

Food Allergy

Catering for the Needs of the Clinician



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KEYWORDS

- Food allergy • Food allergy prevention • Food allergy diagnosis • Serum IgE
- Skin test • Oral food challenge • Oral immunotherapy

KEY POINTS

- Clinicians are caring for an increasing number of patients with food allergy of different ages, gender and ethnic/racial background. This is due to an increased prevalence of the disorder and in part due to increased awareness.
- Early food introduction for the prevention of peanut allergy and oral immunotherapy with peanut have generated a change in paradigm in the approach of the clinician to prevention and management of food allergy. Use of biologics for food allergy is highly anticipated.
- Clinicians have been given much welcomed national and international guidelines for the diagnosis of food allergy and for the prevention of peanut allergy.
- Clinicians continue to be faced with the high sensitivity but low specificity of the available skin tests and serum IgE tests for food allergy, even with the availability of component resolved diagnostics.
- The oral food challenge remains the most reliable confirmatory test for food allergy. Clinicians will welcome novel tests that may avoid the oral food challenge or ameliorate its potential side effects.

A HISTORIC PERSPECTIVE

Other than the rising prevalence of food allergy (FA), as discussed by Warren, Brewer, Grobman et al: Racial/Ethnic Differences in Food Allergy¹ in this issue, over the past decade, several events have led to the heightened awareness of FA in the scientific community and in the population (**Boxes 1** and **2**). These have included guidelines on FA and novel research on prevention and therapy in addition to advocacy efforts.

A landmark event that ushered the changes seen today in the field of FA and those anticipated in the near future is the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) assembling a coordinating committee

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Box 1**Events during the past decade that resulted in a large impact on the field of food allergy in the United States**

- NIAID/NIH expert panel guidelines on food allergy
- Publication of the LEAP study results
- NIAID/NIH expert panel guidelines supplement on the prevention of peanut allergy
- Epidemiologic surveys that demonstrate the widespread diagnosis
- Completion of the clinical trials of peanut oral immunotherapy and the receipt of FDA approval for Palforzia

made up of 35 professional and lay organization stakeholders, which named an expert panel to draft the first guidelines on FA in the United States.² The guidelines were published in 2010 within the same timeframe as other international guidelines, as reviewed by Mennini, Arasi, Fiocchi et al: Developing National and International Guidelines³ in this issue. An important part of the evidence-based guidelines is the segment on the gaps in knowledge, which demonstrated to the NIH, the most reliable funding organization for research, that there are many areas in FA that need to be investigated.

On the prevention front, initial recommendations for prevention of FA by avoiding highly allergenic foods in the first 3 years of life published in 2000 were reversed in 2008, citing no or little evidence that delaying timing of the introduction of complementary foods beyond 4 months to 6 months of age prevents the occurrence of atopic disease. Despite evidence-based publications to promote the reversal of recommendations, it was not universally accepted or implemented, as shown in a study examining the knowledge and implementation differences between urban and suburban populations.^{4,5} It was not until the primary prevention study that has come to be known by its acronym, the Learning Early About Peanut Allergy (LEAP) study, was published and received large publicity, that a change in paradigm occurred.⁶ This was followed by another NIAID/NIH expert panel supplement to the guidelines, this time for the prevention of peanut allergy.⁷ For the first time, the practice of allergists started seeing infants at a very young age, either because parents wanted guidance on implementing the guidelines or for the evaluation of reactions related to early introduction of allergenic food in infants at risk. Using Current Procedural Terminology (CPT) codes to categorize the diagnosis in the authors' practice shows that FA diagnosis has reached 44% and, along with eczema, which constitutes 7% and commonly accompanies FA, makes for patients with FA constituting half the number of patients in the practice (Fig. 1).

On the therapy front, in 2012, the first of the Consortium of Food Allergy Research (CoFar) studies of oral immunotherapy for egg was published, followed by several other results of maintenance therapy and sustained unresponsiveness.^{8–12} Studies of oral immunotherapy for peanut were launched soon after by the CoFar centers and reported

Box 2**Events that are expected to impact in the near future the field of food allergy in the United States**

- FDA review of the data on the effect of epicutaneous immunotherapy on peanut allergy
- Completion of multiple clinical trials of biologics in patients with FA
- The Food Allergy Research and Education patient advocacy organization assembling more than 50 centers of excellence in clinical care and research around the country

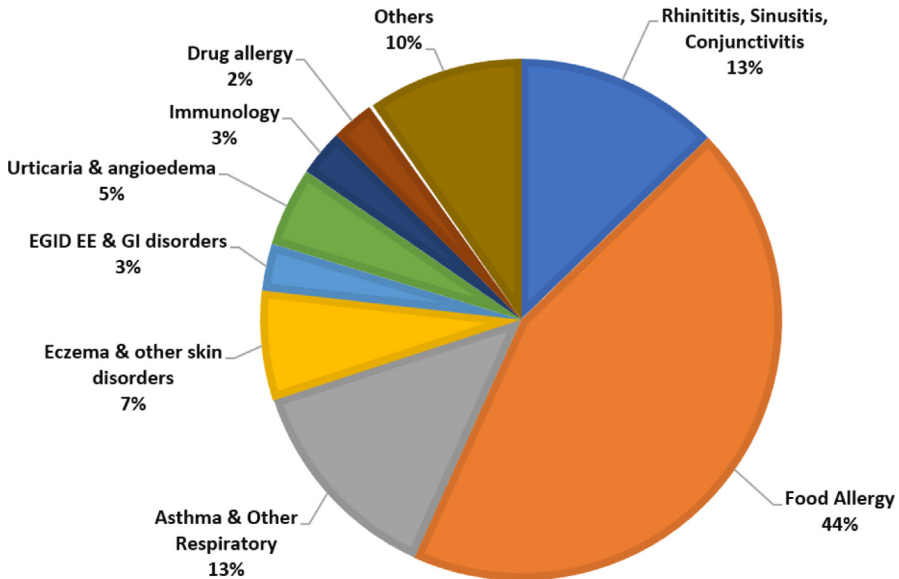


Fig. 1. An example of the current mix of patient diagnosis in an academic allergy practice showing that FA diagnosis and the related eczema diagnosis constitute more than half of the diagnoses. EE, Eosinophilic Esophagitis; EGID, Eosinophilic Gastrointestinal Disorder; GI, Gastrointestinal.

on sublingual immunotherapy for peanuts and moved on to epicutaneous immunotherapy.⁹ Around the same time, 2 pharmaceutical companies launched clinical trials for peanut oral immunotherapy (Allergen Research Corporation, which later became Aim-mune, Brisbane, CA, USA) and for epicutaneous immunotherapy by DBV Technologies, Montrouge, France. This was another paradigm change where exposure to the allergen, albeit in small gradually increasing amounts and under strict medical supervision, rather than avoidance, became an optional therapeutic modality. Several publications chronicled the progress and successes of these forms of therapy.^{13–18} The clinical trials led to the approval by the US Food and Drug Administration (FDA) of AR101, now Palforzia, for the treatment of peanut allergy in 4-year olds to 17-year olds. Oral immunotherapy became another reason that patients with FA flocked to allergists practices. This due to the fact that oral immunotherapy has been conducted with foods in their natural form in practices and under research protocols. The controversy over the practice led to the publication of a white paper by leaders of various national organizations and stake holders.¹⁹

With the rise of numbers of patients with FA seen by clinicians come more questions about the epidemiology of the disorder, the accuracy of the diagnostic tools, and the benefits and potential side effects of the therapies. Besides the topics discussed later, clinicians can avail themselves of collaborations with dietitians, as discussed by Durban, Groetch, Meyer et al: Dietary Management of Food Allergy in this issue,²⁰ and with psychologists, as discussed by Rubeiz and Ernst: Psychosocial Aspects of Food Allergy in this issue.²¹

EPIDEMIOLOGY

Prevalence

Published figures on the prevalence of FA are estimates and vary widely.^{2,22–26} They are influenced by multiple factors, including definitions, foods studied, diagnostic

methods, age of subjects, infant feeding methods, and geographic dietary habits.²⁷ In recent years, survey estimates of the prevalence of food allergy have been 1 in 13 children and 1 and 10 in adults.^{26,28} What is more important is the rising trend that has been well documented by many studies in different countries.^{29–37} Such a trend seems to be more real than due to improved diagnosis and is more conspicuous in Western countries. The prevalence over-estimates, based on self-diagnosis reported on surveys or on positive allergy skin or serum testing that reflect sensitization that may or may not be clinically relevant, still translate to FA. This led to FA patients becoming the largest number of patients seen in an allergy clinic today, patients with asthma and allergic rhinitis and other atopic conditions. (see [Fig. 1](#)).

Figures based on FA confirmed by appropriate challenge testing are scarce and cannot be generalized. Several studies have shown that when food challenges are performed in the office, only approximately a third result in an allergic reaction consistent with FA.³⁸ On the other hand, the patients who are given a diagnosis of an FA, whether clinically significant or not, live the life of patients with FA, with all the stresses and the needs, as discussed by Engel and Bunning: The Unmet Needs of Patients with Food Allergies in this issue.³⁹ This makes the prevalence that may be based on self-reports, even if an over-estimate, still significant. The prevalence of FA among various ethnic and racial backgrounds in the United States and the current state of knowledge and research are discussed in the article by Warren, Brewer, Grobman et al: Racial/Ethnic Differences in Food Allergy¹ in this issue. There are some ethnic groups in the United States, however, who are not yet studied. Attention recently has been drawn to the Asian population in the United States by the authors' research that examined scores for anxiety over FA from a questionnaire. The research found that the Asian population in the United States is highest in anxiety scores compared with whites, blacks, and Latinex.⁴⁰

Causative Foods

Knowledge of the common food allergens can guide a clinician's approach to the diagnosis, even though, theoretically, any food can cause allergy. The most allergenic foods are those with high protein content, with multiplicity of allergenic components, and that are consumed frequently. The NIAID/NIH expert panel guidelines published in 2010 reviewed the evidence-based literature that addressed FA in the United States. At that time, the common food allergens were cow milk, eggs and peanuts, fish, and crustaceans in all ages both by self-report and by self-report combined with skin tests and/or serum IgE. Cow milk allergy was stated to be more common in children than adults.² The guidelines also stated that allergy to fruits, vegetables, nonpeanut legumes, wheat, and soy were much less common compared with the 5 food groups listed. The Food Allergen Labeling and Consumer Protection Act of 2004 listed the top 8 foods as peanut, cow milk, hen egg, shellfish, tree nuts, wheat, fish, and soy.⁴¹ Recently, the US Senate passed the Food Allergy Safety, Treatment, Education, and Research Act, which directs the Centers for Disease Control and Prevention to expand data collection of information related to food allergies and specific allergens and revises the definition of major allergen to specifically include sesame.

FA varies by ethnicity and geographic location. Thus, in the absence of diagnostic modalities with high sensitivity and specificity, clinicians need to be aware of the common food allergies in their communities and in the age range that they serve.

Clinical Manifestations

The clinician usually is presented with 1 or a set of symptoms. IgE-mediated FA can cause symptoms in the skin, the gastrointestinal tract, the respiratory tract, or in

multiple systems simultaneously, that is, anaphylaxis⁴² (Fig. 2). The symptoms of IgE-mediated FA can coexist or overlap with symptoms of other disorders in the same organ system. Multiple manifestations can be caused by a single food or 1 manifestation be caused by multiple foods. The latter may or may not be cross-reactive. The oral allergy syndrome (pollen-FA syndrome) typically is caused by certain food allergens that cross-react with certain pollen allergens.^{43,44} Allergy to galactose-alpha-1,3-galactose (alpha-gal) is a late IgE-mediated hypersensitivity that occurs a couple of hours after eating red mammalian meat in subjects sensitized through the bite of the tick *Ixodes racinus*.⁴⁵

DIAGNOSIS

A diagnosis of FA has 2 main stages. First is a patient's illness an allergic disease? Depending on information from the medical history and findings from the physical examination, a differential diagnosis can be formulated. Second, if FA seems to be the most likely diagnosis, what is (are) the causative food(s)? The latter may be suspected through the medical history and allergy tests.

Medical History

The general population often attribute various symptoms to FA, may not be confirmed in some cases. In a few cases, the relationship between ingesting a certain food and the recurrence of symptoms is so convincing that further testing may not be necessary. Skillful history taking may narrow down the list of suspected foods.

Skin Testing

Percutaneous testing has been well established as the most common allergy testing procedure for IgE-mediated reactions. It is an in vivo test in which the allergen extract (1:10 wt/vol or 1:20 wt/vol) is brought in contact with the cutaneous mast cells using skin prick (or skin puncture) test (SPT). If IgE antibodies specific to the allergen are on the mast cell, histamine and other mediators are released, causing local

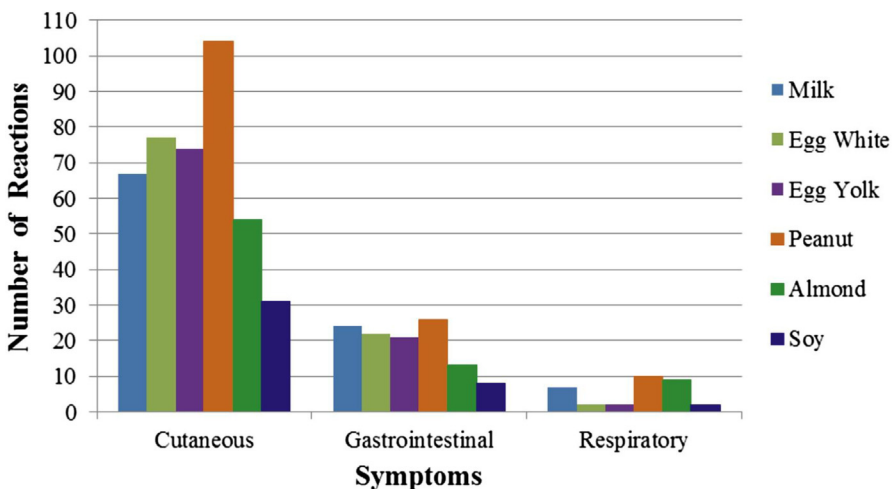


Fig. 2. Frequency distribution of presenting symptoms in patients with FA. Figure from Amin, Khoury and Assa'ad. Food-specific serum immunoglobulin E measurements in children presenting with food allergy. Ann Allergy Asthma Immunol 2014; 112(2):121-5.

vasodilatation, erythema, wheal formation, and irritation of the nerve endings. The area of the reaction is compared with the negative control (diluent) and the positive control (histamine). The larger the reaction, the more likely the allergen is the culprit. The test in patients with eczema and high serum total IgE level usually is positive to many foods, most of which are not clinically relevant. SPT has several advantages and a few disadvantages (**Table 1**). Because the allergenicity of extracts can be different from the consumed food, testing with the actually ingested food (prick-by-prick) may be done.⁴⁶ Some investigators reported SPT wheal size cutoff values that showed high correlation with positive challenge testing. Not surprisingly, such cutoff values vary among different studies because of the variability in the patient populations studied, the age, and the symptoms and their severity. They thus are difficult to generalize or be applied to individual patients in clinical practice.^{47–54}

The general consensus is that a large positive SPT to a food is an indication that the test is a definite positive and an indication of the presence of sensitization to the food, but is not an indication of clinical allergy or the severity of a reaction. The NIH expert panel supplement to the Guidelines for the Prevention of Peanut Allergy, however, has utilized SPT size of the wheal to determine the risk of peanut clinical reactions in infants. The size of the wheal to a peanut SPT is used in the guidelines to determine whether the infant can have peanut introduced at home, introduced in the office through an observed feeding, introduced only after a graded oral challenge in the office determines tolerance to peanut, or avoided because the risk of clinical reaction is high.⁷ These cutoffs were derived from the LEAP study, upon which the guidelines were based, with additional data from the HealthNuts study.⁵⁵ More recent further analysis of the LEAP data, with comparison of the SPT and the basophil activation test (BAT) performance regarding sensitivity, specificity, and prediction of reaction severity, reported that the SPT is best at detecting low threshold reactions to peanut.⁵⁶ The SPT remains one of the most used tests for FA in the allergist office, and intradermal testing, which has not been recommended because of its high false-positive result and potential risk in very sensitive subjects, has been studied and utilized in the diagnosis of red meat allergy produced by sensitization to the cross-reacting allergen alpha-gal.^{57,58}

Patch testing is of little use for IgE-mediated FA. It can be useful in identifying the food causing allergic contact dermatitis in food handlers.

Serologic Testing

Specific IgE antibodies

Serum testing for allergen-specific IgE antibodies (sIgE) was developed in 1968, just a year after the discovery of IgE. The original assay was the radioallergosorbent test,

Table 1 Advantages and potential disadvantages of the skin test procedure for the diagnosis of food allergy	
Advantages of Skin Prick Tests	Disadvantages of Skin Prick Tests
In-office procedure	Variation in test extracts
Easy to perform	Variation in devices
Immediate results	Variation in scoring
Low cost	Effect of skin disease
Large number of allergens can be applied	Suppression by many drugs
High specificity and sensitivity	Potential risk (minimal)
Visual reinforcement (to patient & clinician)	Requires trained personnel
In vivo biologic test mimicking type I reaction	Requires knowledge in interpretation

which went through several modifications by different laboratories that resulted in increasing the test's sensitivity and avoiding the use of radioisotopes. The results of test done by different methods do not correlate well.^{59,60} At present, the ImmunoCAP assay (Thermo Fischer Scientific, Waltham, MA, USA) is the most commonly used in research and in clinical practice. There has been advances in the ImmunoCap measurement that has gotten the approval of the FDA, specifically, that the lower limit of the assay has been taken down to less than 0.1 KU/L.⁴²

As in cases of SPT, the detection of sIgE merely indicates sensitization; the higher the level, the more likely to be clinically relevant. Whereas SPT is a biologic in vivo test, sIgE assay may be considered a passive test in the sense that it merely detects circulating IgE antibodies (Table 2).

In interpreting a sIgE level, several factors need to be considered, in particular the total IgE level. The higher the latter, the less likely for slightly and moderately elevated sIgE to be clinically relevant. Serial follow-up measurement of sIgE level can be helpful in predicting the attainment of tolerance. In 1 study on children with milk or egg allergy, however, even when sIgE decreased to 1% of the initial level, milk was not tolerated in 6% and egg in 5% of children.⁶¹ Several investigators reported cutoff sIgE levels that strongly correlated with positive challenge testing. As with studies on SPT, such levels varied from one study to another, obviously because they were based on different patients' samples that varied in several ways. Hence, they cannot be generalized or applied to individual patients who are not seeking probabilities but expect a definite identification of the culprit food(s).^{62–68}

Component-resolved diagnostic testing

Component-resolved diagnostic test (CRDT) has been developed recently. Whereas routine sIgE testing detects antibodies to the whole protein, CRDT measures the sIgE level to the food's major protein components. Such information was found to have high correlation with diagnostic precision, allergen cross-reactivity, and prognosis.^{69,70} The test currently is available for several foods. It is costly and is not a substitute to conformation by challenge testing. In a study on sera of peanut allergy patients from 3 countries, the results revealed geographic/genetic differences. The most predictive antibodies in Americans were to Ara h 1, Ara h 2, and Ara h 3; in Swedes, to Ara h 8; and in the Spanish, to Ara h 9.⁷¹

Cellular Tests

Basophils, as the circulating cells bearing high-affinity receptors for IgE, have been explored for potential in vitro diagnosis of FA. Two main methods were tried, namely BAT and basophil histamine release (BHR) test.

Table 2

Advantages and potential disadvantages of food-specific, serum-specific IgE test procedure for the diagnosis of food allergy

Advantages of Food-specific, Serum-specific IgE Test	Disadvantages of Food-specific, Serum-specific IgE Test
Quantitative	High cost
Very safe	Delay in result
Unaffected by medications	Less impressive to patient
Provides results for protein components of a single food allergen	Variability among methods, laboratories, and allergens
	Requires knowledge in interpretation

A patient's basophils are incubated with various food allergens. If the cells are bearing IgE antibodies specific to that allergen, activation occurs (BAT) that can be measured by flow cytometry for the cell surface markers CD63 and CD203c.^{72–75} Performing the test in microtiter plates, the basophils release their mediators, mainly histamine (BHR), that become adsorbed to the plate wells and can be measured.⁷³ Both tests have sound scientific basis. They require rapid processing of the blood samples as well as expensive equipment and special expertise. The few published studies showed promising results and work is in progress toward increasing the test's reproducibility and reliability. Although certain kits are marketed, these tests are not available in commercial laboratories and are considered investigational at this time.

Challenge Testing

Because FA commonly is over-diagnosed or misdiagnosed, depending on the diagnostic procedures discussed previously, verification of the offending food by the challenge test is required in most cases.²⁹ The procedure consists of safe administration of the food under supervision for accurate assessment and prompt treatment of any developing reaction.^{76–78}

In patients with persistent symptoms, all suspected foods should be simultaneously strictly avoided to document definite improvement while on no or minimal symptomatic medications. The test material, one at a time, is administered in a titrated fashion. The start dose should be safe, and the cumulative dose should be at least equivalent to the usually consumed quantity. Depending on the degree of concern about bias by the patient or the observer, the procedure may be carried out in any of 3 ways: open, single-blind, or double-blind. A guideline on the oral food challenges was published in 2009 and recently updated in 2020.^{78,79} Another guideline was published on conducting food challenges in infants.^{80,81}

Challenge testing is essential particularly in evaluating reactions to food additives. They are thousands that increasingly are incorporated in foods yet are difficult for patients to suspect or to test reliably by skin or blood tests. Evaluation for suspected reactions to additives and spices require special approaches.^{82,83}

Unproved Tests

Several procedures have been promoted in various countries over the years for FA diagnosis but without proved adequate reliability. They include, but are not limited to, specific IgG or IgG4 antibodies, cytotoxic test, change in leukocytes size, neutralization-provocation test, hair analysis, electrodermal Vega test, kinesiology, and iridology.^{84,85}

MANAGEMENT OF FOOD ALLERGY

Dietary Avoidance

Once the culprit food is identified, management basically is strict avoidance of that food, which can be difficult for patients allergic to multiple foods or to a food that commonly is incorporated in the usual diet. Patients should be provided with lists of foods that may contain that food allergen and be counseled on reading labels of commercially prepared foods, including unfamiliar names, such as casein, whey, ovalbumin, ovomucoid, and so forth. Highly sensitive patients may need to avoid exposure by skin contact, particularly if they have eczema, and by inhalation, particularly if they have asthma.^{86,87}

Although some subjects allergic to milk or egg may tolerate these foods in baked goods, approximately 1 in 5 milk-allergic subjects may react to beef that is not well cooked.^{88–90} Patients should be advised strongly against cross-reacting foods unless

they are sorted out by challenge testing. For example, more than 90% of subjects allergic to bovine milk do not tolerate milks of sheep or goat.^{91–93} A person allergic to a crustacean is unlikely to tolerate another crustacean. Hypoallergenic formulas are needed for infants who are allergic to milk or to multiple foods.⁹⁴ On the other hand, most fish-allergic subjects can tolerate one or more fish species.⁹⁵ Subjects with food-dependent, exercise-induced anaphylaxis should allow at least 4 hours between eating the offending food and exercise.^{96,97} In certain cases, the reaction occurred only when a combination of multiple foods were eaten or when cofactors, such as hormonal changes, occur.^{98,99}

Studies on using probiotics showed inconsistent findings possibly due to differences in study design, age of subjects, and the organism regarding type, dose, duration, and route of administration.^{100–104}

Pharmacotherapy

Pharmacologic agents are used primarily for symptomatic treatment tailored to the clinical manifestation. Patients who had anaphylaxis or severe systemic reaction should be provided with an anaphylaxis treatment plan and epinephrine autoinjector.

New biologic agents have been studied and showed promising results in particular protocols. These are reviewed by Albuhaireh and Rashid: Biologics and Novel Therapies for Food Allergy¹⁰⁵ in this issue. Although none is approved yet by the FDA for treating FA per se, a few are approved for certain allergic disorders that FA may be involved in. In a small series of peanut-allergic patients, omalizumab showed promising results in preventing reaction to small quantities of peanut protein.¹⁰⁶

Immunotherapy

Several immunotherapy protocols for FA treatment have been studied over the past several years. Routes used were sublingual, oral,¹⁰⁷ and epicutaneous.^{107–110} Various degrees of efficacy and safety have been reported, but at the time of preparing this article, only oral immunotherapy to one food is approved by the FDA. The expected benefit from immunotherapy is protection from accidental exposures to small amounts of the allergen and to not eat usual quantities.

In conclusion, several aspects of the care of patients with FA that clinicians can offer have had a breakthrough and a change in paradigms, whereas others have not changed and continue to rely on clinical acumen and tests. Clinicians are encouraged to continue to acquire expertise in the care of patients with FA, to apply the breakthroughs in the science and discoveries and to continue to be advocates for their patients.

CLINICS CARE POINTS

- Several recent advances in the care of patients with FA has led to an increase in the numbers of patients and families seeking care from clinicians for their FAs.
- Clinicians can make use of the advances in recommendations for prevention of peanut allergy and an approved therapy for peanut allergy to better the management of their patients.
- Diagnostic tools have not changed much and accurate diagnosis still relies on a combination of medical history, skin tests, serum IgE measurements, and food challenges.

DISCLOSURE

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