

Diagnosis of Food Allergy



Malika Gupta, MD^a, Amanda Cox, MD^b,
Anna Nowak-Węgrzyn, MD, PhD^b, Julie Wang, MD^{b,*}

KEYWORDS

- Diagnosis • Food allergy • Molecular allergen analysis • Serum-specific IgE
- Skin prick test • Epitope binding • Basophil activation test
- Component-resolved diagnostic testing

KEY POINTS

- Differentiating between clinical allergy and sensitization is challenging but important to prevent overdiagnosis of food allergy.
- Double-blind placebo controlled food-challenges remain the gold standard for the diagnosis of food allergy, although their utility remains limited to research studies. In clinical settings, open oral food challenges are usually considered sufficient.
- Standard food allergy diagnosis involves the use of skin prick tests, allergen-specific immunoglobulin E, and oral food challenges. Molecular allergen analysis is a promising new technique and has increased specificity of testing for peanut and hazelnut allergies, with attention now shifting to other food allergens. Basophil activation tests and epitope binding are actively used in research and may have clinical applications for diagnosis of food allergy in the future.

INTRODUCTION

Food allergy (FA) is defined as “an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food.”¹ FA prevalence increased by almost 50% over the past 2 decades in countries with a Western lifestyle.² FA is estimated to affect 6% to 8% of the children in the United States and approximately 3% to 4% of the adults.³ This has led to an increased focus on all aspects of FA, from prevention to treatment.

Diagnosis of FA is challenging, with pitfalls associated with most testing methods. Despite several advances, a double-blind, placebo-controlled food challenge (DBPCFC) remains the gold standard for FA diagnosis. Correctly identifying FA is

Disclosure Statement: The authors have no relevant financial disclosures or conflicts of interests.

^a Division of Allergy & Immunology, Department of Internal Medicine, University of Michigan, 24 Frank Lloyd Wright Drive, Suite H-2100, Ann Arbor, MI 48106, USA; ^b Department of Pediatrics, Icahn School of Medicine at Mount Sinai, Jaffe Food Allergy Institute, One Gustave Levy Place, Box 1198, New York, NY 10029, USA

* Corresponding author.

E-mail address: Julie.Wang@mssm.edu

Immunol Allergy Clin N Am 38 (2018) 39–52

<https://doi.org/10.1016/j.iac.2017.09.004>

0889-8561/18/© 2017 Elsevier Inc. All rights reserved.

immunology.theclinics.com

important, not only to prevent reactions but also to avoid unnecessary dietary restrictions that negatively affect growth.^{4,5}

This article describes the diagnostic methods for immunoglobulin E (IgE)-mediated FA with a particular focus on molecular allergen analysis (MAA) and basophil activation testing (BAT). This article does not include evaluation of non-IgE-mediated food-allergies, which involve different diagnostic approaches.

CLINICAL HISTORY

As with any disease, a detailed history is important and guides further testing:

- A description of typical symptoms of IgE-mediated allergy (described in [Table 1](#)), timing of symptoms in relation to food ingestion (usually minutes to 1–2 hours), reproducibility of symptoms with subsequent food ingestion, form (eg, raw vs cooked), and amount of food ingested, are all relevant in FA diagnosis.
- It is important to rule out conditions that mimic FA ([Box 1](#)).
- Certain populations are at higher risk of FA: those with eczema, asthma, allergic rhinitis, other FA, and a family history of atopic disease (AD).⁶
- Associated cofactors, including acute febrile illness, asthma exacerbation, exercise, alcohol ingestion, drugs increasing gastric pH, and nonsteroidal antiinflammatory drugs, can worsen the severity of an allergic reaction and should be assessed.⁷
- Knowledge of cross-reactivity within food protein families should guide further tests to exclude allergy to related foods if they have not yet been ingested. This should be done cautiously because testing for all homologous proteins can result in elimination of foods that demonstrate sensitization but may not result in allergic reactions.⁸ [Fig. 1](#) summarizes the approximate rate of cross-reactivity between different foods.⁸ Decisions regarding testing should be based on likelihood of allergy and the nutritional and social importance of the food.

STANDARD TESTING

In addition to a detailed clinical history, several diagnostic tests can be considered in the evaluation of FA.

Table 1 System-based symptoms encountered in acute immunoglobulin E-mediated food reactions	
System Involved	Symptoms (Usual Onset Within Minutes to 1–2 h Following Food Ingestion)
Cutaneous	Pruritus, flushing, urticaria, angioedema, flare of chronic eczematous rash
Ocular	Pruritus, conjunctival erythema, tearing, periorbital edema
Respiratory tract	Nasal congestion, pruritus, sneezing, laryngeal edema and hoarseness, cough, wheeze, chest tightness, dyspnea, cyanosis
Gastrointestinal	Nausea; emesis; crampy abdominal pain; oral pruritus; tongue, lip, palate, or pharyngeal angioedema
Cardiovascular	Tachycardia, bradycardia, hypotension, cardiac arrest, dizziness
Neurologic	Sense of impending doom, syncope, dizziness

Adapted from Sampson HA, Aceves S, Bock SA, et al. Food allergy: a practice parameter update-2014. J Allergy Clin Immunol 2014;134(5):1025.e41; with permission.

Box 1**Differential diagnosis for food allergy**

- Allergic reactions to drugs, venom, inhalants
- Food intolerance (eg, lactose intolerance)
- Toxic reactions or food poisoning (eg, scombroid fish toxin, poisoning due to *Escherichia coli*)
- Pharmacologic reactions (eg, to caffeine, theobromine, alcohol)
- Auriculotemporal syndrome (Frey syndrome)
- Gustatory rhinitis caused by spicy foods
- Panic, anorexia nervosa

Data from Sampson HA, Aceves S, Bock SA, et al. Food allergy: a practice parameter update-2014. *J Allergy Clin Immunol* 2014;134(5):1025.e42.

The diagnostic pathway commonly begins with a skin prick test (SPT) for the suspected allergen with or without a serum-specific IgE (ssIgE). Both tests detect antigen-specific IgE (asIgE). The presence of asIgE is called sensitization and alone does not confirm FA because asIgE can be present in the absence of clinical allergy.¹ Therefore, these tests must be interpreted in the context of clinical history. A larger SPT diameter or a higher ssIgE correspond to a higher likelihood of clinical reaction^{7,9} but do not predict the severity of a reaction. The advent of MAA has made it possible to identify sensitization to allergens predicting systemic reactions.

SKIN PRICK TESTING

During SPT procedure, the skin surface is pricked with allergen to measure the asIgE bound to cutaneous mast cells.⁷ SPT results in a wheal and flare response, which is measured within 15 minutes.¹⁰ SPT has limited utility in patients with dermatographism or who are taking systemic antihistamines.¹ Wheal sizes vary with age, body site used for testing (usually greater on back compared with forearms), device used, the potency and commercial extract manufacturer, or if fresh food is used. The negative predictive value (NPV) of SPT is greater than 90%, making it a useful test for excluding FA in the absence of a convincing clinical history.⁷ This is especially true for the major allergens for which commercial skin test extracts are available.¹¹ False-negative SPT may occur if the commercial extracts are not standardized and lack the allergen in sufficient quantities.¹² This is particularly true for fruits and vegetables in which the antigens are destroyed during the manufacturing process.¹² In these cases, prick-prick testing with the fresh food may be used.⁷

The positive predictive value (PPV) of SPT depends on the patient's age and the food allergen,⁷ and can differ with the SPT method used and presence of atopy. The 95% PPV values have been established for only a few major food allergens (summarized in [Table 2](#)). In general, a larger SPT correlates with an increased likelihood of reaction.⁷

SPT should be performed by a trained personnel in a facility capable of managing anaphylaxis, which can rarely be triggered by SPT. Intradermal skin testing is not recommended in FA diagnosis because it can provoke anaphylaxis and is associated with high rates of false-positive results.⁷

SERUM FOOD ALLERGEN-SPECIFIC IMMUNOGLOBULIN E

Extract-based in vitro testing for allergen-specific IgE in serum (ssIgE) is another diagnostic tool. Physicians can send ssIgE from the office and it can be used in patients

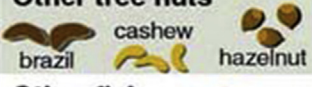
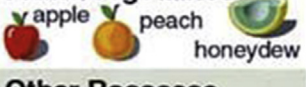
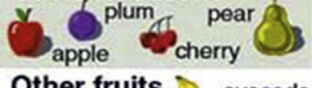
If Allergic to:	Risk of Reaction to at Least One:	Risk:
A legume^a 	Other legumes 	5% 
A tree nut 	Other tree nuts 	37% 
A fish^a 	Other fish 	50% 
A shellfish 	Other shellfish 	75% 
A grain^a 	Other grains 	20% 
Cow's milk^a 	Beef 	10% 
Cow's milk^a 	Goat's milk 	92% 
Cow's milk^a 	Mare's milk 	4% 
Pollen 	Fruits/vegetables 	55% 
Peach^a 	Other Rosaceae 	55% 
Melon^a 	Other fruits 	92% 
Latex^a 	Fruits 	35% 
Fruits 	Latex 	11% 

Fig. 1. Cross-reactive foods.^a Data derived from studies with DBPCFCs. (From Sicherer SH. Clinical implications of cross-reactive food allergens. J Allergy Clin Immunol 2001;108(6):885; with permission.)

Table 2
Predictive values for skin prick testing in positive or negative oral food challenges

Food	95% Positive (mm) ^a	50% Negative (mm) ^b
Egg white	≥7	≤3
Cow's milk	≥8	—
Peanut	≥8	≤3

^a Mean wheal diameters above which 95% of the challenges are expected to be positive (failed).

^b Mean wheal diameters under which 50% of the challenges are expected to be negative (passed).

Adapted from Sampson HA, Aceves S, Bock SA, et al. Food allergy: a practice parameter update-2014. *J Allergy Clin Immunol* 2014;134(5):1025.e42; with permission.

who are unable to cooperate with skin testing, those with extensive skin disease, or those unable to discontinue oral antihistamines.

Serum allergen-specific IgE has high sensitivity but low specificity for FA.¹³ A detectable sslgE by itself is not diagnostic of FA, but increasing sslgE levels correlate with increased likelihood of a true allergy.⁹ Of note, in 10% to 25% of cases, reactions can occur with undetectable sslgE.¹⁴ This may be explained by insufficient sensitivity of the immunoassay and/or loss of minor allergens during extract preparation for the immunoassay.

Predictive values of clinical reactivity have been established for several foods (summarized in [Table 3](#)). When sslgE levels are greater than or equal to 95% PPV, FA is likely. If sslgE levels are less than or equal to 50% PPV, a physician-supervised oral food challenge (OFC) can be considered to exclude FA. These cutoff values have been established based on ImmunoCAP (ThermoFisher, Waltham, Massachusetts, USA) and are not comparable to the levels measured by other immunoassays.¹⁵ The cutoff values differ with age because lower sslgE antibody levels have higher PPV in infants and younger children.⁷ They are also affected by the prior history of reactions, which is associated with a higher pretest probability.⁷

Few studies have suggested interpreting allergen-sslgE in the context of the total IgE for improved accuracy.^{16,17} Further studies are needed before this method can be used clinically. Although no single factor is thought to be an absolute predictor by itself, using a combination of factors might increase the accuracy of predictive models. DunnGalvin and colleagues¹⁸ developed predictive models for peanut, milk, and egg using 6 clinical

Table 3
Predictive values for food allergen-specific immunoglobulin E for children

Allergen	≥95% Predictive Level (kUA/L)	PPV
Egg	7	98
Infants ≤2 y	2	95
Cow milk	15	95
Infants ≤2 y	5	95
Peanut	14	100
Fish	20	100
Tree nuts	15	≈ 95
Soybean	30	73
Wheat	26	74

Adapted from Sampson HA. Update on food allergy. *J Allergy Clin Immunol* 2004;113(5):812 [quiz: 820]; with permission.

factors: SPT, sslgE, total IgE minus sslgE, symptoms, sex, and age. The sensitivity and specificity of the Cork-Southampton algorithm incorporating these 6 variables was higher than using SPT, or sslgE, or a combination of SPT and sslgE. Age tends to be an important predictor in these models, whereas time since the last reaction seems to be less important.¹⁸ Also, the relative importance of an individual factor varies by food.¹⁸

In infants, sslgE might be more sensitive than SPT. In the Learning Early About Peanut Allergy (LEAP) study, which enrolled infants in the 4 to 11 months age group, almost 28% of infants with negative skin tests had detectable peanut-sslgE.¹⁹ Race also affects the PPV of sslgE levels. Black race is more commonly associated with higher sslgE levels^{19,20} but less clinical reactivity. In the LEAP study, it was noted that higher peanut sslgE levels in the black subjects were often associated with negative SPT, and no clinical reactivity compared with other races. Thus, SPT was assumed to be a more accurate predictor in black subjects.^{19,21}

The FA guidelines suggest combining SPT and sslgE to increase the PPV and NPV for the diagnosis of FA.¹

Other uses of sslgE include periodic monitoring of the longitudinal trend to determine the resolution of FA.^{14,22} Regarding egg and milk, a 50% decrease in sslgE over 12 months is more likely predictive of resolution of allergy compared with a slower decrease over a long period of time.²²

Children with higher peak lifetime sslgE (generally above 50 kilounits of allergen-specific IgE per liter [kUA/L]) are more likely to have persistent cow's milk, egg, soy, and wheat allergy.²³

The Consortium for Food Allergy Research developed a Web-based calculator to counsel families about the prognosis of milk allergy in children younger than 15 months (www.cofargroup.org). The calculator is based on milk-sslgE, SPT, and severity of AD, which are most predictive of milk allergy resolution (Fig. 2).²⁴ A prognostic calculator for egg allergy is also available.²⁵

MOLECULAR ALLERGEN ANALYSIS

MAA (aka component-resolved diagnostic testing) augments the accuracy of conventional testing.²⁶ Conventional sslgE measures IgE to the whole food extract, which contains both allergenic and nonallergic components.²⁷ MAA, on the other hand, identifies IgE bound to specific protein antigens in a food.²⁷

MAA can separate the clinically relevant from the irrelevant IgE with prognostic benefit.²⁷ This is most helpful either when 1 main isoform of the protein is associated with the allergic reaction or when the allergen is degraded easily by heat or digestion. Proteins that are resistant to heat or digestion are more likely to cause systemic reactions. For instance, ovomucoid is a heat-resistant egg white protein. Individuals who are predominantly sensitized to ovomucoid are less likely to tolerate baked egg products²⁸ and MAA helps identify this phenotype.

MAA can also be applied to evaluating sensitization to foods that share homologous proteins with aeroallergens.²⁶ Patients primarily sensitized to the hazelnut Cor a 1, which is a homolog of Bet v 1, are more likely to experience mild oral or no symptoms compared with patients sensitized to the storage seed proteins (Cor a 9, Cor a 14) who are more likely to experience systemic symptoms.²⁹

The ratio of component-specific IgE to total IgE does not improve the predictive ability of MAA, high total IgE levels lower the probability of positive challenges at a given Ara h2 and Cor A 14 for peanut and hazelnut, respectively.³⁰

Two commercial immunoassays measure IgE to individual food allergens. Fluorescent enzyme immunoassay (ImmunoCAP) uses purified native or recombinant

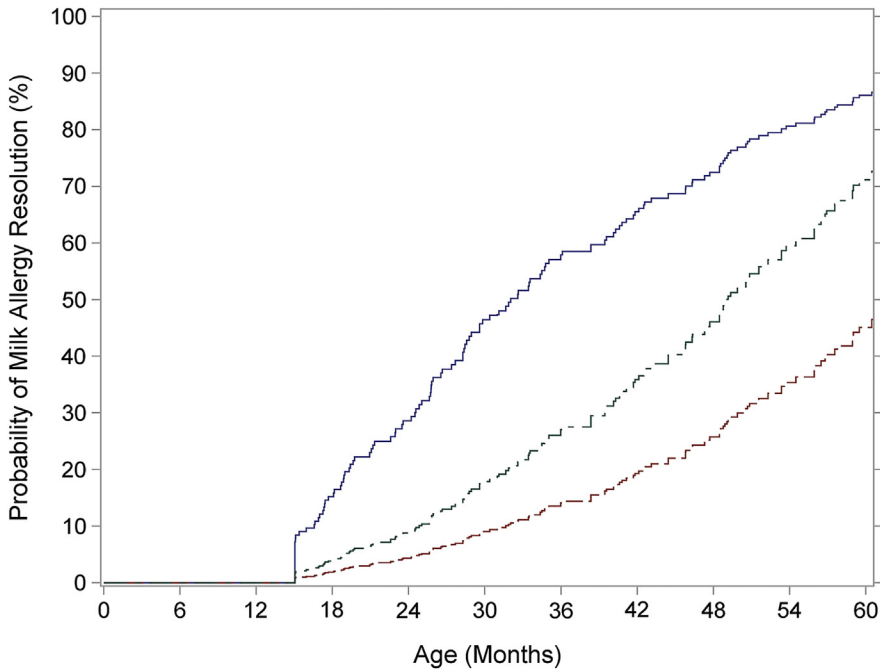


Fig. 2. Predicting the natural history of resolution of milk allergy. Red curve represents a patient with milk sslgE of 20 kUA/L, milk SPT mean of 7 mm, and moderate-to-severe AD. Green curve represents a patient with milk sslgE of 20 kUA/L, milk SPT mean of 7 mm, and mild to no AD. Blue curve represents a patient with milk sslgE of 2 kUA/L, milk SPT mean of 4 mm, and mild to no AD. (From Wood RA, Sicherer SH, Vickery BP, et al. The natural history of milk allergy in an observational cohort. *J Allergy Clin Immunol* 2013;131(3):811; with permission.)

proteins and provides quantitative results expressed as kUA/L. A microarray-based immunoassay (ImmunoCAP ISAC) measures specific IgE to greater than 100 allergens simultaneously.³¹ The results obtained from ISAC are semiquantitative and are expressed in ISAC standardized units (ISUs).³¹ Notably, because ISAC covers a wide spectrum of food allergens, this type of testing has the potential of overdiagnosing food allergies by detecting sensitization to foods that may not be clinically relevant.

Peanut-MAA is best-studied and most often used in practice. Although Ara h 1, 2, and 3 have all been associated with systemic peanut allergy; Ara h 2 has is the best predictor of peanut allergy with sensitivity approaching 100% and specificity approaching 96.1% in 1 study.³² In contrast, monosensitization to Ara h 8 (a homologue of the labile birch protein Bet v 1) is usually associated with mild oral to no symptoms. These patients should undergo physician-supervised OFCs because they are likely to tolerate peanut. Of note, Ara h 6 is also associated with systemic reactions but is only available with ISAC.³³ Clinically important major food allergens are summarized in [Table 4](#).

BASOPHIL ACTIVATION TEST

An allergic reaction is provoked when allergen crosslinks FcεRI-bound surface membrane IgE on basophils and mast cells, which then degranulate to release histamine

Table 4
Clinically important major food allergens

Food	Major Allergen	Clinical Correlation
Cow's milk ²⁸	Bos d 8 (casein)	High levels of casein-IgE indicate higher likelihood of reactivity to baked milk
Egg ²⁸	Gal d 1 (ovomucoid)	High levels of ovomucoid-IgE indicate higher likelihood of reactivity to baked egg
Peanut ³⁴	Ara h 1	Systemic reactivity
	Ara h 2	Systemic reactivity (best predictor)
	Ara h 3	Systemic reactivity
	Ara h 6	Systemic reactivity
	Ara h 8	Cross-reactivity with Bet v 1 (usually tolerant or with mild oral allergy)
	Ara h 9	Systemic reactivity in Mediterranean regions ³⁵
Hazelnut ²⁹	Cor a 1	Cross-reacts with Bet v 1; no correlation with systemic reactions
	Cor a 8	Systemic reactivity in Mediterranean regions ³⁶
	Cor a 9	Systemic reactions
	Cor a 14	Systemic reactions
Cashew ³⁷	Ana o 3	Best predictor of systemic allergy to cashew and pistachio
Walnut ³⁸	Jug r 1	Anaphylactic reactions
Wheat ^{39–41}	Tri a 14	Clinical reactivity in Mediterranean regions
	Tri a 19 (Omega 5-gliadin)	Correlates with severe wheat allergy, WDEIA
	Tri a 20	Wheat allergy
	Tri a 21	Wheat allergy
	Tri a 36	Cross-reactivity with other cereal grains
Soy ⁴²	Gly m 4	Cross-reactivity with Bet v 1, correlates with milder symptoms or oral allergy symptoms
	Gly m 5	Systemic symptoms in the absence of Gly m 5 and 6
	Gly m 6	Anaphylactic reactions
Beef, lamb, pork meat ⁴³	Galactose-alpha-1,3-galactose (alpha-gal)	Predicts delayed reactions to mammalian meat

Abbreviation: WDEIA, wheat-dependent exercise-induced anaphylaxis.

and other mediators. BAT mimics an allergic reaction and reflects a functional response rather than sensitization.⁴⁴ Flow cytometry detects surface activation markers, usually CD63 and CD203c, on the allergen-stimulated basophils.⁴⁴ BAT should ideally be able to distinguish between clinically allergic and sensitized-but-tolerant individuals.⁴⁵ BAT may also predict anaphylaxis.⁴⁶

Crude allergen extracts and purified or recombinant allergens can be used to stimulate basophils for BAT.⁴⁷ BAT results may be reported as basophil reactivity or basophil sensitivity. Basophil reactivity is reported as the maximum proportion (CD-max) of activated basophils measured at any concentration of stimulating allergen. Basophil sensitivity (EC50 or CDsens) is the smallest effective allergen concentration causing 50% of maximal basophil activation.⁴⁴ An area under the dose-responsive curve, which provides a measurement of both basophil reactivity and sensitivity, may also be measured.⁴⁴

BAT has high sensitivity and specificity for diagnosis of peanut, hazelnut, egg, milk, and wheat allergies, as well as for pollen-food syndrome to apple, hazelnut, celery, and carrot.⁴⁵

BAT assays generally have comparable sensitivity to SPT and sIgE but improved specificity as a diagnostic test for FA. In cases in which SPT and sIgE provide equivocal or inconclusive results, BAT may be useful as an intermediate step before proceeding with an OFC to confirm tolerance or FA.

BAT differentiates between FA phenotypes. For example, milk-specific basophil reactivity is greater in baked milk-reactive children compared with baked milk-tolerant but nonheated milk-reactive children.⁴⁸ BAT results also correlate with DBPCFC severity scores in a study of 12- to 45-year-olds with peanut, tree nut, fish, shrimp, and sesame allergy.⁴⁶

BAT may be useful in evaluating for the resolution of food allergies, such as milk,⁴⁹ wheat,⁵⁰ and egg,⁵¹ which are often outgrown, and for helping determine when these may be safely reintroduced into a child's diet. Decreased basophil sensitivity and reactivity have been observed for patients with clinical response (desensitization) to sublingual and oral immunotherapy for peanut,⁵² cow's milk,⁵³ and egg.⁵⁴ BAT may eventually be used to assess the development of clinical tolerance and response to immune-modulating therapies for FA.

BAT remains a research modality and is not likely to be used as a stand-alone test for the diagnosis of FA. Additional studies are needed to standardize the laboratory assay methods and validate BAT values for different food allergens and for different populations, as well as for assessing the utility of BAT for monitoring natural resolution of FA and clinical response to emerging therapies for FA. BAT results may eventually be considered in combination with other diagnostic tests, and may improve the safety of and reduce the number of OFCs.

EPITOPE ANALYSIS

Conventional serologic and MAA testing evaluate sIgE responses to whole proteins, whereas epitope mapping allows for analysis of IgE-binding to specific segments of allergenic proteins (epitopes). Immunodominant epitopes are those that bind the most food-specific IgE and are recognized by most patients with clinical FA. IgE-binding epitopes may be sequential or conformational. Sequential epitopes are composed of a linear sequence of neighboring amino acids in a protein. Conformational epitopes include amino acids that are not sequential and are only brought together when a protein is in its tertiary (or folded) conformation.

Conformational epitopes are more susceptible to degradation by heating and enzymatic digestion, and thus may be less allergenic than linear epitopes.²⁸ Patients with

IgE recognizing sequential epitopes of ovalbumin and ovomucoid have more persistent egg allergy than those who primarily bind conformational epitopes.⁵⁵

Using protein microarray, IgE-binding to multiple short linear allergen peptides in a food allergen can also be analyzed.⁵⁶ This epitope analysis has been applied for milk, egg, and peanut. For milk allergy, patients with IgE to multiple linear allergenic epitopes in beta-lactoglobulin may have persistent cow's milk allergy compared with those who only recognize conformational epitopes on alpha-lactalbumin.⁵⁷ IgE binding to a higher number of epitopes with greater affinity may also be predictive of more severe allergic reactions, reactivity to baked milk, and more persistent milk allergy.⁵⁸ Similarly, higher epitope diversity corresponds to clinical sensitivity and severity of peanut allergy.⁵⁹

Although epitope analysis is still primarily a research modality, it may prove to be an additional tool for diagnosing symptomatic FA, differentiating among various phenotypes, and determining prognosis.

ORAL FOOD CHALLENGE

A DBPCFC is the gold standard for FA diagnosis, although single-blind and open (unblinded) OFCs, despite being more subject to bias and having more frequent false-positive results, are more practical in most clinical settings.⁶⁰

The decision to conduct an OFC should be guided by a patient's clinical history, sIgE, and/or SPT.⁶⁰ Additional diagnostic tests, once standardized, may eventually also factor into the decision to perform an OFC. An OFC should not be considered if history and/or testing are convincing that the food will provoke an acute allergic reaction. An OFC may be performed if the patient history is uncertain, or if diagnostic testing is negative, inconclusive, or below threshold levels predictive of clinical reactivity.⁷

An OFC is also warranted if clinical history or diagnostic testing indicates that FA may have resolved. The social and nutritional benefits of adding the challenge food to a patient's diet should be taken into consideration. The risks, including the potential for provoking a severe allergic reaction, and emotional consequences of not tolerating the food, should be considered carefully when deciding to perform an OFC.

The OFC should be performed in a facility where medical personnel are trained, fully equipped, and prepared to treat anaphylaxis.⁶⁰

During an OFC, the food should be given gradually in incremental doses to minimize the risk of anaphylaxis and help identify the lowest provoking dose.⁶⁰ Various forms and preparations of foods may be used, as well as different starting and total doses. Baking decreases the allergenicity of milk and egg, and may not provoke a reaction in individuals allergic to fresh or raw forms of milk and egg.²⁸ Allergenicity of beef, seafood, fruits, and vegetables can also be affected by preparation and cooking methods.²⁸ For blinded challenges, the food needs to be mixed with an appropriate vehicle that masks its taste, smell, and texture.⁶⁰ A placebo-food may also be incorporated into the challenge. Published protocols differ with regard to number and timing of dosing intervals, as well as observation periods; however, most OFCs are generally performed over several hours.⁶⁰

OFC should be discontinued if symptoms develop and treatment rendered immediately. In negative OFC (absent allergic symptoms), the patient may subsequently introduce the challenged food into their diet at home and they should be instructed to ingest the food regularly to maintain tolerance. Patients should be instructed to continue avoidance of any food that provokes an allergic reaction during OFC. Education and guidance should be provided to families for successful and safe avoidance of food allergens (<https://web.emmes.com/study/cofar/EducationProgram.htm>).

Special considerations need to be taken when conducting OFCs in infants. With current guidelines recommending early introduction of peanut to infants at high risk for developing peanut allergy, there will likely be an increased demand for peanut-OFCs for infants 4 to 11 months of age who have early onset AD (severe eczema and/or egg allergy).¹⁹ A workgroup report from the Adverse Reactions to Foods Committee of the American Academy of Allergy, Asthma, and Immunology provides specific infant peanut-OFC guidance, taking into consideration infant developmental stages and age-appropriate forms, textures, and amounts of peanut that may be offered.⁶¹

UNPROVEN METHODS

Allergen specific-IgG measurement, applied kinesiology, cytotoxicity assays, and gastric juice analysis are not recommended in the diagnosis of FA.⁷ These are discussed (See Catherine Hammond and Jay A. Lieberman's article, "[Unproven Diagnostic Tests for Food Allergy](#)," in this issue for further details).

SUMMARY

FA is rapidly evolving in the wake of increased prevalence and increased awareness among clinicians and parents alike. Promising new diagnostic methods, such as MAA, BAT, and epitope mapping, are under active investigation. Although early data are encouraging, more robust studies must be performed before these tests can be used clinically.

Standard testing for FA involves SPT and sIgE. These tests are sensitive but not specific and must be interpreted with caution. Although some highly predictive SPT and sIgE threshold levels have been determined for milk, egg, and peanut allergies, these levels are not well described for most other allergens. Attention is now focused on MAA, which will likely add to the specificity of FA diagnosis. The future of FA diagnosis perhaps lies in the use of multiple diagnostic parameters, along with clinical history to increase accuracy and to minimize dependence on OFCs.

REFERENCES

1. Boyce JA, Assa'ad A, Burks AW, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol* 2010;126(6 Suppl):S1–58.
2. Jackson KD, Howie LD, Akinbami LJ. Trends in allergic conditions among children: United States, 1997–2011. *NCHS Data Brief* 2013;(121):1–8.
3. Gupta RS, Springston EE, Warrier MR, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. *Pediatrics* 2011;128(1):e9–17.
4. Mehta H, Groetch M, Wang J. Growth and nutritional concerns in children with food allergy. *Curr Opin Allergy Clin Immunol* 2013;13(3):275–9.
5. Robbins KA, Guerrero AL, Hauck SA, et al. Growth and nutrition in children with food allergy requiring amino acid-based nutritional formulas. *J Allergy Clin Immunol* 2014;134(6):1463–6.e5.
6. Spergel JM, Paller AS. Atopic dermatitis and the atopic march. *J Allergy Clin Immunol* 2003;112(6 Suppl):S118–27.
7. Sampson HA, Aceves S, Bock SA, et al. Food allergy: a practice parameter update-2014. *J Allergy Clin Immunol* 2014;134(5):1016–25.e43.
8. Sicherer SH. Clinical implications of cross-reactive food allergens. *J Allergy Clin Immunol* 2001;108(6):881–90.

9. Perry TT, Matsui EC, Kay Conover-Walker M, et al. The relationship of allergen-specific IgE levels and oral food challenge outcome. *J Allergy Clin Immunol* 2004;114(1):144–9.
10. Khan FM, Ueno-Yamanouchi A, Serushago B, et al. Basophil activation test compared to skin prick test and fluorescence enzyme immunoassay for aeroallergen-specific Immunoglobulin-E. *Allergy Asthma Clin Immunol* 2012; 8(1):1.
11. Chokshi NY, Sicherer SH. Interpreting IgE sensitization tests in food allergy. *Expert Rev Clin Immunol* 2016;12(4):389–403.
12. Nowak-Wegrzyn A, Burks W, Sampson HA. Chapter 81: reactions to foods. In: Middleton E, Franklin Adkinson N, Busse WW, et al, editors. *Middleton's allergy: principles and practice*, vol. 2, 8th edition. Philadelphia: W B Saunders; 2014. p. 1237–59.
13. Soares-Weiser K, Takwoingi Y, Panesar SS, et al. The diagnosis of food allergy: a systematic review and meta-analysis. *Allergy* 2014;69(1):76–86.
14. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol* 2001;107(5):891–6.
15. Wang J, Godbold JH, Sampson HA. Correlation of serum allergy (IgE) tests performed by different assay systems. *J Allergy Clin Immunol* 2008;121(5):1219–24.
16. Federly TJ, Jones BL, Dai H, et al. Interpretation of food specific immunoglobulin E levels in the context of total IgE. *Ann Allergy Asthma Immunol* 2013;111(1): 20–4.
17. Gupta RS, Lau CH, Hamilton RG, et al. Predicting outcomes of oral food challenges by using the allergen-specific IgE-total IgE ratio. *J Allergy Clin Immunol Pract* 2014;2(3):300–5.
18. DunnGalvin A, Daly D, Cullinane C, et al. Highly accurate prediction of food challenge outcome using routinely available clinical data. *J Allergy Clin Immunol* 2011;127(3):633–9.e1-3.
19. Du Toit G, Roberts G, Sayre PH, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med* 2015;372(9):803–13.
20. Maloney JM, Nowak-Wegrzyn A, Wang J. Children in the inner city of New York have high rates of food allergy and IgE sensitization to common foods. *J Allergy Clin Immunol* 2011;128(1):214–5.
21. Du Toit G, Roberts G, Sayre PH, et al. Identifying infants at high risk of peanut allergy: the Learning Early About Peanut Allergy (LEAP) screening study. *J Allergy Clin Immunol* 2013;131(1):135–43.e1-12.
22. Shek LP, Soderstrom L, Ahlstedt S, et al. Determination of food specific IgE levels over time can predict the development of tolerance in cow's milk and hen's egg allergy. *J Allergy Clin Immunol* 2004;114(2):387–91.
23. Savage J, Sicherer S, Wood R. The natural history of food allergy. *J Allergy Clin Immunol Pract* 2016;4(2):196–203 [quiz: 204].
24. Wood RA, Sicherer SH, Vickery BP, et al. The natural history of milk allergy in an observational cohort. *J Allergy Clin Immunol* 2013;131(3):805–12.
25. Sicherer SH, Wood RA, Vickery BP, et al. The natural history of egg allergy in an observational cohort. *J Allergy Clin Immunol* 2014;133(2):492–9.
26. Matricardi PM, Kleine-Tebbe J, Hoffmann HJ, et al. EAACI molecular allergology user's guide. *Pediatr Allergy Immunol* 2016;27(Suppl 23):1–250.
27. Treudler R, Simon JC. Overview of component resolved diagnostics. *Curr Allergy Asthma Rep* 2013;13(1):110–7.

28. Nowak-Wegrzyn A, Fiocchi A. Rare, medium, or well done? The effect of heating and food matrix on food protein allergenicity. *Curr Opin Allergy Clin Immunol* 2009;9(3):234–7.
29. Kattan JD, Sicherer SH, Sampson HA. Clinical reactivity to hazelnut may be better identified by component testing than traditional testing methods. *J Allergy Clin Immunol Prac* 2014;2(5):633–4.e1.
30. Grabenhenrich L, Lange L, Hartl M, et al. The component-specific to total IgE ratios do not improve peanut and hazelnut allergy diagnoses. *J Allergy Clin Immunol* 2016;137(6):1751–60.e8.
31. Shreffler WG. Microarrayed recombinant allergens for diagnostic testing. *J Allergy Clin Immunol* 2011;127(4):843–9 [quiz: 850–1].
32. 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.e1-13.
33. Asaranoj A, Glaumann S, Elfstrom L, et al. Anaphylaxis to peanut in a patient predominantly sensitized to Ara h 6. *Int Arch Allergy Immunol* 2012;159(2):209–12.
34. Sicherer SH, Wood RA. Advances in diagnosing peanut allergy. *J Allergy Clin Immunol Prac* 2013;1(1):1–13 [quiz: 14].
35. 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.
36. Flinterman AE, Akkerdaas JH, den Hartog Jager CF, et al. Lipid transfer protein-linked hazelnut allergy in children from a non-Mediterranean birch-endemic area. *J Allergy Clin Immunol* 2008;121(2):423–8.e2.
37. Savvatanos S, Konstantinopoulos AP, Borga A, et al. Sensitization to cashew nut 2S albumin, Ana o 3, is highly predictive of cashew and pistachio allergy in Greek children. *J Allergy Clin Immunol* 2015;136(1):192–4.
38. Ciprandi G, Pistorio A, Silvestri M, et al. Walnut anaphylaxis: the usefulness of molecular-based allergy diagnostics. *Immunol Lett* 2014;161(1):138–9.
39. Le TA, Al Kindi M, Tan JA, et al. The clinical spectrum of omega-5-gliadin allergy. *Intern Med J* 2016;46(6):710–6.
40. Urisu A, Yamada K, Masuda S, et al. 16-kilodalton rice protein is one of the major allergens in rice grain extract and responsible for cross-allergenicity between cereal grains in the Poaceae family. *Int Arch Allergy Appl Immunol* 1991;96(3):244–52.
41. Battais F, Pineau F, Popineau Y, et al. Food allergy to wheat: identification of immunoglobulin E and immunoglobulin G-binding proteins with sequential extracts and purified proteins from wheat flour. *Clin Exp Allergy* 2003;33(7):962–70.
42. Berneder M, Bublin M, Hoffmann-Sommergruber K, et al. Allergen chip diagnosis for soy-allergic patients: Gly m 4 as a marker for severe food-allergic reactions to soy. *Int Arch Allergy Immunol* 2013;161(3):229–33.
43. Commins SP, Satinover SM, Hosen J, et al. Delayed anaphylaxis, angioedema, or urticaria after consumption of red meat in patients with IgE antibodies specific for galactose-alpha-1,3-galactose. *J Allergy Clin Immunol* 2009;123(2):426–33.
44. Hoffmann HJ, Santos AF, Mayorga C, et al. The clinical utility of basophil activation testing in diagnosis and monitoring of allergic disease. *Allergy* 2015;70(11):1393–405.
45. Santos AF, Brough HA. Making the most of in vitro tests to diagnose food allergy. *J Allergy Clin Immunol Prac* 2017;5(2):237–48.

46. Song Y, Wang J, Leung N, et al. Correlations between basophil activation, allergen-specific IgE with outcome and severity of oral food challenges. *Ann Allergy Asthma Immunol* 2015;114(4):319–26.
47. Hauswirth AW, Natter S, Ghannadan M, et al. Recombinant allergens promote expression of CD203c on basophils in sensitized individuals. *J Allergy Clin Immunol* 2002;110(1):102–9.
48. Ford LS, Bloom KA, Nowak-Wegrzyn AH, et al. Basophil reactivity, wheal size, and immunoglobulin levels distinguish degrees of cow's milk tolerance. *J Allergy Clin Immunol* 2013;131(1):180–6.e1-3.
49. Rubio A, Vivinus-Nebot M, Bourrier T, et al. Benefit of the basophil activation test in deciding when to reintroduce cow's milk in allergic children. *Allergy* 2011;66(1):92–100.
50. Nilsson N, Nilsson C, Hedlin G, et al. Combining analyses of basophil allergen threshold sensitivity, CD-sens, and IgE antibodies to hydrolyzed wheat, omega-5 gliadin and timothy grass enhances the prediction of wheat challenge outcome. *Int Arch Allergy Immunol* 2013;162(1):50–7.
51. Sato S, Tachimoto H, Shukuya A, et al. Basophil activation marker CD203c is useful in the diagnosis of hen's egg and cow's milk allergies in children. *Int Arch Allergy Immunol* 2010;152(Suppl 1):54–61.
52. Thyagarajan A, Jones SM, Calatroni A, et al. Evidence of pathway-specific basophil anergy induced by peanut oral immunotherapy in peanut-allergic children. *Clin Exp Allergy* 2012;42(8):1197–205.
53. Frischmeyer-Guerrero PA, Masilamani M, Gu W, et al. Mechanistic correlates of clinical responses to omalizumab in the setting of oral immunotherapy for milk allergy. *J Allergy Clin Immunol* 2017. [Epub ahead of print].
54. Vila L, Moreno A, Gamboa PM, et al. Decrease in antigen-specific CD63 basophil expression is associated with the development of tolerance to egg by SOTI in children. *Pediatr Allergy Immunol* 2013;24(5):463–8.
55. Jarvinen KM, Beyer K, Vila L, et al. Specificity of IgE antibodies to sequential epitopes of hen's egg ovomucoid as a marker for persistence of egg allergy. *Allergy* 2007;62(7):758–65.
56. Lin J, Bardina L, Shreffler WG, et al. Development of a novel peptide microarray for large-scale epitope mapping of food allergens. *J Allergy Clin Immunol* 2009;124(2):315–22, 322.e1-3.
57. Jarvinen KM, Chatchatee P, Bardina L, et al. IgE and IgG binding epitopes on alpha-lactalbumin and beta-lactoglobulin in cow's milk allergy. *Int Arch Allergy Immunol* 2001;126(2):111–8.
58. Wang J, Lin J, Bardina L, et al. Correlation of IgE/IgG4 milk epitopes and affinity of milk-specific IgE antibodies with different phenotypes of clinical milk allergy. *J Allergy Clin Immunol* 2010;125(3):695–702, 702.e691-702.e696.
59. Flinterman AE, Knol EF, Lencer DA, et al. Peanut epitopes for IgE and IgG4 in peanut-sensitized children in relation to severity of peanut allergy. *J Allergy Clin Immunol* 2008;121(3):737–43.e10.
60. Nowak-Wegrzyn A, Assa'ad AH, Bahna SL, et al. Work Group report: oral food challenge testing. *J Allergy Clin Immunol* 2009;123(6 Suppl):S365–83.
61. Bird JA, Groetch M, Allen KJ, et al. Conducting an oral food challenge to peanut in an infant. *J Allergy Clin Immunol Prac* 2017;5(2):301–11.e1.