Food Allergy Testing

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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.
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Clin Lab Med 39 (2019) 625–642
https://doi.org/10.1016/j.cll.2019.07.009 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 immunoenzematic 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 immunoenzematic 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%

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Table 1
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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 NVP 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] • [a]0.35 = 97%–98% • 0.35 = 86.7% • 1.5 = 52.2% • [a]3.4 = 82% • [a]6 = 64% • [a]7 = 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] • [a]0.35 = 45%–51% • 0.35 = 39.6% • 1.5 = 90.6% • [a]3.4 = 84% • [a]6 = 90% • [a]7 = 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] • [a]0.35 = 80%–84% • 0.35 = 70.9% • 1.5 = 90.4% • [a]3.4 = 94% • [a]6 = 95%–96% • [a]7 = 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] • [a]0.35 = 88%–89% • 0.35 = 63.6% • 1.5 = 52.7% • [a]3.4 = 62% • [a]6 = 39% • [a]7 = 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 (kU_A/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%

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Table 2
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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 (kUA/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 (*Glycine max*)[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; lrgumin) • Gly m 7 (seed biotinylated protein) • Gly m 8 (2S albumin)	• Gly m 5 • Gly m 6	• Gly m 4
Peanut (*Arachis hypogaea*)[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

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Table 3
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Food	Protein Components	Components Associated with Severe Reactions/Anaphylaxis	Components Associated with Food-Pollen Allergy Syndrome
Cow's milk (*Bos domesticus*)[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 (*Gallus domesticus*)[48]	• Gal d 1 (ovomucoid) • Gal d 2 (ovalbumin), • Gal d 3 (ovotransferrin/conalbumin) • Gal d 4 (lysosyme) • 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 (*Triticum aestivum*)[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 (*Corylus avellana*)[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 (*Juglans regia*)[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 (*Anacardium occidentale*)[53]	• Ana o 1 (vicilin-like protein) • Ana o 2 (legume-like protein) • Ana o 3 (2S albumin)	• Ana o 3	-
Apple (*Malus domestica*)[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

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Table 3
(*continued*)

Food	Protein Components	Components Associated with Severe Reactions/Anaphylaxis	Components Associated with Food-Pollen Allergy Syndrome
Peach (*Prunus persica*)[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 (*Actinidia deliciosa*)[45]	• Act d 1 (cysteine protease—actinidin) • Act d 2 (thaumatin-like protein) • Act d 4 (phytocystatin) • Act d 5 (kiwellin) • 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.

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