or less were responders if the post treatment eliciting dose was 300 mg or more; participants with baseline eliciting dose greater than 10 to 300 mg were responders if the posttreatment eliciting dose was 1000 mg or more. A threshold of 15% or more on the lower bound of a 95% CI around responder rate difference was prespecified to determine a positive trial result. Adverse event evaluation included collection of treatment-emergent adverse events (TEAEs). Mean treatment adherence was 98.5% with 89.9% participants completing the trial. The responder rate was 35.3% with peanut-patch treatment vs 13.6% with placebo ($p<0.001$). The prespecified lower bound of the CI threshold was not met. TEAEs, primarily patch application site reactions, occurred in 95.4% and 89% of active and placebo groups, respectively. The all-causes rate of discontinuation was 10.5% in the peanut-patch group vs 9.3% in the placebo group. The authors concluded that the percentage difference in responders at 12 months with the peanut-patch therapy vs placebo was 21.7% which was statistically significant, but did not meet the prespecified lower bound of the confidence interval criterion for a positive trial result. The clinical relevance of not meeting this lower bound of the confidence interval with respect to the treatment of peanut-allergic children with epicutaneous immunotherapy remains to be determined.

Helminth trichuris suis therapy: Treatment with helminth trichuris suis has been proposed as a treatment for allergic rhinitis. A therapeutic approach has been suggested in different experimental models of allergic disease showing that live ova from trichuris suis, an intestinal helminth of pigs, can protect against allergic reactivity by

helminth-induced regulatory T cells and cytokines. Bager et al. (2010) conducted a double-blind, placebo-controlled study (n=100) to evaluate the effectiveness of trichuris suis therapy for the treatment of allergic rhinitis. The authors reported that repeated treatment with the helminth trichuris suis induced a substantial clinical and immunologic response, but had no therapeutic effect on allergic rhinitis. This allergy treatment method remains unproven due to a lack of supporting evidence published in the peer-reviewed scientific literature.

Homeopathic remedies: A homeopathic remedy administers a causative agent of a disease and is administered therapeutically in small amounts. There is no scientific evidence to support homeopathic practice as a method for treating allergies.

Injection of food extracts: An injection of food extracts consists of a combination of foods based on skin test results or a patient's report of intolerance to foods. There is a lack of clinical trials support this treatment.

Intranasal immunotherapy: Treatment with intranasal immunotherapy has been proposed as a treatment for allergic rhinitis. Local adverse reactions are common with this approach and are the most frequent reason for discontinuing treatment. This allergy treatment method remains unproven due to a lack of supporting evidence published in the peer-reviewed scientific literature (Cox, et al., 2011).

Low-dose immunotherapy or ultra-low dose enzyme activated immunotherapy/low dose allergens (LDA): Both of these methods involve the use of extremely low doses of antigens alone or in conjunction with beta-glucuronidase in an attempt to down regulate an inappropriate immune response. These allergy treatment methods remains unproven due to a lack of supporting evidence published in the peer-reviewed scientific literature.

Oral immunotherapy (OIT) for food hypersensitivity: Please refer to Pharmacy Coverage Policy: Peanut (arachis hypogaea) allergen powder-dnfp for information regarding FDA-approved oral immunotherapy.

Oral immunotherapy (OIT) refers to feeding an allergic individual an increasing amount of an allergen with the goal of increasing the threshold that triggers a reaction. The current standard of care for treatment of food allergy is avoidance of the allergen and treatment of anaphylaxis with auto-injectable epinephrine.

Nowak-Węgrzyn et al. (2019) conducted a multicenter, randomized, double-blind, placebo-controlled trial to determine the efficacy and safety of vital wheat gluten oral immunotherapy (VWG OIT). Patients (n=46) aged 4–30 years with wheat allergy documented by a baseline double-blind, placebo-controlled food challenge (DBPCFC) were randomized 1:1 to active low-dose VWG OIT (n=23) or placebo (n=23) with biweekly escalation to 1445 mg of wheat protein (WP). Dose escalation was performed every 2 weeks for up to 44 weeks to a maximum dose of 1445 mg of wheat protein (WP), followed by daily home maintenance dosing. After one year the placebo group crossed over to a high dose VWG OIT and underwent DBPCFC at the end of year two.. The primary outcome of the study was to determine whether one year of daily oral administration of VWG relative to placebo escalated to a maximum of 1445 mg of WP increased desensitization, as measured by consuming (without dose-limiting symptoms) 4443 mg of WP. Secondary outcomes included the following: the percentage of patients in the low-dose VWG OIT group who successfully consumed 7443 mg of WP during a sustained unresponsiveness (SU) DBPCFC at the two year time point; the percentage of patients who achieved the targeted maintenance dose of low-dose VWG OIT during the desensitization phase of the study; the percentage of patients who achieved desensitization in the placebo crossover group after one year of dosing at the two year study time point; immunologic changes associated with OIT; and incidence of all dosing reactions and serious adverse events during the study. After 52 weeks of treatment (minimum of 8 weeks of maintenance dosing), DBPCFCs were performed up to a cumulative dose of 7443 mg of WP to evaluate for desensitization (roughly equivalent to 2-3 slices of bread). After a year one DBPCFC, active patients continued low-dose VWG OIT for another year and underwent a year two DBPCFC and, if passed, a subsequent off-therapy DBPCFC. Placebo-treated patients crossed over to high-dose VWG OIT (maximum, 2748 mg of WP). Eleven (24%) subjects discontinued the study. At year one, 12 (52.2%) of 23 low-dose VWG OIT–treated and 0 (0%) of 23 placebo-treated patients achieved the primary end point of a successfully consumed dose (SCD) of 4443 mg of WP or greater ($p<0.0001$). The low-dose VWG OIT group had a significantly higher median SCD (4443 mg of WP) versus the placebo group (median SCD, 143 mg of WP; $p<0.0001$). At year two, seven (30.4%) of 23 low-dose VWG OIT–treated patients were desensitized to an SCD of 7443 mg of WP; three (13%) achieved sustained

unresponsiveness 8–10 weeks off therapy. Among placebo-treated patients who crossed over to high-dose VWG OIT, 12 (57.1%) of 21 were desensitized after one year (median SCD, 7443 mg of WP; nonsignificant vs low-dose VWG OIT). The median time to maintenance was significantly longer (p=0.004) in the high-dose crossover VWG OIT group compared to the low-dose VWG OIT group. At year one, skin prick test responses and wheat and omega-5 gliadin–specific IgE levels did not differ between groups. However, the low-dose VWG OIT median specific IgG4 level was significantly greater than placebo (wheat, p=0.0005; omega-5 gliadin, p=0.0001). Year one SCDs correlated with wheat-specific (p=0.0003) and omega-5 gliadin–specific (p=0.001) IgG4 levels in all subjects. Among 7822 low-dose VWG OIT doses in year one, 15.4% were associated with adverse reactions: 0.04% were severe, and 0.08% subjects received epinephrine. Among 7921 placebo doses, 5.8% were associated with adverse reactions; none were severe. Author noted limitations included the small sample size and the results might not be representative of the majority of the patients with wheat allergy.

There is limited evidence that single-food OIT (eg, cow's milk, egg, wheat, sesame) can be used to achieve desensitization. Additionally, the studies have not been shown to reduce the risk of anaphylaxis and may increase the risk. In addition, there are no approved preparations of these allergens (Nachshon, et al., 2020; Jones, et al., 2016; Brożek, et al., 2012; Burks, et al., 2012; Cox, et al., 2011). This allergy treatment method remains unproven due to a lack of supporting evidence published in the peer-reviewed scientific literature.

Peptide therapy: The concept that the clinical response to allergen immunotherapy probably reflects the induction of nonresponsiveness in Th2 lymphocytes led to the concept of immunotherapy with allergen-derived peptides representing T cell activating epitopes that do not react with IgE antibodies.

Provocation-neutralization therapy: This treatment involves the injection of substances under the skin that are suspected of triggering an allergic reaction in sufficient quantity to cause symptoms similar to the patient's complaints. This is then followed by an immediate injection of a weaker or stronger dilution of the same antigen to relieve the symptoms.

Rhinophototherapy: Rhinophototherapy uses UV-B, UV-A, and visible light to treat allergic rhinitis. This allergy treatment method remains unproven due to a lack of supporting evidence published in the peer-reviewed scientific literature.

Rotational and multiple food elimination diets: Proponents of the concept of multiple food allergies sometimes recommend a “rotary diversified diet,” in which the patient rotates foods so that the same food is eaten only once every 4–5 days to help identify foods that may cause allergic responses. This allergy treatment method remains unproven due to a lack of supporting evidence published in the peer-reviewed scientific literature.

Sublingual Antigen Extract Drop Immunotherapy Preparations: Please refer to Pharmacy Coverage Policy: Sublingual Allergen Immunotherapy for information regarding FDA-approved sublingual allergen immunotherapy.

There are no accepted CPT codes for sublingual antigen extract drop immunotherapy preparations.

Standardized antigen extract drop immunotherapy preparations administered under the tongue allows absorption through the sublingual mucosa. This therapy has been proposed for the treatment of patients with asthma and/or allergic rhinitis. Questions remain about the optimal dosing, duration of treatment, and the use of multiple allergens. Because of mixed study results, the therapy is controversial. There is insufficient evidence in the published, peer-reviewed scientific literature regarding improved outcomes using this therapy. Clinical trial data comparing sublingual antigen extract drop immunotherapy with other immunotherapy treatments are also lacking. Further, professional society support in the form of published consensus guidelines is lacking. In a Practice Parameter Update (2017) regarding the use of liquid extract drops the American Academy of Allergy, Asthma, and Immunology (AAAAI) and the American College of Allergy, Asthma, and Immunology (ACAAI) note that although alternative regimens and preparations for liquid sublingual immunotherapy or use of specific sublingual drops have been proposed and may be used off-label, these products and formulations have not been systematically studied in a rigorous manner in US populations. Use of such products or formulations is without recommendation for any current particular indication in the US populations and is not endorsed. (Strength of Recommendation: Strong; Evidence: D: Directly based on category IV evidence or extrapolated recommendation

from category I, II, or III evidence.) At present there are no U.S. Food and Drug Administration (FDA)-approved sublingual antigen extract drop preparations.

Several meta-analyses and systematic reviews have examined outcomes with subcutaneous antigen extract drop immunotherapy (Calderon, et al., 2011; DiBona, et al., 2010; Calamita, et al., 2006; Wilson, et al., 2004; update Radulovic, et al., 2010). Other studies have evaluated the comparative clinical effectiveness of this immunotherapy compared with subcutaneous immunotherapy, placebo and other interventions for the treatment of allergic rhino-conjunctivitis and/or asthma (Chelladurai and Lin, 2014; de Bot, et al., 2013). Study authors noted randomized controlled trials with head-to-head direct comparisons of subcutaneous immunotherapy and sublingual antigen extract drop immunotherapy are needed to strengthen the evidence base. Indirect comparisons of treatment options have many limitations and must be taken into consideration for clinical decision making.

Liu et al. (2019) conducted a multi-center, double-blind, randomized placebo-controlled trial with four parallel groups to evaluate the efficacy and safety of sublingual immunotherapy (SLIT) with Dermatophagoides farinae (D. farina) drops on patients with house dust mites (HDM) induced atopic dermatitis (AD). The study included patients (n=239) aged 18–60 years, a severity score of atopic dermatitis between 10 and 40 on the scoring atopic dermatitis (SOCRAD) scale, and a positive skin prick test results to D. farinae stimulation. Patients were randomly divided into four groups: placebo (n=60), high-dose sublingual D. farinae drops (n=60), medium-dose sublingual D. farinae drops (n=60) and low-dose sublingual D. farinae drops (n=59). Treatment was conducted by two phases: up-dosing phase (1st–10th weeks) and maintenance phase (11th–36th weeks). In up-doing phase, patients received low to high dose of sublingual D. farinae drops or placebo treatment. In the maintenance phase, patients took a high dose of sublingual D. farinae drops or placebo daily. The primary outcome assessed the therapeutic efficacy and safety of SLIT drops. Patients were assigned to receive relevant treatment for 36 weeks with follow-ups at four, 10, 16, 24 and 36 weeks. The therapeutic efficacy of SLIT with D. farinae drops was assessed using the SCORAD scale, the use of concomitant drugs to relieve clinical symptoms in maintenance phase, the dermatology life quality index (DLQI) and the skin lesion area. The safety was evaluated by adverse events (AE) and general clinical laboratory evaluations. 48 cases withdrew before the end of study. There were no significant differences in withdraw rates between the placebo group and D. farinae Drops groups. There was significant decreases in scoring atopic dermatitis and total medication score in the medium-dose and high-dose D. farinae drops groups. At the sixth visit, the skin lesion area showed a statistically significant difference between high-dose/medium-dose D. farinae drops group and placebo group ($p<0.05$). Most adverse events were minimal, and no life-threatening adverse drug reactions occurred. Author noted limitations included short term follow-up and children were not included as test subjects. The authors concluded that the study demonstrated the beneficial effect of SLIT with high or medium dose D. farinae drops on AD, and the treatment was well tolerated. However, further studies should include a longer time frames and a more suitable D. farina drops dosage.

Pfaar et al. (2019) conducted a parallel-group, multicenter, double-blind, randomized placebo-controlled trial to investigate the efficacy and safety of sublingual high-dose liquid birch pollen extract (40,000 allergy units native [AUN]/mL) in adults with birch pollen allergy. The study included adult patients (n=406) aged 18-65 years with moderate-to-severe birch pollen-induced allergic rhinoconjunctivitis with or without mild-to-moderate controlled asthma. Patients were randomized into the active treatment group (n=208) or the placebo group (n=198). Treatment was started three to six months before the birch pollen season and continued co-seasonally during the pollen season followed by an open-label safety extension period over six months that included 343 patients treated exclusively with the active product (n=169/active treatment group and n=174/placebo group). The primary outcome measured the difference in mean combined symptom and medication score (CSMS) between the active and placebo treatment groups. The CSMS is the European Academy of Allergy and Clinical Immunology (EAACI) recommended end point for pivotal studies. Primary outcome analysis was carried out in the intention-to-treat (ITT) population (n=357), with 179 patients in the active treatment group and 178 patients in the placebo group. The Secondary outcomes assessed quality-of-life, immunologic parameters, and safety. Thirty-two patients were lost to follow-up primarily due to the development of adverse events (AEs). Primary efficacy results demonstrated a significant ($p<0.0001$) and clinically relevant (32%) reduction in the combined symptom and medication score compared with placebo after three to six months of sublingual allergen immunotherapy (SLIT) in the intention to treat (ITT) population. Significantly better rhinoconjunctivitis quality-of-life scores ($p<0.0001$) and the patient's own overall assessment of his or her health status, including the visual

analog scale score (Euro Quality of Life Visual Analogue Scale; p=0.0025), were also demonstrated. In total, a good safety profile of SLIT was observed. The local and systemic treatment-emergent adverse events (TEAEs) in the double blind period of the study totaled 342 local reactions in 165 (40.6%) patients and 83.0% of all reactions were mild. Four (1.9%) patients of the active treatment group experienced at least one severe local reaction. Local and systemic adverse reactions were mainly of mild intensity and well controlled in the open label extension, 123 of 343 patients reported a local reaction, 88 of whom belonged to the former placebo group. Most local reactions were of mild-to-moderate intensity (> 97%). Regarding clinical and laboratory safety parameters, no safety issues were observed.

On behalf of the Agency for Healthcare Research and Quality, Lin et al. (2013) and colleagues reported results of a comparative effectiveness review of 60 studies comparing sublingual antigen extract drop therapy to placebo or another intervention for the treatment of allergic rhinoconjunctivitis and/or asthma. Authors note overall quality of evidence is assessed to be low to moderate due in part to limitations with the description of allocation concealment in some studies, moderate statistical heterogeneity and possible publication bias. Large definitive trials are required as well as head-to-head comparative studies with currently available anti-allergic drugs. Further studies evaluating the mechanisms of sublingual antigen extract drop immunotherapy preparations are needed as is a need to develop and validate standard instruments, such as questionnaires with adequate psychometrical properties. There is need for further large rigorously designed studies that examine long-term effectiveness after discontinuation of treatment and establish the cost-effectiveness of sublingual antigen extract drop immunotherapy preparations.

In a Cochrane review, Wilson et al. (2004; update Radulovic, et al., 2010), conducted a systematic review and meta-analysis of sublingual antigen extract drop immunotherapy for the treatment for allergic rhinitis. The authors identified 22 randomized controlled trials involving 979 patients. Only two of the studies compared injection therapy with sublingual extract drop therapy. The studies reported similar improvements in symptoms and medication requirements. The authors found heterogeneity in the findings, due to varying methods used to administer sublingual extract drop therapy and different clinical response scoring systems. Overall, sublingual antigen extract drop immunotherapy was followed by a significant reduction in mean symptom scores (p=0.002) and medication use (p=0.0003) when compared to placebo therapy. There were no significant variations in response to the use of different allergens in the studies. The authors noted total amount of allergen delivered may be a determinant of success, but the increasing time duration of sublingual extract drop therapy did not clearly increase efficacy. Sublingual extract drop therapy did not appear to be effective in studies limited to allergic children; however, the numbers of children in such studies were too small to draw definitive conclusions. The subgroup analyses did not suggest a benefit of treatment in any particular patient or disease group. The updated review of 2010 resulted in no change to the conclusions.

Professional Societies/Organizations
The American Board of Internal Medicine's (ABIM) Foundation Choosing Wisely® Initiative: 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 (2014)
- Don't routinely do diagnostic testing in patients with chronic urticaria (2012)
- Don't perform food IgE testing without a history consistent with potential IgE-mediated food allergy (2014)

American Academy of Pediatrics:

- Don't perform screening panels for food allergies without previous consideration of medical history (2014)

American Academy of Dermatology:

- Don't use skin prick tests or blood tests such as the radioallergosorbent test (RAST) for the routine evaluation of eczema (2015)

Use Outside the US

In 2019 Agache et al. published EAACI Guidelines on Allergen Immunotherapy: House dust mite (HDM) driven allergic asthma. The guidelines stated that HDM SLIT drops are recommended for children with controlled HDM-driven allergic asthma as the add-on to regular asthma therapy to decrease symptoms and medication needs (conditional recommendation, low-quality evidence).

On behalf of the 2015 European Academy of Allergy and Clinical Immunology (EAACI) de Waard vander Spek et al. published a position paper with recommendations for practical patch testing in allergic contact dermatitis in children. According to the EAACI, patch testing is recommended in children for: suggestive history, suggestive clinical distribution of skin lesions, severe eczema, especially if unresponsive to topical therapies, Hand or foot eczema and therapy-resistant (atopic) dermatitis.

European Society of Contact Dermatitis (2015)
On behalf of this Society Johansen et al. published recommendations on best practice for diagnostic patch testing. According to the guidelines, patch testing should be considered in patients with: suspected contact dermatitis, acute or chronic, including dermatitis related to occupational exposures; other types of (chronic) dermatitis (eczema) not improving with treatment and skin and mucous membrane eruptions (including delayed-type drug eruptions) in which delayed-type hypersensitivity is suspected.

National Institute for Health and Clinical Excellence (NICE) (United Kingdom)
A clinical guideline on food allergy in children and young people states that, if IgE-mediated allergy is suspected, a skin prick best and/or blood tests for specific IgE antibodies to the suspected foods and likely co-allergens may be offered. The choice of test is based on the clinical history, suitability for, safety for and acceptability to the child (or their parent or caregiver), and the available competencies of the healthcare professional (NICE 2011; update 2018).

Medicare Coverage Determinations

	Contractor	Determination Name/Number	Revision Effective Date
NCD	National	Food Allergy Testing and Treatment (110.11)	10/31/88
NCD	National	Antigens Prepared for Sublingual Administration (110.9)	11/17/96
NCD	National	Challenge Ingestion Food Testing (110.12)	8/1/78
NCD	National	Cytotoxic Food Tests (110.13)	8/5/85
LCD	CGS Administrators, LLC	RAST Type Tests (L34063)	12/5/19
LCD	CGS Administrators, LLC	Allergy Immunotherapy (L32553)	11/7/19
LCD	National Government Services, Inc.	RAST Type Tests (L33591)	11/7/19
LCD	Novitas Solutions, Inc	Allergy Testing (L36241)	7/1/20
LCD	Novitas Solutions, Inc	Allergen Immunotherapy (L36240)	11/14/19
LCD	Noridian Healthcare Solutions, LLC	Allergy Testing (L34313)	10/1/19
LCD	First Coast Service Options, Inc.	Allergy Testing (L33261)	7/2/20
LCD	First Coast Service Options, Inc.	Allergen Immunotherapy (L37800)	10/15/19
LCD	Wisconsin Physicians Service Insurance Corporation	Allergy Testing (L36402)	11/26/20

	Contractor	Determination Name/Number	Revision Effective Date
LCD	Wisconsin Physicians Service Insurance Corporation	Allergy Immunotherapy (L36408)	5/28/20
LCD	Palmetto GBA	Allergy Skin Testing (L33417)	10/10/19

Note: Please review the current Medicare Policy for the most up-to-date information.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Testing

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
86003	Allergen specific IgE; quantitative or semiquantitative, crude allergen extract, each
86005	Allergen specific IgE; qualitative, multiallergen screen (eg, disk, sponge, card)
86008	Allergen specific IgE; quantitative or semiquantitative, recombinant or purified component, each
86353	Lymphocyte transformation, mitogen (phytomitogen) or antigen induced blastogenesis
95004	Percutaneous tests (scratch, puncture, prick) with allergenic extracts, immediate type reaction, including test interpretation and report, specify number of tests
95017	Allergy testing, any combination of percutaneous (scratch, puncture, prick) and intracutaneous (intradermal), sequential and incremental, with venoms, immediate type reaction, including test interpretation and report, specify number of tests
95018	Allergy testing, any combination of percutaneous (scratch, puncture, prick) and intracutaneous (intradermal), sequential and incremental, with drugs or biologicals, immediate type reaction, including test interpretation and report, specify number of tests
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
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)
95070	Inhalation bronchial challenge testing (not including necessary pulmonary function tests); with histamine, methacholine, or similar compounds
95071	Inhalation bronchial challenge testing (not including necessary pulmonary function tests); with antigens or gases, specify Code deleted (12/31/2020)
95076	Ingestion challenge test (sequential and incremental ingestion of test items, eg, food, drug or other substance); initial 120 minutes of testing
95079	Ingestion challenge test (sequential and incremental ingestion of test items, eg, food, drug or other substance); each additional 60 minutes of testing (List separately in addition to code for primary procedure)

Considered Experimental/Investigational/Unproven:

CPT®* Codes	Description
82784	Gammaglobulin (immunoglobulin); IgA, IgD, IgG, IgM, each
83516	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; qualitative or semiquantitative, multiple step method
83518	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; qualitative or semiquantitative, single step method (eg, reagent strip)
83519	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, by radioimmunoassay (eg, RIA)
83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified
86001	Allergen specific IgG quantitative or semiquantitative, each allergen
86160	Complement antigen; each component
86343	Leukocyte histamine release test (LHR)
86807	Serum screening for cytotoxic percent reactive antibody (PRA); standard method
86808	Serum screening for cytotoxic percent reactive antibody (PRA); quick method
86849	Unlisted immunology procedure
95060	Ophthalmic mucous membrane tests
95065	Direct nasal mucous membrane test
95199	Unlisted allergy/clinical immunologic service or procedure
0165U	Peanut allergen-specific quantitative assessment of multiple epitopes using enzyme-linked immunosorbent assay (ELISA), blood, individual epitope results and probability of peanut allergy
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

Treatment

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
95115	Professional services for allergen immunotherapy not including provision of allergenic extracts; single injection
95117	Professional services for allergen immunotherapy not including provision of allergenic extracts; 2 or more injections
95120	Professional services for allergen immunotherapy in the office or institution of the prescribing physician or other qualified health care professional, including provision of allergenic extract; single injection
95125	Professional services for allergen immunotherapy in the office or institution of the prescribing physician or other qualified health care professional, including provision of allergenic extract; 2 or more injections
95130	Professional services for allergen immunotherapy in the office or institution of the prescribing physician or other qualified health care professional, including provision of allergenic extract; single stinging insect venom
95131	Professional services for allergen immunotherapy in the office or institution of the prescribing physician or other qualified health care professional, including provision of allergenic extract; 2 stinging insect venoms
95132	Professional services for allergen immunotherapy in the office or institution of the prescribing physician or other qualified health care professional, including provision of allergenic extract; 3 stinging insect venoms
95133	Professional services for allergen immunotherapy in the office or institution of the prescribing physician or other qualified health care professional, including provision of allergenic extract; 4 stinging insect venoms

CPT®* Codes	Description
95134	Professional services for allergen immunotherapy in the office or institution of the prescribing physician or other qualified health care professional, including provision of allergenic extract; 5 stinging insect venoms
95144	Professional services for the supervision of preparation and provision of antigens for allergen immunotherapy, single dose vial(s) (specify number of vials)
95145	Professional services for the supervision of preparation and provision of antigens for allergen immunotherapy, (specify number of doses); single stinging insect venom
95146	Professional services for the supervision of preparation and provision of antigens for allergen immunotherapy, (specify number of doses); 2 stinging insect venoms
95147	Professional services for the supervision of preparation and provision of antigens for allergen immunotherapy, (specify number of doses); 3 stinging insect venoms
95148	Professional services for the supervision of preparation and provision of antigens for allergen immunotherapy, (specify number of doses); 4 stinging insect venoms
95149	Professional services for the supervision of preparation and provision of antigens for allergen immunotherapy, (specify number of doses); 5 stinging insect venoms
95165	Professional services for the supervision of preparation and provision of antigens for allergen immunotherapy; single or multiple antigens (specify number of doses)
95170	Professional services for the supervision of preparation and provision of antigens for allergen immunotherapy; whole body extract of biting insect or other arthropod (specify number of doses)
95180	Rapid desensitization procedure, each hour (eg, insulin, penicillin, equine serum)

Considered Experimental/Investigational/Unproven:

CPT®* Codes	Description
30999	Unlisted procedure, nose
95199	Unlisted allergy/clinical immunologic service or procedure
97810	Acupuncture, 1 or more needles; without electrical stimulation, initial 15 minutes of personal one-on-one contact with the patient
97811	Acupuncture, 1 or more needles; without electrical stimulation, each additional 15 minutes of personal one-on-one contact with the patient, with re-insertion of needle(s) (List separately in addition to code for primary procedure)
97813	Acupuncture, 1 or more needles; with electrical stimulation, initial 15 minutes of personal one-on-one contact with the patient
97814	Acupuncture, 1 or more needles; with electrical stimulation, each additional 15 minutes of personal one-on-one contact with the patient, with re-insertion of needle(s) (List separately in addition to code for primary procedure)

Sublingual Antigen Extract Drop Immunotherapy Preparations

Experimental/Investigational/Unproven when used to report sublingual antigen extract drop immunotherapy preparations:

CPT®* Codes	Description
95165	Professional services for the supervision of preparation and provision of antigens for allergen immunotherapy; single or multiple antigens (specify number of doses)
95199	Unlisted allergy/clinical immunologic service or procedure

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