Allergen Testing

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Policy Description

Allergic disease is characterized by inappropriate or exaggerated immune reactions to foreign antigens (allergens) that are generally innocuous to most people, but when introduced into a genetically-predisposed individual, elicit a hypersensitivity reaction (R. Hamilton, 2018). Hypersensitivity reactions can be classified into four types, two of which are associated with allergy, type I immediate immunoglobulin (IgE) reactions and type IV T cell mediated reactions (K.-L. Chang & J. C. Guarderas, 2018). Type I reactions involve the formation of IgE antibodies specific to the allergen. When the subject is re-exposed to that allergen, the allergen binds multiple IgE molecules, resulting in the release of an array of inflammatory mediators, including histamines, that precipitate the symptoms of allergic disease (R. Hamilton, 2018).

Allergen testing in serum is designed to detect the presence of allergen-specific IgE. A positive test for allergen-specific IgE confirms the presence of the antibody only. Actual reactivity must be determined by history or supervised challenge (Kowal & DuBuske, 2019). Several diagnostic procedures have been developed to elicit and assess hypersensitivity reactions including epicutaneous, intradermal, patch, bronchial, exercise, and ingestion challenge tests (Bernstein et al., 2008).

Related Policies

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Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual’s benefit coverage at the time of the request

1. Specific IgE in-vitro allergy testing MEETS COVERAGE CRITERIA:
   
   a. In lieu of skin testing for an INITIAL allergy screen. When in-vitro testing is ordered, the medical record must clearly document the indication and why it is being used instead of skin testing.
b. When skin testing is either contraindicated (see Policy Guidelines below for details), or when direct skin testing results are not consistent with the history of an anaphylactic or other severe reaction to an allergen and further treatment decisions would be impacted by confirmation of sensitivity, in the evaluation of:

i. individuals with asthma, or

ii. individuals with suspected allergen-induced chronic rhinitis, or

iii. individuals with suspected food allergy, or

iv. individuals with suspected insect venom allergy, or

v. individuals with suspected allergy to specific drugs

2. In-vitro specific IgE testing MEETS COVERAGE CRITERIA when:

   a. Allergens chosen for testing are based on the individual’s history, physical examination, and environment.

   b. It is limited to 20 allergen specific antibodies per year.

3. In-vitro testing for total serum IgE MEETS COVERAGE CRITERIA for:

   a. Individuals with moderate to severe asthma being considered for Xolair therapy, or

   b. Individuals suspected of allergic bronchopulmonary aspergillosis

4. Routine re-testing for allergies to the same allergens DOES NOT MEET COVERAGE CRITERIA in the absence of a new clinical presentation.

5. The Antigen Leukocyte Antibody test (ALCAT) DOES NOT MEET COVERAGE CRITERIA.

   The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of a patient’s illness.

6. In-vitro testing of allergen specific IgG or non-specific IgG, IgA, IgM, and/or IgD in the evaluation of suspected allergy DOES NOT MEET COVERAGE CRITERIA.

7. Basophil Activation flow cytometry testing (BAT) for measuring hypersensitivity to allergens DOES NOT MEET COVERAGE CRITERIA.

Policy Guidelines

Skin testing is contraindicated in the following situations:

- Patients who have certain skin conditions (for e.g. dermatographism, urticaria, cutaneous mastocytosis, atopic dermatitis, severe diffuse psoriasis)

- Patient who are taking medications that may interfere with the treatment of anaphylaxis (for e.g. Beta-blockers and Angiotensin Converting Enzyme inhibitors) or may impair skin test sensitivity (for e.g. tricyclic antidepressants, antihistamines)

- Patients who are at high risk to testing (for e.g., poorly controlled asthma, clinical history of severe reaction to minute amounts of allergen, cardiac arrhythmia, unstable angina)
- Patients who have experienced an anaphylactic event within the past one month
- Uncooperative patients (e.g., small children, individuals with mental or physical impairments)

**Scientific Background**

Allergies affect over 50 million Americans, as many as 30 percent of adults and 40 percent of children (Jackson, Howie, Akinbami, & CDC, 2013; NASEM, 2016). The incidence of allergic disease is increasing (Pawankar, Holgate, Canonica, Lockey, & Blaiss, 2013) and is estimated to result in over $17 billion in health care costs and 200,000 emergency department visits annually (Adams, Kirzinger, & Martinez, 2013).

A majority of environmental, food, and medication allergies with clinical significance are type I immunoglobulin E (IgE)-mediated allergies (Kowal & DuBuske, 2019). Diagnosis of an IgE-mediated allergy involves identification of the allergen, demonstration of IgE specific to that allergen, and confirmation that symptoms occur when the patient is exposed to the allergen. The IgE response to an allergen can be assessed using skin or serum testing. Patch testing is preferred for delayed T-cell mediated response (K.-L. Chang & J. C. Guarderas, 2018; Zug et al., 2014).

Allergic diseases, respiratory infections, and autoimmune conditions have similar clinical presentations and self-reported symptoms have a relatively low PPV (Sampson et al., 2014). Thus, laboratory allergy and immunologic testing are useful in clarifying diagnosis and guiding treatment when the frequency, duration, and sequelae of upper respiratory infections exceed the norm or when rhinosinusitis or asthma symptoms persist despite treatment (Chow et al., 2012). Allergy testing is also useful in identifying causative allergen in atopic dermatitis (eczema), contact dermatitis, urticaria, angioedema, and food or drug allergies. Knowing the causal allergen helps provide clinically relevant information for avoidance and treatment (K.-L. Chang & J. C. Guarderas, 2018).

**Skin Testing**

Skin testing is the most rapid, sensitive, and cost-effective testing modality for the detection of immunoglobulin E (IgE)-mediated disease. The procedure lasts less than an hour with minimal patient discomfort. There are several published practice parameters for allergen skin testing (Bernstein et al., 2008; K.-L. Chang & J. C. Guarderas, 2018; Kowal & DuBuske, 2019).

**Serum IgE**

IgE is one of five immunoglobulins and the one primarily involved in allergic disease. At the cellular level, the allergic response starts with “atopy”, a genetic predisposition to produce specific IgE after exposure to allergens. CD4+ helper T cells are predisposed to the “T helper type 2” response, which causes the Th2 cells to secrete large amounts of interleukins 4 and 13, which then promotes production of the allergen-specific IgE. From there, the allergen-specific IgE binds to high-affinity receptors on mast cells and basophils. At this point, if the relevant allergen is ingested in large enough amounts, the IgE molecules may cluster (cross-linking). This cross-linking causes the mast cells and basophils to release chemical and protein mediators, resulting in the characteristic allergic response (Stokes & Casale, 2019).

Immunoassays measuring both total IgE and allergen-specific IgE in serum and other bodily fluids have been developed. Specific IgE immunoassays do not require patient cooperation, are not limited in patients with skin disease, are not blocked by antihistamines, and pose no risk of adverse reactions (Bernstein et al., 2008; K.-L. Chang & J. C. Guarderas, 2018; Stokes & Casale, 2019). Total IgE is usually unrelated to IgE levels for a specific allergen but may be useful in other conditions, such as asthma (Stokes & Casale, 2019).
Other tests

Patch testing is the gold standard for identification of a contact allergen (Mowad, 2006; Rietschel, 1997). Although occlusive patch testing is the most common technique, open, prophetic (provocative), repeated insult, photopatch, and atopy patch tests are also available if special situations indicate their use (Bernstein et al., 2008).

Cellular activation assays measuring the release of histamine from basophils (Kim et al., 2016; Santos & Lack, 2016) or mast cells (Bahri et al., 2018) as diagnostic or prognostic indicators of allergy have been the subject of intense research. Basophil and eosinophilic reactivity tests have been shown to be associated with food-induced allergic responses and have been shown in current research to be modified over time during immunotherapy (Sampson et al., 2014). The basophil activation test (BAT) in particular has emerged as having superior specificity and comparable sensitivity to diagnose food allergy when compared with skin prick test and specific IgE (Santos & Shreffler, 2017). Histamine release from leukocytes of allergic persons is an excellent in vitro correlate of allergy; however, it is currently still considered a research test by the AAAAI (Bernstein et al., 2008).

BAT has the potential of being a useful tool for measuring hypersensitivity to allergens, especially for patients who are not suitable for skin testing due to skin status or prior severe reactions since it is an ex vivo, flow cytometry-based assay. BAT, for use as standard clinical practice, is currently limited by its lack of standardization in methodology as well as between systems used. A study by Depince-Berger and colleagues has proposed standardization between systems and instruments using whole blood-EDTA samples with instrumentation standardization. “BAT would strongly benefit from easy implementation [EDTA, one step stimulation/labeling, wash, full sample analysis over time parameter, B cell relative basophil count] and standardization of instrument settings on MFI targets whatever system or instrument is used (Depince-Berger, Sidi-Yahya, Jeraiby, & Lambert, 2017).” Hemmings et al note that standardization, quality assurance, and clinical validation will facilitate the transition of the BAT from research to clinical practice (Hemmings, Kwok, McKendry, & Santos, 2018).

The Antigen Leukocyte Antibody Test (ALCAT) is another test available for assessment of allergens. ALCAT measures food/immune reactions through stimulation of leukocytes. The immunological reactions to this stimulation are intended to identify sensitivities regardless of pathway as antibodies do not necessarily need to be involved. CellScienceSystems suggests individuals with a variety of disorders (such as gastrointestinal, neurological, et al) to take this test (CellScienceSystems, 2019). Although the ALCAT machine is FDA registered and there are a few papers published, results are not reproducible when subject to rigorous testing and do not correlate with clinical evidence of allergy (Beyer & Teuber, 2005; Hammond & Lieberman, 2005; Wuthrich, 2005).

Panels encompassing a large number of analytes are also offered by labs. For example, Genova Labs offers a blood test for IgG and IgE antibodies for 87 different foods. Genova also offers several variations on this test, such as “Vegetarian” (21 foods), “Spices” (24 spices), “Molds” (15 molds), and more. (Genova, 2019b). A similar test measuring IgG4 antibodies for 90 commonly consumed foods is also offered (Genova, 2019a).

Spiriplex offers a microarray-style panel for allergen testing, called “Allergenex”. This test contains many purified allergen proteins to which a patient’s blood sample can bind. This binding creates a quantifiable signal that allows the user to identify the number of IgE antibodies present, and therefore provide a picture of allergy. Spiriplex offers a test for 26 common food allergens, a test for 37 inhalant allergens, and 63 combined food and inhalant allergens (Spiriplex, 2017). AllerGenis offers a test based on microarrays as well; their “Component Resolved Diagnostic” approach divides the allergenic proteins into smaller segments called “epitopes” then measures the reactivity of IgE or IgG4 levels to these epitopes. These reactivity levels are combined into a patient allergy profile (AllerGenis, 2019).
Analytical Validity

Variables that can influence the wheal size when performing skin prick tests (SPT) include multiple operators, extract concentrations and quality, skin test devices, time of day, location on the skin, and the measuring of results (Nelson, 2001; Werther et al., 2012).

In 2006, Oppenheimer and Nelson evaluated variability and analytical validity of skin testing finding that “Overall, a significant degree of variability was reported with regard to number of skin tests performed, extract concentrations, skin test devices, interpretation and documentation of results, and quality assurance procedures. The average number of skin prick tests performed ranged from 5.09 (grasses) to 10.9 (trees), whereas the average number of intradermal tests performed ranged from 2.03 (grasses) to 5.6 (perennial). The allergen extract concentrations used for intradermal testing varied widely. Expressed as a dilution of the concentrated extracts, 20.8% use 1:100 dilutions, 10.3% use 1:500 dilutions, and 59.4% use 1:1,000 dilutions. Significant variability also occurred regarding devices and the technique with which the devices were used. Most clinicians (92.1%) used the most concentrated extract available for skin prick testing. For reporting the results of skin testing, 53.8% used a 0 to 4+ scale, and only 28.3% measured orthogonal diameters. Of those using a 0 to 4+ scale, two thirds related the results to the size of the histamine control. Quality assurance testing was reportedly performed by 61.2% of responders. However, less than 10% of responders used an objective test protocol for this purpose (Oppenheimer & Nelson, 2006).”

CLSI has evaluated the analytical validity of serum IgE measurements and found that “Clinical/diagnostic sensitivity and specificity of IgE antibody assays cannot be accurately determined due to the absence of definitive gold standard methods for defining allergic disease. Total and allergen-specific IgE analyses achieve among the highest analytical performance of any antibody assay by following consensus procedures in CLSI-ILA20-A3 (R. G. Hamilton et al., 2015).”

Knight et al “examined the qualitative concordance between SPT and sIgE as measured on the HYTEC™288 platform for 10 commonly encountered inhalant allergens” 232 subjects were included. Overall concordance between SPT and sIgE was >70% for all allergens tested. Sensitivity ranged from 25% to 95% depending on the allergen, while specificity was significantly higher for all allergens (78-97%). NPV was >85% for all allergens tested, while PPV was more variable, ranging from 22% to 88%. The authors noted that “these results are similar to findings in other studies comparing SPT with sIgE” (Knight et al., 2018).

Carlsson et al examined the inter- and intra- variability of IgE and IgE receptor expression in blood of seasonal allergic rhinitis (SAR) subjects. 32 patients with SAR were included, and FcεRI (high-affinity) and CD23 (low affinity) expression was measured. The authors found that “FcεRI expression on basophils and CD23 expression on B cells showed low intrasubject variability both in and out of the pollen season”, although there was a small seasonal difference with lower total IgE levels and FcεRI expression during the pollen season (Carlsson, Thorell, Sjolander, & Larsson-Faria, 2015).

Siroux et al explored the effect of allergen nature, route of exposure, and dose of exposure on IgE and IgG responses. 340 patients (170 with asthma, 170 without) were included, and IgE/IgG responses to 47 inhalant and food allergens were analyzed and compared between 5 French regions according to route of allergen exposure (inhaled or food). “Ubiquitous” allergens (grass, olive/ash pollen, house dust mites) did not show marked difference in specific IgE level between regions. For region-specific allergens (ragweed, birch, cypress), IgE sensitization was associated with regional pollen exposure. Airborne allergens cross-reacting with food allergens led to frequent IgG recognition. The authors concluded that “the variability in allergen-specific IgE and IgG frequencies depends on exposure, route of exposure, and overall immunogenicity of the allergen. Allergen contact by the oral route might preferentially induce IgG responses (Siroux et al., 2017).”
Clinical Validity and Utility

In 1998 Tshcopp et al compared three diagnostic tests for atopic diseases. Total serum IgE, Phadiatop, and the skin prick test (SPT) were compared for 8329 individuals. Current allergic asthma (CAA) and current allergic rhinitis (CAR) were the conditions studied. The prevalence of CAA was 1.8% and prevalence for CAR was 16.3%. The prevalence of positive tests was 29%, 23%, and 23% for Phadiatop, SPT, and IgE, respectively. The results were as follows: “To diagnose current allergic asthma (CAA) and current allergic rhinitis (CAR), the sensitivity of Phadiatop was significantly higher than that of SPT (72.5% vs 65.4%, 77.1% vs 68.4% respectively) and IgE (72.5% vs 56.9%, 77.1% vs 43.9%, respectively. The sensitivity of SPT was significantly higher (68.4% vs 43.9%) than that of IgE to diagnose CAR. When CAA and CAR were excluded, the SPT specificity was significantly higher than that of Phadiatop (77.8% vs 71.9% and 85.9% vs 80.5%, respectively): when CAR was excluded, SPT was significantly higher than 85.9% vs 81.4%). SPT had significantly the best positive predictive value for CAA (5.2% for SPT vs 4.6% for both IgE and Phadiatop) and CAR (48.7% for SPT vs 43.5% for Phadiatop and 31.6% for IgE). The three markers of atopy had roughly the same negative predictive value (NPV) for CAA, but IgE had a significantly lower NPV for CAR than SPT and Phadiatop (88.1% vs 93.3% and 94.7%, respectively). The diagnostic efficiency of SPT was significantly higher than that of Phadiatop (83.1% vs 79.9% and 77.6 vs 71.9%, respectively) to diagnose CAR and CAA. IgE and SPT had equal efficiency (77.6%), which was significantly higher than that of Phadiatop, to diagnose CAA (71.9%). The authors concluded that "SPT have the best positive predictive value and the best efficiency to diagnose respiratory atopic diseases. Furthermore, SPT give information on sensitivity to individual allergens and should therefore be used primarily by clinicians to assess respiratory allergic diseases (Tschopp et al., 1998).”

Usmani and Wilkinson (2007) performed a retrospective analysis of patients who had been prick tested to "establish whether an incomplete diagnosis would have been reached if patch testing had been omitted." The authors observed that if "investigation of allergic skin disease is undertaken by a non-dermatologist, it is unlikely that patch testing will be performed". 330 patients had been prick tested in the time period specified. 68 patients had positive reactions on prick testing, and 36 of those had positive patch tests. Of the 262 patients who had negative prick tests, 121 had positive patch tests (46.1%) of current relevance to patient history in 92 subjects (35.1%). The authors concluded that “omission of patch testing from the investigation of allergic skin disease, even when contact urticaria may be the sole suspected diagnosis, would result in the frequent missed diagnosis of contact allergy (Usman & Wilkinson, 2007).”

In 2014, a meta-analysis examined the clinical validity of SPT and IgE for food allergy. 24 studies consisting of 2831 participants were included. The results were as follows: “For cows' milk allergy, the pooled sensitivities were 88% (SPT), and 87% (IgE) and specificities were 68% and 48%. For egg, pooled sensitivities were 92% and 93% and specificities were 58% and 49% for SPT and specific-IgE. For wheat, pooled sensitivities were 73% and 83% and specificities were 73% and 43% for SPT and sIgE. For soy, pooled sensitivities were 55% and 83% and specificities were 68% and 38% for SPT and sIgE. For peanut, pooled sensitivities were 95% and 96%, and specificities were 61% and 59% for SPT and sIgE (Soares-Weiser et al., 2014).”

Klemans et al (2015) examined the diagnostic accuracy of using sIgE to peanut components to improve sensitivity and specificity of peanut allergen testing. 22 studies were included. The authors found that "sIgE to Ara h 2 [a peanut component] showed the best diagnostic accuracy of all diagnostic tests to diagnose peanut allergy. Compared to the currently used SPT and sIgE to peanut extract, sIgE to Ara h 2 was superior in diagnosing peanut allergy.” The authors also found that the worst accuracy was observed to be sIgE to Ara8 and Ara9. The authors concluded that “sIgE to Ara 2 should replace SPT and sIgE to peanut extract in daily clinical practice (Klemans et al., 2015).”

Sozmen et al (2015) examined the diagnostic accuracy of using the patch test to avoid oral food challenge (OFC). They found that in 243 children that underwent OFC to suspected food,
clinically relevant food allergies were seen in 40 (65%) children to egg and in 22 (35%) to cow's milk. The sensitivity of skin prick test for both milk and egg was 92%, specificity 91%, positive predictive value 35%, and negative predictive value of 93%. Sensitivity, specificity, positive predictive value, and negative predictive value of atopy patch test for both milk and egg were 21%, 73%, 20%, and 74%, respectively.

Santos et al (2014) studied the performance of basophil activation tests (BAT) as a diagnostic marker for peanut allergy. 43 peanut-allergic children, 36 peanut-sensitized but tolerant and 25 non–peanut-sensitized nonallergic children underwent SPT, sIgE, and BAT. The authors found that BAT in peanut-allergic children showed a peanut dose-dependent upregulation of CD63 and CD203c while there was no significant response in the other two cohorts. BAT optimal diagnostic cutoffs showed 97% accuracy, 95% positive predictive value, and 98% negative predictive value. BAT allowed reduction of required oral food challenges (OFCs) by two-thirds. BAT proved particularly useful in cases in which specialists could not accurately diagnose peanut allergy with SPT and sIgE to peanut and to Arah2. Using a 2-step diagnostic approach in which BAT was performed only after equivocal SPT or Arah2-sIgE, BAT had a major effect (97% reduction) on the number of OFCs required.

Santos et al also studied the utility of BAT to predict the severity and reactivity to peanut during OFCs. They found that of the 124 children submitted to OFCs to peanut, 52 reacted with clinical symptoms that ranged from mild oral symptoms to anaphylaxis. Severe reactions occurred in 41% of cases, and 57% reacted to 0.1 g or less of peanut protein. The ratio of the percentage of CD63(+) basophils after stimulation with peanut and after stimulation with anti-IgE (CD63 peanut/anti-IgE) was independently associated with severity, whereas the basophil allergen threshold sensitivity CD-sens (1/EC50 × 100, where EC50 = half maximal effective concentration) value was independently associated with the threshold of allergic reactions to peanut during OFCs. Patients with CD63 peanut/anti-IgE levels of 1.3 or greater had an increased risk of severe reactions (relative risk, 3.4). Patients with a CD-sens value of 84 or greater had an increased risk of reacting to 0.1 g or less of peanut protein (relative risk, 1.9). Basophil reactivity is associated with severity, and basophil sensitivity is associated with the threshold of allergic reactions to peanut. CD63 peanut/anti-IgE and CD-sens values can be used to estimate the severity and threshold of allergic reactions during OFCs (Santos et al., 2015).

Davila et al explored the association between total IgE and severity of asthma. 383 patients were included (129 mild, 82 moderate, and 172 severe). Serum IgE levels were noted to vary “markedly” (147% coefficient of variation). The authors did not find an association between total IgE and forced expiratory volume in 1 second (FEV1) or asthma severity; although, the severe subgroup had a higher percentage of patients with >400 IU/mL. Independent predictors of higher IgE were found to be younger age, sensitization to ≥ 2 allergens, male gender, and family history of asthma. The authors concluded that “we did not find a significant association between serum total IgE levels and asthma severity or airflow limitation, except for a higher percentage of patients with IgE > 400 IU/mL in the severe subgroup” (Davila, Valero, Entrenas, Valveny, & Herraez, 2015).

Tannert et al investigated the relevance of a positive skin test and positive IgE test to penicillin allergy. 25 patients with positive results were given penicillin, and another 19 patients deemed allergic were included. However, only 9 of the 25 patients given penicillin were challenge-positive. Positive results from each test alone did not predict allergy. The authors concluded that “the best predictor for a clinically significant (IgE-mediated) penicillin allergy is a combination of a positive case history with simultaneous positive ST result and s-IgE or a positive challenge result (Tannert, Mortz, Skov, & Bindslev-Jensen, 2017).”

Guidelines and Recommendations

The American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) published practice
parameters in 2008 for allergy testing (Bernstein et al., 2008) which noted that “For individual patients, the choice of test allergens is guided by the history and physical examination and the physician’s knowledge, training, and experience.” The guidelines recommended that “Specific IgE immunoassays may be preferable to skin testing under special clinical conditions, such as widespread skin disease, patients receiving skin test suppressive therapy, uncooperative patients, or when the history suggests an unusually greater risk of anaphylaxis from skin testing.” They also note that for both skin testing and in-vitro specific IgE testing, “the allergens selected ... should be determined based on the patient’s age, history, environment and living conditions (eg, region of the country), occupation, and activities.” Also, “The best indicators in the selection of appropriate pollens for clinical use are extensive prevalence in the air and concurrent allergy symptoms during annually recurrent seasons when such pollens are expected to be present in the ambient air.”

They AAAAI and ACAAI guidelines also state, “As is the case with skin tests, a direct correlation cannot be assumed between the presence of specific IgE (sIgE) antibodies and clinical disease.” Additionally, “sensitivity and the positive predictive value of both prick/puncture and specific IgE tests generally tend to be higher among pollens, stable anaphylactogenic foods, house dust mite, certain epidermals, and fungi compared with venoms, drugs, and chemicals.”

With regards to total IgE testing, these groups indicate, “Measurements of total serum IgE concentration are of modest clinical value when used as a screen for allergic disease or for predicting the risk of allergic disease.”

The AAAAI and ACAAI also note that “IgG and IgG subclass antibody tests for food allergy do not have clinical relevance, are not validated, lack sufficient quality control, and should not be performed.”

In regard to basophil activation assays they state, “Histamine and leukotriene release measurements from human basophils after incubation with allergen are valuable research tools for in vitro investigations of allergy (Bernstein et al., 2008).”

Their practice parameter on drug allergy also states that “The basophil activation test is a recently described method of evaluating expression of CD63 on basophils after stimulation with an allergen. There are limited data using this method to evaluate patients with possible allergies to β-lactam antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs)” (Boyce et al., 2010).

They also recommend, “Because anaphylactic reactions cannot be distinguished from anaphylactoid, nonimmune occurrences, it has been recommended that plasma histamine, tryptase, and specific IgEs (if available) may be ordered at the time of reaction and skin tests be performed later” (Boyce et al., 2010).

In their 2014 practice parameter on food allergy (Sampson et al., 2014) they acknowledge: "Basophil and eosinophilic reactivity tests have been shown to be associated with food-induced allergic responses and have been shown in current research to be modified over time during immunotherapy.”

Their 2014 practice parameter on rhinosinusitis also recommends to "Perform an evaluation for specific IgE antibodies to airborne allergens in patients with RARS or CRS.”

In their 2015 practice parameter on anaphylaxis (Lieberman et al., 2015), they recommend “Skin tests and/or in vitro tests for specific IgE and challenge tests might be appropriate to help define the cause of the anaphylaxis.”

They also recommend against routinely obtaining total serum IgE levels for the diagnosis of food allergy, however because of the low PPV of self-reported symptoms and lack of pathognomonic signs on physical examination, they recommend that the accurate diagnosis of IgE-mediated food allergy should be aided by laboratory allergy testing, including skin prick and/or serum IgE testing. The clinician should use specific IgE tests (skin prick tests, serum tests, or both) to foods as diagnostic tools; however, testing should be focused on foods suspected of provoking the reaction, and test results alone should not be considered diagnostic of food allergy.
In a ChoosingWisely (CW) report, the AAAAI recommends against performing “unproven diagnostic tests, such as immunoglobulin G (IgG) testing or an indiscriminate battery of immunoglobulin E (IgE) tests, in the evaluation of allergy” (AAAAI, 2012).

In another CW report, the AAAAI recommends against routine diagnostic testing in patients with chronic urticaria, stating that “skin or serum-specific IgE testing for inhalants or foods is not indicated, unless there is a clear history implicating an allergen as a provoking or perpetuating factor for urticaria” (AAAAI, 2012)

National Institute of Allergy and Infectious Diseases (NIAID) convened an expert panel to review current information and to make recommendations related to the evaluation of food allergy (FA), including the use of specific IgE (sIgE) testing (Boyce et al., 2010). With regards to allergen-specific serum IgE determination, NIAID recommended that “sIgE tests for identifying foods that potentially provoke IgE-mediated food-induced allergic reactions, but alone these tests are not diagnostic of FA.” It stated that “sIgE testing and skin prick testing both depend on the presence of allergen-specific antibodies. Because the former test measures sIgE in the serum and the latter reflects IgE bound to cutaneous mast cells, their results may not always correlate. Serum testing can be especially useful when SPTs cannot be done (for example, due to extensive dermatitis or dermatographism), or when antihistamines cannot be discontinued.” The NIAID also recommended not using the combination of skin prick test (SPT), sIgE tests and atopy patch test (ATP) for the routine diagnosis of food allergy.

Additionally, the NIAID notes that “the routine use of measuring total serum IgE should not be used to make a diagnosis of FA.”

“Non-standardized tests” such as basophil histamine release/activation, lymphocyte stimulation, allergen-specific IgG, cytotoxicity assays, and mediator release assays should not be used in the routine evaluation of FA, according to the NIAID guidelines (Boyce et al., 2010).

American Academy of Pediatrics (AAP)

In 2012, AAP released a clinical report on allergy testing in childhood. It stated that “Both serum sIgE tests and SPT are sensitive and have similar diagnostic properties.” The AAP summary included the following:

- “Treatment decisions for infants and children with allergy should be made on the basis of history and, when appropriate, identified through directed serum sIgE or SPT testing. Newer in vitro sIgE tests have supplanted radioallergosorbent tests.”
- “Positive sIgE test results indicate sensitization but are not equivalent to clinical allergy. Large panels of indiscriminately performed screening tests may, therefore, provide misleading information.”
- “Increasingly higher levels of sIgE (higher concentrations on serum tests or SPT wheal size) generally correlate with an increased risk of clinical allergy.”
- “Use of a multiallergen serum test can be helpful for screening for atopic disease if there is a clinical suspicion. If positive, allergen-specific testing may be considered.
- “Tests for allergen-specific IgG antibodies are not helpful for diagnosing allergies (AAP, 2012).”

Xolair (FDA, 2007)

The availability of Xolair for treatment of allergic asthma also has implications for allergy testing. According to the package insert, “Xolair is indicated for adults and adolescents (12 years of age and above) with moderate to severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids. Determine doses (mg) and dosing frequency by serum total IgE level (IU/mL), measured before the start of treatment, and body weight (kg).” The
prescribing information also notes that “Total IgE levels are elevated during treatment and remain elevated for up to one year after the discontinuation of treatment. Therefore, re-testing of IgE levels during Xolair treatment cannot be used as a guide for dose determination (FDA, 2007).”

**Medicare Regulations and Coding Guidelines (CMS, 2017)**

- “Evaluation and management codes reported with allergy testing or allergy immunotherapy are appropriate only if a significant, separately identifiable service is administered.”
- “Allergy testing is not performed on the same day as allergy immunotherapy in standard medical practice. These codes should, therefore, not be reported together. Additionally, the testing becomes an integral part to rapid desensitization kits (CPT code 95180) and would therefore not be reported separately.”

**International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis**

The authors reviewed the existing evidence behind various aspects of evaluation and diagnosis of the AR patient, and developed the following recommendations (Wise et al., 2018):

- “History taking is essential in the diagnosis of AR. Physical examination is recommended in the diagnosis of AR, and when combined with patient history, it increases diagnostic accuracy and excludes alternative causes. Making a presumptive diagnosis of AR on history (ideally combined with physical examination) is reasonable and would not delay treatment initiation. Confirmation with diagnostic testing is required for progression to AIT, or desirable with inadequate response to initial treatment.”
- “Skin-prick testing (SPT) is recommended for evaluation of allergen sensitivities in appropriately selected patients. Regular use of the same SPT device will allow clinicians to familiarize themselves with it and interpretation of results may therefore be more consistent. The use of standardized allergen extracts can further improve consistency of interpretation. Patients can benefit from identification of their specific sensitivities. SPT is a quick and relatively comfortable way to test several antigens with accuracy similar to other available methods of testing.”
- “Total IgE assessment is an option to assess atopic status. However, the evidence does not support a routine use.”
- “Serum sIgE testing may be used in the evaluation of AR. Using standardized allergens and rigorous proficiency testing on the part of laboratories may improve accuracy. Patients can benefit from identification of their specific sensitivities. Further, in some patients who cannot undergo skin testing, sIgE testing is a safe and effective alternative.”
- “The average pooled sensitivity of SPT is 85% which is often slightly higher than that of serum sIgE testing; however, this is not universally true depending on the allergen tested and the characteristics of the patient. Based on accuracy, convenience, cost, and promptness of results, SPT is often chosen as the first line diagnostic instrument to detect sensitivity to aeroallergens. Intradermal testing can be used as a second line test to exclude reactivity if the clinical suspicion is very high. In cases where dermatographism is present and/or patients are unable to wean off medications that affect skin testing, sIgE testing may be a better choice.”
- “BAT is an option for AR diagnosis when first-line tests are inconclusive or for measuring response to AIT. Basophil sensitivity may be a useful marker for following response to immunotherapy.”
- “Skin testing is not appropriate in all patients. Absolute or relative contraindications to SPT include uncontrolled or severe asthma, severe or unstable cardiovascular disease, concurrent beta-blocker therapy, and pregnancy. Certain medications and skin conditions may interfere with skin testing.”
- The list of medications that may interfere with skin testing are as follows: H1, H2, or topical antihistamines, anti-IgE (omalizumab), leukotriene receptor antagonists, tricyclic
antidepressants, selective serotonin reuptake inhibitors (SSRIs), benzodiazepines, topical (cutaneous) or systemic corticosteroids, and topical calcineurin inhibitors (ie. tacrolimus, picrolimus).

The guideline states that because of the “lack of published studies on this topic, an Aggregate Grade of Evidence and evidence based recommendation cannot be provided.” However, they mention dermatitis and dermatographism as two skin conditions that may interfere with skin testing. (Wise et al., 2018)

The National Academies of Science, Engineering and Medicine

The National Academies of Science, Engineering and Medicine convened an expert committee to review the science and management practices of food allergy. Overall, they found that:

- “Currently, no simple diagnostic tests exist for food allergy.”
- “Food allergy evaluation procedures include a medical history and physical examination, and also may include food-specific skin prick test, food-specific serum immunoglobulin E test, diagnostic food elimination diet, and oral food challenge (OFC). Selection of the specific tests needs to be individualized based on the medical history of each patient.”
- “The BAT shows promising preliminary data, the potential utility is recognized and will require additional validation and standardization. “Guidelines suggest not using the BAT clinically on the grounds that it is nonstandardized, but recognize its use as a research tool (NASEM, 2016).”

American Academy of Family Physicians (AAFP, 2018)

AAFP’s recommendations for practice state: “Allergy and immunologic testing can help clarify the diagnosis and guide treatment. Immediate immunoglobulin E (IgE) and delayed T cell-mediated reactions are the main types of allergic responses. The allergens suspected in an immediate IgE-mediated response are identified through serum IgE-specific antibody or skin testing. For patients with an inhalant allergy, skin or IgE-specific antibody testing is preferred. In patients with food allergies, eliminating the suspected allergenic food from the diet is the initial treatment. If this is ineffective, IgE-specific antibody or skin testing can exclude allergens. An oral food challenge should be performed to confirm the diagnosis. Patients with an anaphylactic reaction to an insect sting should undergo IgE-specific antibody or skin testing. Skin testing for penicillin has a high negative predictive value and can help when penicillin administration is indicated and there are limited alternatives. Testing for other drug allergies has less well-determined sensitivity and specificity, but can guide the diagnosis. Patch testing can help identify the allergen responsible for contact dermatitis (K. L. Chang & J. C. Guarderas, 2018).”

ChoosingWisely Canada (2016)

ChoosingWisely Canada recommends that food allergen testing should include consideration of medical history. They also state that “testing should be selected based on the history and should not include large screening panels” (ChoosingWisely, 2016).

European Academy of Allergy and Clinical Immunology (EAACI, 2017)

The EAACI published guidelines on “Biomarkers for monitoring the clinical efficacy of allergen Immunotherapy (AIT)”. In it, they concluded that “to date, there are no validated and generally accepted candidate biomarkers that are predictive or indicative of the clinical response to AIT”. However, they did note sIgE/tIgE ratio and IgE-FAB as candidate biomarkers for future research (Shamji et al., 2017).

National Institute for Health and Care Excellence (NICE)

NICE published a guideline on asthma, recommending against use of serum total or specific IgE for diagnosing asthma. Specific IgE should only be used to identify triggers to asthma (NICE, 2017).

NICE also released a statement on multiplex allergen testing, particularly “ImmunoCAP ISAC 112 and Microtest”. Although they acknowledge the test’s promise, they state that there is
“insufficient evidence to recommend the routine adoption of multiplex allergen testing, ImmunoCAP ISAC 112 or Microtest, to help diagnose allergy and predict the risk of an allergic reaction in people with allergy that is difficult to diagnose, when used with standard clinical assessment (NICE, 2016).”

**European Academy of Allergy and Clinical Immunology (EAACI, 2015)**

The EAACI released a position statement on the BAT. In it, they concluded that “Basophil activation test has been established as a routine diagnostic test with standardized allergen preparations in a number of service laboratories... An important next step is the standardization and automation of analysis of BAT. Once that is achieved, it will be possible to do large multicenter trials to characterize the diagnostic performance of BAT and broaden its use as a clinical tool (Hoffmann et al., 2015).”

**State and Federal Regulations, as applicable**

The FDA has cleared 43 assays for total IgE, and 62 assays for allergen specific IgE as of August 9, 2019 (FDA, 2019). Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA ‘88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

**Applicable CPT/HCPCS Procedure Codes**

<table>
<thead>
<tr>
<th>Code Number</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>82784</td>
<td>Gammaglobulin (immunoglobulin); IgA, IgD, IgG, IgM, each</td>
</tr>
<tr>
<td>82785</td>
<td>Gammaglobulin; IgE</td>
</tr>
<tr>
<td>82787</td>
<td>Immunoglobulin subclasses (eg: IgG 1, 2, 3, or 4) each</td>
</tr>
<tr>
<td>83516</td>
<td>Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; qualitative or semiquantitative, multiple step method (ALCAT)</td>
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<tr>
<td>83520</td>
<td>Immunoassay, analyte quantitative; not otherwise specified [anti-IgE receptor antibody testing]</td>
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<tr>
<td>86001</td>
<td>Allergen specific IgG quantitative or semi-quantitative, each allergen</td>
</tr>
<tr>
<td>86003</td>
<td>Allergen specific IgE quantitative or semi-quantitative, each allergen</td>
</tr>
<tr>
<td>86005</td>
<td>Qualitative, multi-allergen screen (dipstick, paddle or disk)</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
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<tr>
<td>--------</td>
<td>-----------------------------------------------------------------------------</td>
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<tr>
<td>86008</td>
<td>Allergen specific IgE; quantitative or semiquantitative, recombinant or purified component, each</td>
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<tr>
<td>88184</td>
<td>Flow cytometry, cell surface, cytoplasmic, or nuclear marker, technical component only; first marker <a href="BAT">anti-IgE receptor antibody testing</a></td>
</tr>
</tbody>
</table>


*Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.*

**Evidence-based Scientific References**

AllerGenis. (2019). PIONEERING PRECISION DIAGNOSTICS FOR FOOD ALLERGY.


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