Medical Coverage Policy

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Allergy Testing and Non-Pharmacologic Treatment

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Complementary and Alternative Medicine
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Odactra
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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 vivo allergy testing that exceeds the following limits is not covered or reimbursable:

- 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

Allergen specific IgE; quantitative or semiquantitative testing that exceeds 80 units is not covered or reimbursable.

Bead-based epitope assay (e.g., VeriMAP™ Peanut Dx, VeriMAP™ Peanut Sensitivity) is not covered or reimbursable.

<u>Treatment</u>:

Medically Necessary

Subcutaneous allergen immunotherapy is considered medically necessary for the treatment of allergic asthma and allergic rhinitis (with or without allergic conjunctivitis).

Professional services for the supervision of preparation and provision of antigens for allergen immunotherapy, single or multiple antigens (CPT® code 95165) that exceeds a maximum of 150 doses per year (i.e., rolling 12 months) are not covered or reimbursable.

Sublingual antigen extract drop immunotherapy preparations are not covered or reimbursable.

Note: Please refer to Drug and Biologic Coverage Policies IP0515: Grass Pollen Sublingual Products, IP0516: Odactra, IP0518: Ragwitek, and 2004: Peanut (arachis hypogaea) allergen powder-dnfp for information regarding FDA-approved non-subcutaneous allergen immunotherapy.

Health Equity Considerations

Health equity is the highest level of health for all people; health inequity is the avoidable difference in health status or distribution of health resources due to the social conditions in which people are born, grow, live, work, and age.

Social determinants of health are the conditions in the environment that affect a wide range of health, functioning, and quality of life outcomes and risks. Examples include safe housing, transportation, and neighborhoods; racism, discrimination and violence; education, job opportunities and income; access to nutritious foods and physical activity opportunities; access to clean air and water; and language and literacy skills.

The American Academy of Allergy, Asthma and Immunology (AAAAI) published a workgroup report on health disparities in allergic and immunologic conditions in racial and ethnic underserved populations. Allergic rhinitis (AR) is underdiagnosed and underappreciated in certain racial and ethnic populations. Black children without a personal or family history of atopy had a higher odds of sensitization to any allergen as well as discrete sensitization to mold, cockroach, grass, weed and tree pollen compared to white children. Latino populations are also significantly affected by AR and under diagnosed in Puerto Rican and urban populations. Clinical studies have demonstrated that low-income and minority groups are less likely to receive allergen immunotherapy (AIT) and Medicaid insurance is associated with more emergency room care for acute nasal symptoms compared to private insurance. The studies highlight that additional burdens faced by lower income families can contribute to a lack of resources necessary to adhere to AIT rigorous schedules. Disparities in food allergies (FA) are predominately seen among under-represented racial and ethnic groups and lower income populations in the United States, with higher rates of FA-related anaphylaxis and ED visits. Black children have higher odds of wheat, soy, corn, fish, and shellfish allergy, and Hispanic children have higher odds of corn, fish, and shellfish allergy. Children belonging to under-represented racial and ethnic groups are less likely to have prescribed FA action plans, have a shorter duration of specialist follow-up, and have higher rates of FA related anaphylaxis and ED visits. Food insecurity is a risk factor in milk and egg allergy and was associated with lower health literacy (Davis, et al., 2021).

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 month 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).

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 issued by 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

When there is a clear history of sting anaphylaxis and skin test results are negative, then serum IgE antibodies should be measured, and if necessary, skin tests should be repeated after 3 to 6 months (Kowal and DuBuske, 2021; Golden, et al., 2017).

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.

Arthroplasty Implants: In Vitro 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 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.

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. 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 testing modalities.

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.

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

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 categories 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 (Fortescue, et al., 2020; 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.

Medicare Coverage Determinations

	Contractor	Determination Name/Number	Revision Effective Date
NCD	National	Food Allergy Testing and Treatment (110.11)	10/31/1988
NCD	National	Antigens Prepared for Sublingual Administration (110.9)	11/17/1996
NCD	National	Challenge Ingestion Food Testing (110.12)	08/01/1978
NCD	National	Cytotoxic Food Tests (110.13)	08/05/1985
LCD	CGS Administrators, LLC	RAST Type Tests (L34063)	08/03/2023

	Contractor	Determination Name/Number	Revision Effective Date
LCD	CGS Administrators, LLC	Allergy Immunotherapy (L32553)	11/02/2023
LCD	National Government Services, Inc.	RAST Type Tests (L33591)	11/07/2019
LCD	Novitas Solutions, Inc	Allergy Testing (L36241)	07/11/2021
LCD	Novitas Solutions, Inc	Allergen Immunotherapy (L36240)	07/11/2021
LCD	Noridian Healthcare Solutions, LLC	Allergy Testing (L34313)	10/01/2019
LCD	First Coast Service Options, Inc.	Allergy Testing (L33261)	07/11/2021
LCD	First Coast Service Options, Inc.	Allergen Immunotherapy (L37800)	07/11/2021
LCD	Wisconsin Physicians Service Insurance Corporation	Allergy Testing (L36402)	10/01/2022
LCD	Wisconsin Physicians Service Insurance Corporation	Allergy Immunotherapy (L36408)	10/26/2023
LCD	Palmetto GBA	Allergy Skin Testing (L33417)	04/15/2021

Note: Please review the current Medicare Policy for the most up-to-date information.
(NCD = National Coverage Determination; LCD = Local Coverage Determination)

Coding Information

Notes:

1. This list of codes may not be all-inclusive since the American Medical Association (AMA) and Centers for Medicare & Medicaid Services (CMS) code updates may occur more frequently than policy updates.
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
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
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)

Not Covered or Reimbursable:

CPT®* Codes	Description
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
95144	Professional services for the supervision of preparation and provision of antigens for allergen immunotherapy, single dose vial(s) (specify number of vials)
95165†	Professional services for the supervision of preparation and provision of antigens for allergen immunotherapy; single or multiple antigens (specify number of doses)

†**Note: Professional services for the supervision of preparation and provision of antigens for allergen immunotherapy, single or multiple antigens that exceeds a maximum of 150 doses per year (i.e., rolling 12 months) are not covered or reimbursable.**

Sublingual Antigen Extract Drop Immunotherapy Preparations

Not covered or reimbursable 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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Revision Details

Type of Revision	Summary of Changes	Date
Annual Review	• Removed policy statements related to: in vitro metal LTT for joint replacement surgery, and LHR in vitro allergy testing.	04/15/2025
Annual Review	• No changes to coverage.	05/15/2024
Focused Review	• Added policy statements regarding testing limits on allergy testing and preparation of allergen immunotherapy. • Removed the not medically necessary policy statement for in vitro allergy testing and subcutaneous allergen immunotherapy. • Updated the experimental/investigational or unproven policy statement for allergy testing.	12/03/2023