Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

***Current Policy Effective Date: 7/1/24**
(See policy history boxes for previous effective dates)

Title: Allergy Testing and Immunotherapy

Description/Background

ALLERGY TESTING

Allergic diseases, such as allergic rhinitis (hay fever), food allergy and atopic dermatitis (eczema) affect more than 50 million people in the U.S. and are the 6th leading cause of chronic illness.[1] An allergy is a reaction of the body's immune system to a foreign substance, an allergen. The immune system generates an immunoglobulin E (IgE) antibody in response to the allergen exposure.

Allergic or hypersensitivity disorders may be manifested by generalized systemic reactions, as well as localized reactions in any organ system of the body. The reactions may be acute, sub-acute or chronic, immediate or delayed and may be caused by numerous offending agents, which may include pollen, mold, dust, mites, animal dander, stinging insect venoms, food or drugs.

Allergy testing, in conjunction with the use of a history and physical examination, may be necessary to differentiate allergic disorders from other types of diseases and to guide treatment. Allergy tests are performed to verify or exclude the presence of IgE-mediated hypersensitivity and to identify the causative allergen(s).

Allergy testing may be broadly subdivided into either in vivo or in vitro procedures. In vivo procedures 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). In vivo methodologies include skin allergy testing (eg, skin prick/puncture testing, skin scratch testing, intradermal testing, skin patch testing and skin endpoint titration), photo patch testing, bronchial challenge, provocation tests and food

challenges. In vitro methodologies determine the presence of specific IgE or elevated IgE by analyzing patient serum. In vitro allergy tests include RAST, FAST, MAST, ELISA and ImmunoCAP.

In addition to the above tests that assess the presence of specific IgE, many other in vivo and in vitro tests have been proposed as being useful in the management of allergic disorders.

ALLERGY TREATMENT

Once an allergen is identified, treatment may include avoidance of the allergen, pharmacologic therapy and/or immunotherapy. Avoidance of the allergen is the most effective treatment for allergy. In cases where the allergen cannot be avoided completely, medication therapy including antihistamines may be helpful. Allergy immunotherapy (also known as desensitization, allergy injection therapy or "allergy shots") involves regular injections of extracts prepared from the allergen(s) to which a patient is sensitized. It begins with low doses of the allergen (to prevent reactions), followed by gradually-increasing doses, as immunity to the antigen develops. After the maintenance dose is achieved, the interval between injections may range between two and six weeks. Immunotherapy is usually continued for several years. Clinical benefits from multiple years of subcutaneous injections for allergen-specific immunotherapy may persist for several years after treatment is discontinued.

Serial endpoint titration (SET) testing (ie, skin endpoint titration, serial dilution endpoint titration, the Rinkel test/method) is a technique to determine the starting dose for testing or immunotherapy when there is potential for the specific allergen in question to produce a severe systemic allergic reaction or anaphylaxis.

An alternative to subcutaneous injections is Sublingual Immunotherapy (SLIT). SLIT targets absorption to the sublingual and buccal mucosa. Allergen preparations used for SLIT are held under the tongue and then swallowed or spit out. The U.S. Food and Drug Administration (FDA) approved 3 sublingual immunotherapy agents (see medical policy: "Sublingual Immunotherapy as a Technique of Allergen-Specific Therapy", retired).

Oral mucosal immunotherapy (OMIT) is similar to SLIT in that allergen preparations are introduced to the oral mucosa. However, rather than the sublingual region, the targeted area is the vestibule of the mouth. The delivery platform, Allerdent® (Allovate, LLC) is a toothpaste base that can be customized by physicians to include allergens that are specific to the patient. The toothpaste base can be compounded by the physician or in a pharmacy. Taking a similar approach, Intrommune Therapeutics is developing a toothpaste product to desensitize those with peanut allergy. This product does not require compounding.

Oral immunotherapy (OIT) has received increasing attention as a new approach in the treatment of food allergy. An individual consumes gradually-increasing amounts of an allergen, with the goal of raising the threshold that may trigger a reaction, thus providing the individual protection against accidental ingestion of the allergen. Individuals begin

with a dose that is lower than what may trigger an allergic reaction. The dose is escalated about every two weeks with medical supervision; daily doses are given at home. At four to six months, a maintenance dose is reached, and is continued indefinitely. OIT is not a curative therapy.[2,3]

There are many other proposed treatments for allergies, among them enzyme-potentiated desensitization, provocation-neutralization therapy, autogenous urine immunization, repository emulsion therapy and rhinophototherapy.

Regulatory Status:

On January 31, 2020 the U.S. Food and Drug Administration approved Palforzia™ (Peanut [Arachis hypogaea] Allergen Powder-dnfp) (Aimmune Therapeutics, Inc.) as an oral immunotherapy indicated for the mitigation of allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanut. The FDA requires that Palforzia™ is available only through a restricted program under a Risk Evaluation and Mitigation Strategies called the Palforzia REMS.[4]

In April 2014, the first sublingual allergen extract tablets were approved by the U.S. Food and Drug Administration (FDA) through the biologics license application process for treatment of pollen-induced allergic rhinitis with or without conjunctivitis:

- On April 1, the FDA approved Oralair (Stallergenes) allergen extract for individuals 10 to 65 years of age (product is now approved for individuals 5 to 65 years of age). Oralair contains freeze-dried pollen allergen extracts of 5 grasses: Kentucky Blue Grass, Orchard, Perennial Rye, Sweet Vernal, and Timothy.
- On April 11, the FDA approved Grastek (Merck) Timothy grass pollen (*Phleum pretense*) allergen extract for individuals 5 to 65 years of age (Grastek is marketed in Europe as Grazax®).
- On April 17, the FDA approved Ragwitek (Merck) short ragweed pollen allergen extract for individuals 18 to 65 years of age. On April 16, 2021, Ragwitek received FDA approval for use in individuals age 5 to 17 years of age.

In March 2017, the FDA approved Odactra (Merck) allergan extract for individuals 18 to 65 years of age who have house dust mite-induced allergic rhinitis with or without conjunctivitis. Odactra contains freeze-dried extracts of dust mites (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*).

Medical Policy Statement

The safety and effectiveness of selected allergy testing and immunotherapy treatment of allergies have been established. They may be considered useful diagnostic and therapeutic options when indicated.

Inclusionary and Exclusionary Guidelines

INCLUSIONS:

- **Allergy testing:**
  - Bronchial challenge tests
  - Direct skin test (percutaneous [scratch, prick or puncture] or intracutaneous [intradermal])
  - Double blind food challenge test
  - Patch test (application test)
  - Photo patch test
  - In vitro IgE antibody tests (RAST, MAST, FAST, ELISA, ImmunoCAP)
  - Total serum IgE concentration
  - Serial (skin) endpoint titration (SET) when there is a high likelihood for a severe allergic reaction to specific agents

- **Immunotherapy treatments:**
  - Appropriate in individuals with demonstrated allergic hypersensitivity that cannot be managed by medications or avoidance.
  - Oral immunotherapy with Palforzia™, when Pharmacy and Therapeutics Policy criteria are met

EXCLUSIONS:

- **Allergy Testing (this list may not be all-inclusive)**
  - Antigen leukocyte cellular antibody (ALCAT) automated food allergy testing (see policy: “Antigen Leukocyte Antibody Test”)
  - Applied kinesiology or Nambudripad’s allergy elimination test (NAET; i.e., muscle strength testing or measurement after allergen ingestion)
  - Anti-Fc Epsilon receptor antibodies testing
  - Anti-IgE receptor antibody testing
  - Blood, urine or stool micro-nutrient assessments
  - Candidiasis test
  - Chemical analysis of body tissues (eg, body fluids, hair, etc.)
  - Chlorinated pesticides (serum)
  - Clifford materials reactivity testing
  - Complement (total or components)
  - Complement antigen testing (Sage)
  - C-reactive protein
  - Cytokine and cytokine receptor assay
  - Cytotoxic food, environmental or clinical ecological tests (Bryan’s test, ACT)
  - Direct mucous membrane test (conjunctival/ophthalmic, nasal)
  - Electrodermal testing or electro-acupuncture
  - Electromagnetic sensitivity syndrome/disorder (allergy to electricity, electro-sensitivity, electro-hypersensitivity and hypersensitivity to electricity)
  - Environmental cultures and chemicals
  - Eosinophil cationic protein (ECP) test
  - Food immune complex assay (FICA) or food allergenic extract immunotherapy

- General immune system assessments
- Immune complex assay
- Iridology
- Leukocyte antibodies testing
- Leukocyte histamine release test (LHRT)/basophil histamine release test
- Live cell analysis
- Lymphocytes (B or T subsets)
- Lymphocyte function assay
- Mediator Release test (MRT)
- Metabolic assessments
- Multiple chemical sensitivity syndrome (a.k.a., idiopathic environmental intolerance (IEI), clinical ecological illness, clinical ecology, environmental illness, chemical AIDS, environmental/chemical hypersensitivity disease, total allergy syndrome, cerebral allergy, 20th century disease)
- Nasal challenge test
- Prausnitz-Kustner or P-K testing/passive cutaneous transfer test
- Provocation-neutralization tests (food, inhalant or environmental chemical allergies)
- Pulse response test
- Qualification of nutritional assessments
- Rebuck skin window test
- Secretory IgA (saliva, and other mucous secretions)
- Allergen specific IgG (RAST/ELISA) testing
- Sublingual provocative neutralization testing and treatment with hormones
- Venom blocking antibodies
- Volatile chemical panels (blood testing for chemicals)

- **Immunotherapy**
  - Oral immunotherapy (OIT)*
  - Oral mucosal immunotherapy (OMIT), including compounded toothpaste
  - Provocation-neutralization therapy
  - Rinkel injection therapy (RIT), also known as serial dilution endpoint titration therapy, for ragweed pollen hay fever
  - Enzyme-potentiated desensitization (EPD)
  - Repository emulsion therapy
  - Autogenous urine immunization (urine auto injections)
  - Rhinophototherapy

  *EXCEPTION: Palforzia™ (FDA-approved oral immunotherapy), when the Pharmacy and Therapeutics Policy criteria are met

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CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

95004	95017	95018	95024	95027	95028
95044	95052	95056	95070	95071	95076

95079

Specified Immunotherapy Codes:

95115	95117	95120	95125	95130	95131
95132	95133	95134	95144	95145	95146
95147	95148	95149	95165	95170	95180

Specified Laboratory CPT Codes:

82785	86003	86005	86008

Other codes (investigational, not medically necessary, etc.):

30999	86001	86343	95060	95065	95199

Note: Immunotherapy may not be covered by all contracts or certificates. Please consult customer or provider inquiry resources at BCBSM or BCN to verify coverage.

Note: Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

Rationale

ALLERGY TESTING

In Vivo Diagnostic Testing

Immunoglobulin E (IgE)-mediated allergies account for the majority of environmental, food and medication allergies**.** Skin testing is rapid, sensitive and cost-effective for the detection of IgE-mediated disease. Skin testing may be used to diagnose allergic asthma, rhinitis, food allergy, some medication allergies, venom allergies and latex allergy. The testing may be focused or more general depending on the clinical setting.

Skin Test Methods

Percutaneous (scratch, prick or puncture tests): a drop of allergen extract is placed on the skin. The skin is then gently scratched, pricked or punctured through the drop into the underlying epidermis. The skin is evaluated for redness and/or swelling. Issues associated with this method include false-positive reactions, low reproducibility and patient discomfort. These tests are generally less sensitive than intracutaneous (intradermal) tests, but they are more specific.

The American Academy of Allergy Asthma and Immunology's Allergy Diagnostic Testing: An Updated Practice Parameter, 2008[5]:
Summary Statement 1. First described in 1867 by Dr Charles Blackley, skin tests (prick/puncture and intracutaneous) have evolved as reliable, cost effective techniques for the diagnosis of IgE-mediated diseases.

Summary Statement 2. Prick/puncture tests are used to confirm clinical sensitivity induced by aeroallergens, foods, some drugs, and a few chemicals.

Intracutaneous/Intradermal tests: a small amount of allergen extract is injected by a very fine needle into the dermis. The skin is observed for any reaction. Intradermal testing is more sensitive but less specific than percutaneous testing for the detection of IgE antibodies.

AAAAI's Allergy Diagnostic Testing: An Updated Practice Parameter, 2008[5]:
Summary Statement 19: Intracutaneous tests will identify a larger number of individuals with lower skin sensitivity and are used when increased sensitivity is the main goal of testing.

Summary Statement 25: the diagnostic sensitivity of intracutaneous tests is probably greater than prick/puncture tests when testing for penicillin, insect venom, or certain drug class (eg, insulin, heparin, muscle relaxants) hypersensitivity).

Skin endpoint titration (SET) or intradermal dilutional testing (IDT): a variation of intradermal skin testing that uses increasing does of antigen to determine the endpoint at which the reaction changes from negative to positive. SET testing can be used to determine the starting dose for immunotherapy for individuals highly sensitive to hymenoptera venom or inhalants.

AAAAI's Allergy Diagnostic Testing: An Updated Practice Parameter, 2008[5]:
Summary Statement 21. When compared with specific nasal challenge testing, skin end point titration (SET) is equivalent to prick/puncture skin tests.

Patch test: allergens are applied to patches which are placed on the arm or back for 48 hours. Patches are removed at the physician office and reactions are noted. The test can be re-assessed at 72 to 96 hours following the initial placement. This test is generally performed for those with contact dermatitis.

AAAAI's Contact Dermatitis: A Practice Parameter Update 2015[6]:
"Summary Statement 2: In individuals suspected of ACD [acute contact dermatitis], patch testing is the gold standard to confirm the diagnosis."

Photo patch test: used to detect light-induced antigens in individuals with photosensitive dermatitis. Two identical sets of allergen patches are placed on a patient's back. One set is exposed to UVA light then examined for a reaction. A positive test is recorded when an allergic reaction appears only on the light-exposed site.

AAAAI's Allergy Diagnostic Testing: An Updated Practice Parameter, 2008[5]:
Summary Statement 238: If photosensitization is suspected, photo patch tests should be performed by a physician with expertise in UV radiation.

Challenge / Provocation Tests

Bronchial challenge: baseline lung function is measured via spirometry. Then either methacholine or histamine is introduced via a nebulizer, and lung function is again evaluated. Increasing doses are given until there is a change in lung function. This testing identifies bronchial hyperresponsiveness and may be valuable in diagnosing atypical mild asthma or effectiveness of asthma medication.

> AAAAI's Allergy Diagnostic Testing: An Updated Practice Parameter, 2008[5]:
> *Summary Statement 49:* Specific (allergic) bronchial challenge provides a measure of lower airway clinical sensitivity when there is uncertainty or dispute.

Double blind oral food (food ingestion) challenge: this test is performed to diagnose a food allergy. Increasing doses of a suspected food allergen and a placebo are given, usually on different days. Neither the patient nor the physician knows which substance is being ingested on which day. Responses or symptoms to the food are evaluated.

> AAAAI's Allergy Diagnostic Testing: An Updated Practice Parameter, 2008[5]:
> Summary Statement 129: The probability distribution of specific IgE for several anaphylactogenic foods (peanuts, egg white, cow's milk, and codfish) can define clinical sensitivity as verified by double-blind oral challenge tests; similar relationships have been defined for several respiratory allergens.

In Vitro Diagnostic Testing

In vitro testing may be a reasonable alternative to skin testing in individuals with: skin conditions such as severe dermatographism, ichthyosis or generalized eczema that would obscure wheal and flare results; individuals who have been receiving long-acting antihistamines, tricyclic antidepressants or medications that may put the patient at undue risk if discontinued; uncooperative individuals with mental or physical impairments; or when clinical history suggests a high risk of anaphylaxis from skin testing. The American Academy of Allergy, Asthma and Immunology (AAAAI) states that appropriate diagnosis and treatment of allergies requires specific IgE testing (either skin or serum tests) based on the patient's clinical history.

IgE (RAST, MAST, FAST, ELISA and ImmunoCAP): detect IgE antibody in the serum.. This testing is considered equivalent to percutaneous skin testing for inhalant allergens and foods. Testing for drug and insect sting sensitivity should be by intradermal testing.

> AAAAI's Allergy Diagnostic Testing: An Updated Practice Parameter, 2008[5]:
> *Summary Statement 117.* As with skin tests, the interpretation of specific IgE results requires correlation with the history, physical examination, and, in some cases, symptoms directly observed after natural or laboratory exposure to allergens. This cannot be accomplished by commercial remote practice laboratories, which base recommendations for immunotherapy on a history form submitted by the patient and specific IgE results.
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> *Summary Statement 122*. Specific IgE immunoassays may be preferable to skin testing under special clinical conditions, such as widespread skin disease,

individuals receiving skin test suppressive therapy, uncooperative individuals, or when the history suggests an unusually greater risk of anaphylaxis from skin testing.

Total IgE: may be helpful in the evaluation of clinical disorders specifically associated with very high levels of total IgE (eg, parasitic infections, allergic bronchopulmonary aspergillosis). Total IgE may also help determine eligibility for treatment with anti-IgE therapy in individuals with moderate to severe allergic asthma.

> AAAAI's Allergy Diagnostic Testing: An Updated Practice Parameter, 2008[5]: *Summary Statement 112*. The clinical applications of total serum IgE are of modest value. High serum IgE concentrations occur in allergic bronchopulmonary Aspergillosis (ABPA), the therapeutic response of which is evaluated by serial IgE values.

Non-Covered Tests

AAAAI's Allergy Diagnostic Testing: An Updated Practice Parameter, 2008[5]: *Summary Statement 154*. Procedures for which there is no evidence of diagnostic validity include cytotoxic tests, provocation-neutralization, electrodermal testing, applied kinesiology, iridology, hair analysis, or food specific IgG, IgG4, and IgG/IgG4 antibody tests.

The American Academy of Allergy, Asthma & Immunology has no statements of support for additional tests which are listed in the Inclusionary and Exclusionary Guidelines, Exclusions, Allergy Testing section of this policy; therefore, these tests do not meet utility criteria.

ALLERGY TREATMENT

Avoidance therapy, pharmacologic therapy and immunotherapy are the basic treatments for allergy conditions. Complete avoidance of the known allergen that causes the signs and symptoms is the most effective treatment. When avoidance is not possible, pharmacologic therapy (eg, antihistamines, corticosteroids, adrenergic agonists, anticholinergics, beta-adrenergic agonists, cromolyn sodium and methylxanthines) is initiated. Immunotherapy may be indicated for individuals whose symptoms are not controlled adequately by avoidance measures and medications or those experiencing adverse effects of medications or who wish to reduce long-term use of medications.

Allergen immunotherapy:

The American Academy of Allergy, Asthma & Immunology and the American College of Allergy, Asthma & Immunology: Allergen immunotherapy: A practice parameter third update[7]:

> "… allergen immunotherapy is efficacious in the treatment of allergic rhinitis, allergic conjunctivitis, allergic asthma and stinging insect hypersensitivity. Randomized controlled studies showed that allergen immunotherapy prevents the development of asthma in subjects with allergic rhinitis. There is some evidence of immunotherapy's efficacy in the treatment of individuals with atopic dermatitis with aeroallergen sensitization … (Allergen immunotherapy) should be

differentiated from unproved methods, such as neutralization-provocation therapy and low-dose subcutaneous regimens based on Rinkel technique, which have been found to be ineffective in double-blind, placebo-controlled trials."

Under "Conditions for which immunotherapy is investigational, Food hypersensitivity,":
Summary Statement 12:"Clinical trials do not support the use of subcutaneous immunotherapy for food hypersensitivity".

Oral Immunotherapy (OIT): for the treatment of food allergy; a structured, increased ingestion of an allergen with a goal of desensitization.

A Cochrane Review (2018) focused on oral immunotherapy for egg allergy.[8] A total of 10 RCTs included 439 children, ages ranging from 1 year to 18 years. Study groups were compared to control groups which either involved an egg-avoidance diet or placebo. The reviewers found that fewer than half (45%) of children receiving oral immunotherapy were able to tolerate a full serving of egg compared to 10% of the control group (RR 4.25, 95% CI 2.77 to 6.53; RD 0.35, 95% CI 0.28 to 0.43). All 10 trials reported numbers of children with serious adverse events (SAEs) and numbers of children with mild-to-severe adverse events. SAEs requiring epinephrine/adrenaline presented in 21/249 (8.4%) of children in the oral immunotherapy group, and none in the control group. Mild-to-severe adverse events were frequent; 75% of children presented mild-to-severe adverse events during oral immunotherapy treatment versus 6.8% of the control group (RR 8.35, 95% CI 5.31 to 13.12). The reviewers concluded that it appears oral immunotherapy for egg allergy is effective, but confidence in the trade-off between benefits and harms is low; because there was a small number of trials with few participants, and there were methodological problems with some trials.

De Schryver et al (2019) evaluated the risk of allergic reactions during cow's milk OIT in children.[9] Among 41 children undergoing CM-OIT, 11 discontinued the treatment (N = 26.8%). The mean age at challenge was 12.1 years (standard deviation [SD], 3.6) and half were male (56.1%). The mean number of anaphylactic allergic reactions per patient was 6.0 (SD, 3.5) versus a mean of 17.4 (SD, 11.9) non-AARs per patient. Among withdrawals from OIT, the mean number of AARs per patient was 8.3 versus 5.1 in non-withdrawals. AARs were more frequent in children with higher specific IgE (sIgE) for α-lactalbumine and casein at baseline (1.11 [95% confidence interval (CI): 1.01, 1.22] and 1.01 [1.0, 1.03], respectively). Children with resolved eczema and higher sIgE for β-lactoglobuline at baseline (0.13 [95% CI: 0.04, 0.46] and 0.96 [95% CI: 0.94, 0.99], respectively) were less likely to develop AARs. The authors concluded that although the majority of Ars during OIT are non-anaphylactic, AARs occur frequently. Children with higher sIgE for α-lactalbumine and casein at baseline seem to be at higher risk for AARs during OIT.

Chu et al (2019) reported on the Peanut Allergen immunotherapy, Clarifying the Evidence (PACE) systematic review and meta-analysis.[10] In a total of 12 trials and 1,041 patients with peanut allergy, high-certainty evidence showed that available peanut oral immunotherapy regimens considerably increase allergic and anaphylactic reactions over avoidance or placebo, despite effectively inducing desensitization. The reviewers

felt that safer peanut allergy treatment approaches and rigorous randomized controlled trials are needed.

Chinthrajah et al (2019) reported on a study of the sustained effects of peanut allergy oral immunotherapy in a randomized long-term study in adults and children.[11] A total of 120 individuals with peanut allergy, aged 7-55 years, with a positive result from a double-blind, placebo-controlled, food challenge (DBPCFC; ≤500 mg of peanut protein), a positive skin-prick test (SPT) result (≥5 mm wheal diameter above the negative control), and peanut-specific immunoglobulin (Ig)E concentration of more than 4 kU/L were followed during a 23-month period. Participants were randomly assigned in a two-by-two block design to be built up and maintained on 4000 mg peanut protein through to week 104 then discontinued on peanut (peanut-0 group, n=60), to be built up and maintained on 4000 mg peanut protein through to week 104 then to ingest 300 mg peanut protein daily (peanut-300 group, n=35) for 52 weeks, or to receive oat flour (placebo group, n=25). Double-blind, placebo-controlled food challenges to 4000 mg peanut protein were performed at baseline and weeks 104, 117, 130, 143, and 156. The pharmacist assigned treatment on the basis of a randomized computer list. The primary endpoint was the proportion of participants who passed Double-blind, placebo-controlled food challenges to a cumulative dose of 4000 mg at both 104 and 117 weeks. Results of the study were as follows: 21 (35%) of peanut-0 group participants and one (4%) placebo group participant passed the 4000 mg challenge at both 104 and 117 weeks (odds ratio [OR] 12.7, 95% CI 1.8 to 554.8; p=.0024). Over the entire study, the most common adverse events were mild gastrointestinal symptoms, which were seen in 90 of 120 patients (50/60 in the peanut-0 group, 29/35 in the peanut-300 group, and 11/25 in the placebo group) and skin disorders, which were seen in 50/120 (26/60 in the peanut-0 group, 15/35 in the peanut-300 group, and 9/25 in the placebo group). Adverse events decreased over time in all groups. In the peanut-0 group, in which eight (13%) of 60 participants passed Double-blind, placebo-controlled food challenges at week 156, higher baseline peanut-specific IgG4 to IgE ratio and lower Ara h 2 IgE and basophil activation responses were associated with sustained unresponsiveness. The authors' interpretation of the data was that peanut OIT could desensitize individuals with peanut allergy to 4000 mg peanut protein but discontinuation, or even reduction to 300 mg daily, could increase the likelihood of regaining clinical reactivity to peanut.

Summary of OIT

The goal of OIT for food allergy is to induce permanent tolerance to the food, ultimately to prevent allergic reactions. However, there is no consensus on the OIT procedure, including dosing schedule, maintenance dose and treatment duration. OIT products, other than Palforzia, are not standardized. Further studies are needed.

Oral mucosal immunotherapy (OMIT): exposure of the oral mucosa to an allergen, via a toothpaste base.

Reisacher et al (2016) reported on a pilot study comparing novel oral mucosal IT to SLIT.[12] Twenty-four individuals with allergic rhinitis received IT by applying allergenic extracts daily to either the oral vestibule plus oral cavity mucosa by using a glycerin-based toothpaste or to the sublingual mucosa by using 50% glycerin liquid drops. Adverse events, adherence rates, total combined scores, rhinoconjunctivitis quality-of-

life questionnaire scores, changes in skin reactivity, and changes in serum antibody levels were measured for each participant. The adherence rate was 80% for the OMIT group and 62% for the SLIT group (p=.61). Decreased total combined scores were demonstrated for both the OMIT group (15.6%) and the SLIT group (22.3%), although this decrease did not reach statistical significance in either group. Both groups achieved a meaningful clinical improvement of at least 0.5 points on rhinoconjunctivitis quality-of-life questionnaire. A statistically significant rise in specific immunoglobulin G4 (IgG4) was seen in both groups over the first 6 months of treatment. The authors concluded that OMIT and SLIT demonstrated similar safety profiles and adherence rates. Measurements of clinical efficacy improved for both groups, but only changes in IgG4 achieved statistical significance. The authors felt that the pilot data provided enough evidence to proceed with a full-scale investigation to explore the role of OMIT in the long-term management of allergic rhinitis; however no subsequent studies have been found.

The American Academy of Allergy, Asthma & Immunology states that the following are unproved methods of immunotherapy[7]:

Neutralization-provocation therapy

Low-dose subcutaneous regimens based on the Rinkel technique

The American Academy of Allergy, Asthma & Immunology has no statements of support for the following modalities of treatment for allergen responses.

Enzyme potentiated desensitization (EPD): a cell-mediated method of immunotherapy in which combinations of extremely low dose allergens are given with the enzyme beta-glucuronidase. EPD appears to stimulate the production of activated T-suppressor cells, which inactivate the T-helper cells that are producing the symptoms of allergy. It is promoted as an improvement over conventional allergy immunotherapy in that it requires fewer injections and eliminates escalating dose immunotherapy which drastically reduces the risk of life-threatening reactions. EPD is widely used in England; however, it is not approved by the U.S. Food and Drug Administration (FDA).

Ultra-low dose enzyme activated immunotherapy / low dose allergens (LDA): patterned after EPD in that LDA includes mixtures of over 300 allergens enhanced by the enzyme beta-glucuronidase. The mixture is only available by prescription through compounding pharmacies for specific physicians' patients and is not available as a retail product. There are no published studies on the efficacy of LDA.

Urine auto injection (autogenous urine injection/immunization): based on the theory that urine of allergic individuals contains the antigen receptors, and re-introducing the urine would result in the production of antibodies that would stop the allergic response. The use of this procedure has no proven efficacy and can predispose the patient to potential harmful effects.

Repository emulsion therapy: allergens are added to vegetable and mineral oils, which are then injected intramuscularly. In theory, there would be slow release of the allergens at the injection site. This therapy is outdated and was discontinued after it was found it had the potential to induce plasma cell myelomas.

Rhinophototherapy: Phototherapy has been used in treating immune-mediated dermatological conditions such as psoriasis and atopic dermatitis. It has been proposed that phototherapy to the nasal mucosa may be effective in treating allergic rhinitis. This treatment method remains unproven as there is limited peer reviewed literature.

The American Academy of Allergy, Asthma & Immunology has no statements of support for modalities that are listed in the Inclusionary and Exclusionary Guidelines, Exclusions, Immunotherapy section of this policy; therefore, these modalities do not meet utility criteria.

Government Regulations

National:

NCD 110.11 Food Allergy Testing and Treatment (Rev 1, 10-03-03)[13]
Effective October 31, 1988, sublingual intracutaneous and subcutaneous provocative and neutralization testing and neutralization therapy for food allergies are excluded from Medicare coverage because available evidence does not show that these tests and therapies are effective. This exclusion was published as a Final Notice in the "Federal Register" on September 29, 1988.

NCD 110.12 – Challenge Ingestion Food Testing (Rev. 1, 10-03-03)[14]
Challenge ingestion food testing is a safe and effective technique in the diagnosis of food allergies.

Indications and Limitations of Coverage
This procedure is covered when it is used on an outpatient basis if it is reasonable and necessary for the individual patient.

Challenge ingestion food testing has not been proven to be effective in the diagnosis of rheumatoid arthritis, depression, or respiratory disorders. Accordingly, its use in the diagnosis of these conditions is not reasonable and necessary within the meaning of §1862(a)(1) of the Act, and no program payment is made for this procedure when it is so used.

NCD 110.13 Cytotoxic Food Tests (Rev. 1, 10-03-03)[15]
Not Covered
Prior to August 5, 1985, Medicare covered cytotoxic food tests as an adjunct to in vivo clinical allergy tests in complex food allergy problems. Effective August 5, 1985, cytotoxic leukocyte tests for food allergies are excluded from Medicare coverage because available evidence does not show that these tests are safe and effective. This exclusion was published as a CMS Ruling in the "Federal Register" on July 5, 1985.

Local:

Wisconsin Physicians Service Insurance Corporation
Local Coverage Determination (LCD): Allergy Testing (L36402)
Original Effective Date: For services performed on or after 03/18/2016
Revision Effective Date For services performed on or after 10/1/22

Indications:
Allergy skin testing is a clinical procedure that is used to evaluate an immunologic response to allergenic material. It would not be expected that all patients would receive the same tests or the same number of sensitivity tests. The number and type of antigens used for testing must be chosen judiciously given the patient's presentation, history, physical findings, and clinical judgment.

To be covered by Medicare, the antigens must meet all of the following criteria:
1. Skin testing must be performed based on a complete history and physical exam,
2. Proven efficacy as demonstrated through scientifically valid peer reviewed published medical studies, and
3. Exist in the patient's environment with a reasonable probability of exposure

Allergy testing can be broadly subdivided into two methodologies:

A. In vivo testing (skin tests): this testing correlates the performance and evaluation of selective cutaneous and mucous membrane tests with the patient's history, physician examination, and other observations.

1. Percutaneous Testing (scratch, puncture, prick) and is used to evaluate immunoglobulin E (IgE) mediated hypersensitivity. Percutaneous tests require medical supervision, since there is a small but significant risk of anaphylaxis. Overall, skin testing is quick, safe, and cost effective. It remains the test of choice in most clinical situations where immediate hypersensitivity reactions are suspected.

Percutaneous testing is the usual preferred method for allergy testing. Medicare covers percutaneous (scratch, prick or puncture) testing when IgE-mediated reactions occur with **any** of the following:
a. Inhalants.
b. Foods. (Patients present with signs and symptoms such as urticarial, angioedema, eosinophilic esophagitis, or anaphylaxis after ingestion of specific foods. Testing for food allergies in patients who present with wheezing is occasionally required.)
c. Hymenoptera (stinging insects).
d. Specific drugs (penicillins, macromolecular agents, enzymes, and egg-containing vaccines). Skin testing is unreliable with other drugs.

2. Intracutaneous/Intradermal Tests are usually performed when increased sensitivity is the main goal such as when percutaneous tests are negative and there is a strong suspicion of allergen sensitivity. Intradermal tests are injections of small amounts of antigen into the superficial layers of the skin. The usual testing program may include 2 concentrations of an extract: a weaker concentration and a stronger concentration. It would not be expected that 3 or more concentrations of one extract would be medically necessary. Medicare covers intradermal (intracutaneous) testing when IgE-mediated reactions occur to **any** of the following:
a. Inhalants.
b. Hymenoptera (stinging insects).
c. Specific drugs (penicillins and macromolecular agents).
d. Vaccines.

3. Patch Testing is the gold standard method of identifying the cause of allergic contact dermatitis. This testing is indicated to evaluate a nonspecific dermatitis, pruritus, to differentiate allergic contact dermatitis (ACD) and irritant contact dermatitis (ICD) and determine the causative antigen. It is a diagnostic test reserved for patients with skin eruptions for which a contact allergy source is likely.

The patch test procedure can induce an eczematous reaction in miniature by applying suspect allergens to normal skin, allowing the physician to determine a specific patient allergy. Patch tests are applied to the skin on the patient's back and left in place for 48 hours. The test is interpreted after 48 hours, and typically once again at 72 or 96 hours, and the reactions are systematically scored and recorded. The patient is then informed and educated regarding specific allergies and avoidance of exposure. Avoidance of the identified allergen(s) is critical to patient improvement and resolution of the dermatitis.

Allergy patch testing is a covered procedure only when used to diagnose allergic contact dermatitis after the following exposures: dermatitis due to detergents, oils and greases, solvents, drugs and medicines in contact with skin, other chemical products, food in contact with skin, plants (except food), cosmetics, metals, rubber additives, other and unspecified. Patch tests may also be used and may be helpful when a distribution and persistence of dermatitis suggests a possible contact allergy, but the exact etiology of the dermatitis is unknown.

The clinician should recognize that contact sensitization to metals or bone cement that is used in orthopedic, cardiac, dental, and gynecological implants has been associated with both dermatitis and noncutaneous complications. These complications may include localized pain, swelling, erythema, warmth, implant loosening, decreased range of motion, stent stenosis, and pericardial effusions in the case of cardiac implants. Patch testing to implant or device components has been recommended to help determine the etiology of the adverse reaction.

4. Photo Patch Testing uses two patches, with one of them being irradiated with ultraviolet light half way through the occlusive period. It is indicated to evaluate unique allergies resulting from light exposure. Some chemicals or medications produce an allergic reaction only when exposed to light (usually ultraviolet type A, UVA). Patients who are over-sensitive to light and those with a rash that appears on parts of the body normally exposed to light but that does not appear in areas shielded from the light should have a photo-patch test.

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

6. Skin Endpoint Titration (SET) Testing or Intradermal Dilutional Testing (IDT) analyzes the highest dilution of a substance that produces a reaction, and may be used to determine the starting dose(s) of allergen immunotherapy.

7. Delayed Hypersensitivity Skin Testing has been commonly used in three ways: anergy testing, testing for infection with intracellular pathogens, and testing for

sensitivity to contact allergens. Accurate testing for contact allergy requires careful attention to technique, and limitation of testing to the specific allergens known to be associated with a contact reaction.

8. Ophthalmic Mucous Membrane Tests and Direct Nasal Mucous Membrane Tests are rarely indicated. They are allowed when skin testing cannot test allergens. Ophthalmic mucous membrane tests and direct nasal mucous membrane tests are approved if levels of allergic mediators (such as histamine and tryptase) are measured and a placebo control is performed. This is usually performed in allergy research laboratories. It is also approved in the office setting if the physician is there to observe objective measurement of reactions which might include redness of the eyes, tearing and sneezing.

9. Inhalation Bronchial Challenge Testing involves the inhalation of agents that can trigger respiratory responses and are often used to evaluate new allergens and/or substantiate the role of allergens in patients with significant symptoms. Results of these tests are ordinarily evaluated by objective measures of pulmonary function and occasionally by characterization of bronchoalveolar lavage samples.

a. Inhalation bronchial challenge tests should be performed as dose-response assays where in provocation concentration thresholds can be determined on the basis of allergen concentration required to cause a significant decrease in measured pulmonary function.

b. Inhalation bronchial challenge tests with occupational allergens need to be carefully controlled with respect to dose and duration of exposure. When industrial small molecular weight agents are assessed, tests should be performed under conditions of continuous monitoring of the specific chemical being assessed so as not to exceed the threshold limit level permitted in the workplace.

10. Ingestion (Oral) Challenge Test involves the administration of sequentially or incrementally larger doses of the test item. The test items may include food or antibiotics. The service is allowed once per patient encounter, regardless of the number of items tested, and includes evaluation of the patient's response to the test items.

Challenge ingestion food testing is covered for the following indications:

- Food allergy, dermatitis
- Anaphylactic shock due to adverse food reaction
- Allergy to medicinal agents
- Allergy to foods

Challenge Ingestion is not payable when used to diagnose rheumatoid arthritis, depression, or respiratory disorders. (CMS Pub. 100-03 *Medicare National Coverage Determination (NCD) Manual*, Chapter 1- Coverage Determinations, Part 2 Section 110.12- Challenge Ingestion Food Testing).

11. Intracutaneous testing, delayed reaction – more than 6 tests, may be covered but requires additional justification and case-by-case review for the number of tests performed and the medical necessity except when the skin test is used:
For collagen implant therapy. Refer to: CMS Pub 100-03 *Medicare National Coverage*

Determinations (NCD) Manual, Chapter 1 – Coverage Determinations, Part 4, Section 230.10 – Incontinence Control Devices.

12. Organ challenge test materials may be applied to the mucosae of the conjunctivae, nares, GI tract, or bronchi. Considerable experience with these methods is required for proper interpretation and analysis. All organ challenge tests should be preceded by a control test with diluent and, if possible, the procedure should be performed on a double blind or at least single-blind basis.

B. In vitro testing (blood serum analysis): immediate hypersensitivity testing by measurement of allergen-specific serum IgE in the blood serum. They are useful when testing for inhalant allergens (pollens, molds, dust mites, animal danders), foods, insect stings, and other allergens such as drugs or latex, when direct skin testing is impossible due to extensive dermatitis, marked dermatographism, or in children younger than four years of age.

In-vitro testing is covered when skin testing is not possible or would be unreliable; or in vitro testing is medically reasonable and necessary as determined by the physician. When invitro testing is ordered or performed, the medical record must clearly document the indication and why it is being used instead of skin testing.

It is not covered when done in addition to a skin test for the same antigen, except in the case of suspected latex sensitivity, hymenoptera, or nut/peanut sensitivity where both the skin test and the in-vitro test may be performed. The number of tests done, choice of antigens, frequency of repetition and other coverages issues are the same as skin testing.

Testing must be based on a careful history/physical examination which suggests IgE-medicated disease. Total Serum IgE is not appropriate in most general allergy testing. Instead, individual IgE tests are performed against a specific antigen.

Special clinical situations in which specific IgE immunoassays are performed against a specific antigen may be appropriate in the following situations:

1. Patients with extensive dermatitis, severe dermatographism, ichthyosis or generalized eczema that will not make direct skin testing possible.
2. Patients needing continued use of H-1 blockers (antihistamines), or in the rare patient with persistent unexplained negative histamine control.
3. Patients who cannot be safely withdrawn from medications that interfere with skin testing, such as long-acting antihistamines, tricyclic antidepressants, beta-blockers, or medications that may put the patient at undue risk if they are discontinued long enough to perform skin tests.
4. Uncooperative patients with mental or physical impairments.
5. For evaluation of cross-reactivity between insect venoms (e.g., fire ant, bee, wasp, yellow jacket, hornet).
6. As adjunctive laboratory testing for disease activity of allergic bronchopulmonary aspergillosis and certain parasitic disease.
7. To diagnose atopy in small children.

8. Patients at increased risk for anaphylactic response from skin testing based on clinical history (e.g., when an unusual allergen is not available as a licensed skin test extract), or who have a history of a previous systemic reaction to skin testing.
9. Patients in who skin testing were equivocal/inconclusive and in vitro testing is required as a confirmatory test.

Total IgE is reasonable and necessary for follow-up of Allergic Bronchopulmonary Aspergillosis (ABPA) and to diagnosis atopy in children.

Retesting with the same antigen(s) should rarely be necessary within a three-year period. Exceptions include young children with negative skin tests, or older children and adults with negative skin tests in the face of persistent symptoms. Routine repetition of skin tests is not indicated (i.e., annually) and not covered.

Limitations:
The following tests are considered not medically reasonable and necessary:
1. Ingestion (Oral) Challenge Food Testing performed by the patient in the home, and not in the office setting, will not be covered.
2. Provocative Testing for which there is limited or no evidence of validity include the cytotoxic test, the provocation-neutralization procedure, electrodermal diagnosis, applied kinesiology, the “reaginic” pulse test, and chemical analysis of body tissues. Controlled studies for the cytotoxic and provocation-neutralization tests demonstrated that the results are not reproducible and do not correlate with clinical evidence of allergy. Electrodermal diagnosis and applied kinesiology have not been evaluated for efficacy. Similarly, the “reaginic” pulse test and chemical analysis of body tissues for various exogenous chemicals have not been substantiated as valid tests for allergy.

Provocative and neutralization testing and neutralization therapy (Rinkel test) of food allergies (sublingual, intracutaneous and subcutaneous) are excluded from Medicare coverage because available evidence does not show these tests and therapies are effective.
3. IgG and IgG Subclass Antibody Tests measure allergen-specific IgG and IgG subclasses by using immunoabsorption assays and IgG and IgG subclass antibody tests for food allergy/delayed food allergic symptoms or intolerance to specific foods. These tests are considered experimental and investigational since there is insufficient evidence in the published peer-reviewed scientific literature to support the diagnostic value of these tests.
4. Antigens for which no clinical efficacy is documented in peer reviewed literature include the following: newsprint, tobacco smoke and leaf, dandelion, orris root, phenol, alcohol, sugar, yeast, grain mill dust, soybean dust (except when the patient has a known exposure to soybean dust such as a food processing plant), honeysuckle, marigold, goldenrod, fiberglass, wool, green tea, or chalk.
5. Radioallergosorbent test (RAST), fluoroallergosorbent test (FAST), and multiple antigen simultaneous test (MAST) are in vitro techniques for determining whether a patient’s serum contains IgE antibodies against specific allergens of clinical importance. As with any allergy testing, the need for such tests is based on the findings during a complete history and physical examination of the patient. These tests are not

appropriate in most general allergy testing. Instead, individual IgE tests should be performed against a specific antigen.

6. **ELISA (enzyme-linked immunosorbent assay) test** is another in vitro method of allergy testing for specific IgE antibodies against allergens. It is used to determine in vitro reaction to various foods and relies on lymphocyte blastogenesis in response to certain food antigens.
7. **Quantitative multi-allergen screen** is a non-specific screen that does not identify a specific antigen. It is does not have sufficient literature demonstrating clear cut clinical implication. It is a screening tool and therefore not covered by Medicare.
8. **Cytotoxic leukocyte tests** are excluded. (CMS Pub. 100-03 *Medicare National Coverage Determination (NCD) Manual*, Chapter 1- Coverage Determinations, Part 2 Section 110.13-Cytotoxic Food Tests).
9. **Sublingual intracutaneous and subcutaneous provocative and neutralization testing and neutralization therapy for food allergies** are excluded. (CMS Pub 100-03 *Medicare National Coverage Determinations Manual*, Chapter 1- Coverage Determinations, Part 2, Section 110.11 – Food allergy testing and Treatment).
10. The following tests are considered **experimental and investigational for allergy testing** as these have not been proven to be effective or appropriate for the evaluation and/or management of IgE-mediated allergic reactions. This list is not all inclusive:

a. Antigen leukocyte cellular antibody (ALCAT) automated food allergy testing
b. Applied kinesiology or Nambudripad's allergy elimination test (NAET (i.e., muscle strength testing or measurement after allergen ingestion)
c. Anti-Fc epsilon receptor antibodies testing
d. Anti-IgE receptor antibody testing
e. Blood, urine, or stool micro-nutrient assessments
f. Candidiasis test
g. Chemical analysis of body tissues (e.g., hair)
h. Chlorinated pesticides (serum)
i. Chronic urticarial index testing
j. Clifford materials reactivity testing
k. Complement (total or components)
l. Complement antigen testing
m. C-reactive protein
n. Cytokine and cytokine receptor assay
o. Cytotoxic testing for environmental or clinical ecological allergy testing (Bryans Test, ACT)
p. Electrodermal testing or electro-acupuncture
q. Electromagnetic sensitivity syndrome/disorder (allergy to electricity, electro-sensitivity, electrohypersensitivity, and hypersensitivity to electricity)
r. Environmental cultures and chemicals
s. Eosinophil cationic protein (ECP) test
t. Food immune complex assay (FICA) or food allergenic extract immunotherapy
u. General immune system assessments
v. Immune complex assay
w. Immunoglobulin G (IgG) testing for allergy
x. Iridology
y. Leukocyte antibodies testing
z. Leukocyte histamine release test (LHRT)/basophil histamine release test

aa. Lymphocytes (B or T subsets)
ab. Lymphocyte function assay
ac. Mediator release test (MRT) or the LEAP program
ad. Metabolic assessments
ae. Multiple chemical sensitivity syndrome (a.k.a., idiopathic environmental intolerance (IEI), clinical ecological illness, clinical ecology, environmental illness, chemical AIDS, environmental/chemical hypersensitivity disease, total allergy syndrome, cerebral allergy, 20th century disease)
af. Prausnitz-Kustner or P-K testing – passive cutaneous transfer test
ag. Pulse response test
ah. Qualification of nutritional assessments
ai. Rebuck skin window test
aj. Secretory IgA (salvia)
ak. Sage Complement Antigen Test
al. Specific Immunoglobulin (IgG) (e.g., by Radioallergosorbent (RAST) or Enzyme-linked immunosorbent assay (ELISA)
am. Sublingual provocative neutralization testing and treatment with hormones.
an. Total serum IgG, immunoglobulin A (IgA) and immunoglobulin M (IgM)
ao. Venom blocking antibodies
ap. Volatile chemical panels (blood testing for chemicals)
aq. Live Cell Analysis
ar. Passive Transfer
as. Cytotoxic Food Testing

Routine allergy re-testing does not meet the definition of medically necessity according to the practice parameters and recommendations from the American College of Allergy, Asthma, and Immunology (ACAAI), the American Academy of Allergy, Asthma, and Immunology (AAAAI), and the Joint Council of Allergy, Asthma, and Immunology (JCAAI).

Wisconsin Physicians Service Insurance Corporation
Local Coverage Determination (LCD): Allergy Immunotherapy (L36408)
Original Effective Date For services performed on or after 03/18/16
Revision Effective Date For services performed on or after 10/26/2023
[Please refer to the LCD for complete information, the following is an excerpt]

Indications:
Indications for immunotherapy are determined by appropriate diagnostic procedures coordinated with clinical judgment and knowledge of the natural history of allergic diseases. The following indications are considered medically reasonable and necessary for allergy immunotherapy:

1. Controlled studies have shown that allergen immunotherapy is effective for patients with
   a. Allergic rhinitis,
   b. Allergic conjunctivitis,
   c. Allergic asthma, and
   d. Stinging insect hypersensitivity.

Allergen-induced asthma is an indication for immunotherapy along the guidelines for allergic rhinitis when there is a poor response to environmental control or pharmacologic treatment. Allergen immunotherapy in asthmatic patients should not be initiated unless the patient's asthma is stable. Patients with severe or uncontrolled asthma are at increased risk for systemic reactions to immunotherapy injections.

2. The necessity of allergen immunotherapy depends on the
    a. Degree to which symptoms can be reduced by medications,
    b. Ability of the patient to tolerate possible side effects of the medication,
    c. Amount, type and cost of the medications required to control symptoms,
    d. Significant exposure to an allergen in which there is a significant level of sensitivity and the pattern of symptoms conform to the pattern of exposure, and
    e. Whether conservative therapies (including avoidance) have failed to control the symptoms, or avoidance of the relevant antigen (e.g., dust mites, pollen, and mold) is impractical.
3. Animal dander sensitivity (epidermal) may respond to immunotherapy. While removal of the offending allergen is recommended, this is often not possible or there may be occupational or other sources of exposure. Antihistamines are used first before immunotherapy but a trial of immunotherapy may be warranted if the antihistamines do not relieve symptoms.
4. Aeroallergen immunotherapy is indicated for patients with allergic rhinitis due to:
    a. Seasonal pollinosis caused by trees, grasses and weeds.
    b. The treatment of mold-induced rhinitis.
    c. Perennials such as cat and dog dander, dust mite and cockroach.
5. Standardized dust mite extracts appear effective for immunotherapy. Other environmental allergens (e.g., kapok, jute, feathers, and unstandardized house dust extracts) are of questionable value in immunotherapy, however, and generally should not be used.
6. Venom immunotherapy is indicated for patients who have a severe systemic anaphylactic reaction after an insect sting and a positive skin test or other documented IgE sensitivity to specific insect venom.
7. Patients with delayed systemic reactions, with symptoms of anaphylaxis or serum sickness and with a positive skin test or presence of venom specific IgE by in vitro testing are also recommended for treatment.
8. Rapid desensitization is indicated in cases of allergy to insulin, penicillin and horse serum, as well as sulfonamides, cephalosporins and other commonly used drugs (e.g. aspirin). Rush desensitization can also be sued in select patient with stinging insect allergies. In patients with a positive history of reaction and with documented skin test reactivity, every effort should be made to avoid the use of these substances. When circumstances require the use of one of these substances, the patient will have to be desensitized. Desensitization may need to be repeated if future circumstances require an additional course of the offending allergen. Full-dose therapy should be initiated immediately after reactions (treated and controlled), requiring strict physician monitoring in a setting with continuous monitoring of vital signs and cardio-respiratory status. In most cases, this can be performed in a physician's office if a physician trained to treat anaphylaxis is physically present for the entire duration. In cases where the initial reaction was severe, desensitization should be performed in the ambulatory care department of a hospital.

Limitations:
The following allergy immunotherapy are considered investigational and experimental, therefore, are not medically necessary. The effectiveness also has not been established, therefore, these indications will not be covered:

1. Angioedema.
2. Food hypersensitivity/allergy.
3. Intrinsic (non-allergic) asthma.
4. Migraine headaches.
5. Non-allergic vasomotor rhinitis.

The following allergy immunotherapy services are considered investigational and experimental, and are therefore not medically necessary. The effectiveness also has not been established, therefore, these indications will not be covered:

1. Therapy with allergoids or adjuvants.
2. Therapy via other administration:
   a. Oral or sublingual food immunotherapy*,
   b. Epicutaneous immunotherapy,
   c. Intralymphatic immunotherapy,
   d. Intranasal immunotherapy, or
   e. Sublingual immunotherapy
3. Desensitization with commercially available extracts of poison ivy, poison oak, or poison sumac.
4. Desensitization for hymenoptera sensitivity using whole body extracts, with the exception of fire ant extracts**.
5. Desensitization with bacterial vaccine (BAC: bacterial, antigen complex, streptococcus vaccine, staphylo-strepto vaccine, serobacterin, staphylococcus phage lysate).
6. Food allergenic extracts immunotherapy.
7. Intracutaneous desensitization (Rinkel Injection Therapy, RIT).
8. Intracutaneous titration.
9. Neutralization therapy (intradermal and subcutaneous).
10. Repository emulsion therapy.
11. Sublingual desensitization***.
12. Sublingual provocative therapy***.
13. Urine auto-injection (autogenous urine immunotherapy).
14. Allergen immunotherapy for the management of skin and mucous membrane disease such as atopic dermatitis, chronic urticaria, and Candida vulvovaginitis.
15. Postmortem examination for IgE antibodies to identify allergens responsible for lethal anaphylaxis (post mortem work is not-covered by Medicare).

Patients who are mentally or physically unable to communicate clearly with the allergist and those with a history of noncompliance are not good candidates for allergy immunotherapy. If a patient cannot communicate clearly with the physician; it will be difficult for the patient to report signs and symptoms, especially early symptoms, suggestive of systemic reactions.

*Several clinical trials with oral and sublingual immunotherapy demonstrate an increased tolerance to oral food challenge in subjects with food hypersensitivity while

receiving therapy. Oral and sublingual food immunotherapy is investigational. At present, the only treatment for food hypersensitivity is avoidance.

**Immunotherapy with whole-body extracts of biting insects or other arthropod is covered only for fire ant extracts.

***Sublingual immunotherapy (SLIT) involves the use of FDA approved allergenic extracts administered orally. In early 2014, the FDA approved oral administration of 3 allergenic extracts, two for grasses and one for ragweed. These extracts are not approved by the FDA for anyone over the age of 65 years. Medicare does not cover sublingual immunotherapy. Effective October 31, 1988, sublingual intracutaneous and subcutaneous provocative and neutralization testing and neutralization therapy for food allergies are excluded from Medicare coverage because available evidence does not show that these tests and therapies are effective. (CMS Pub 100-03 Medicare National Coverage Determinations Manual, Chapter 1- Coverage Determinations, Part 2, Section 110.11 – Food Allergy Testing and Treatment).

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Antigen Leukocyte Antibody Test
- Sublingual Immunotherapy as a Technique of Allergen-Specific Therapy (Retired)
- Xolair® (Omalizumab/ruhMab-E25)
- Diagnostic and/or Treatment Services (Idiopathic Environmental Intolerances) (Retired)

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 1/22/24, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
3/21/02	3/21/02	3/21/02	Joint policy established
9/9/03	9/9/03	10/3/03	Routine maintenance
5/7/04	5/7/04	6/22/04	Added enzyme-potentiated desensitization to policy, updated resources
9/6/05	9/6/05	8/27/05	Combined four allergy testing and treatment policies
9/1/06	7/10/06	7/3/06	Routine maintenance code change from investigational to established
1/1/08	10/16/07	11/17/07	Routine maintenance
1/1/09	10/13/08	12/29/08	Routine maintenance
9/1/10	9/15/10	8/25/10	Status change for serial endpoint testing (CPT 95027) from experimental/investigational to established
9/1/11	6/21/11	6/21/11	Routine maintenance
7/1/13	4/16/13	4/22/13	Routine maintenance, Code updates
2/1/14	10/15/13	10/25/13	Routine maintenance, updated information for ALCAT testing
9/1/14	6/17/14	6/23/14	Routine maintenance. Removed Antigen Leukocyte Antibody Test from this policy. New policy titled Antigen Leukocyte Antibody Test created with effective date 9/1/14
7/1/16	4/19/16	5/23/16	• Routine maintenance • ImmunoCAP added to Inclusions • Eosinophilic cationic protein serum levels, anti-IgE antibodies & anti Fc Epsilon receptor antibodies testing added to Exclusions

7/1/17	4/18/17	4/18/17	• Routine maintenance • References and Government Regulations section updated.
7/1/18	4/17/18	4/17/18	• Routine maintenance, revision of description, rationale; inclusions and exclusions verbiage updated to eliminate duplications; references and government sections updated. Code 86008 added.
7/1/19	4/16/19		Routine maintenance
7/1/20	4/14/20		Routine maintenance Oral immunotherapy, OMIT, Palforzia information added. References 25-31 added.
7/1/21	4/20/21		Routine maintenance Code 86001 moved to E/I section
7/1/22	4/19/22		Routine maintenance
7/1/23	4/18/23		Routine maintenance (jf) Vendor Managed: Avalon 86003 and 86005 nomenclature updated
7/1/24	4/16/24		Routine maintenance (jf) Vendor Managed: Avalon

Next Review Date: 2nd Qtr, 2025

Pre-Consolidation Medical Policy History

Original Policy Date	Comments
BCN: N/A	Revised: N/A
BCBSM: 3/31/96 (Immunotherapy) 7/26/01 (Allergy Testing)	Revised: 12/15/00 (Immunotherapy)

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: ALLERGY TESTING AND ALLERGY IMMUNOTHERAPY

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply.
BCNA (Medicare Advantage)	See Government Regulations section of policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service. If BCN65 member has an “exact-fill” option, BCN may cover the service even if Medicare does not.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member’s certificate and is not guaranteed. Please consult the individual member’s certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.