

Food Allergy Testing



Nicole A. LaHood, MD^a, Sarita U. Patil, MD^{b,c,d,*}

KEYWORDS

- Food allergy • Immunoglobulin E • Skin testing • Oral food challenge
- Component testing

KEY POINTS

- Serum-specific immunoglobulin E (IgE) measurement can be helpful in the diagnosis of IgE-mediated food allergies, and clinically useful values vary by individual foods.
- Skin prick testing using whole-food allergen extracts provides an in vivo surrogate of IgE sensitization, and clinically useful values have been defined for various foods.
- For particular foods, component-specific IgE testing to particular protein components can provide additional diagnostic discrimination.

INTRODUCTION

Food allergy is “an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food.”¹ The gold standard for diagnosis of food allergy is an oral food challenge (OFC) to the culprit allergen that elicits reproducible clinical symptoms. Whether open, blinded, or placebo controlled, OFCs can occur in the outpatient setting under close clinical observation by trained providers who are equipped to manage potential reactions, including anaphylaxis. In an OFC, the potential food is ingested in predefined, incrementally increasing doses until a full serving size is ingested.² Objective symptoms, such as hives, swelling, vomiting, and wheezing, confirm an immunoglobulin E (IgE)-mediated allergy.

OFCs are resource intensive, however, and place patients at risk for an allergic reaction.^{1,3,4} Although most individuals with IgE-mediated food allergies also have sensitization, or detectable levels of IgE, allergen-specific IgE is not sufficient for a diagnosis of food allergy. Therefore, the ability to risk stratify patients prior to OFC

Disclosure Statement: Dr. Patil is funded by NIH grant NIAID K23AI121491, and Dr. LaHood is funded by NIH grant NHLBI T32 HL116275.

^a Allergy and Immunology, Department of Medicine, Division of Rheumatology, Allergy, and Immunology, Massachusetts General Hospital, 55 Fruit Street, Cox 201, Boston, MA, USA;

^b Department of Medicine, Division of Rheumatology, Allergy, and Immunology, Massachusetts General Hospital, 55 Fruit Street, Cox 201, Boston, MA, USA; ^c Food Allergy Center, Massachusetts General Hospital for Children, Boston, MA, USA; ^d Harvard Medical School, Boston, MA, USA

* Corresponding author. 55 Fruit Street, Cox 201, Boston, MA 02114.

E-mail address: sarita.patil@mgh.harvard.edu

Clin Lab Med 39 (2019) 625–642

<https://doi.org/10.1016/j.cll.2019.07.009>

0272-2712/19/© 2019 Elsevier Inc. All rights reserved.

labmed.theclinics.com

is important for patient safety. This article focuses on the various commercially available methods of testing for sensitization to aid clinicians to risk stratify and diagnose patients with IgE-mediated food allergies.

SKIN TESTING

Since the 1950s, skin prick testing (SPT) has been the preferred cutaneous method for food allergy testing.^{5,6} Epicutaneous SPT technique involves application of a small amount of allergen extract and subsequent or simultaneous bloodless prick of the skin, depending on the device used. Exposure of relevant antigens to cutaneous mast cells cross-links their surface IgE and induces degranulation. The resulting local wheal and flare reaction can be measured as a surrogate of food sensitization. Local application of histamine serves as a positive control and normal saline serves as a negative control.

SPT can be performed with a variety of tools, including hypodermic or solid bore needles, or more modern devices, such as plastic or metal lancets with or without bifurcated tips and multiple head devices that simultaneously deliver up to 10 pricks. Comparison of modern skin prick devices have not found significant advantages of one over another.^{5,7–9} Due to interdevice variability, however, in wheal size, technique, and acceptable control concentrations, providers should select one device for use and ensure proper training of technicians for reproducible results.⁵ Testing reagents include both fresh in-office preparations and commercially available extracts, and there is no clear consensus on any individual reagent's superiority.^{10–14} Although intradermal testing is used in evaluation of environmental allergies, intradermal testing to foods may increase false-positive results as well as the incidence of serious, sometimes fatal, adverse reactions and, therefore, is contraindicated.^{3,15}

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for SPT vary based on age, study design, prevalence of food allergy in the study population, SPT cutoffs, and testing techniques. Despite this variability, among study populations presenting to allergy clinics with concern for food allergy or with a clinical history consistent with IgE-mediated food allergy, the utility of SPT at various cutoffs for different age ranges has been described in several publications, as outlined in **Table 1**. Compared with the general population, these values have a higher PPV because the pretest probability is higher. Generally, a larger SPT wheal size increases specificity but decreases sensitivity across all ages. There is a higher frequency of non-IgE-mediated milk reactions in children under 2 years of age, and this should be taken into consideration when a child has a history of reaction with negative SPT to cow's milk.¹⁶

SERUM IMMUNOGLOBULIN E TESTING

Reliable and widely available in vitro tests for specific IgE (sIGE) to allergens were introduced in the 1990s. The first commercially available test, radioallergosorbent test, has been largely replaced by sIGE immunoenzymatic assays, such as ImmunoCAP (Phadia, ThermoFisher Scientific, Uppsala, Sweden) testing, in which serum antibodies bind to allergen and are quantified with enzyme-labelled anti-IgE antibody. For the purpose of this article, only studies that use immunoenzymatic testing most commonly used are discussed.

There are many factors modulating the interpretation of sIGE allergy test results to foods, because a positive value is not always predictive of clinical food allergy. Pretest probability, therefore, greatly influences test interpretation. For example, a clinical

Table 1
Skin prick testing sensitivity, specificity, positive predictive value, and negative predictive value at various cutoffs

Skin Prick Testing	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Hen's egg (Challenge to raw or partially cooked egg)	Age <18 ^{16-18,20,23,24} • 3 mm = 73%–98% • 5 mm = 74% • 6 mm = 68%–95% • 7 mm = 48%–52% • 9 mm = 22% Age <14 ^{19,25} • 3 mm = 93% Age <2 ^{20-22,26} • 3 mm = 79%–97% • 4 mm = 46% • 5 mm = 62% • ^a 3 mm = 66.6%–78% • ^a 4 mm = 26.4% • ^a 5 mm = 4.2%	Age <18 ^{16-18,20,23,24} • 3 mm = 42.9%–72% • 5 mm = 69.6%–92% • 6 mm = 70%–92% • 7 = 92.9%–100% • 9 mm = 98.2% Age <14 ^{19,25} • 3 mm = 54%–59% Age <2 ^{20-22,26} • 3 mm = 71%–75% • 4 mm = 93% • 5 mm = 100% • 7 mm = 100% • ^a 3 mm = 88%–88.6% • ^a 4 mm = 94.3% • ^a 5 mm = 100%	Age <18 ^{17,18,20,23,24} • 3 mm = 61%–93% • 5 mm = 81.3% • 6 mm = 95%–100% • 7 mm = 92.3%–100% • 9 mm = 95.6% Age <14 ^{19,25} • 3 mm = 79%–80% Age <2 ^{20-22,26} • 3 mm = 93% • 4 mm = 94%–95% • 5 mm = 100% • ^a 3 mm = 92%–96% • ^a 4 mm = 90.5% • ^a 5 mm = 100%	Age <18 ^{17,18,20,23,24} • 3 mm = 50%–90% • 5 mm = 60.0% • 6 mm = 35%–95% • 7 mm = 29%–50% • 9 mm = 41.3% Age <14 ^{19,25} • 3 mm = 81%–83% Age <2 • 3 mm = 86% • 4 mm = 38.4%–44% • ^a 3 mm = 50%–56.3% • ^a 5 mm = 33.6%–42%
Hen's egg (Challenge to baked egg)	Age <18 ²⁸ • 3 mm = 100% • 4 mm = 96.2% • 11 mm = 69.2% • 25 mm = 0% Age <2 ²⁶ • 11 mm = 0%	Age <18 ²⁸ • 3 mm = 16.5% • 4 mm = 17.3% • 11 mm = 55.6% • 25 mm = 95.5% Age <2 ²⁶ • SPT 11 mm = 99%	Age <18 ^{27,28} • 3 mm = 19% • 4 mm = 18.5% • 11 mm = 23.4% • 15 mm = 60% • 25 mm = 0% Age <2 ²⁶ • 11 mm = 82%	Age <18 ²⁸ • 3 mm = 100% • 4 mm = 95.8% • 11 mm = 90.2% • 25 mm = 83% Age <2 ²⁶ • 11 mm = 82%
Peanut	Age <18 ^{16-18,20,29,30} • 3 mm = 78.9%–100% • 6 mm = 47.4%–78% • 8 mm = 31.6%–51% Age <2 ^{20,26} • 3 mm = 100% • 4 mm = 93% • 8 mm = 54%	Age <18 ^{16-18,29,30} • 3 mm = 29%–98.1% • 6 mm = 94%–99.8% • 8 mm = 99.9%–100% Age <2 ^{20,26} • 3 mm = 67% • 4 mm = 100% • 8 mm = 98%	Age <18 ^{17,18,20,29,30} • 3 mm = 28.1%–99.5% • 6 mm = 81.8%–98% • 8 mm = 85.7%–100% Age <2 ^{20,26} • 3 mm = 94% • 4 mm = 100% • 8 mm = 96%	Age <18 ^{16-18,20,29,30} • 3 mm = 75%–100% • 6 mm = 59%–98.9% • 8 mm = 40%–98.5% Age <2 ^{20,26} • 3 mm = 100% • 4 mm = 75% • 8 mm = 80%

(continued on next page)

Table 1
(continued)

Skin Prick Testing	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Cow's milk Challenge to raw milk	Age <18 ^{16-18,20} • 3 mm = 74%–96% • 6 mm = 49% • 8 mm = 30% Age <14 ^{19,25} • 3 mm = 85% Age <2 ²⁰ • 3 mm = 58% • 6 = 20% Age <1 ³¹ • 3 mm = 72%	Age <18 ^{16-18,20} • 3 mm = 51%–89% • 6 mm = 95% • 8 mm = 100% Age <14 ^{19,25} • 3 mm = 70%–75% Age <2 ²⁰ • 3 mm = 91% • 6 mm = 100% Age <1 ³¹ • 3 mm = 62%	Age <18 ^{17,18,20} • 3 mm = 50%–75% • 6 mm = 91% • 8 mm = 100% Age <14 ^{19,25} • 3 mm = 73%–76% Age <2 ²⁰ • 3 mm = 79% • 6 mm = 90%–100% Age <1 ³¹ • 3 mm = 60%	Age <18 ^{17,18,20} • 3 mm = 77%–97% • 6 mm = 64% • 8 mm = 58% Age <14 ^{19,25} • 3 mm = 83% Age <2 ²⁰ • 3 mm = 78% • 6 mm = 68% Age <1 ³¹ • 3 mm = 73%
Cow's milk (Challenge to baked milk)	Age <18 ³² • 3 mm = 100% • 7 mm = 100% • 10 mm = 66.7% • 12 mm = 66.7% • 15 mm = 50% • 20 mm = 33.3%	Age <18 ³² • 3 mm = 6.9% • 7 mm = 17.2% • 10 mm = 41.4% • 12 mm = 69% • 15 mm = 86.2% • 20 mm = 96.6%	Age <18 ³² • 3 mm = 18.2% • 7 mm = 20% • 10 mm = 19% • 12 mm = 30.8% • 15 mm = 42.9% • 20 mm = 66.7%	Age <18 ³² • 3 mm = 100% • 7 mm = 100% • 10 mm = 85.7% • 12 mm = 90.9% • 15 mm = 89.3% • 20 mm = 87.5%
Soy	Age <18 ^{17,18} • 3 mm = 76%–100% Age <14 ^{19,25} • 3 mm = 21%–29%	Age <18 ^{17,18} • 3 mm = 47%–72% Age <14 ^{19,25} • 3 mm = 85%–88%	Age <18 ^{17,18} • 3 mm = 30%–35% Age <14 ^{19,25} • 3 mm = 29%–33%	Age <18 ^{17,18} • 3 mm = 84%–100% Age <14 ^{19,25} • 3 mm = 82%–83%
Wheat	Age <18 ^{17,18} • 3 mm = 75%–90% Age <14 ^{19,25} • 3 mm = 65%–75%	Age <18 ^{17,18} • 3 mm = 51%–97% Age <14 ^{19,25} • 3 mm = 64%–77%	Age <18 ^{17,18} • 3 mm = 35%–75% Age <14 ^{19,25} • 3 mm = 49%–52%	Age <18 ^{17,18} • 3 mm = 94%–97% Age <14 ^{19,25} • 3 mm = 85%
Fish	Age <18 ^{17,18} • 3 mm = 90%–100%	Age <18 ^{17,18} • 3 mm = 57%	Age <18 ^{17,18} • SPT 3 mm = 25%–77%	Age <18 ^{17,18} • 3 mm = 80%–100%
Sesame	Age <2 ²⁶ • 8 mm = 48%	Age <2 ²⁶ • 8 mm = 99%	Age <2 ²⁶ • 8 mm = 95%	Age <2 ²⁶ • 8 mm = 82%

^a SPT using egg yolk extract only. Age in years.

history of immediate hypersensitivity, young age, and relative prevalence increases pretest probability, whereas atopic dermatitis and concomitant inhalant allergies decrease pretest probability.³³ These factors can also vary based on geographic region and, therefore, should be taken into consideration when sending in vitro allergy testing.^{33,34}

The sensitivity, specificity, PPV, and NPV of various sIgE cutoffs to predict positive OFC have been described in the literature (**Table 2**) and vary by individual foods. For instance, compared with peanut and milk, soy sIgE and wheat sIgE were not found as reliably correlative to clinical symptoms.^{35,36} The performance of sIgE also may vary by the degree of clinical sensitivity. A subset of patients with milk and egg sensitivity may be tolerant of baked products. SPT and sIgE cutoffs, however, have less utility in evaluation of individuals who may tolerate baked milk and egg as opposed to identification of those with sensitivity to all forms of milk and egg.²⁷ Despite these caveats, used correctly in conjunction with SPT when possible, serum IgE testing can be a useful tool to detect clinically relevant sensitization to foods and identify high-risk individuals.

Although meat allergy is rare, alpha-gal hypersensitivity syndrome, described in 2009, occurs in individuals with tick exposure, classically to the lone star tick (*Amblyomma americanum*), resulting in sensitization to a mammalian oligosaccharide epitope, which is present in mammalian meats. Unlike most IgE-mediated reactions, clinical manifestation of alpha-gal allergy is delayed 3 hours to 6 hours after consumption of mammalian meat, and reactions range from urticaria and angioedema to life-threatening anaphylaxis with known cross-reactivity to gelatin and medications like cetuximab.^{37,38} Testing for alpha-gal IgE is commercially available, and the value above which there is a 95% probability of meat allergy is 5.5 kilounits of allergen-specific IgE per liter (kU_A/L) and/or an alpha-gal IgE to total IgE ratio of 2.12%.³⁹

Foods contain complex mixtures of allergenic proteins. Component testing allows assessment of sIgE to individual allergenic proteins within a food. In particular foods, studies have shown that certain protein components are linked to increased severity in clinical allergy and can indicate a higher risk of reaction to OFC.^{42,43,45–53} This allows practitioners to better risk stratify whole-allergen-sensitized patients and identify those at a higher risk of severe reaction versus those who are pollen cross-sensitized, with lower risk of systemic reactions. The protein fractionation and clinical relevance of major allergens are outlined in **Table 3**.

Sensitization to certain protein components and their clinical relevance can vary by geographic region. For example, peanut sensitization in the United States occurs earlier in life and children are more likely to be sensitized to high-risk protein components like Ara h 1, Ara h 2 or Ara h 3 compared with children in other parts of the world.³⁴

Pollen-food syndrome, also known as oral allergy syndrome, is the most common form of food allergy in adults, in which ingestion of certain foods, such as fresh fruits, vegetables, and nuts, leads to immediate-onset oropharyngeal symptoms. The most common cross-reactive allergens are birch, ragweed, mugwort, and grasses. Although pollen-food syndrome usually is indicative of mild limited reactions in US adults, in Mediterranean regions, certain pollen cross-reactive lipid transfer proteins have been associated with severe systemic reactions and anaphylaxis.⁵⁴

More recently, component testing has been especially helpful in identifying pollen cross-reactive components to peanut and tree nut, notably hazelnut. The sensitivity, specificity, PPV, and NPV for various cutoffs for peanut and hazelnut are outlined in **Table 4**.

Table 2

Serum-specific immunoglobulin E sensitivity, specificity, positive predictive value, and negative predictive value at various cutoffs

Specific Immunoglobulin E Testing (ImmunoCAP)	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Hen's egg white IgE (kUA/L) (Challenge to raw or partially cooked egg)	Age <18 ^{18,23,24,35,36} • ^a0.35 = 97%–98% • 0.35 = 86.7% • 1.5 = 52.2% • ^a3.4 = 82% • ^a6 = 64% • ^a7 = 61% • 7 = 48.2% • 25 = 4.4% Age <14 ²⁵ • 0.35 = 96% Age <2 ^{21,26} • 0.35 = 91% • 1.7 = 48%	Age <18 ^{18,23,24,35,36} • ^a0.35 = 45%–51% • 0.35 = 39.6% • 1.5 = 90.6% • ^a3.4 = 84% • ^a6 = 90% • ^a7 = 95% • 7 = 100% • 25 = 100% Age <14 ²⁵ • 0.35 = 48% Age <2 ^{21,26} • 0.35 = 77% • 1.7 = 98%	Age <18 ^{18,20,23,24,35,36} • ^a0.35 = 80%–84% • 0.35 = 70.9% • 1.5 = 90.4% • ^a3.4 = 94% • ^a6 = 95%–96% • ^a7 = 98% • 7 = 100% • 25 = 100% Age <14 ²⁵ • 0.35 = 79% Age <2 ^{20,21,26} • 0.35 = 94%–95% • 1.7 = 95%	Age <18 ^{18,23,24,35,36} • ^a0.35 = 88%–89% • 0.35 = 63.6% • 1.5 = 52.7% • ^a3.4 = 62% • ^a6 = 39% • ^a7 = 38% • 7 = 38% • 25 = 38.1% Age <14 ²⁵ • 0.35 = 85% Age <2 ^{21,26} • 0.35 = 68% • 1.7 = 47%
Hen's egg white IgE (kUA/L) (Challenge to baked egg)	Age <19 ^{28,40} • 0.35 = 92.6% • 2.5 = 87% • 5 = 56% • 6 = 51.9% • 9.65 = 37% • 10 = 20% Age <2 ²⁶ • 50 = 9%	Age <19 ^{28,40} • 0.35 = 19% • 2.5 = 48% • 5 = 69% • 6 = 85.8% • 9.65 = 95% • 10 = 94% Age <2 ²⁶ • 50 = 100%	Age <19 ^{28,40} • 0.35 = 18% • 2.5 = 44% • 5 = 46% • 6 = 41.2% • 9.65 = 58.8% • 10 = 60% Age <2 ²⁶ • 50 = 95%	Age <19 ^{28,40} • 0.35 = 93.1% • 2.5 = 89% • 5 = 77% • 6 = 90.3% • 9.65 = 88.7% • 10 = 71% Age <2 ²⁶ • 50 = 85%

Cow's milk IgE (kUA/L) (Challenge to raw milk)	Age <18 ^{18,35,36} • 0.35 = 83%–100% • 5.8 = 80% • 15 = 57% • 32 = 34% Age <14 ²⁵ • 0.35 = 87% Age <1 ³¹ • IgE 0.35 = 84% • IgE 0.7 = 74% • IgE 2.5 = 48% • IgE 5 = 30%	Age <18 ^{18,35,36} • 0.35 = 30%–53% • 5.8 = 81% • 15 = 94% • 32 = 100% Age <14 ²⁵ • IgE 0.35 = 49% Age <1 ³¹ • IgE 0.35 = 56% • IgE 0.7 = 71% • IgE 2.5 = 95% • IgE 5 = 99%	Age <18 ^{18,20,35,36} • 0.35 = 57%–63% • IgE 5.8 = 80% • IgE 15 = 95% • IgE 32 = 95%–100% Age <14 ²⁵ • IgE 0.35 = 62% Age <1 ³¹ • IgE 0.35 = 61% • IgE 0.7 = 67% • IgE 2.5 = 90% • IgE 5 = 95%	Age <18 ^{18,35,36} • 0.35 = 76%–100% • 5.8 = 81% • 15 = 53% • 32 = 44% Age <14 ²⁵ • 0.35 = 79% Age <1 ³¹ • 0.35 = 81% • 0.7 = 77% • 2.5 = 69% • 5 = 64%
Cow's milk IgE (kUA/L) (Challenge to baked milk)	Age <18 ⁴¹ • 1.21 = 95% • 9.97 = 62% • 24.5 = 30%	Age <18 ⁴¹ • 1.21 = 27% • 9.97 = 85% • 24.5 = 95%	Age <18 ⁴¹ • 1.21 = 33% • 9.97 = 60% • 24.5 = 69%	Age <18 ^{32,41} • 1.0 = >90% • 1.21 = 94% • 9.97 = 86% • 24.5 = 78%
Peanut IgE (kUA/L)	Age <18 ^{18,30,36,42,43} • 0.35 = 87.6%–97% • 1.0 = 89.5% • 5.0 = 73.7% • 10.0 = 63.2%–76% • 15 = 57%–57.9% • 45.0 = 20% Age <2 ^{26,44} • 0.35 = 91% • 0.4 = 90% • 2.21 = 68% • 6.20 = 44% • 14.9 = 26% • 34 = 14% • 54.2 = 3%	Age <18 ^{18,30,36,42,43} • 0.35 = 17%–92.9% • 1.0 = 95.2% • 5.0 = 98.9% • 10.0 = 88%–99.5% • 15 = 99.8%–100% • 45.0 = 100% Age <2 ^{26,44} • 0.35 = 68% • 0.4 = 69% • 2.21 = 90% • 6.20 = 95% • 14.9 = 98% • 34 = 99% • 54.2 = 100%	Age <18 ^{18,20,30,36,43} • 0.35 = 31%–78% • 1.0 = 38.6% • 5.0 = 70% • 10.0 = 80%–94% • 15 = 91.7%–100% • 45.0 = 100% Age <2 ²⁶ • 34 = 95%	Age <18 ^{18,30,36,43} • 0.35 = 59%–99.8% • 1.0 = 99.6% • 5.0 = 99.1% • 10.0 = 62%–98.8% • 15 = 36%–98.6% • 45.0 = 76% Age <2 ²⁶ • 34 = 69%

(continued on next page)

Table 2
(continued)

Specific Immunoglobulin E Testing (ImmunoCAP)	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Soy IgE (kU _A /L)	Age <18 ^{18,35,36} • 0.35 = 69%–94% • 5 = 68% • 30 = 44% • 65 = 24% Age <14 ²⁵ • 0.35 = 65%	Age <18 ^{18,35,36} • 0.35 = 25%–50% • 5 = 63% • 30 = 94% • 65 = 99% Age <14 ²⁵ • 0.35 = 50%	Age <18 ^{18,35,36} • 0.35 = 21%–22% • 5 = 28% • 30 = 73% • 65 = 50%–86% Age <14 ²⁵ • 0.35 = 22%	Age <18 ^{18,35,36} • 0.35 = 88%–95% • 5 = 90% • 30 = 82% • 65 = 78% Age <14 ²⁵ • 0.35 = 86%
Wheat IgE (kU _A /L)	Age <18 ^{18,35,36} • 0.35 = 79%–96% • 8.1 = 70% • 26 = 61% • 100 = 13% Age <14 ²⁵ • 0.35 = 82%	Age <18 ^{18,35,36} • 0.35 = 20%–38% • 8.1 = 73% • 26 = 92% • 100 = 100% Age <14 ²⁵ • 0.35 = 34%	Age <18 ^{18,35,36} • 0.35 = 14%–41% • 8.1 = 25% • 26 = 74% • 100 = 75%–100% Age <14 ²⁵ • 0.35 = 41%	Age <18 ^{18,35,36} • 0.35 = 77%–97% • 8.1 = 95% • 26 = 87% • 100 = 76% Age <14 ²⁵ • 0.35 = 77%
Fish IgE (kU _A /L)	Age <18 ^{18,36} • 0.35 = 94% • 1.8 = 85% • 3 = 63% • 20 = 25%	Age <18 ^{18,36} • 0.35 = 65% • 1.8 = 88% • 3 = 91% • 20 = 100%	Age <18 ^{18,36} • 0.35 = 49% • 1.8 = 71% • 3 = 56% • 20 = 95%–100%	Age <18 ^{18,36} • 0.35 = 97% • 1.8 = 94% • 3 = 93% • 20 = 89%
Sesame IgE (kU _A /L)	Age <2 ²⁶ • 50 = 4%	Age <2 ²⁶ • 50 = 98%	Age <2 ²⁶ • 50 = 95%	Age <2 ²⁶ • 50 = 69%

^a Hen's whole egg IgE (kU_A/L). Age in years.

Table 3
Protein components of major food allergens and clinical relevance

Food	Protein Components	Components Associated with Severe Reactions/Anaphylaxis	Components Associated with Food-Pollen Allergy Syndrome
Soybean (<i>Glycine max</i>) ⁴²	• Gly m 3 (profilin) • Gly m 4 (pathogenesis-related protein 10/Bet v 1-like) • Gly m 5 (7s globulin, beta-conglycinin; vicilin) • Gly m 6 (11S globulin, glycerin; Irgumin) • Gly m 7 (seed biotinylated protein) • Gly m 8 (2S albumin)	• Gly m 5 • Gly m 6	• Gly m 4
Peanut (<i>Arachis hypogaea</i>) ^{42,43,45,46}	• Ara h 1 (7/8S globulins (vicilin) of seed transfer protein) • Ara h 2 (2S albumins (conglutin) of seed transfer protein) • Ara h 3 (11S globulins (legumins) of seed transfer protein) • Ara h 4 (11S globulins (legumins) of seed transfer protein) • Ara h 5 (profilin—Bet v 2-like) • Ara h 6 (2S albumins (conglutin) of seed transfer protein) • Ara h 7 (2S albumins (conglutin) of seed transfer protein) • Ara h 8 (pathogenesis-related protein 10/Bet v 1-like) • Ara h 9 (nonspecific lipid transfer protein) • Ara h 10 (oleosin plant lipid storage bodies) • Ara h 11 (oleosin plant lipid storage bodies) • Ara h 12 (defensin) • Ara h 13 (defensin) • Ara h 14 (oleosin plant lipid storage bodies) • Ara h 15 (oleosin plant lipid storage bodies) • Ara h 16 (nonspecific lipid transfer protein) • Ara h 17 (nonspecific lipid transfer protein)	• Ara h 1 • Ara h 2 • Ara h 3 • Ara h 6	• Ara h 8 • Ara h 9

(continued on next page)

Table 3
(continued)

Food	Protein Components	Components Associated with Severe Reactions/Anaphylaxis	Components Associated with Food-Pollen Allergy Syndrome
Cow's milk (<i>Bos domesticus</i>) ⁴⁷	• Bos d 4 (α-lactalbumin) • Bos d 5 (β-lactoglobulin) • Bos d 6 (bovine serum albumin) • Bos d 7 (lactoferrin and immunoglobulins) • Bos d 8 (whole casein) • Bos d 9 (alpha S1-casein) • Bos d 10 (alpha S2-casein) • Bos d 11 (beta-casein) • Bos d 12 (kappa-casein)	• Bos d 4 • Bos d 5 • Bos d 8	-
Hen's egg (<i>Gallus domesticus</i>) ⁴⁸	• Gal d 1 (ovomucoid) • Gal d 2 (ovalbumin), • Gal d 3 (ovotransferrin/conalbumin) • Gal d 4 (lysozyme) • Gal d 5 (alpha-livetin) • Gal d 7 (myosin light chain) • Gal d 8 (alpha-parvalbumin) • Gal d 9 (beta-enolase) • Gal d 10 (aldolase)	• Gal d 1 • Gal d 2 • Gal d 4	• Gal d 5 (bird-egg cross-reactive)
Wheat (<i>Triticum aestivum</i>) ^{46,49}	• Tri a 14 (nonspecific lipid transfer protein) • Tri a 17 (beta-amylase) • Tri a 18 (agglutinin isolectin 1) • Tri a 19 (omega-5 gliadin seed storage protein) • Tri a 20 (gamma gliadin) • Tri a 25 (thioredoxin) • Tri a 26 (high-molecular-weight glutenin) • Tri a 36 (low-molecular-weight glutenin GluB3-23) • Tri a 37 (alpha purothionin)	• Tri a 19	-

Hazelnut (<i>Corylus avellana</i>) ^{45,46,50,51}	• Cor a 1 (pathogenesis-related protein 10/Bet v 1-like) • Cor a 2 (profilin) • Cor a 6 (isoflavone reductase homologue) • Cor a 8 (nonspecific lipid transfer protein) • Cor a 9 (seed storage protein—11S globulin) • Cor a 10 (luminal binding protein) • Cor a 11 (7S seed storage globulin [vicilin-like]) • Cor a 12 (oleosin plant lipid storage bodies) • Cor a 13 (oleosin plant lipid storage bodies) • Cor a 14 (seed storage protein—2S albumin)	• Cor a 9 • Cor a 11 • Cor a 14	• Cor a 1
Walnut (<i>Juglans regia</i>) ^{51,52}	• Jug r 1 (2S albumin) • Jug r 2 (vicilin seed storage protein) • Jug r 3 (nonspecific lipid transfer protein) • Jug r 4 (11S globulin seed storage protein) • Jug r 5 (pathogenesis-related protein 10/Bet v 1-like) • Jug r 6 (vicilin-like cupin) • Jug r 7 (profilin) • Jug r 8 (nonspecific lipid transfer protein)	• Jug r 1 • Jug r 2 • Jug r 4	• Jug r 5
Cashew (<i>Anacardium occidentale</i>) ⁵³	• Ana o 1 (vicilin-like protein) • Ana o 2 (legume-like protein) • Ana o 3 (2S albumin)	• Ana o 3	-
Apple (<i>Malus domestica</i>) ⁴⁵	• Mal d 1 (pathogenesis-related protein 10/Bet v 1-like) • Mal d 2 (thaumatin-like protein) • Mal d 3 (nonspecific lipid transfer protein) • Mal d 4 (profilin)	• Mal d 3	• Mal d 1 • Mal d 4

(continued on next page)

Table 3
(continued)

Food	Protein Components	Components Associated with Severe Reactions/Anaphylaxis	Components Associated with Food-Pollen Allergy Syndrome
Peach (<i>Prunus persica</i>) ⁴⁵	• Pru p 1 (pathogenesis-related protein 10/Bet v 1-like) • Pru p 2 (thaumatin-like protein) • Pru p 3 (nonspecific lipid transfer protein) • Pru p 4 (profilin) • Pru p 7 (gibberellin-regulated protein) • Pru p 9 (pathogenesis-related protein 10/Bet v 1-like)	• Pru p 3 (severe reactions in Mediterranean regions/Europe)	• Pru p 1
Kiwifruit (<i>Actinidia deliciosa</i>) ⁴⁵	• Act d 1 (cysteine protease—actinidin) • Act d 2 (thaumatin-like protein) • Act d 4 (phytocystatin) • Act d 5 (kiwelling) • Act d 6 (pectin methylesterase inhibitor) • Act d 7 (pectin methylesterase) • Act d 8 (pathogenesis-related protein 10/Bet v 1-like) • Act d 9 (profilin) • Act d 10 (nonspecific lipid transfer protein) • Act d 11 (major latex protein/ripening-related protein/Bet v 1-like) • Act d 12 (cupin, 11S globulin) • Act d 13 (2S albumin)	• Act d 1	• Act d 8 • Act d 9

Table 4

Protein components sensitivity, specificity, positive negative predictive value, and negative predictive value at various cutoffs for egg, milk, peanut, and hazelnut

Immunoglobulin E Component Testing	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Hen's egg • Yolk IgE (kU _A /L)	Age <18 ²⁴ • 0.35 = 55.4% • 1.0 = 26.5% Age <2 ²¹ • 0.35 = 63%	Age <18 ²⁴ • 0.35 = 92.3% • 1.0 = 98.1% Age <2 ²¹ • 0.35 = 93%	Age <18 ²⁴ • 0.35 = 92% • 1.0 = 95.6% Age <2 ²¹ • 0.35 = 98%	Age <18 ²⁴ • 0.35 = 56.5% • 1.0 = 45.5% Age <2 ²¹ • 0.35 = 37%
Hen's egg • Ovomucoid IgE (kU _A /L)	Age <19 ^{24,28} • 0.35 = 65.5%–66.7% • 1.0 = 41.4% • 2.0 = 28.7% • 3.38 = 18.5% • 4.85 = 11.1% • 9.74 = 7.41% Age <2 ²¹ • 0.35 = 73%	Age <19 ^{24,28} • 0.35 = 61.3%–78.4% • 1.0 = 94.1% • 2.0 = 98% • 3.38 = 95.1% • 4.85 = 97.9% • 9.74 = 99.3% Age <2 ²¹ • 0.35 = 82%	Age <19 ^{24,28} • 0.35 = 24.7%–83.8% • 1.0 = 92.3% • 2.0 = 96.1% • 3.38 = 41.7% • 4.85 = 50% • 9.74 = 66.7% Age <2 ²¹ • 0.35 = 96%	Age <19 ^{24,28} • 0.35 = 57.1%–90.6% • 1.0 = 48.5% • 2.0 = 44.6% • 3.38 = 86% • 4.85 = 85.3% • 9.74 = 84.9% Age <2 ²¹ • 0.35 = 35%
Hen's egg • Ovalbumin IgE (kU _A /L)	Age <18 ²⁴ • 0.35 = 87.6% • 1.3 = 55.4% • 2 = 49.4% Age <2 ²¹ • 0.35 = 72%	Age <18 ²⁴ • 0.35 = 47.1% • 1.3 = 90.2% • 2 = 96.1% Age <2 ²¹ • 0.35 = 83%	Age <18 ²⁴ • 0.35 = 72.7% • 1.3 = 90.2% • 2 = 95.3% Age <2 ²¹ • 0.35 = 96%	Age <18 ²⁴ • 0.35 = 68.6% • 1.3 = 55.4% • 2 = 53.8% Age <2 ²¹ • 0.35 = 36%
Cow's milk (baked) • Casein IgE (kU _A /L)	Age <18 ⁴¹ • 0.94 = 95% • 4.95 = 74% • 20.2 = 30%	Age <18 ⁴¹ • 0.94 = 32% • 4.95 = 77% • 20.2 = 95%	Age <18 ⁴¹ • 0.94 = 34% • 4.95 = 54% • 20.2 = 69%	Age <18 ⁴¹ • 0.94 = 96% • 4.95 = 89% • 20.2 = 78%

(continued on next page)

Table 4
(continued)

Immunoglobulin E Component Testing	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Peanut • Ara h 1 IgE (kU _A /L)	Age <18 ⁴³ • 0.35 = 56%	Age <18 ⁴³ • 0.35 = 87%	Age <18 ⁴³ • 0.35 = 88%	Age <18 ⁴³ • 0.35 = 54%
Peanut • Ara h 2 IgE (kU _A /L)	Age <18 ^{42,43} • 0.35 = 80%–100% Age <2 ⁴⁴ • 0.1 = 95% • 0.35 = 81% • 1.0 = 60% • 1.19 = 60% • 3.51 = 43%	Age <18 ^{42,43} • 0.35 = 92%–96.1% Age <2 ⁴⁴ • 0.1 = 86% • 0.35 = 93% • 1.0 = 97% • 1.19 = 98% • 3.51 = 100%	Age <18 ⁴³ • 0.35 = 94%	Age <18 ⁴³ • 0.35 = 73%
Peanut • Ara h 3 IgE (kU _A /L)	Age <18 ⁴³ • 0.35 = 48%	Age <18 ⁴³ • 0.35 = 90%	Age <18 ⁴³ • 0.35 = 89%	Age <18 ⁴³ • 0.35 = 50%
Peanut • Ara h 8 IgE (kU _A /L)	Age <18 ⁴³ • 0.35 = 35%	Age <18 ⁴³ • 0.35 = 43%	Age <18 ⁴³ • 0.35 = 51%	Age <18 ⁴³ • 0.35 = 27%
Hazelnut • Cor a 9 IgE (kU _A /L)	Age >18 ⁵⁰ • 0.35 = 36% • 1.0 = 33% • 5.0 = 13% Age <18 ⁵⁰ • 0.35 = 83% • 1.0 = 75% • 5.0 = 48%	Age >18 ⁵⁰ • 0.35 = 95% • 1.0 = 100% • 5.0 = 100% Age <18 ⁵⁰ • 0.35 = 80% • 1.0 = 95% • 5.0 = 98%	—	—
Hazelnut • Cor a 14 IgE (kU _A /L)	Age >18 ⁵⁰ • 0.35 = 38% • 1.0 = 31% • 5.0 = 18% Age <18 ⁵⁰ • 0.35 = 70% • 1.0 = 70% • 5.0 = 60%	Age >18 ⁵⁰ • 0.35 = 95% • 1.0 = 98% • 5.0 = 100% Age <18 ⁵⁰ • 0.35 = 76% • 1.0 = 76% • 5.0 = 98%	—	—

Age in years.

Testing for sIgE components does not improve risk stratification for all foods. For instance, egg white was found to have a higher sensitivity, specificity, and PPV than other egg components like egg yolk, ovomucoid, and ovalbumin in children less than 2 years of age.^{21,24}

SUMMARY

In conclusion, using both SPT and sIgE, with component testing where available, allows for more accurate assessment of food allergy and can effectively risk stratify those who may benefit from OFCs. Serial evaluation of children with IgE-mediated food allergies every 1 year to 2 years with SPT and sIgE can identify those with decreasing values who may benefit from OFC to evaluate clinical tolerance.

REFERENCES

1. Boyce JA, Assa'ad A, Burks AW, et al. Guidelines for the diagnosis and management of food allergy in the United States: summary of the NIAID-sponsored expert panel report. *J Am Acad Dermatol* 2011;64(1):175–92.
2. Sampson HA, Van Wijk RG, Bindslev-Jensen C, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology–European Academy of Allergy and Clinical Immunology PRACTALL consensus report. *J Allergy Clin Immunol* 2012;130(6):1260–74.
3. Harris MC, Shure N. Sudden death due to allergy tests. *J Allergy Clin Immunol* 1950;21(3):208–16.
4. Burks AW, Sampson HA. Anaphylaxis and food allergy. *Clin Rev Allergy Immunol* 1999;17(3):339–60.
5. Bernstein IL, Li JT, Bernstein DI, et al. Allergy diagnostic testing: an updated practice parameter. *Ann Allergy Asthma Immunol* 2008;100(3):S1–48.
6. Sampson HA, Aceves S, Bock SA, et al. Food allergy: a practice parameter update—2014. *J Allergy Clin Immunol* 2014;134(5):1016–25.
7. Nelson HS. Variables in allergy skin testing. *Allergy Proc* 1994;15(6):265. Ocean-Side Publications.
8. Oppenheimer J, Nelson HS. Skin testing. *Ann Allergy Asthma Immunol* 2006;96(2):S6–12.
9. Tversky JR, Chelladurai Y, McGready J, et al. Performance and pain tolerability of current diagnostic allergy skin prick test devices. *J Allergy Clin Immunol Pract* 2015;3(6):888–93.
10. Rance F, Juchet A, Bremont F, et al. Correlations between skin prick tests using commercial extracts and fresh foods, specific IgE, and food challenges. *Allergy* 1997;52(10):1031–5.
11. Ferrer Á, Huertas ÁJ, Larramendi CH, et al. Usefulness of manufactured tomato extracts in the diagnosis of tomato sensitization: comparison with the prick-prick method. *Clin Mol Allergy* 2008;6(1):1.
12. Łoś-Rycharska E, Sterkowicz A, Romańczuk B, et al. Comparison of results and clinical value of skin prick tests with synthetic and native food allergens in patients at the age of up to 3 years. *Postepy Dermatol Alergol* 2016;33(6):485.
13. Rosen JP, Selcow JE, Mendelson LM, et al. Skin testing with natural foods in patients suspected of having food allergies: is it a necessity? *J Allergy Clin Immunol* 1994;93(6):1068–70.

14. Sampson HA. Comparative study of commercial food antigen extracts for the diagnosis of food hypersensitivity. *J Allergy Clin Immunol* 1988;82(5):718–26.
15. Bock SA, Buckley J, Holst A, et al. Proper use of skin tests with food extracts in diagnosis of hypersensitivity to food in children. *Clin Exp Allergy* 1977;7(4):375–83.
16. Sporik R, Hill DJ, Hosking CS. Specificity of allergen skin testing in predicting positive open food challenges to milk, egg and peanut in children. *Clin Exp Allergy* 2000;30(11):1541–6.
17. Sampson HA, Albergo R. Comparison of results of skin tests, RAST, and double-blind, placebo-controlled food challenges in children with atopic dermatitis. *J Allergy Clin Immunol* 1984;74(1):26–33.
18. Sampson HA, Ho DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. *J Allergy Clin Immunol* 1997;100(4):444–51.
19. Verstege A, Mehl A, Rolinck-Werninghaus C, et al. The predictive value of the skin prick test weal size for the outcome of oral food challenges. *Clin Exp Allergy* 2005;35(9):1220–6.
20. Hill DJ, Heine RG, Hosking CS. The diagnostic value of skin prick testing in children with food allergy. *Pediatr Allergy Immunol* 2004;15(5):435–41.
21. Boyano-Martínez T, García-Ara C, Díaz-Pena JM, et al. Prediction of tolerance on the basis of quantification of egg white-specific IgE antibodies in children with egg allergy. *J Allergy Clin Immunol* 2002;110(2):304–9.
22. Monti G, Muratore MC, Peltran A, et al. High incidence of adverse reactions to egg challenge on first known exposure in young atopic dermatitis children: predictive value of skin prick test and radioallergosorbent test to egg proteins. *Clin Exp Allergy* 2002;32(10):1515–9.
23. Tripodi S, Di Rienzo Businco A, Alessandri C, et al. Predicting the outcome of oral food challenges with hen's egg through skin test end-point titration. *Clin Exp Allergy* 2009;39(8):1225–33.
24. Diéguez MC, Cerecedo I, Muriel A, et al. Utility of diagnostic tests in the follow-up of egg-allergic children. *Clin Exp Allergy* 2009;39(10):1575–84.
25. Mehl A, Rolinck-Werninghaus C, Staden U, et al. The atopy patch test in the diagnostic workup of suspected food-related symptoms in children. *J Allergy Clin Immunol* 2006;118(4):923–9.
26. Peters RL, Allen KJ, Dharmage SC, et al. Skin prick test responses and allergen-specific IgE levels as predictors of peanut, egg, and sesame allergy in infants. *J Allergy Clin Immunol* 2013;132(4):874–80.
27. Leonard SA. Debates in allergy medicine: baked milk and egg ingestion accelerates resolution of milk and egg allergy. *World Allergy Organ J* 2016;9(1):1.
28. Bartnikas LM, Sheehan WJ, Larabee KS, et al. Ovomucoid is not superior to egg white testing in predicting tolerance to baked egg. *J Allergy Clin Immunol Pract* 2013;1(4):354–60.
29. Pucar F, Kagan R, Lim H, et al. Peanut challenge: a retrospective study of 140 patients. *Clin Exp Allergy* 2001;31(1):40–6.
30. Nicolaou N, Poorafshar M, Murray C, et al. Allergy or tolerance in children sensitized to peanut: prevalence and differentiation using component-resolved diagnostics. *J Allergy Clin Immunol* 2010;125(1):191–7.
31. García-Ara C, Boyano-Martínez T, Díaz-Pena JM, et al. Specific IgE levels in the diagnosis of immediate hypersensitivity to cows' milk protein in the infant. *J Allergy Clin Immunol* 2001;107(1):185–90.

32. Bartnikas LM, Sheehan WJ, Hoffman EB, et al. Predicting food challenge outcomes for baked milk: role of specific IgE and skin prick testing. *Ann Allergy Asthma Immunol* 2012;109(5):309–13.
33. Santos AF, Brough HA. Making the most of in vitro tests to diagnose food allergy. *J Allergy Clin Immunol Pract* 2017;5(2):237–48.
34. Vereda A, van Hage M, Ahlstedt S, et al. Peanut allergy: clinical and immunologic differences among patients from 3 different geographic regions. *J Allergy Clin Immunol* 2011;127(3):603–7.
35. Celik-Bilgili S, Mehl A, Verstege A, et al. The predictive value of specific immunoglobulin E levels in serum for the outcome of oral food challenges. *Clin Exp Allergy* 2005;35(3):268–73.
36. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol* 2001;107(5):891–6.
37. Wilson JM, Platts-Mills TA. Meat allergy and allergens. *Mol Immunol* 2018;100:107–12.
38. Hilger C, Fischer J, Wölbing F, et al. Role and mechanism of Galactose- α -1,3-Galactose in the elicitation of delayed anaphylactic reactions to red meat. *Curr Allergy Asthma Rep* 2019;19(1):3.
39. Mabelane T, Basera W, Botha M, et al. Predictive values of alpha-Gal IgE levels and alpha-Gal IgE: total IgE ratio and oral food challenge-proven meat allergy in a population with a high prevalence of reported red meat allergy. *Pediatr Allergy Immunol* 2018;29(8):841–9.
40. Lieberman JA, Huang FR, Sampson HA, et al. Outcomes of 100 consecutive open, baked-egg oral food challenges in the allergy office. *J Allergy Clin Immunol* 2012;129(6):1682–4.
41. Caubet JC, Nowak-Węgrzyn A, Moshier E, et al. Utility of casein-specific IgE levels in predicting reactivity to baked milk. *J Allergy Clin Immunol* 2013;131(1):222–4.
42. Nicolaou N, Custovic A. Molecular diagnosis of peanut and legume allergy. *Curr Opin Allergy Clin Immunol* 2011;11(3):222–8.
43. Lieberman JA, Glaumann S, Batelson S, et al. The utility of peanut components in the diagnosis of IgE-mediated peanut allergy among distinct populations. *J Allergy Clin Immunol Pract* 2013;1(1):75–82.
44. Dang TD, Tang M, Choo S, et al. Increasing the accuracy of peanut allergy diagnosis by using Ara h 2. *J Allergy Clin Immunol* 2012;129(4):1056–63.
45. Hoffmann-Sommergruber K, Pfeifer S, Bublin M. Applications of molecular diagnostic testing in food allergy. *Curr Allergy Asthma Rep* 2015;15(9):56.
46. Hamilton RG, Kleine-Tebbe J. Molecular allergy diagnostics: analytical features that support clinical decisions. *Curr Allergy Asthma Rep* 2015;15(9):57.
47. Kattan JD, Cocco RR, Järvinen KM. Milk and soy allergy. *Pediatr Clin North Am* 2011;58(2):407–26.
48. Caubet JC, Wang J. Current understanding of egg allergy. *Pediatr Clin North Am* 2011;58(2):427–43.
49. Czaja-Bulsa G, Bulsa M. What do we know now about IgE-mediated wheat allergy in children? *Nutrients* 2017;9(1):35.
50. Masthoff LJ, Mattsson L, Zuidmeer-Jongejan L, et al. Sensitization to cor a 9 and cor a 14 is highly specific for a hazelnut allergy with objective symptoms in Dutch children and adults. *J Allergy Clin Immunol* 2013;132(2):393–9.
51. Valcour A, Lidholm J, Borres MP, et al. Sensitization profiles to hazelnut allergens across the United States. *Ann Allergy Asthma Immunol* 2019;122(1):111–6.

52. Blankestijn MA, Blom WM, Otten HG, et al. Specific IgE to Jug r 1 has no additional value compared with extract-based testing in diagnosing walnut allergy in adults. *J Allergy Clin Immunol* 2017;139(2):688–90.
53. Van der Valk JP, Gerth van Wijk R, Vergouwe Y, et al. sIgE Ana o 1, 2 and 3 accurately distinguish tolerant from allergic children sensitized to cashew nuts. *Clin Exp Allergy* 2017;47(1):113–20.
54. Katelaris CH. Food allergy and oral allergy or pollen-food syndrome. *Curr Opin Allergy Clin Immunol* 2010;10(3):246–51.