LCD - Allergy Testing (L36241)

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Contractor Information

CONTRACTOR NAME	CONTRACT TYPE	CONTRACT NUMBER	JURISDICTION	STATES
Novitas Solutions, Inc.	A and B MAC	04111 - MAC A	J - H	Colorado
Novitas Solutions, Inc.	A and B MAC	04112 - MAC B	J - H	Colorado
Novitas Solutions, Inc.	A and B MAC	04211 - MAC A	J - H	New Mexico
Novitas Solutions, Inc.	A and B MAC	04212 - MAC B	J - H	New Mexico
Novitas Solutions, Inc.	A and B MAC	04311 - MAC A	J - H	Oklahoma
Novitas Solutions, Inc.	A and B MAC	04312 - MAC B	J - H	Oklahoma
Novitas Solutions, Inc.	A and B MAC	04411 - MAC A	J - H	Texas
Novitas Solutions, Inc.	A and B MAC	04412 - MAC B	J - H	Texas
Novitas Solutions, Inc.	A and B MAC	04911 - MAC A	J - H	Colorado New Mexico Oklahoma Texas
Novitas Solutions, Inc.	A and B MAC	07101 - MAC A	J - H	Arkansas
Novitas Solutions, Inc.	A and B MAC	07102 - MAC B	J - H	Arkansas
Novitas Solutions, Inc.	A and B MAC	07201 - MAC A	J - H	Louisiana
Novitas Solutions, Inc.	A and B MAC	07202 - MAC B	J - H	Louisiana
Novitas Solutions, Inc.	A and B MAC	07301 - MAC A	J - H	Mississippi
Novitas Solutions, Inc.	A and B MAC	07302 - MAC B	J - H	Mississippi
Novitas Solutions, Inc.	A and B MAC	12101 - MAC A	J - L	Delaware
Novitas Solutions, Inc.	A and B MAC	12102 - MAC B	J - L	Delaware
Novitas Solutions, Inc.	A and B MAC	12201 - MAC A	J - L	District of Columbia
Novitas Solutions, Inc.	A and B MAC	12202 - MAC B	J - L	District of Columbia
Novitas Solutions, Inc.	A and B MAC	12301 - MAC A	J - L	Maryland
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Novitas Solutions, Inc.	A and B MAC	12401 - MAC A	J - L	New Jersey
Novitas Solutions, Inc.	A and B MAC	12402 - MAC B	J - L	New Jersey
Novitas Solutions, Inc.	A and B MAC	12501 - MAC A	J - L	Pennsylvania
Novitas Solutions, Inc.	A and B MAC	12502 - MAC B	J - L	Pennsylvania
Novitas Solutions, Inc.	A and B MAC	12901 - MAC A	J - L	Delaware

CONTRACTOR NAME	CONTRACT TYPE	CONTRACT NUMBER	JURISDICTION	STATES
				District of Columbia Maryland New Jersey Pennsylvania

LCD Information

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CMS National Coverage Policy

This LCD supplements but does not replace, modify or supersede existing Medicare applicable National Coverage Determinations (NCDs) or payment policy rules and regulations for allergy testing services. Federal statute and subsequent Medicare regulations regarding provision and payment for medical services are lengthy. They are not repeated in this LCD. Neither Medicare payment policy rules nor this LCD replace, modify or supersede applicable

state statutes regarding medical practice or other health practice professions acts, definitions and/or scopes of practice. All providers who report services for Medicare payment must fully understand and follow all existing laws, regulations and rules for Medicare payment for allergy testing services and must properly submit only valid claims for them. Please review and understand them and apply the medical necessity provisions in the policy within the context of the manual rules. Relevant CMS manual instructions and policies may be found in the following Internet-Only Manuals (IOMs) published on the CMS Web site.

IOM Citations:

- CMS IOM Publication 100-02, *Medicare Benefit Policy Manual,*
    - Chapter 15, Sections 20.2 Physician Expense for Allergy Treatment and 50.4.4.1 Antigens
- CMS IOM Publication 100-03, *Medicare National Coverage Determinations (NCD) Manual,*
    - Chapter 1, Part 2, Sections 110.11 Food Allergy Testing and Treatment, 110.12 Challenge Ingestion Food Testing, and 110.13 Cytotoxic Food Tests
    - Chapter 1, Part 4, Section 230.10 Incontinence Control Devices

- CMS IOM Publication 100-08, *Medicare Program Integrity Manual*,
    - Chapter 13, Section 13.5.4 Reasonable and Necessary Provisions in LCDs

Social Security Act (Title XVIII) Standard References:

- Title XVIII of the Social Security Act, Section 1862(a)(1)(A) states that no Medicare payment shall be made for items or services which are not reasonable and necessary for the diagnosis or treatment of illness or injury.
- Title XVIII of the Social Security Act, Section 1862(a)(7). This section excludes routine physical examinations.

Coverage Guidance

Coverage Indications, Limitations, and/or Medical Necessity

Compliance with the provisions in this LCD may be monitored and addressed through post payment data analysis and subsequent medical review audits.

History/Background and/or General Information

Allergy is a form of exaggerated sensitivity or hypersensitivity to a substance that is either inhaled, ingested, injected, or comes in contact with the skin or eye. The term allergy is used to describe situations where hypersensitivity results from heightened or altered reactivity of the immune system in response to external substances. Allergic or hypersensitivity disorders may be manifested by generalized systemic reactions as well as localized reactions in any part of the body. The reactions may be acute, subacute, or chronic, immediate or delayed, and may be caused by a variety of offending agents; pollen, molds, mites, dust, feathers, animal fur or dander, stinging insect venoms, foods, drugs, etc.

Allergy testing is performed to determine a patient's immunologic sensitivity or reaction to particular allergens for the purpose of identifying the cause of the allergic state, and is based on findings during a complete medical and immunologic history and appropriate physical exam. There are several different types of diagnostic modalities available for allergy testing. Positive and negative controls should be performed with all tests and tests used should have proven efficacy as demonstrated through scientifically valid medical studies published in peer review journals. 1,2,3,4

This policy addresses immediate (IgE-mediated) hypersensitivity and delayed (cell mediated) hypersensitivity and

includes in vivo testing (skin tests), organ challenge tests, in vitro testing, limitations, and provider qualifications. The specific allergy testing described below is considered medically reasonable and necessary in accordance with the criteria noted in accordance with evidence-based guidelines.

Covered Indications

A. In Vivo Testing (skin tests):

In vivo testing (skin tests) include the performance and evaluation of selective cutaneous and mucous membrane tests in correlation with history, physician examination, and other observations of the patient. The tests are performed to determine body sensitivity and reaction to the antigen for the purpose of diagnosing the presence of allergic reaction to antigenic stimuli. Prick/puncture tests or intracutaneous tests are the preferred techniques for immunoglobulin E (IgE)-mediated hypersensitivity.[1]

1. Percutaneous testing (scratch, puncture, prick), immediate type reaction, will be considered medically reasonable and necessary when used to evaluate IgE mediated hypersensitivity to inhalants, foods, Hymenoptera (stinging insects), chemicals, and specific drugs (e.g., penicillins and macromolecular agents).[1]

2. Intracutaneous (intradermal) testing, immediate type reaction, will be considered medically reasonable and necessary when used to evaluate IgE mediated hypersensitivity to inhalants, Hymenoptera venoms (e.g., bee venom), drugs (e.g., penicillin, insulin, heparin, muscle relaxants) and/or chemicals.[1,2]

3. Patch testing is used to differentiate allergic contact dermatitis (ACD) and irritant contact dermatitis (ICD). Patch testing is the gold standard method of identifying the cause of allergic contact dermatitis. This testing is indicated to evaluate a nonspecific dermatitis, allergic contact dermatitis, pruritus, and other dermatitis to determine the causative antigen. It is a diagnostic test reserved for patients with skin eruptions for which a contact allergy source is likely.[1,2]

   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 hours or 96 hours, and the reactions are systemically 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.[1]

   Allergy patch testing will be considered medically reasonable and necessary when used to diagnose allergic contact dermatitis for patients with a clear-cut clinical suspicion of contact allergy, and they are tested with the chemicals relevant to the problem, which may include the following:

   - 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, and metals, such as nickel and rubber additives (this is not an all-inclusive list).[1,2,3]

4. Photo patch testing will be considered medically reasonable and necessary to evaluate unique allergies resulting from photosensitization (e.g., photo-allergic contact dermatitis).[1]

5. Photo testing will be considered medically reasonable and necessary to evaluate skin abnormalities (e.g., itching, blisters, hives) resulting from exposure to sunlight.[1]

6. Intracutaneous (intradermal) Dilutional Testing (IDT) (also known as Skin Endpoint Titration [SET]), immediate

type reaction is intradermal testing of sequential and incremental dilutions of a single antigen. The endpoint is determined by intradermal testing with the use of approximately 0.1 ml of serial five-fold dilution extract. The endpoint is the weakest dilution that produces a positive skin reaction and initiates progressive increase in the diameter of the wheals with each stronger dilution. For example, if Hymenoptera venom sensitivity is suspected, initial prick/puncture tests followed by serial endpoint titration with intracutaneous tests may be required.[1,5]

- Intracutaneous (intradermal) dilutional testing will be considered medically reasonable and necessary when used for determining the starting dose for immunotherapy for individuals with Hymenoptera venom sensitivity and significant aeroallergen sensitivity.

7. Intracutaneous (intradermal) testing, delayed reaction

- Intracutaneous (intradermal) testing will be considered medically reasonable and necessary when used in epidemiologic testing of susceptible populations exposed to bacterial and fungal pathogens (e.g., tuberculin skin test). The tuberculin skin test is elicited by the intracutaneous injection of 0.1 mL of standardized purified protein derivative (PPD) starting with the intermediate strength of 5 tuberculin units. The size of the delayed skin test response is measured 48 hours after antigen challenge, and the largest diameter of the palpable firm area that outlines the induration reaction should be measured to the nearest millimeter.[1]

B. Organ Challenge Tests:

Controlled challenges or supervised exposure are considered the gold standard for assessing whether clinical sensitivity is present. When tests for IgE-mediated immunity are ambiguous, organ challenge testing is used to determine if clinical sensitivity exists. Organ challenge test material may be applied to the mucosae of the conjunctivae, nares, GI tract, or bronchi. 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. Considerable experience with these methods is required for proper interpretation and analysis. Specific organ challenge tests will be considered medically reasonable and necessary under the following conditions[1,4,6]:

1. Ophthalmic mucous membrane challenge tests and direct nasal mucous membrane challenge tests provided that levels of allergic mediators (such as histamine and tryptase) are measured.
2. Inhalation bronchial challenge tests to evaluate new allergens and to 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.

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

3. Oral food challenge (OFC) testing is a physician-supervised oral provocation procedure where a patient ingests gradually increasing amounts of a food under medical supervision until an age-appropriate serving is reached or the feeding is terminated because of symptoms. Prior to conducting an OFC, the patient’s medical history, age, past adverse food reactions, skin prick testing (SPT), and serum food allergen-specific IgE results must be considered.

- Oral food challenge testing will be considered medically reasonable and necessary when the diagnosis is uncertain for:
  - Food allergy dermatitis
  - Anaphylactic shock due to an adverse food reaction
  - Allergy to medicinal agents
  - Allergy to foods

C. In Vitro Testing:

Specific IgE In Vitro Tests

- Examples include[1,7]:
  - ELISA (Enzyme linked immunosorbent assay)
  - MAST (Multiple thread allergosorbent test)
  - IP (Immuno-peroxidase test)
  - PRIST (Paper radioimmunosorbent test)
  - CAP (ImmunoCap assay)

Specific IgE immunoassays detect antigen-specific IgE antibodies in the patient's serum. Testing must be based on a careful history/physical examination which suggests IgE- mediated disease. The choice of specific allergen specificities for testing should be guided by a comprehensive physical exam that includes objective symptoms to select appropriate testing. In situations in which a high pretest probability has been determined, confirmation of sensitization is frequently conducted by IgE antibody testing due to the possible risk of life-threatening anaphylaxis and/or the possibility of starting a course of immunotherapy. Specific IgE in vitro tests are useful when testing for inhalant allergens (pollens, molds, dust mites, animal dander), specific foods, insect stings, and other allergens such as drugs or latex, when direct skin testing is impossible due to extensive dermatitis, or in marked dermatographism.[1,5,7]

In-vitro allergen specific IgE testing will be considered medically reasonable and necessary under the following conditions[1,5,7]:

- Direct skin testing is not possible due to extensive dermatitis, dermographism, ichthyosis, or generalized eczema.
- For patients who cannot be safely withdrawn from medications that interfere with skin testing (such as long-acting antihistamines, tricyclic antidepressants).
- Testing of uncooperative patients with mental or physical impairments.
- As adjunctive laboratory testing for disease activity of allergic bronchopulmonary Aspergillosis (ABPA) and certain parasitic diseases.
- The evaluation of cross-reactivity between insect venoms (e.g., fire ant, bee, wasp, yellow jacket, hornet).
- When the pretest probability of Hymenoptera venom allergy is strong and the skin test result is negative, serological detection of IgE antibodies is recommended for vespid, wasp, honeybee, bumblebee, and fire ant venoms.
- When clinical history suggests an unusually greater risk of anaphylaxis from skin testing than usual (e.g., when a patient has a history of a previous systemic reaction to skin testing or when an unusual allergen is not available as a licensed skin test extract).
- Measurements of total IgE serum levels are not appropriate in most general allergy testing which is performed to determine a patient’s immunologic sensitivity or reaction to particular allergens for the purpose of identifying the cause of the allergic state. Total serum IgE levels will only be considered medically reasonable and necessary for the following[1]:
  - Follow up of bronchopulmonary Aspergillosis (ABPA),

- Select immunodeficiency such as the syndrome of hyper-IgE,
- Eczematous dermatitis,
- Recurrent pyogenic infections, or
- Evaluation for omalizumab therapy.

Limitations

1. The number of allergy tests performed should be judicious and dependent upon the patient's history, physical findings and provider's clinical judgment. All patients should not necessarily receive the same tests or the same number of sensitivity tests. Rather, testing should be patient specific based on the history and physical examination.[1]

    - Per evidence-based guidelines, the number of skin tests (e.g., ≤70 prick/puncture and 40 intracutaneous tests) for inhalant allergens is justified as an initial diagnostic evaluation. Also, up to 80 patch tests may be required for ACD diagnosis.[1,8-10]

2. In-vitro testing performed in addition to skin testing for the same antigen is not usually necessary, 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.[1]
3. Intracutaneous (intradermal) tests for food sensitivity are not recommended because of numerous false-positive test findings and possible risks.[1]
4. Food allergy tests are inappropriate for investigation of chronic idiopathic urticaria (CIU) or angioedema.[1]
5. Routine utilization of a large number of skin tests or routine annual tests without a discernable indication is not acceptable.[1]
6. Please refer to the CMS IOM Publication 100-03, *Medicare National Coverage Determinations (NCD) Manual*, Chapter 1, Part 2, Section 110.11 Food Allergy Testing and Treatment, Section 110.12 Challenge Ingestion Food Testing, and Section 110.13 Cytotoxic Food Tests for additional limitations.
7. Please refer to the CMS IOM Publication 100-03, *Medicare National Coverage Determinations (NCD) Manual*, Chapter 1, Part 4, Section 230.10 Incontinence Control Devices for additional limitations.

The following tests are considered not medically reasonable and necessary:

- Allergen specific IgE; qualitative, multiallergen screen and multiplex microarray chip for IgE antibody detection are non-specific screening tests that do not identify a specific antigen.[1,5] These tests are screening tools and therefore are not covered by Medicare.
- Provocation-neutralization[1,11]
- Electrodermal testing[1,6,11]
- Applied kinesiology[1,6,11]
- Iridology[1]
- Hair analysis[1,6,11]
- Lymphocyte proliferation test[1,11]
- Basophil activation tests (BAT) to diagnose food or drug allergies[1,6,11,12]
- T-cell proliferation assay[6]
- Facial thermography[6]
- Breath condensate analysis[1]
- In vitro tests for delayed hypersensitivity to contact allergens (e.g., metals and bone cement)[3]
- Immunoglobulin G (IgG) allergy testing[13]
- Tests to diagnose Food Allergy:

- Food specific IgG, IgG4, and IgG/IgG4 antibody tests[1,6,11]
- Atopy patch tests to diagnose non-contact food allergy[1,11]
- Intradermal testing to diagnose food allergy[6]
- Component-resolved diagnostics (CRD) to diagnose food allergy[6]
- Epitope binding testing to diagnose food allergy[6]
- T-cell responses to food allergens[6]
- Platelet activating factor (PAF) to diagnose food allergy[6]
- Gastric juice analysis[6,11]
- Mediator release assay (LEAP diet)[11]
- Cytotoxic food testing[1,11]
- Please refer to the CMS IOM Publication 100-03, *Medicare National Coverage Determinations (NCD) Manual*, Chapter 1, Part 2, Section 110.11 Food Allergy Testing and Treatment, Section 110.12 Challenge Ingestion Food Testing, and Section 110.13 Cytotoxic Food Tests for additional coverage restrictions.

Provider Qualifications

Services will be considered medically reasonable and necessary when all aspects of care are within the scope of practice of the provider's professional licensure; and when all procedures are performed by appropriately trained providers in the appropriate setting.

Notice: Services performed for any given diagnosis must meet all of the indications and limitations stated in this LCD, the general requirements for medical necessity as stated in CMS payment policy manuals, any and all existing CMS national coverage determinations, and all Medicare payment rules.

Summary of Evidence

Multiple guidelines and appropriate use criteria are available for allergy testing.

Pretest probability is used to determine if allergy testing is appropriate and is based on the patient's clinical history.

A literature search was conducted using the following key words: allergy; allergen; allergy testing; guideline; practice parameters; meta-analysis; systematic review; diagnosis; IgE; pretest probability; clinical history; skin testing; skin prick tests; food allergy; drug allergy; venom allergy; insect hypersensitivity; Hymenoptera venom; anaphylaxis; urticaria; in vitro allergy tests; in vivo allergy tests; specific IgE antibodies; allergic contact dermatitis; patch testing; oral food challenge; immediate IgE-mediated hypersensitivity; delayed (cell mediated) hypersensitivity; atopic dermatitis; multiallergen screen; photoallergy; allergic rhinitis; asthma; cockroach; house dust mites; and inhalant allergy.

Evidence-based guidelines

Skin Tests (prick/puncture and intracutaneous)

Bernstein et al has provided practice parameters for allergy diagnostic testing. There are many diagnostic methods for use in diagnosing hypersensitivity disorders. Positive and negative controls should be performed with all allergy tests and tests used should have proven efficacy as demonstrated through scientifically valid medical studies.[1]

Prick/Puncture Tests and Intracutaneous Tests

Prick/puncture tests or intracutaneous (intradermal) tests, which have an immediate type reaction, are the preferred techniques for IgE-mediated hypersensitivity.[14] Skin tests (prick/puncture and intracutaneous) are beneficial to verify sensitivity caused by aeroallergens, foods, some drugs, and a few chemicals.[11] Skin test allergens utilized for prick/puncture tests should also be potent and stable. The dependability of prick/puncture tests rests on the skill of the tester, the test instrument, color of the skin, skin reactivity on the day of the test, potency, and stability of test reagents. The diagnostic validity of prick/puncture tests has been proven not only in patients subjected to allergens under natural conditions but also in patients undergoing controlled organ challenge tests. Many studies have confirmed the sensitivity and specificity of prick/puncture tests for both inhalant and food allergens when correlated with nasal and oral challenge tests. Skin tests should not be conducted on skin locations with active dermatitis or severe dermatographism. Literature indicates that life-threatening, generalized systemic reactions are rarely generated by prick/puncture tests. In a recent retrospective survey, one death was reported in a patient who received 90 food prick/puncture tests at one time. In general, skin prick/puncture testing is more sensitive for detecting sensitization to inhalant allergens and confirming clinical allergy. However, specific IgE assays with defined quantifiable threshold levels can also predict positive respiratory responses following allergen exposure.[1]

Intracutaneous (intradermal) tests will recognize a greater number of patients with lower skin test sensitivity and are utilized when increased sensitivity is the main goal of testing.[1] Intracutaneous tests are beneficial for evaluation of anaphylaxis, particularly drug (e.g., penicillin) and Hymenoptera venom anaphylaxis. They have been assessed and validated in analysis of several significant IgE-mediated drug reactions, including anaphylactic reactions caused by penicillin, succinylcholine analogs, and cancer chemotherapeutic agents.

Intracutaneous (Intradermal) Dilutional Testing (skin endpoint titration)

Intracutaneous (intradermal) dilutional testing (also known as skin endpoint titration [SET]) is intradermal testing of sequential and incremental dilutions of a single antigen. The endpoint is determined by intradermal testing with the use of approximately 0.1 ml of serial five-fold dilution extract. The endpoint is the weakest dilution that produces a positive skin reaction and initiates progressive increase in the diameter of the wheals with each stronger dilution.[1] In comparison with specific nasal challenge, skin endpoint titration (SET) is equivalent to prick/puncture skin tests. This type of testing is beneficial for determining the starting dose for immunotherapy for individuals with Hymenoptera venom sensitivity and significant aeroallergen sensitivity. For example, if Hymenoptera venom sensitivity is suspected, initial prick/puncture tests followed by serial endpoint titration with intracutaneous tests may be required.

The sensitivity of intracutaneous tests may be greater than prick/puncture tests for penicillin, insect venom, or certain drug classes (e.g., insulin, heparin, muscle relaxants) hypersensitivity. Concurrent medications may affect the validity of prick/puncture and intracutaneous tests (e.g., antihistamines, tricyclic antidepressant doxepin, histamine antagonists, oral prostaglandin D2 inhibitors). The dependability of intracutaneous tests rests on the same variables as those described for prick/puncture tests; the age of the skin, the location of the body where the tests are applied, skin pigmentation, concurrent medications, and potency and biologic stability of the allergen test extracts. Prompt systemic reactions are more common with intracutaneous tests.

The late-phase cutaneous reaction is an extension of the prick/puncture or intracutaneous testing, generally the latter, and is described by erythema, induration or edema, and dysesthesia.[1] The late-phase cutaneous reaction can occur following immune and nonimmune activation. Numerous allergens have been implicated. The late-phase cutaneous reaction should be read between the 6th and 12th hours after the skin tests are performed; measurements of average diameter and/or area of induration or edema should be documented.

Delayed-Type Hypersensitivity Skin Testing

Delayed-type hypersensitivity skin testing is key in epidemiologic screening of susceptible populations exposed to bacterial and fungal pathogens.[1] The standardized purified protein derivative (PPD) antigen has a long history for use as a predictor of active or latent tuberculosis infection. Variables, such as vulnerable populations and cross-

sensitization with other atypical mycobacterial species affect the diagnostic accuracy of the tuberculin skin test and, by extrapolation, other delayed-type hypersensitivity tests. A late phase cutaneous reaction and a delayed-type hypersensitivity reaction might not look entirely different except that the latter typically has prolonged induration. No life-threatening occurrences or deaths have been reported as a result of late-phase cutaneous reactions in recent surveys.

Purified protein derivative (PPD) of tuberculin is the prototype antigen recall test and offers explicit evidence that hypersensitivity, as opposed to toxicity, is elicited by the antigens in Mycobacterium hominis or related mycobacterial species. The tuberculin skin test is elicited by the intracutaneous injection of 0.1 mL of standardized PPD starting with the intermediate strength of 5 tuberculin units. Recall antigen skin tests are used to assess cellular immunity in patients with infection (e.g., life-threatening sepsis), cancer, pretransplantation screening, and end-stage debilitating diseases. Decreased or absent recall antigen tests are termed anergy, which develops frequently in certain diseases, such as hematogenous tuberculosis, sarcoidosis, and atopic dermatitis. The size of the delayed skin test response is measured 48 hours after antigen challenge, and the largest diameter of the palpable firm area that outlines the induration reaction should be measured to the nearest millimeter.[1]

When a single intracutaneous antigen (other than PPD) is utilized to assess prior sensitization to a potential pathogen, a reaction of 5 mm or larger may serve as the cutoff point for a positive test, but smaller reactions (2 to 4 mm) may be clinically significant. The absence of delayed-type hypersensitivity to all the test antigens would imply an anergic state. The largest application of recall antigen testing is the recognition of anergy and as an in vivo clinical correlate of cell-mediated immunoincompetency.[1] Although the standardized PPD antigen has been used for many years as a predictor of active or latent tuberculosis infection, confounders, such as susceptible populations, bacilli Calmette-Guerin (BCG), a vaccination for tuberculosis that is not widely used in the United States, and cross-sensitization with other atypical mycobacterial species, have all affected the diagnostic accuracy of the tuberculin skin test and, by extrapolation, other delayed-type hypersensitivity tests.

Patch Tests

The epicutaneous patch test is considered to be the definitive diagnostic method for the diagnosis of allergic contact dermatitis (ACD), which is a unique form of delayed hypersensitivity.[1] Leading triggers of ACD are chemicals, plant resins, and lipid components. Direct irritants may cause irritant contact dermatitis (ICD), which often is indistinguishable from ACD; however, the clinical presentation of ICD is more limited to the skin site directly in contact with the offending agent(s) with little or no extension beyond the site of contact. Irritant contact dermatitis is generally the result of nonimmunologic, direct tissue reaction and must be clearly differentiated from ACD. Irritant contact dermatitis is usually a multifactorial response that involves contact with a substance that chemically abrades, physically irritates, or damages the skin. Irritation is usually a direct cytotoxic reaction produced by a multitude of various agents (e.g., chemicals, detergents, solvents, alcohol, creams, lotions, ointments, and powders) and by contributing physical factors that include excessive scrubbing, washing, overhydration, improper drying, perspiration, and temperature extremes. Patch testing is recommended for any dermatitis for which contactant exposure, either natural or secondary to topical agents, might be implicated. The diagnosis of ACD is suspected from the clinical presentation of the rash, which then must be supported by a history of exposure to a causative agent and subsequently confirmed by patch testing. Patch tests are most beneficial for patients with a clear-cut clinical suspicion of contact allergy, and they are tested with the chemicals relevant to the problem; these conditions satisfy the prerequisites of high pretest probability.

Patch tests are recommended for patients with chronic, pruritic, eczematous, or lichenified dermatitis if underlying or secondary ACD is speculated. Contact dermatitis is a frequent concern following exposure to topical medications, including lanolin, para-aminobenzoic acid (PABA), caine derivatives, antihistamines, iodochlorhydroxyquin, nonsteroidal anti-inflammatory drugs (NSAIDs), and corticosteroids. When clinical evaluations imply that exposure to a specific contactant has occurred either in an occupational or nonoccupational setting, patch testing may be used to confirm the diagnosis.[8,10] As indicated previously, patch tests should be used for patients based on a clear-cut clinical inference of contact allergy, and tested with the chemicals pertinent to the issue; these conditions satisfy the

prerequisites of high pretest probability. Certain contactants (e.g., antibiotics, PABA) may induce photo contact ACD or phototoxic contact dermatitis (CD) (e.g., carrot, celery, fennel, lemon-lime, grapefruit). If photosensitization is suspected, photo patch tests should be performed by a physician with expertise in UV radiation. If photo contact sensitivity is suspected, the appropriate allergens should be subjected to photo patch test primarily in the UV-A range of 320 to 400 nm. Photosensitizers are substances that lead to photobiologic reactions after UV exposure, showing either toxic or allergic reaction patterns. Cutaneous manifestations in photoallergic reactions are predominantly eczematous lesions. Photo patch testing is the diagnostic testing recommended for photosensitization, whereas, photo tests are used to evaluate skin abnormalities (e.g., itching, blisters, and hives) resulting from exposure to sunlight. Patch test findings are affected by oral corticosteroids but not by antihistamines. Usually, patch tests stay in place for 48 hours. Following the 48-hour patch test reading, additional readings at 3 to 4 days and, in some instances, 7 days following the original application of the patch generate the greatest overall reading reliability.

Specific IgE Immunoassays

Under specific circumstances, IgE immunoassays may be preferable to skin testing, such as widespread skin disease, patients receiving skin test suppressive therapy, uncooperative patients, or when the patient's history proposes an extraordinarily greater risk of anaphylaxis from skin testing. Also, antihistamines and drugs such as tricyclic antidepressants decrease or block skin test reactivity. Therefore, when a patient cannot be safely withdrawn from a medication that would interfere with skin testing, an immunoassay may be appropriate. The sensitivity of these immunoassays compared with prick/puncture skin tests range from less than 50% to greater than 90%, with the mean at about 70% to 75% for most studies. Consequently, skin tests are highly beneficial for the diagnosis of IgE-mediated sensitivity.[1,14]

As indicated previously, skin prick/puncture testing is more sensitive for recognizing sensitization to inhalant allergens and proving clinical allergy. However, specific IgE assays with defined quantifiable threshold levels can also predict positive respiratory responses following allergen exposure.[1]

Diagnostic skin and/or specific IgE tests are utilized to verify sensitivity to venoms in a patient with a history of a prior systemic reaction. While diagnostic tests distinguish species specificity of venom sensitization, they do not reliably predict severity of the sting reaction. A small percentage of individuals (1%) with negative findings to both skin and in vitro tests may experience anaphylaxis following a field sting.[1]

Assessment of drug-specific IgE antibodies caused by many high-molecular-weight and several low-molecular-weight agents is often beneficial for validating the diagnosis and prediction of future IgE-mediated reactions, such as anaphylaxis and urticaria.[1]

Examples of specific IgE in vitro tests include[1,7]:

- ELISA (Enzyme linked immunosorbent assay)
- MAST (Multiple thread allergosorbent test)
- IP (Immuno-peroxidase test)
- PRIST (Paper radioimmunosorbent test)
- CAP (ImmunoCap assay)

Total Serum IgE

The clinical applications of total serum IgE are of limited value. Elevated serum IgE concentrations occur in allergic bronchopulmonary Aspergillosis (ABPA). Total serum IgE is recommended to assess select immunodeficiency syndromes such as hyper-IgE, eczematous dermatitis, and recurrent pyogenic infections. Total serum IgE is also recommended to evaluate the appropriateness of a patient for omalizumab therapy and to establish the initial dose.[1] Allergic bronchopulmonary Aspergillosis is an inflammatory disease of the lungs distinguished by severe asthma,

sputum production, peripheral blood eosinophilia, and an increased total serum IgE concentration. If untreated, it could progress to central bronchiectasis and, eventually, pulmonary fibrosis and death. Following suitable treatment with corticosteroids, total serum IgE levels generally decrease. Total serum IgE should be monitored during the disease as an increase in IgE may signal a relapse.

Food Allergy Testing

Tests for food specific IgE antibodies include percutaneous skin tests (prick/puncture tests) and serum assays. Overall, these tests are very sensitive (generally 85%) but modestly specific (approximately 40% to 80%) and therefore are recommended for use when a specific food is highly suspected.[1] They are not effective for indiscriminate screening (e.g., using panels of tests without consideration of likely causes) and therefore generally should not be used for that purpose.

The probability distribution of specific IgE for several anaphylactogenic foods (peanuts, egg whites, cow's milk, and codfish) can outline sensitivity as confirmed by double-blind oral challenge tests.[1]

Organ Challenge Tests

Controlled challenges or supervised exposure are considered the gold standard for assessing whether clinical sensitivity is present. In challenge testing, a suspected allergen in a clinically relevant exposure is administered in an attempt to reproduce symptoms. Challenge tests have been broadly applied under research conditions for many years, but they may also be useful in clinical situations for confirmation of clinical disease. For example, when tests for IgE-mediated immunity are ambiguous, organ challenge testing may be used to determine if clinical sensitivity exists. Specific organ challenge tests may facilitate or support clinical diagnosis under certain conditions: 1) investigation of potential "new" allergens, 2) validation of diagnosis when the history is suggestive but skin and/or in vitro test findings are negative, 3) verifying food allergy, and 4) monitoring of therapy, either pharmacologic or immunologic. In general, these tests require cooperative patients with respect to both age and mental status. The site of the specific organ challenge is history dependent (i.e., conjunctival, nasal, bronchial, or skin) (e.g., patch tests for ACD; supervised insect stings).[1]

Respiratory challenge tests are utilized when an objective gold standard for determining clinical sensitivity is indicated. Conjunctival challenge tests are generally performed for suspected localized eye allergy but they may also be helpful in assessing nasal allergy. Conjunctival challenge tests are assessed by symptoms of itching and objective indices, including tear volume, amount of mucus, and palpebral or bulbar erythema. Nasal challenge testing is rare but may be used to offer objective evidence of sensitivity when the diagnosis is uncertain or to evaluate the effectiveness of therapeutic management. Nasal challenge reactions are assessed by subjective symptoms and objective measurements of nasal airway resistance, the number of sneezes, and the measurement of inflammatory mediators in nasal secretions (such as histamine and tryptase). Specific (allergic) bronchial challenge yields a measure of lower airway clinical sensitivity when there is doubt. Possible new asthma triggers can be investigated and confirmed with specific bronchial challenge. Since late-phase asthmatic responses may occur, arrangements should be made for peak flow monitoring or direct observation of such reactions, which usually appear 6 to 12 hours later.[1]

Many inflammatory correlates can be assessed and studied serially in respiratory and other body fluids, such as nasal smears or lavage, induced sputum, and bronchoalveolar lavage (BAL).[1] These may identify specific phenotypes or in some cases predict severity.

Number and Frequency of Tests

The number of skin tests and the allergens chosen for skin testing should be based on the patient's age, history, environment and living conditions (e.g., region of the country), occupation, and activities.[1] Regular use of a

significant number of skin tests or routine annual tests without a distinct clinical indication are clearly not necessary. Evidence-based sources should be used to determine whether specific allergen tests based on pretest probability are likely to confirm a suspected clinical diagnosis. Because ACD is frequently caused by unsuspected substances, up to 80 patch tests may be required for diagnosis.[8-10] The Joint Task Force on Practice Parameters concludes the number of skin tests (e.g., ≤70 prick/puncture and 40 intracutaneous tests) for inhalant allergens is justified as an initial diagnostic evaluation.[1] However, routine annual tests without a definite clinical indication are clearly not indicated.

If Hymenoptera venom sensitivity is suspected, initial prick/puncture tests followed by serial end point titration with intracutaneous tests may be required.[1]

If a patient presents with idiopathic anaphylaxis, up to 30 screening prick/puncture tests have been reported to distinguish causal foods in a small percentage of such individuals.[1] A subsequent overview of this study questioned whether the diagnostic yield of such a strategy was useful. However, in the diagnostic assessment of speculated anaphylaxis, it would be wise to spread the total number of tests over several clinic visits to prevent the likelihood of severe anaphylaxis if multiple reactions occurred.

Unproven Tests

The role of lymphocyte proliferation as measured in vitro in the pathogenesis of the delayed-type hypersensitivity tissue reaction and delayed-type hypersensitivity skin reactions is unclear.[1]

Procedures for which there is no evidence of diagnostic validity include cytotoxic tests, provocation-neutralization, electrodermal testing, applied kinesiology, iridology, hair analysis, and food specific IgG, IgG4, and IgG/IgG4 antibody tests. Also, atopy patch tests, lymphocyte proliferation tests, and basophil activation tests are additional diagnostic tests for drug allergy. However, further studies are required to confirm their clinical utility in the evaluation of drug allergic patients.[1]

Intracutaneous (intradermal) skin tests for foods are potentially dangerous as they can provoke a systemic reaction (seldom a concern for prick test), are overly sensitive, increase the chance of a false-positive test result, and are not recommended.[1]

Food allergy tests are inappropriate for investigation of chronic idiopathic urticaria (CIU) or angioedema.[1]

Although breath condensate analysis is an evolving noninvasive method for evaluation of asthma, results are still variable and further refinements are required before it can be accepted as a valid diagnostic method.[1]

A positive multiple allergen test result does not provide adequate information to make a specific diagnosis or to initiate therapy. In addition, a negative multiple allergen test finding does not exclude clinical sensitivity since the commercially-available multiallergen screening tests only screen for approximately 15 aeroallergens.[1]

Unproven tests, such as immunoglobulin G (IgG) testing or an indiscriminate battery of immunoglobulin E (IgE) tests, should not be conducted in the evaluation of allergy as these tests may lead to inappropriate diagnosis and treatment.[13]

Evidence-Based Guideline for Drug Allergy Testing

An evidenced-based updated practice parameter for drug allergy testing[2] provides important considerations in the assessment of drug hypersensitivity which includes the patient's history, physical exam, objective clinical and laboratory tests, previous and current drug use, toxicity and allergenicity of previous current drug use and the timing between initiation of therapy and onset of symptoms. All body systems potentially responsible for symptoms should be assessed. Cutaneous manifestations are the most common presentation for drug allergic reactions. Although drug allergic reactions may present with noncutaneous physical findings, these findings are generally nonspecific and are

not nearly as helpful in diagnosis and management decisions.

The immediate hypersensitivity skin test is considered the most useful test for detecting IgE-mediated drug reactions caused by many large-molecular-weight biologicals and penicillin.[2]

Limited trials with small numbers of individuals have assessed the specificity and sensitivity of third-generation assays for detection of penicillin specific IgE in vitro. These studies show relatively high specificity (97%-100%) but lower sensitivity (29%-68%) for penicillin specific IgE. Consequently, although a positive in vitro test result for penicillin specific IgE is highly predictive of penicillin allergy, a negative in vitro test result does not adequately exclude penicillin allergy. The basophil activation test is a recently described method of evaluating expression of CD63 on basophils after stimulation with an allergen. Data is limited for this method to assess patients with possible allergies to β-lactam antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs). Further confirmatory studies, especially with commercially available tests, are needed before its general acceptance as a diagnostic tool.[2]

The most dependable method for diagnosis of contact dermatitis caused by topically applied drugs is patch testing. Recent literature indicates concerns regarding the diagnostic utility of patch tests with systemically administered drugs in non–IgE-mediated cutaneous drug reactions. While drug patch testing may be beneficial for certain types of cutaneous drug reactions, including maculopapular exanthems, acute generalized exanthematous pustulosis, and fixed drug eruptions, generally drug patch testing is not helpful for Stevens-Johnson syndrome (SJS) or urticarial eruptions.[2]

Evidence-Based Guidelines for Contact Dermatitis

Fonacier et al provided an updated practice parameter for contact dermatitis. These evidence-based guidelines signify that patch testing (PT) is the gold standard to confirm the diagnosis in individuals suspected of allergic contact dermatitis (ACD). The consideration of ACD is recommended in the differential diagnosis of individuals with chronic eczematous or noneczematous dermatitis. Patch testing for patients with the following conditions/situations is recommended: 1) hand dermatitis; 2) generalized and anatomically localized skin eruptions (such as the hands, face, eyelids); 3) facial rash involving the periorbital areas (e.g., eyelids); 4) lip dermatitis (cheilitis) and perioral dermatitis; 5) dermatitis that involves the scalp and neck; 6) acute or chronic hand eczema; 7) axillary dermatitis; 8) anogenital dermatitis; 9) a generalized ACD rash from systemic exposure (e.g., ingestion, infusion, or transcutaneous exposure) of a drug, chemical, or food to which the patient previously experienced ACD; 10) chronic dermatitis involving the lower extremities, feet and/or soles; 11) preoperative patch testing for metal sensitization in patients with a significant history of metal allergy; and 12) in patients with joint replacement failure after infection and biomechanical causes have been excluded.[3]

Currently, there are no guidelines or recommendations for symptomatic patients with positive PT to metals or bone cement components.[3] Therefore, a determination concerning an implant revision after a positive PT test must be made following a conversation between the patient and their healthcare team. Furthermore, in addition to the probability of metal sensitization as a possible cause of joint replacement failure, reports also show implant failure associated with bone cement or its components including benzoyl peroxide, hydroquinone, methyl methacrylate, and n-dimethyl para-toluidine.

Tests Not Recommended for Hypersensitivity to Contact Allergens

In vitro tests are available for delayed hypersensitivity to contact allergens (i.e., metals and bone cement). However, routine use of such assays is not currently recommended as their sensitivity and specificity for diagnosing ACD has not been determined and should be considered investigational.[3]

Evidence-Based Guidelines for Atopic Dermatitis

Schneider et al provided an evidenced-based, updated practice parameter for atopic dermatitis (AD). These

evidence-based guidelines indicate that atopic dermatitis (AD) is often the first manifestation of allergic disease. Most patients with AD will also have another atopic disorder, such as allergic rhinitis, asthma, or food allergy. Pruritus and chronic or relapsing eczematous lesions with typical morphology and distribution in patients with a history of atopy are essential for diagnosis. In older children and adults, the skin lesions often involve lichenification (thick, leathery skin, usually the result of constant scratching and rubbing) and are usually localized to the flexural folds of the extremities. Factors that can exacerbate symptoms in patients with AD include temperature, humidity, irritants, infections, food, inhalant and contact allergens, and emotional stress.[4]

The diagnosis of AD is based on its clinical presentation rather than the results of diagnostic testing. Potential causes of AD can be verified by percutaneous skin tests or in vitro tests for specific IgE antibodies and in some situations by using patch tests that can produce immediate or delayed reactions to protein allergens. To establish the significance of specific food ingestion to symptoms, double-blind food challenges are frequently needed. It has been established that most patients with AD have increased serum IgE levels that correlate with the degree of disease severity.[4] Management of AD involves a combination of trigger avoidance, measures to restore skin barrier function, and anti-inflammatory medication.

IgE Testing

Hamilton et al provided a clinical management review to examine the role that IgE antibody measurements play in the diagnostic algorithm when considering the pretest likelihood of disease on the basis of the patient's clinical history. In this regard, the choice of specific allergen specificities for testing should be guided by a comprehensive physical exam that includes objective symptoms to select appropriate testing.

In situations in which a high pretest probability has been determined, confirmation of sensitization is frequently conducted by IgE antibody testing due to the possible risk of life-threatening anaphylaxis and/or the possibility of starting a course of immunotherapy.[5] Verification of sensitization may also encourage the patient to avoid situations for improved quality of life and provide a baseline for future monitoring of IgE antibody levels.

The multiallergen screen is recognized as a serological test with the highest negative predictive value for ruling out allergic sensitization. The multiallergen screen is a single test that detects IgE antibody to a balanced mixture of extracted aeroallergens (n =~10) including selections of tree, grass, and weed pollens, molds, dust mites, pet epidermals, but not foods, drugs, or venoms. These specific aeroallergen specificities have been chosen for inclusion on the multiallergosorbent following research to distinguish the group of aeroallergens that principally contributes to sensitization in individuals in North America with allergic asthma and rhinitis symptoms. This is considered a screening assay, and does not identify the precise allergen specificity or the quantitative level of IgE antibody to which the patient is sensitized.[5] Also, the allergen specificities are highly targeted and consequently they will not detect sensitization (IgE antibody) to less common aeroallergens and food allergens.

A quantitative singleplex IgE antibody assay assessment can be beneficial in situations in which there is a moderate pretest likelihood of aeroallergen-related allergic disease and the suspected allergen can be distinguished from the patient's history.[5] The age of the individual is considered in selecting the specific IgE antibody assay used to determine sensitization (skin test or serology). Serological assays are typically used for children possibly because pediatricians seldom conduct skin testing and serology can decrease the fear of potential risk of adverse events after allergen administration. While skin tests are performed more frequently for adults.

The intradermal skin test is the diagnostic test of choice for assessment in patients with a potential Hymenoptera venom allergy.[5] This test is recommended regardless of the level of pretest probability for individuals who do not qualify for skin testing due to dermatographism or antihistamine premedication or if there is a suspected false-negative skin test result due to a recent sting reaction. Also, in situations in which the pretest probability of Hymenoptera venom allergy is strong and the skin test result is negative, serological detection of IgE antibodies is recommended for vespid, wasp, honeybee, bumblebee, and fire ant venoms.

A World Allergy Organization survey reported that the most frequently tested drugs for IgE antibody-mediated reactions using serology assays were the penicillins (93.7%; beta-lactam antibiotics), cephalosporins (61.9%), general anesthetic agents (36.5%), and nonsteroidal anti-inflammatory drugs. Infrequently tested drug specificities included platinum-based chemotherapeutic agents, quinine, and sulfamides. However, evidenced-based guidelines indicate that intradermal skin testing is currently the diagnostic test of choice for the assessment in individuals for sensitization to these drugs. Studies of penicilloyl-specific IgE antibody analysis have documented a high diagnostic specificity (97%-100%) but low diagnostic sensitivity (29%-68%) of clinically used tests. Consequently, when a serological IgE antipenicilloyl measurement is positive, it is highly predictive of penicillin allergy when in agreement with the patient's medical history.[5] However, a negative test (absence of IgE antibody) result does not rule out penicillin allergy.

IgE antibody serology is frequently used in pediatrics for the detection of sensitization to foods. In this regard, molecular allergen tests have been used in the assessment of food allergies for the recognition of several defined allergenic protein families. The five chief food related allergen families include the pathogenesis-related proteins (PR10, Bet v 1 homologue); the nonspecific lipid transfer proteins, which are present in tree pollen, fruits, nuts, vegetables, and legumes; the parvalbumins in fish; tropomyosins in crustaceans; and possibly most important, the storage proteins in seeds and nuts. The most commonly used application of molecular allergen (component) resolved diagnostics has been the testing of IgE antibodies to five peanut allergen molecules. However, panel testing is not without issues. For instance, when the outcome of panel testing is positive (clinically irrelevant positive IgE antibody response) for a food that has been safely consumed by the individual with no obvious symptoms, the result is a clinical false-positive result. Therefore, a comprehensive history is imperative to guide the appropriate selection of allergen in testing for IgE antibody to confirm allergic sensitization.[5]

Currently, individual single allergenic molecules on a singleplex autoanalyzer such as the ImmunoCAP or Immulite are most frequently used.[5] Also, literature indicates that the use of extracts in IgE antibody assays will remain the principal source of allergen used in serological IgE antibody assay allergosorbents due to their comprehensive nature.

The multiplex microarray chip is an impressive technology that detects IgE antibody to a broad spectrum of clinically relevant allergenic molecules using a small quantity of serum. However, using this type of panel testing encourages abuse by providing measurements of unwanted or unneeded IgE antibody specificities that are not indicated by the patient's clinical history. Also, this chip-based microarray tends to be less quantitative and potentially less analytically sensitive than singleplex autoanalyzers.

Food Allergy Testing

Kattan et al performed a review of evidenced-based literature to assess current testing methods used to diagnose food allergy and methods under study that show potential to diagnose food allergy. In this regard, the National Institute of Allergy and Infectious Diseases-sponsored expert panel published recommendations (2010) on the diagnosis of food allergy, endorsing use of the medical history and physical examination, elimination diets, skin prick testing (SPT), serum food specific IgE (sIgE) levels, and oral food challenges (OFCs). The OFC is recommended when the diagnosis is uncertain.[6]

Skin prick testing (SPT) is particularly sensitive and has a negative predictive value of greater than 90% and is frequently able to quickly rule out an IgE-mediated food allergy.[6] Also, SPT can assist to verify a food allergy when positive results correlate with the patient's recent medical history of an acute allergic reaction to the tested food. In addition, studies suggest that the likelihood of a reaction to the tested food increases with increasing SPT wheal size. While skin tests offer quick results and are considered highly sensitive, they require the patient to be off antihistamines and to have an area of skin free of rash for testing. Furthermore, studies show that predictive values may differ according to various foods, ages, and populations, and that skin test results cannot be used as an isolated diagnostic tool without a thorough history and possibly other testing.

Serum immunoassays that measure food-specific IgE antibodies are sometimes used in the assessment of IgE-medicated food allergy with higher concentrations of food sIgE being associated with a higher risk of true food allergy. However, as with skin testing, predictive values may differ among populations for various reasons. Also, sIgE levels do not always correlate with reaction severity.[6] Therefore, the routine use of measuring total serum IgE should not be used to make a diagnosis of food allergy.[11]

An OFC may be performed to determine if a patient is sensitized to an allergen or is clinically reactive to the allergen. An OFC is a physician-supervised oral provocation procedure conducted in a hospital or outpatient office, where a patient ingests gradually increasing amounts of a food under medical supervision until an age-appropriate serving is reached or the feeding is terminated because of symptoms. Prior to conducting an OFC, the patient's medical history, age, past adverse food reactions, SPT, and serum food allergen-specific IgE results must be considered. The OFC may be conducted as an open feeding or as a single blind, or double-blind, placebo-controlled food challenge (DBPCFC).[11] Currently, the DBPCFC is considered the gold standard test for diagnosing food allergy; however, due to the time and labor intensive nature of this approach it is typically only performed in research studies and select cases in clinical practice.[6]

Tests Under Investigation that Require Further Evaluation

In recent years, several testing modalities have been under investigation that may improve food allergy diagnostics, including component-resolved diagnostics (CRD), epitope binding, T-cell responses, basophil activation studies, T-cell proliferation assays, and measurement of platelet activating factor (PAF).[6]

The allergen CRD test measures IgE to individual allergen proteins. This method has been used on a variety of food allergens, including peanuts, hazelnuts, eggs, milk, wheat, soy, fruits, cow's milk, hen's eggs, and shrimp. However, the results from these studies have differed, possibly due to varying study populations and methods, manners of sensitization, environmental exposures, and degree of sensitization to various food components. Consequently, CRD is not considered ready to be used solely in ruling out a food allergy on its own.[6]

Similar to immune responses against various proteins within a food, the location (epitope) and strength of binding (affinity) of IgE antibodies within a protein can also have clinical implications. Having IgE antibodies directed to a greater number of epitopes, or to epitopes that are not easily destroyed by denaturation and digestion (e.g., sequential or linear epitopes rather than ones dependent upon folding and conformation) may be linked with clinical allergy. Studies for epitope binding testing have been performed in relation to cow's milk, shrimp, eggs, and wheat allergies. Studies for epitope binding assays continue to evolve in diagnosing food allergy.[6]

Studies have recently investigated T cell responses to food allergens and reported that assessment of allergen-specific T-cell responses may be beneficial in differentiating sensitization from clinical reactivity. These studies have primarily focused on peanut allergens. Additional studies are needed to verify the efficacy of T-cell proliferative responses in the diagnosis of food allergy.[6]

A few studies have reported that markers of basophil activation, particularly upregulation of cell-surface molecules such as CD63 and CD203c using flow cytometry, may be useful in the diagnosis of food allergy. Studies have focused mainly on allergies related to eggs and cow's milk. Additional studies are needed to clarify the effectiveness of basophil activation in the diagnosis of food allergy.[6]

Santos et al[12] indicates that the basophil activation test (BAT) is an emerging diagnostic test for food allergy. The BAT is a flow cytometry-based assay in which the expression of activation markers is calculated on the surface of basophils after stimulation with allergen. A positive BAT is described as an in vitro surrogate of an acute allergic reaction in vivo. However, there is a large degree of inconsistency in the basophil response to allergens between patients. Additional issues in transforming the BAT from a research technique to a diagnostic test for a broader application is associated with standardization of the assay and its reproducibility as well as the cost-effectiveness of using this method for patients with suspected food allergy. Additional studies are needed to define and validate

diagnostic cut-off values for the BAT.

Currently, there's no established method to accurately predict the severity of an allergic reaction. In this regard, studies have assessed serum platelet activating factor (PAF) and PAF acetylhydrolase (PAF-AH) levels as potential markers of allergy severity. The PAF is a pro-inflammatory phospholipid synthesized and secreted by mast cells, basophils, monocytes, and macrophages. It has a variety of biological activities, including platelet activation, airway constriction, hypotension, and vascular permeation. Circulating levels of PAF are somewhat controlled by the activity of PAF-AH, an enzyme that controls activity by cleaving PAF, leaving it inactive. Additional studies are needed to determine the role of PAF and its associated catabolic enzymes in the prediction and validation of anaphylaxis in regard to food allergy.[6]

Unproven/Not Recommended Tests for the Diagnosis of Food Allergy

Several tests have been investigated and a determination has been made that these tests are unproven/not recommended in the diagnosis of food allergy: a) intradermal testing-the intradermal injection of allergens is too sensitive and involves a greater risk of adverse reactions than SPT; b) per the National Institute of Allergy and Infectious Diseases expert guidelines published in 2010, atopy patch testing (APT) should not be utilized in the assessment of non-contact food allergy as the sensitivity and specificity fluctuates between studies and there is no agreement on the suitable reagents or methods to use, or on how to interpret these tests; c) a measurement of the total serum IgE level is not recommended for routine use as studies have shown no benefit when comparing the predictive value of the ratio of serum food specific IgE (sIgE) used in a double-blind, placebo-controlled food challenge (DBPCFC) to a measurement of the total IgE for the diagnosis of food allergy; and d) other non-standardized tests which are not recommended in the diagnosis of food allergy include facial thermography, gastric juice analysis, applied kinesiology, allergen-specific IgG4 levels, hair analysis, and electrodermal testing.[6,11]

Analysis of Evidence (Rationale for Determination)

Allergy and hypersensitivity conditions are widespread and may be caused by a variety of offending agents; pollen, molds, mites, dust, feathers, animal fur or dander, stinging insect venoms, foods, drugs, etc. Allergy is a form of exaggerated sensitivity or hypersensitivity to a substance that is either inhaled, ingested, injected, or comes in contact with the skin or eye. The term allergy is used to describe situations where hypersensitivity results from heightened or altered reactivity of the immune system in response to external substances. Allergic or hypersensitivity disorders may be manifested by generalized systemic reactions as well as localized reactions in any part of the body. The reactions may be acute, subacute, or chronic, immediate or delayed with varying severity and usually have a considerable effect on the quality of life for the individual affected.

Allergy testing is performed to determine a patient's immunologic sensitivity or reaction to particular allergens for the purpose of identifying the cause of the allergic state and is based on findings during a complete medical and immunologic history and appropriate physical exam. There are several different types of diagnostic modalities available for allergy testing. Positive and negative controls should be performed with all tests and tests used should have proven efficacy as demonstrated through scientifically valid medical studies published in peer reviewed journals. The number of skin tests and the allergens chosen for skin testing should be based on the patient's age, history, environment and living conditions (e.g., region of the country), occupation, and activities. In this regard, regular use of a significant number of skin tests or routine annual tests without a distinct clinical indication are clearly not necessary.[1,2,3,4]

The value of in vivo allergy skin tests, which include skin prick tests, intracutaneous (intradermal) tests, and skin patch tests, is well established as safe diagnostic tools. These tests have been used for more than 100 years and are recognized worldwide. These tests are the preferred techniques for IgE-mediated hypersensitivity. Concerning this, evidence-based guidelines recommend percutaneous testing (scratch, puncture, prick), immediate type reaction, to evaluate IgE mediated hypersensitivity to inhalants, foods, Hymenoptera (stinging insects), chemicals, and specific drugs (e.g., penicillins and macromolecular agents). Also, evidence-based guidelines recommend intracutaneous

(intradermal) testing, immediate type reaction to evaluate IgE mediated hypersensitivity to inhalants, Hymenoptera venoms (e.g., bee venom), drugs (e.g., penicillin, insulin, heparin, muscle relaxants) and/or chemicals.

Per evidence-based guidelines, the epicutaneous patch test is considered to be the definitive diagnostic method for the diagnosis of allergic contact dermatitis (ACD), which is a unique form of delayed hypersensitivity. Direct irritants may cause irritant contact dermatitis (ICD), which often is indistinguishable from ACD; however, the clinical presentation of ICD is more limited to the skin site directly in contact with the offending agent(s) with little or no extension beyond the site of contact.

Evidence-based guidelines recommend patch tests for patients with chronic, pruritic, eczematous, or lichenified dermatitis if underlying or secondary ACD is speculated. Patch tests should be used for patients based on a clear-cut clinical inference of contact allergy, and tested with the chemicals pertinent to the issue; these conditions satisfy the prerequisites of high pretest probability. Evidence-based guidelines support the use of allergy patch testing 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, and metals (this is not an all-inclusive list). Also, photo patch testing is recommended to evaluate unique allergies resulting from photosensitization (e.g., photo-allergic contact dermatitis). Additionally, photo testing is recommended to evaluate skin abnormalities (e.g., itching, blisters, hives) resulting from exposure to sunlight.

Evidence-based guidelines indicate intracutaneous (intradermal) testing, delayed reaction tests are key in epidemiologic testing of susceptible populations exposed to bacterial and fungal pathogens (e.g., tuberculin skin test). The standardized purified protein derivative (PPD) antigen has a long history for use as a predictor of active or latent tuberculosis infection.

Intracutaneous (intradermal) dilutional testing (IDT) (also known as skin endpoint titration [SET]) has an immediate type reaction and consists of sequential and incremental dilutions of a single antigen. The endpoint is the weakest dilution that produces a positive skin reaction and initiates progressive increase in the diameter of the wheals with each stronger dilution. Evidence-based guidelines indicate this type of testing is beneficial for determining the starting dose for immunotherapy for individuals with Hymenoptera venom sensitivity and significant aeroallergen sensitivity.

Specific IgE immunoassays detect antigen-specific IgE antibodies in the patient's serum. Testing must be based on a careful history/physical examination which suggests IgE- mediated disease. Specific IgE immunoassays are useful when testing for inhalant allergens (pollens, molds, dust mites, animal dander), foods, insect stings, and other allergens such as drugs or latex, when direct skin testing is impossible due to extensive dermatitis, or in marked dermatographism. In this regard, evidence-based guidelines recommend in-vitro allergen specific IgE testing under the following conditions: 1) Direct skin testing is not possible due to extensive dermatitis, dermographism, ichthyosis, generalized eczema, 2) For patients who cannot be safely withdrawn from medications that interfere with skin testing (such as long-acting antihistamines, tricyclic antidepressants), 3) Testing of uncooperative patients with mental or physical impairments, 4) The evaluation of cross-reactivity between insect venoms (e.g., fire ant, bee, wasp, yellow jacket, hornet), 5) As adjunctive laboratory testing for disease activity of allergic bronchopulmonary Aspergillosis and certain parasitic diseases, and 6) When clinical history suggests an unusually greater risk of anaphylaxis from skin testing than usual (e.g., when a patient has a history of a previous systemic reaction to skin testing or when an unusual allergen is not available as a licensed skin test extract).

Measurements of total IgE serum levels are not suitable in most general allergy testing, which is performed to determine a patient’s immunologic sensitivity or reaction to particular allergens for the purpose of identifying the cause of the allergic state. In this regard, evidence-based guidelines recommend total IgE diagnostic evaluations for patients with the following conditions: 1) Allergic bronchopulmonary Aspergillosis (ABPA), 2) Select immunodeficiency syndromes, such as hyper-IgE, 3) Eczematous dermatitis, 4) Recurrent pyogenic infections, and 5) To evaluate the appropriateness of a patient for omalizumab therapy and to establish the initial dose.

Organ challenge tests (also referred to as controlled challenges or supervised exposure tests) are considered the gold standard for assessing whether clinical sensitivity is present. In challenge testing, a suspected allergen in a clinically relevant exposure is administered in an attempt to reproduce symptoms. When tests for IgE-mediated immunity are ambiguous, organ challenge testing is used to determine if clinical sensitivity exists. Organ challenge test material may be applied to the mucosae of the conjunctivae, nares, GI tract, or bronchi. 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. Considerable experience with these methods is required for proper interpretation and analysis.

Specific organ challenge tests may facilitate or support clinical diagnosis under certain conditions: 1) investigation of potential "new" allergens, 2) validation of diagnosis when the history is suggestive but skin and/or in vitro test findings are negative, 3) verifying food allergy, and 4) monitoring of therapy, either pharmacologic or immunologic. In general, these tests require cooperative patients with respect to both age and mental status. The site of specific organ challenge is history dependent (i.e., conjunctival, nasal, bronchial, or skin) (e.g., patch tests for ACD; supervised insect stings).

Evidenced-based guidelines recommend the following for challenge tests: 1) Ophthalmic mucous membrane challenge tests and direct nasal mucous membrane challenge tests provided levels of allergic mediators (such as histamine and tryptase) are measured and a placebo control is performed. This test is usually performed in the office setting with the provider present to observe objective measurement of reactions which might include redness of the eyes, tearing and sneezing. 2) Inhalation bronchial challenge tests to evaluate new allergens and to substantiate the role of allergens in patients with significant symptoms. This test should be performed as a dose-response assay wherein provocation concentration thresholds can be determined on the basis of allergen concentration required to cause a significant decrease in pulmonary function measurements. 3) Challenge ingestion food testing for food allergy dermatitis, anaphylactic shock due to an adverse food reaction, allergy to medicinal agents, and allergy to foods.

The quality of evidence in the literature is insufficient to support the diagnostic validity regarding allergy testing for the following procedures: 1) Allergen specific IgE qualitative, multiallergen screen and multiplex microarray chip for IgE, 2) Provocation-neutralization, 3) Electrodermal testing, 4) Applied kinesiology, 5) Iridology, 6) Hair analysis, 7) Lymphocyte proliferation test, 8) Basophil activation tests (BAT) to diagnose food or drug allergies, 9) T-cell proliferation assay, 10) Facial thermography, 11) Breath condensate analysis, and 12) In vitro tests for delayed hypersensitivity to contact allergens (e.g., metals and bone cement). In this regard, the following tests are not considered appropriate in testing for food allergy: 1) Food specific IgG, IgG4, and IgG/IgG4 antibody tests, 2) Atopy patch tests to diagnose non-contact food allergy, 3) Intracutaneous (intradermal) testing to diagnose food allergy, 4) Component-resolved diagnostics (CRD) to diagnose food allergy, 5) Epitope binding testing to diagnose food allergy, 6) T-cell responses to food allergens, 7) Platelet activating factor (PAF) to diagnose food allergy, 8) Gastric juice analysis, 9) Mediator release assay (LEAP diet), and 10) Immunoglobulin G (IgG) testing. Further research is needed to clarify the utility and efficacy of these procedures for allergy testing.

General Information

Associated Information

Please refer to the related Billing and Coding Article: Billing and Coding: Allergy Testing, A56558 for documentation requirements, utilization parameters, and all coding information as applicable.

Sources of Information

N/A

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Revision History Information

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASONS FOR CHANGE
07/11/2021	R14	LCD posted for notice on 05/27/2021 to become effective 07/11/2021. Proposed LCD posted for comment on 01/14/2021.	• Creation of Uniform LCDs With Other MAC Jurisdiction
07/01/2020	R13	LCD revised and published on 06/25/2020 effective for dates of service on and after 07/01/2020, as a non-discretionary update to remove the limitation for IgG (ELISA) testing noted under limitation 1 and limitation 4. Minor formatting changes have been made.	• Other (revised in response to CMS direction)
10/17/2019	R12	LCD revised and published on 10/17/2019. Consistent with CMS Change Request 10901, the entire coding section has been removed from the LCD and placed into the related Billing and Coding Article, A56558. All CPT codes and coding information within the text of the LCD has been placed in the Billing and Coding Article. The following has been removed from the Documentation Requirements: The submitted medical record must support the use of the selected ICD-10-CM code(s). The submitted CPT/HCPCS code must describe the service performed.	• Other (CMS Change Request 10901)
05/16/2019	R11	LCD revised and published on 5/16/2019. The IOM Citations have been updated to add applicable sections. One Social Security Act reference has been removed. Consistent with CMS Change Request (CR) 10901 IOM language has been removed from the covered indications and limitations sections of the LCD and replaced with a reference to the applicable manual. Consistent with CR 10901 all CPT and ICD-10 codes have been removed from the LCD and placed in the related Billing and Coding Article, A56558. One limitation referencing InVitro testing was moved from the Utilization Guidelines section since it is a limitation and not a frequency guideline. Statements about 86001 and 86005 being non-covered were removed from the Utilization Guidelines since these services are addressed in the body of the LCD and CPT codes have been removed from the LCD. There has been no change in coverage with this revision.	• Other (Change in LCD process per CMS CR 10901.)
01/01/2018	R10	LCD revised and published on 01/25/2018 effective for dates of service on and after 01/01/2018 to reflect the annual CPT/HCPCS code updates. For the following CPT/HCPCS codes either the short description and/or the long description was changed: 86003, 86005. Depending on which description is used in this LCD there may not be any change in how the code displays in the document. Limitation language for CPT code 86005 has been	• Revisions Due To CPT/HCPCS Code Changes

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASONS FOR CHANGE
		changed to properly reflect the CPT code descriptor. The following CPT/HCPCS code has been added to CPT Code Group 1 and ICD-10 Diagnosis Code Group 1 Paragraph and Group 2 Paragraph of the LCD: 86008. At this time 21st Century Cures Act will apply to new and revised LCDs that restrict coverage which requires comment and notice. This revision is not a restriction to the coverage determination; therefore, not all the fields included on the LCD are applicable as noted in this policy.	
08/10/2017	R9	LCD revised and published on 08/10/2017 effective for dates of service on and after 08/10/2017 to remove "(Patch Test)" language from Group 3 Paragraph. At this time 21st Century Cures Act will apply to new and revised LCDs that restrict coverage which requires comment and notice. This revision is not a restriction to the coverage determination; and, therefore not all the fields included on the LCD are applicable as noted in this policy.	• Other (Inquiry)
05/04/2017	R8	LCD revised and published on 05/04/2017 effective for dates of service on and after 05/04/2017 to add sources submitted from a reconsideration request to add ICD-10 diagnosis codes for CPT code 82785. No change has been made to the content of the policy.	• Reconsideration Request
01/01/2017	R7	LCD revised and published on 01/12/2017 effective for dates of service on and after 01/01/2017 to reflect the annual CPT/HCPCS code updates. For the following CPT/HCPCS code either the short description and/or the long description was changed. Depending on which description is used in this LCD, there may not be any change in how the code displays in the document: 95076.	• Revisions Due To CPT/HCPCS Code Changes
10/01/2015	R6	LCD revised and published on 09/08/2016 effective for dates of service on or after 10/01/2015 to add the following ICD-10 diagnosis codes to Group 3: L25.8 and L25.9.	• Other (Inquiry)
10/01/2015	R5	LCD revised on 06/09/2016 to remove an additional asterisk (*) from the ICD-10 Asterisk Explanation for Group 2.	• Typographical Error
10/01/2015	R4	LCD revised and published on 05/12/2016, effective for dates of service on or after 10/01/2015, to add the following ICD-10	• Reconsideration Request

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASONS FOR CHANGE
		codes to Group 2: J31.0, J45.20-J45.22, J45.30-J45.32, J45.40-J45.42, J45.50-J45.52, J45.990-J45.991, J45.998, L50.1, L50.6, L50.8, L50.9, and R06.02. Sources added from reconsideration request. The content of the LCD has not been changed in response to the reconsideration to revise policy language regarding specific IgE testing.	
10/01/2015	R3	LCD revised and published on 04/14/2016 effective for dates of service on or after 10/01/2015 to add the following ICD-10 code to Group 1: J31.0. The R1 Revision History Explanation incorrectly lists 'CPT/HCPCS' codes rather than 'ICD-10' codes added.	• Typographical Error • Reconsideration Request
10/01/2015	R2	Missed T63.441a-T63.444S in Group 1 ICD-10 codes.	• Typographical Error
10/01/2015	R1	LCD revised and published on 02/11/2016 to add the following CPT/HCPCS codes effective for dates of service 10/01/2015 or after: J30.2, J30.81, J30.89, J30.9, T36.0X5D, T36.0X5S, T36.1X5D, T36.1X5S, T36.4X5D, T36.4X5S, T36.8X5D, T36.8X5S, T37.0X5D, T37.0X5S, T37.8X5D, T37.8X5S, T39.015D, T39.015S, T39.1X5D, T39.1X5S, T45.0X5D, T45.0X5S, T50.905D, T50.905S, T50.995D, T50.995S, T63.421A-T63.424S, T63.431A-T63.434S, T63.441A-T63.444S, T63.451A-T454S, T63.461A-T63.464S, T63.481A-T63.484S,T63.91XD, T63.91XS, T63.92XD, T63.92XS, T63.93XD, T63.93XS, T63.94XD, T63.94XS, T78.00XA-T78.09XS, T78.2XXD, T78.2XXS, T78.3XXD, T78.3XXS, T78.49XD, T78.49XS, T80.51XD, T80.51XS, T80.52XD, T80.52XS, T80.59XD, T80.59XS, T80.61XD, T80.61XS, T80.62XD, T80.62XS, T80.69XD, T80.69XS to Group 1; T63.91XD, T63.91XS, T63.92XD, T63.92XS, T63.93XD, T63.93XS, T63.94XD, T63.94XS, T65.811D, T65.811S, T65.812D, T65.812S, T65.813D, T65.813S, T65.814D, T65.814S, T78.00XD, T78.00XS, T78.01XD, T78.01XS, T78.02XD, T78.02XS, T78.03XD, T78.03XS, T78.04XD, T78.04XS, T78.05XD, T78.05XS, T78.06XD, T78.06XS, T78.07XD, T78.07XS, T78.08XD, T78.08XS, T78.09XD, T78.09XS, T78.2XXD, T78.2XXS to Group 2; T78.00XD, T78.00XS, T78.01XD, T78.01XS, T78.02XD, T78.02XS, T78.03XD, T78.03XS, T78.04XD, T78.04XS, T78.05XD, T78.05XS, T78.06XD, T78.06XS, T78.07XD, T78.07XS, T78.08XD, T78.08XS, T78.09XD, T78.09XS to Group 4.	• Reconsideration Request

Associated Documents

Attachments

N/A

Related Local Coverage Documents

Articles

A56558 - Billing and Coding: Allergy Testing

A58750 - Response to Comments: Allergy Testing

LCDs

DL36241 - (MCD Archive Site)

Related National Coverage Documents

N/A

Public Versions

UPDATED ON	EFFECTIVE DATES	STATUS
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