

Cigna Medical Coverage Policy



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Subject **Allergy Testing**

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Coverage Policy

Cigna covers the following in vivo allergy tests as medically necessary:

- prick/puncture and/or intradermal allergy testing to diagnose suspected immunoglobulin E (IgE) mediated hypersensitivity to inhalants, foods, 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 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)

Cigna covers 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) as 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 have 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

Cigna covers in vitro metal lymphocyte transformation testing (LTT) performed prior to joint replacement surgery as medically necessary when ALL of the following criteria are met:

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

Cigna covers in vitro metal lymphocyte transformation testing (LTT) performed following joint replacement surgery as medically necessary when ALL of the following criteria are met:

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

Cigna does not cover in vitro allergy testing for ANY of the following, because it is considered not medically necessary:

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

Cigna does not cover in vivo or in vitro allergy testing for any other indication because it is considered experimental, investigational or unproven.

Cigna does not cover the following in vivo and in vitro allergy tests in the diagnosis or management of allergic disease because they are considered experimental/investigational or unproven (this list may not be all-inclusive):

- nasal challenge/provocation

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

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

General Background

Allergies result from an overreaction of the immune system to foreign substances. 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.

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

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.

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

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

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

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

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

offers no additional clinical information beyond that obtained by a well-taken clinical history and a carefully performed skin test.

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

Additional In Vivo Diagnostic Procedures

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

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

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

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

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

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

In Vitro Allergy Testing

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

developed and employ the same principles as the RAST but use an enzymatic (MAST) or fluorogenic (FAST) detection system in place of a radioactive label.

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

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

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

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

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

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

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

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

reviewed scientific literature to support the use of specific IgG antibody testing by RAST or ELISA in the diagnosis or treatment of allergic disease without suspected immunodeficiency.

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

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

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

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

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

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

Body chemical analysis is typically seen in the diagnosis of a condition known as "idiopathic environmental intolerances" (IEIs) or "multiple food and chemical sensitivities." Samples of whole blood, serum, erythrocytes, urine, fat and hair are tested for the presence of environmental chemicals. The most common chemicals measured are organic solvents, other hydrocarbons, pesticides and metals. Some proponents of this testing also recommend measurements of the quantity of vitamins, minerals and amino acids in blood and urine in a search for "environmental sensitivities." The concept of multiple food and chemical sensitivities manifested by numerous symptoms in the absence of objective physical findings lacks scientific foundation. There is no evidence to suggest that these patients suffer from an immunological abnormality. The existence of such an illness is based on anecdotal reports with no verification using well-designed clinical trials. There is no scientific evidence to support the value of diagnostic testing associated with IEIs or multiple food and chemical sensitivities, including body chemical analysis. Body chemical analysis is therefore considered unproven.

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

Alpha gal (galactose-alpha 1, 3-galactose) is an oligosaccharide that has been associated with an unusual delayed allergic reaction to meat, including beef, pork and lamb. Most allergic responses to food are directed against protein epitopes (the part of an antigen molecule to which an antibody attaches), rather than an oligosaccharide (a carbohydrate composed of simple sugars). In addition, most allergic reactions to food occur

within thirty minutes of ingestion. With alpha-gal, however, reaction has been observed to occur three to six hours after ingestion. Symptoms are similar to those seen with other food allergies, and may include urticarial, dyspnea, hypotension, angioedema, and anaphylaxis. It has been suggested that the original sensitizing allergen is exposure to the tick *Amblyomma americanum* (lone star tick) rather than to red meat, with antibodies to alpha-gal produced after a tick bite ((Saleh et al., 2012, Adkinson, 2013).

The link between alpha-gal allergy and exposure to ticks has not been definitively demonstrated, nor has a specific test been established as an accurate diagnostic method.

Complement antigen testing has been proposed for the diagnosis of delayed food allergies. Complement activation is a multi-component immune system response commonly present in inflammatory conditions (e.g., rheumatoid arthritis, arthritis, systemic lupus erythematosus). The degree of complement activation may be used to indicate the intensity of the inflammatory process. The role of complement antigen testing in the diagnosis of allergy has not been established.

Arthroplasty Implants: Testing for Metal Allergy/Hypersensitivity

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

Evidence evaluating the relationship between metal allergy/sensitivity and implant outcomes is limited. In reviewing the approach to the clinical work-up of patients with putative allergic disease to metallic orthopedic implants, Thyssen et al. (2012) 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.

Use Outside the U.S.

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

Summary

In vivo allergy testing (i.e., skin test, organ challenge/provocation test) is the most commonly used and preferred method of allergy testing. In vivo allergy tests are designed to confirm hypersensitivity and identify the antigen(s) responsible for the allergic reaction. In vitro allergy testing has been demonstrated to be an effective alternative for patients with suspected IgE-mediated food or inhalant allergies who cannot be tested using in vivo methods, or as an alternative to skin testing for the evaluation of cross-reactivity between insect venoms. In addition, specific IgE immunoassays may be used as adjunctive testing for disease activity of allergic bronchopulmonary aspergillosis and certain parasitic diseases.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.

2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

Covered when medically necessary:

| CPT [®] * Codes | Description |
|--------------------------|---|
| 86001 | Allergen specific IgG quantitative or semiquantitative, each allergen |
| 86003† | Allergen specific IgE; quantitative or semiquantitative, each allergen |
| 86005 | Allergen specific IgE; qualitative, multiallergen screen (dipstick, paddle or disk) |
| 86353 | Lymphocyte transformation, mitogen (phyto mitogen) or antigen induced blastogenesis |
| 95004 | Percutaneous tests (scratch, puncture, prick) with allergenic extracts, immediate type reaction, including test interpretation and report, specify number of tests |
| 95017 | Allergy testing, any combination of percutaneous (scratch, puncture, prick) and intracutaneous (intradermal), sequential and incremental, with venoms, immediate type reaction, including test interpretation and report, specify number of tests |
| 95018 | Allergy testing, any combination of percutaneous (scratch, puncture, prick) and intracutaneous (intradermal), sequential and incremental, with drugs or biologicals, immediate type reaction, including test interpretation and report, specify number of tests |

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|-------|---|
| 95024 | Intracutaneous (intradermal) tests with allergenic extracts, immediate type reaction, including test interpretation and report, specify number of tests |
| 95027 | Intracutaneous (intradermal) tests, sequential and incremental, with allergenic extracts for airborne allergens, immediate type reaction, including test interpretation and report, specify number of tests |
| 95028 | Intracutaneous (intradermal) tests with allergenic extracts, delayed type reaction, including reading, specify number of tests |
| 95044 | Patch or application test(s) (specify number of tests) |
| 95052 | Photo patch test(s) (specify number of tests) |
| 95070 | Inhalation bronchial challenge testing (not including necessary pulmonary function tests); with histamine, methacholine, or similar compounds |
| 95071 | Inhalation bronchial challenge testing (not including necessary pulmonary function tests); with antigens or gases, specify |
| 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) |

†**Experimental/Investigational/Unproven/Not Covered when used to report alpha-gal allergy testing.**

Experimental/Investigational/Unproven/Not Covered when used to report any procedure listed as such in this Coverage Policy.

| CPT* Codes | Description |
|------------|---|
| 82784 | Gammaglobulin (immunoglobulin); IgA, IgD, IgG, IgM, each |
| 83516† | Immunoassay for analyte other than infectious agent antibody or infectious agent antigen, qualitative or semiquantitative; multiple step method |
| 86160†† | Complement antigen, each component |
| 86343 | Leukocyte histamine release test (LHR) |
| 95060 | Ophthalmic mucous membrane tests |
| 95065 | Direct nasal mucous membrane test |
| 95199 | Unlisted allergy/clinical immunologic service or procedure |

†**Note: Experimental/Investigational/Unproven and not covered when used to report antigen leukocyte cellular antibody (ALCAT) automated food allergy testing.**

††**Note: Experimental/Investigational/Unproven and not covered when used for allergy testing.**

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