

Food Allergen Panel Testing Often Results in Misdiagnosis of Food Allergy

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Objective To determine the utility of food allergy panel testing among patients referred to a pediatric food allergy center.

Study design Retrospective chart review of all new patients seen between September 2011 and December 2012 by 1 provider in a tertiary referral pediatric food allergy center. A cost analysis was performed to calculate the estimated cost of evaluation for patients who have received a food allergy panel.

Results Of 797 new patient encounters, 284 (35%) patients had received a food allergy panel. Only 90 (32.8%) individuals had a history warranting evaluation for food allergy; 126 individuals were avoiding a food based on recommendations from the referring provider and 112 (88.9%) were able to re-introduce at least 1 food into their diet. The positive predictive value of food allergy panel testing in this unselected population was 2.2%. The estimated cost of evaluation for this population was \$79 412.

Conclusions Food allergy panel testing often results in misdiagnosis of food allergy, overly restrictive dietary avoidance, and an unnecessary economic burden on the health system. (*J Pediatr* 2014; ■: ■-■).

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The prevalence of food allergy has increased over the past decade with recent studies estimating nearly 1 in 13 children are diagnosed with a food allergy.^{1,2} Specific IgE testing plays an important role in diagnosing food allergy although currently available serum testing modalities are overly sensitive and carry a high false positive rate.^{3,4} The potential of having a life-threatening food allergy significantly impacts the quality of life for food allergic individuals⁵; in addition, food avoidance carries a risk of nutritional deficiency.⁶⁻⁸ Misdiagnosis also leads to an increased economic burden on the health care system with increased costs associated with specialist referral, additional testing, and unnecessary medication prescriptions. This retrospective chart review was performed to better understand the utility of commonly used serum testing modalities and to analyze the economic consequences of food allergy testing in patients seen by 1 provider in a tertiary referral allergy clinic.

Methods

A retrospective chart review was conducted to analyze all new patient encounters seen by 1 provider in a tertiary referral food allergy center between September 2011 and December 2012. Patients were identified in whom a standard panel of food-specific IgE tests had been obtained by their primary care provider (eg, pediatrician, family practitioner, or primary care nurse practitioner). Records were excluded if individuals had a diagnosis of eosinophilic esophagitis or if a food panel had been ordered but test results were not found in the medical record.

Records were stratified based on a patient history of food allergy and whether or not the testing was warranted based on National Institute of Allergy and Infectious Diseases (NIAID) guidelines,⁹ which recommend testing for patients with: (1) a history of anaphylaxis or any combination of cutaneous, ocular, respiratory, gastrointestinal, or cardiovascular symptoms consistent with allergy that occurs within minutes to hours of ingesting food; or (2) a history of moderate-to-severe atopic dermatitis (AD). A cost analysis was performed to calculate the costs of specialty consultation, diagnostics including repeat serum testing as well as skin prick testing, and observed food challenges.

Results

A total of 797 new patient encounters were recorded. The patient population is diagrammed in **Figure 1** (available at www.jpeds.com). A standard panel of food-specific IgE tests was performed in 284 patients (35% of all visits). Food panels

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AD	Atopic dermatitis
NIAID	National Institute of Allergy and Infectious Diseases
PPV	Positive predictive value

typically included specific IgE testing for milk, egg, peanut, wheat, soy, codfish, and shrimp. Some standard panels also included scallop, corn, sesame seed, clam, beef, pork, chocolate, and/or walnut. Ten charts were excluded because of a history of eosinophilic esophagitis or food panel results were not in the medical record. Of the remaining 274 encounters, only 90 individuals (32.8%) had a history warranting evaluation for IgE-mediated food allergy. The most common reason for ordering the test in individuals without a history of IgE-mediated food allergy was allergic rhinitis (99), followed by mild AD (42), and idiopathic urticaria (19) (**Figure 2**).

The most frequently positive serum test was peanut (184), followed by wheat (176), soy (152), milk (149), and egg (130). Repeat serum testing was ordered after evaluation in our food allergy clinic for 52 individuals resulting in 314 repeat serum-specific IgE tests ordered. Repeat testing was typically performed if specific IgE testing sent with the referral had been obtained more than 1 year before evaluation or if testing was performed using an in vitro specific IgE quantification modality other than through the ImmunoCAP (Phadia, Uppsala, Sweden) platform.

Skin testing was deemed necessary after allergy specialist evaluation in our clinic, and we performed skin prick testing in 149 of the 274 (54.4%) encounters with a total of 810 pricks. Diets were altered by 126 of the 274 (45.9%) individuals based on test results and recommendations from the referring provider. Parents who did not alter their child's diet stated a num-

ber of reasons which included: (1) the parent was told to not change the diet until evaluated by an allergy specialist; (2) the parent was told to modify the diet, but she or he did not think their child had a food allergy and did not feel dietary modification was necessary; and (3) the parent was given the results but was not given further instructions.

Of the 126 who altered their diet, only 54 (42.8%) had a history warranting evaluation for IgE-mediated food allergy. None of the 72 individuals without a history of IgE-mediated food allergy was determined to have food allergy after taking a careful history, repeating testing when necessary, and performing a food challenge in 1 individual who passed the challenge.

A total of 99 food challenges were recommended after allergy specialist evaluation for 81 individuals resulting in only 6 positive challenges. Food challenges were recommended when: (1) repeat serum or skin prick testing did not surpass previously established predictive values indicating a likelihood of reacting with ingestion^{10,11}; or (2) parents were not comfortable reintroducing the food at home for fear of having a reaction. Forty-two of the scheduled challenges were not performed secondary to the individual not arriving for the appointment. Fifty-one food challenges did not result in an allergic reaction and the tested food was re-incorporated into the individual's diet.

The 54 individuals who had altered their diet and had a history of food allergy warranting testing were avoiding an average of 4.8 foods (range 2-9 foods) at the time of initial allergy evaluation. The most commonly avoided foods were peanut (50 individuals avoiding), followed by egg (43 avoiding), tree nuts (38 avoiding), and milk (32 avoiding). An average of 2 foods per individual was reintroduced (range 0-7 foods). Out of all 126 individuals avoiding foods based on testing and recommendations from a provider, 112 (88.9%) were able to reintroduce at least 1 food.

All individuals avoiding corn and chocolate based on testing and recommendations from a previous provider were advised to reintroduce these foods because history, repeat testing, and observed challenges when necessary, did not support a diagnosis of corn or chocolate allergy. Wheat was reintroduced by 75% of individuals avoiding wheat based on the same reasoning, followed by 74% of those avoiding soy, 67% of those avoiding beef, 53% of those avoiding milk, and 41% of those avoiding fish (**Figure 3**).

Of all 274 individuals tested, a previously unknown allergen was identified in only 42 patients. Milk, egg, and peanut were the most commonly identified previously unknown allergens. Food testing was deemed warranted in 38 of the 42 individuals based on either a history of food allergy (27 patients) or moderate to severe AD (11 patients). No allergen was known prior to testing in 15 of the 42 individuals. Test results for all 15 patients exceeded the 95% positive predictive value (PPV) for either specific IgE¹² or skin testing,¹¹ indicating a high likelihood of reacting with ingestion. Out of these 15 individuals without a previously known allergen, 11 had a history of moderate to severe AD. Only 4 individuals had a new allergen identified in those tested without testing warranted, giving a

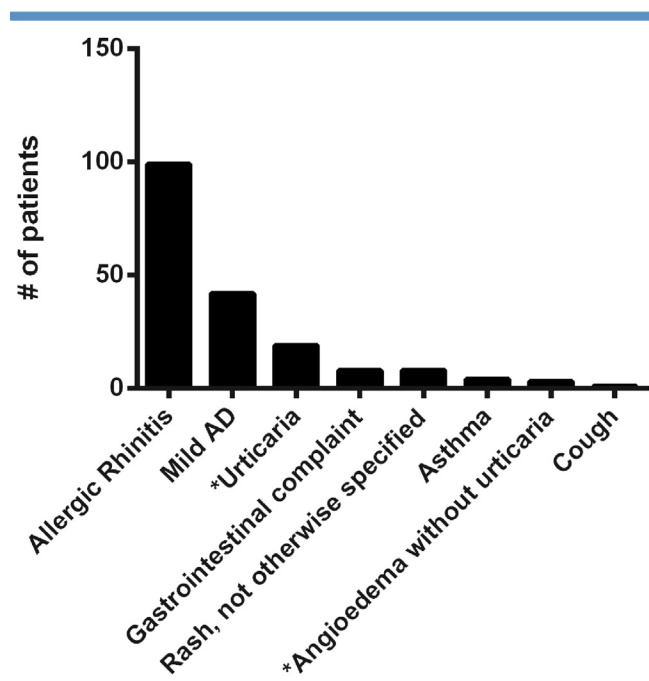


Figure 2. Diagnoses prompting food-specific IgE panel testing in patients not meeting NIAID criteria for evaluation of IgE-mediated food allergy. *Refers to cases of urticaria and angioedema that did not develop within minutes to 2 hours of food ingestion.

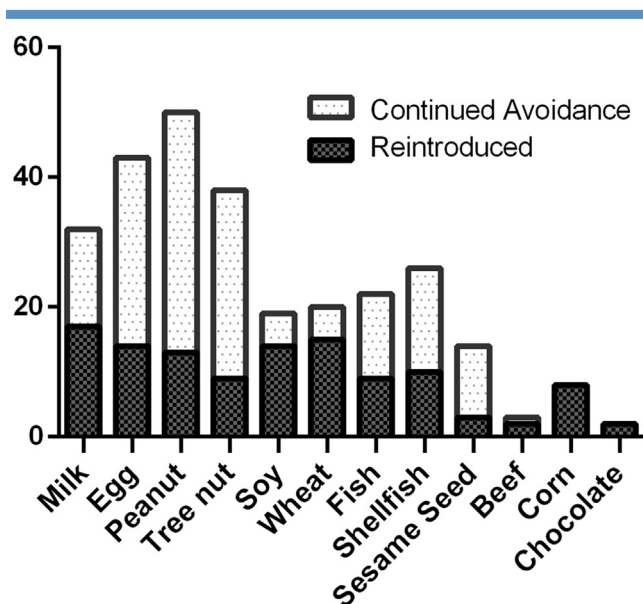


Figure 3. Foods avoided and reintroduced.

PPV of 2.2% in this population (Figure 1). The clinical characteristics of these 4 individuals are outlined in Table I (available at www.jpeds.com).

Based on 2013 Texas Medicaid fee schedules, the charge for a level 4 new patient consult visit is \$90.07, or a total cost of \$24 679.18 for the recorded 274 new patient allergy evaluations in patients whom did not merit food allergy evaluation based on NIAID guidelines.⁹ For the 149 patients who underwent skin testing, total charges for skin test evaluation were \$4317.33, or an average of \$28.97 per encounter. Charges for additional serum specific IgE testing for 52 patients (the number of patients who had repeat serum IgE testing performed at the allergy evaluation) totaled \$1786.66, or an average of \$34.36 per patient. In total, 2882 serum specific IgE tests were ordered. Average price per antigen is \$6.77, with a total charge of \$19 511.14. Of note, many state Medicaid programs limit the number of serum allergen-specific IgE tests per year (typically limited to 12 allergens per year per provider); therefore, additional allergen-specific IgE testing is not always reimbursed.

NIAID guidelines⁹ recommend providing auto-injectable epinephrine for food allergic individuals with the following characteristics: (1) any patient with a history of a prior systemic allergic reaction; (2) any patient with both food allergy and asthma; and (3) patients with a known food allergy to peanut, tree nuts, fish, and crustacean shellfish.

If an auto-injectable epinephrine device were prescribed for all individuals warranting a prescription per these recommendations, 221 individuals would have received a prescription. An EpiPen twin pack costs \$106.81, and an EpiPen, Jr twin pack costs \$107.24. Considering an average cost of \$107 per twin pack, the total costs would amount to \$23 647.

The base charge for a supervised food challenge is \$95.99 for the first 120 minutes, amounting to a conservative estimate of

\$5471.43 for all food challenges performed. This does not take into account charges for challenges extending beyond 120 minutes, treatment of reactions, and secondary costs such as time off of work and school. We also did not account for the loss of time in clinic from the patients who did not return for the scheduled food challenges (42 total scheduled food challenges). The total costs of additional evaluation in this population, conservatively amounts to \$79 412 (Table II).

Discussion

History and physical examination remain the cornerstones of food allergy diagnosis. Key features of the patient's history guide the diagnostic work-up. These important factors include the amount of time between ingestion and symptom development, the organ system(s) affected, and reproducibility of symptoms with subsequent ingestion. As stated in the NIAID guidelines, food allergy testing is not indicated for the evaluation of mild AD or isolated respiratory symptoms, such as rhinitis or asthma.

Food-specific IgE testing is a vital tool used to confirm food allergy but must be directed by clinical suspicion. Our data shows that panels of food-specific IgE tests have little utility as a screening tool prior to food introduction. More than 45% of patients in our cohort were avoiding foods based on test results and recommendations from a provider, and 88.9% of these individuals were able to safely reintroduce at least one food. Even more striking is that the PPV of testing in our population not warranting evaluation was only 2.2%.

Food allergen panels often result in over-diagnosis of food allergy.³ The gold standard for food allergy diagnosis remains the supervised oral food challenge, which is recommended to confirm food allergy in cases in which history and/or testing is inconclusive or to evaluate the development of tolerance. Food challenges must be performed by trained medical personnel in a facility equipped to recognize and treat anaphylaxis.

In this referral population, 35% of patients had inappropriate food allergy testing for a history of allergic rhinitis, mild AD, or nonspecific urticaria. The majority of these individuals were unnecessarily avoiding foods at the time of the initial allergy visit. Additional evaluation resulted in the reintroduction of an average of 2 foods per patient.

Eight foods cause 90% of food-induced allergic reactions. Those foods are milk, egg, peanuts, tree nuts, wheat, soy, fish,

Table II. Total costs

	Number of patients	Cost
Charge for new patient visits (level 4)	274	\$24 679.18
Skin testing at allergy evaluation	149	\$4317.33
Serum IgE testing at referring provider's office	274	\$19 511.14
Repeat serum IgE testing at allergy evaluation	52	\$1786.66
Food challenges performed	57	\$5471.43
Cost of auto-injectable epinephrine	221	\$23 647.00
Total		\$79 412.74

and shellfish. Testing should be based on a careful history, keeping in mind the most common food allergens. The presence of allergen-specific IgE indicates sensitization, which must be differentiated from clinical allergy. Allergy refers to the presence of allergen-specific IgE and symptoms with allergen exposure. A significant portion of sensitized individuals do not have symptoms with allergen exposure, and are therefore not clinically allergic. This explains the high rate of false positives seen with all modalities of allergy testing. Predictive values for the most common food allergens have been established¹⁰ and can aid the clinician in interpretation of testing and by improving PPV. However, it is important to keep in mind that predictive values are influenced heavily by the prevalence of the disorder. For example, Sampson et al demonstrated that the presence of milk-specific IgE (>0.35 kU/L) had a PPV of 57% in the study population but only 2% in a normalized population,¹⁰ similar to our findings.

Misdiagnosis of food allergy has many potential consequences. Food avoidance because of food allergy diagnosis has been identified as a risk factor for nutritional deficiencies,⁶ and we recently reported a child with severe malnutrition resulting from misdiagnosed food allergy.⁸ Anxiety because of food allergy affects quality of life measures for both patients and their caregivers.¹³ With the rising prevalence of food allergy, it is even more important to identify those with true food allergy and not misdiagnose those sensitized to foods that can be consumed without symptoms. Moreover, in the current era of rising health care costs, further medical evaluation, prescription drug dispensing, and additional testing have important economic consequences that must be considered.

In conclusion, food allergy evaluation must be guided by the clinical history. Our data is limited by representation of 1 provider's experience, and estimation of costs based on Texas Medicaid fee schedules. The cost estimation, however, is a most likely a conservative estimate of actual costs and the economic effects to the healthcare system are likely much greater when looking at charges to private insurance, costs of missed work, and lost revenue to healthcare providers for "no show" appointments, factors that we did not take into account. Allergy testing plays an important role in the confirmation of food allergy but has dangerous pitfalls if used inappropriately. Careful diagnostic work-up and consultation can ensure correct identification and

treatment of children with food allergy and can prevent dietary restrictions and unnecessary testing in those without food allergy. ■

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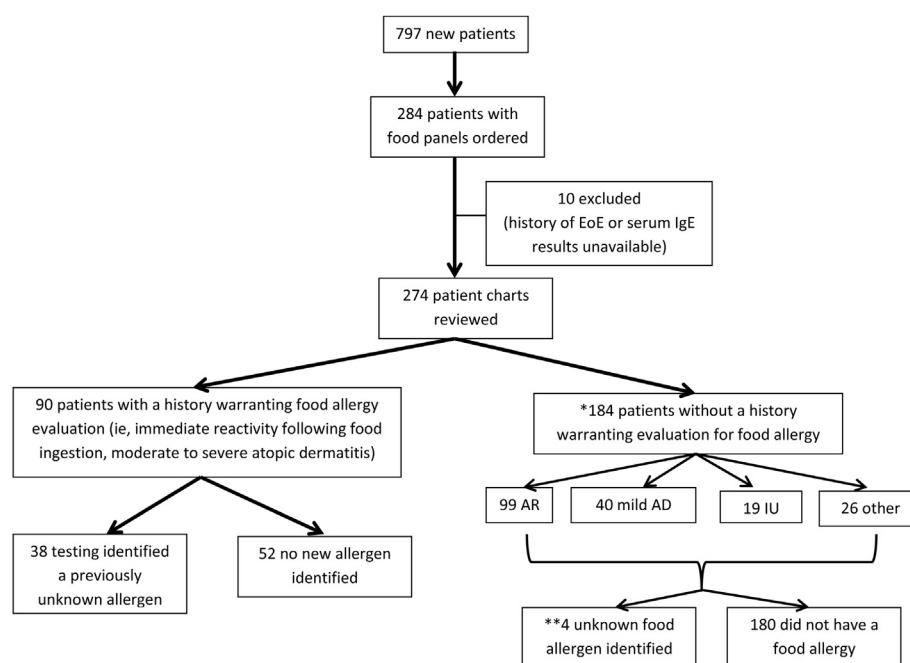


Figure 1. Patient population and stratification. *See Figure 2; **see Table I. AR, allergic rhinitis; EoE, eosinophilic esophagitis; IU, idiopathic urticaria.

Table I. Characteristics of children without a history of food allergy and likely food allergen identified

Age (years, months)	Reason test ordered	Test results exceed established 95% PPVs	Food-related history
3 y, 9 mo	Allergic rhinitis	Peanut (IgE 39.8), egg (IgE 9.86 kU/L)	Always avoided egg and peanut.
1 y, 5 mo	Perioral dermatitis	Egg (SPT 12 mm, IgE 2.11 kU/L)	Refuses to eat eggs.
7 y, 5 mo	Unclear why testing was performed in first year of life	Peanut (IgE >100 kU/L)	Avoided secondary to test result.
8 y, 4 mo	Chronic abdominal pain	Peanut (SPT 11 mm, IgE 13.5 kU/L)	Previously ingested peanut without immediate symptoms.

SPT, skin prick test.