

The use of serum specific IgE measurements for the diagnosis of peanut, tree nut, and seed allergy

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Background: The gold standard for diagnosing food allergy is the double-blind, placebo-controlled food challenge. Diagnostic food-specific IgE levels might assist in diagnosing food allergies and circumventing the need for food challenges.

Objectives: The purpose of this study was to determine the utility of food-specific IgE measurements for identifying symptomatic peanut, tree nut, and seed allergies and to augment what is known about the relationships among these foods.

Methods: Patients referred for suspected peanut or tree nut allergies answered a questionnaire about their perceived food allergies. Allergen-specific diagnoses were based on questionnaire, medical history, and, when relevant, skin prick tests and serum specific IgE levels. Sera from the patients were analyzed for specific IgE antibodies to peanuts, tree nuts, and seeds by using ImmunoCAP Specific IgE (Phadia, Inc, Uppsala, Sweden).

Results: Three hundred twenty-four patients (61% male; median age, 6.1 years; range, 0.2-40.2 years) were evaluated. The patients were highly atopic (57% with atopic dermatitis and 58% with asthma). The majority of patients with peanut allergy were sensitized to tree nuts (86%), and 34% had documented clinical allergy. The relationship between diagnosis and allergen-specific IgE levels were estimated by using logistic regression. Diagnostic decision points are suggested for peanut and walnut. Probability curves were drawn for peanut, sesame, and several tree nuts. High correlations were found between cashew and pistachio and between pecan and walnut.

Conclusions: Quantification of food-specific IgE is a valuable tool that will aid in the diagnosis of symptomatic food allergy and might decrease the need for double-blind, placebo-

controlled food challenges. (*J Allergy Clin Immunol* ■■■■;■■■:■■■-■■■.)

Key words: Food allergy, peanut allergy, tree nut allergy, serum-specific IgE

Food allergies affect approximately 6% to 8% of young children,¹ and the number of children affected appears to be increasing. In fact, 2 separate studies have reported significant increases in the rates of peanut allergy. Over a 5-year period, the rate of peanut allergy in the United States appears to have doubled in young children.^{2,3} Similarly, a cohort of children from the Isle of Wight was compared with a previous cohort in terms of clinical reactivity and sensitization to peanut, and a 2-fold increase in clinical reactivity and a 3-fold increase in peanut sensitization was reported.⁴

There is less information available regarding tree nut and seed allergies. Approximately 0.4% of the United States population is allergic to tree nuts.³ It is thought that the majority of patients retain tree nut allergy throughout their lives.⁵ Both children and adults are affected,⁶ and reactions can be severe. In fact, tree nuts are implicated as the causative foods in a large percentage of fatal anaphylactic reactions.⁷⁻⁹

The exact prevalence of seed hypersensitivity is unknown. In 2002, the French national databank reported that 2.14% of children and 5.14% of adults were affected by sesame allergy.¹⁰ The Anaphylaxis Campaign in the United Kingdom conducted a survey of its members who were avoiding sesame. The survey was prompted because the number of members avoiding sesame had doubled between April 2002 and December 2003. Approximately half of the persons surveyed reported clinical reactivity to sesame, with 18% of reactions characterized by symptoms consistent with anaphylaxis.¹¹ Recently, a report was published about the natural history of sesame allergy. The investigators of the study found that most patients had sesame allergy before the age of 2 years, and approximately 20% of those studied eventually had tolerance to the food,¹² which is similar to what is reported for peanut allergy.¹³

The diagnosis of patients with clinically reactive food allergies remains a challenge for the allergist. The double-blind, placebo-controlled food challenge is the gold standard for the diagnosis of food allergies.¹⁴ Food challenges can be traumatic for the patient, are time-consuming, and are potentially dangerous.¹⁵ Clinical diagnostic tests aid in the differentiation of patients who have favorable probabilities of tolerating foods during food challenges compared with those who are likely to react. The detection of food-specific IgE antibodies to certain foods (ImmunoCAP Specific IgE; Phadia, Inc, Uppsala, Sweden) has been shown to be predictive of symptomatic IgE-mediated food allergy.^{16,17} Diagnostic decision points have been suggested for common food

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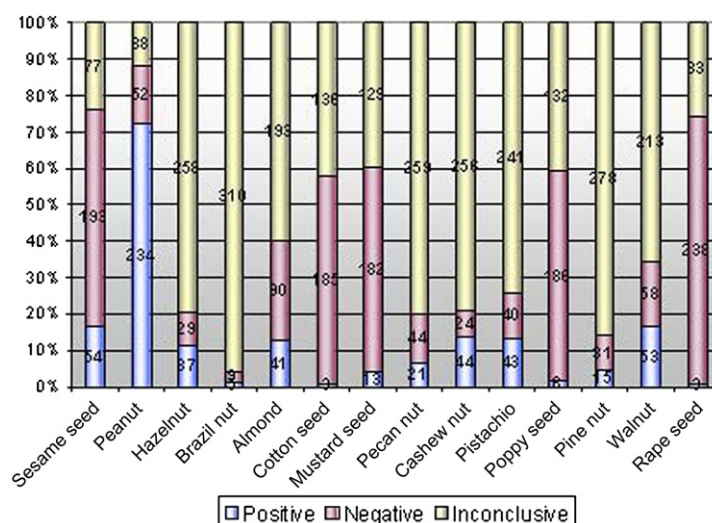


FIG 1. Characterization of the study population.

allergens, namely milk, egg, peanut, and fish. The decision points indicate reaction likelihood but do not predict reaction severity.¹⁷ Diagnostic decision points for tree nuts and seeds that could accurately be used to diagnose symptomatic allergy would greatly assist decision making in clinical practice.

The purpose of this study was to determine the usefulness of peanut-, tree nut-, and seed-specific IgE measurements (ImmunoCAP Specific IgE) for the diagnosis of symptomatic allergies and to learn more about the relationships among these food proteins.

METHODS

Children, adolescents, and adults referred to the Mount Sinai Pediatric Allergy Clinic and the Boulder Valley Asthma and Allergy Clinic in Boulder, Colorado, for evaluation of suspected IgE-mediated peanut, tree nut, or seed (sesame, mustard, poppy, rape, and cotton seed) hypersensitivity were enrolled in the study. The Mount Sinai informed consent procedure was used for all patients enrolled in the study. The physicians involved in the study protocol determined the diagnosis of food allergy. A physician's diagnosis of allergy (positive, negative, or inconclusive) was determined for peanut, each tree nut, and each seed based on the available clinical information. A patient was labeled as having a positive diagnosis if he or she had a history of clinical reactivity to the individual food, and when questionable, this reaction was supported by serologic or skin test evidence of IgE-mediated allergy to that food; a patient was considered to have a negative diagnosis if he or she could tolerate ingestion of the food; and a patient was considered to have an inconclusive diagnosis if it was unknown whether the patient could tolerate the food regardless of serologic or skin test evidence of IgE mediated allergy. A questionnaire was administered to the patients prospectively pertaining to their food allergies. Questions included demographic information, age of onset of allergy, number of accidental exposures, severity of reactions, history of concurrent food allergies, resolution of other food allergies, and history of other atopic diseases. Subjects were enrolled in the study if they had a history of a reaction that was attributed to a peanut, tree nut, or seed; had evidence of food allergy, as demonstrated by an increased serum specific IgE level and, when relevant, by skin prick testing; or both. Food challenges were not performed on the majority of patients. Although considered the gold standard methodology for the diagnosis of food hypersensitivity, the investigators did not judge food challenges to be ethically justified, and parents frequently refused to allow challenges in this highly allergic study population, which consisted predominantly of pediatric patients.

Serum samples from all patients were collected at the time of the visit and analyzed for food allergen-specific IgE antibodies by using the ImmunoCAP

Specific IgE, as previously described.¹⁶ In brief, venous blood samples were collected and analyzed with the automated ImmunoCAP System. Fifty microliters of standards or patients' sera was added to the solid matrix (ImmunoCAP) and incubated for 30 minutes. After washing, enzyme-labeled anti-IgE was added to the ImmunoCAP and incubated for 2.5 hours, after which it was washed again, and then 50 μ L of developing solution was added to each sample. After a 10-minute incubation, stopping solution was added, and fluorescence was determined and compared with values from the standard curve.

The study was approved by the Mount Sinai School of Medicine Institutional Review Board.

All statistical tests were 2-sided, and a *P* value of less than .05 was regarded as statistically significant. In patients with tree nut allergy, the Fischer exact test was used to test the hypothesis of an enhanced prevalence of allergy to a specific tree nut in relation to peanut allergy.

For single nuts and seeds, the relationship between diagnosis (positive or negative) and allergen-specific IgE antibody levels was estimated by using logistic regression. Observations with inconclusive diagnoses were not included in the analyses. The logistic regression models were formulated as the probability of receiving a positive clinical diagnosis as a function of the natural logarithm of the specific IgE concentration. Fitted predicted probability curves, using the results derived from the logistic regression models, were plotted. Performance characteristics (sensitivity, specificity, efficiency, and positive and negative predictive values) of ImmunoCAP Specific IgE were calculated at allergen-specific IgE antibody levels with a fitted predicted probability of 90% and 95%.

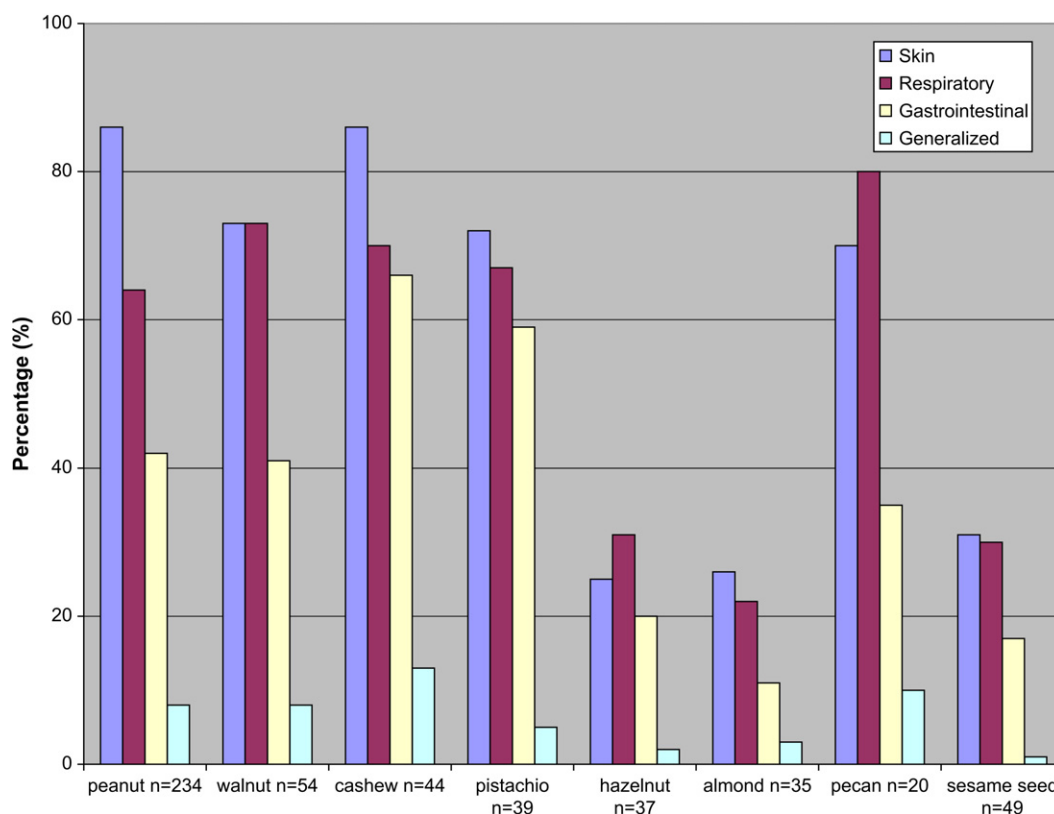
The Spearman rank order correlation coefficient was used to measure the strength of the relationship between allergen-specific IgE levels to peanut, tree nuts, and/or seeds.

RESULTS

Three hundred twenty-four patients with suspected peanut, tree nut, and/or seed allergies were enrolled in the study. The patients ranged in age from 2.4 months to 40.2 years (median, 6.1 years), and the majority of patients were male (male/female ratio, 198:126). Fifty-seven percent of patients had atopic dermatitis at some point in their lifetimes, and 58% had asthma. Many patients had other food allergies (either "outgrown" or present at the time of inclusion in the study), which occurred with the following frequencies: egg, 36.8%; milk, 29.6%; soy, 17.9%; fish, 13.3%; shellfish, 11.7%; and wheat, 10.5%.

TABLE I. Ranges of food-specific IgE levels for patients clinically allergic to each food

Allergen	n	<0.35 kUA/L (n [%])	Minimum	25th Percentile	Median	75th Percentile	Maximum
Sesame seed	54	0 (0)	0.62	2.63	7.74	29.1	>100
Peanut	234	10 (4)	<0.35	4.46	38.3	>100	>100
Hazelnut	37	8 (22)	<0.35	0.75	1.27	4.17	27.0
Almond	41	14 (34)	<0.35	<0.35	0.82	3.42	39.2
Pecan nut	21	2 (10)	<0.35	1.23	3.93	12.3	57.8
Cashew	44	3 (7)	<0.35	2.79	5.48	10.1	>100
Pistachio	43	3 (7)	<0.35	1.71	9.01	21.3	>100
Walnut	53	6 (11)	<0.35	1.39	6.51	12.0	82.3

**FIG 2.** Organ system involvement with peanut, tree nut, and seed reactions.

Seventy-two percent of the patients reported and had a convincing history of peanut allergy. Fewer patients had convincing histories of tree nut allergy; however, the majority of patients had never ingested tree nuts, making it difficult to determine the true prevalence of these nut allergies. Of the patients enrolled, tree nut allergy affected the patients with the following frequencies: walnut, 16.4%; cashew, 13.6%; pistachio, 13.3%; almond, 12.7%; hazelnut, 11.4%; pecan nut, 6.5%; pine nut, 4.6%; and Brazil nut, 1.5%. Seventeen percent of patients reported reactions to sesame seed, whereas the majority of patients (59.6%) were able to eat sesame. Few patients were allergic to the other seeds (mustard seed, 4%; poppy seed, 1.9%; cotton seed, 0.9%; and rape seed, 0.9%); however, a large number of patients did not know whether they had ever ingested the seeds or were purposely avoiding the seeds as a prophylactic measure (mustard, 40%; cotton seed, 42%; poppy seed, 41%; and rape seed, 26%). Fig 1 displays a characterization of the study population.

The ranges of increased serum specific IgE levels for each food varied widely among patients with positive diagnoses. In addition, there was marked variability among the various foods (Table I). For most of the food allergens, there were clinically allergic patients who had undetectable food-specific IgE levels. The number of patients with negative food-specific IgE levels who were labeled as clinically allergic based on a convincing history of reactivity occurred as follows: peanut, 10 (4%); hazelnut, 8 (22%); almond, 14 (34%); pecan nut, 2 (10%); cashew, 3 (7%); pistachio, 3 (7%); and walnut, 6 (11%). The median peanut-specific IgE level for allergic subjects was high (38.28 kUA/L) compared with levels for the other foods.

After peanut, tree nut, or seed ingestion, allergic subjects had cutaneous, respiratory, gastrointestinal, and/or generalized reactions. Skin and respiratory symptoms occurred commonly after the ingestion of each food. Reactions to hazelnut and pecan were accompanied by upper and/or lower respiratory tract symptoms in 84% and 80% of cases, respectively. Cashew and pecan resulted

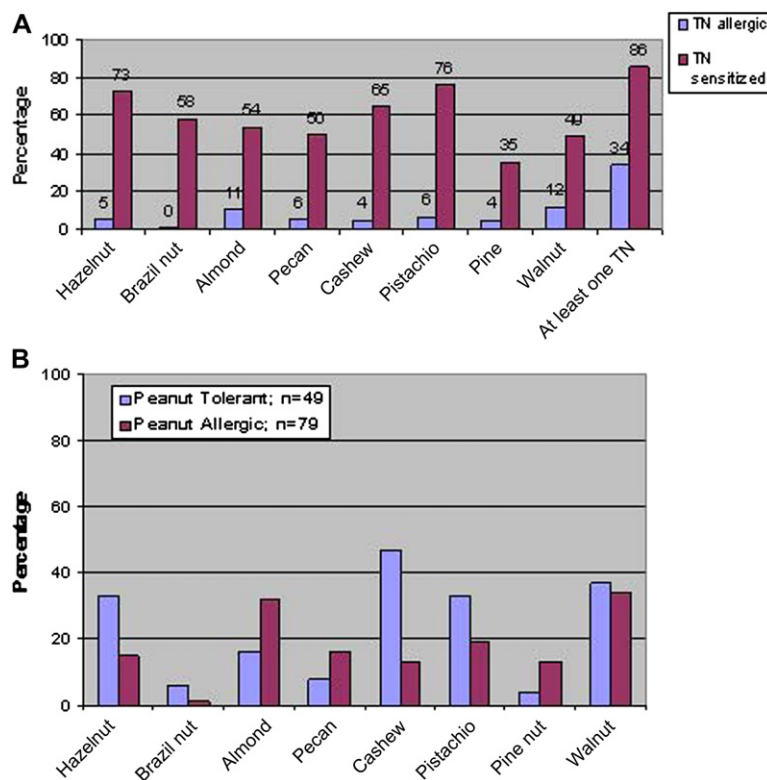


FIG 3. A, Tree nut allergy and sensitization rates in patients with peanut allergy (n = 234). B, Tree nut allergy rates in relation to peanut allergy for patients with tree nut allergy (n = 128). TN, Tree nut.

TABLE II. Allergen-specific IgE antibody levels with an estimated 90% and 95% predicted probability of clinical reactivity

Food	90% Predicted probability	95% Predicted probability
Peanut	6.0	13.0
Walnut	9.0	18.5
Pistachio	88	

TABLE III. Performance characteristics of ImmunoCAP Specific IgE at the decision points

Allergen	Decision point (kUA/L)		Sensitivity	Specificity	Efficiency	PPV	NPV
Peanut	13		60	96	67	99	35
Walnut	18.5		17	98	59	99	56

PPV, Positive predictive value; NPV, negative predictive value.

in the highest percentages of generalized reactions. Fig 2 displays the organ systems affected by the ingestion of each food.

Studies have shown an increased prevalence of tree nut allergy in individuals with peanut allergy.^{6,18-20} Similarly, in our patient population 86% of patients with peanut allergy (n = 234) had positive test results (>0.35 kUA/L; ie, were "sensitized") to at least 1 tree nut. Thirty-four percent of patients with peanut allergy were clinically reactive to at least 1 tree nut. There was a high degree of tree nut sensitization in the patients with peanut allergy compared with true allergy (Fig 3, A). When evaluating only patients with definitive tree nut allergy (n = 128), excluding those with negative and inconclusive diagnoses to all tree nuts, an enhanced prevalence of cashew ($P < .0001$) and hazelnut ($P = .03$) allergies occurred in peanut-tolerant patients compared with that seen in patients with peanut allergy (Fig 3, B).

The relationships between diagnoses and allergen-specific IgE levels were estimated by using logistic regression and illustrated in graphs for peanut, sesame, and several tree nuts. The curves illustrate the likelihood of receiving a positive clinical diagnosis in relation to the specific IgE concentration in the present study.

Allergen-specific IgE levels to the individual foods that reached a 90% and 95% predicted probability of a diagnosed allergen-specific IgE-mediated reaction are shown in Table II. The performance characteristics of the allergen-specific IgE levels that reached 95% predictive probability are also shown (Table III).

Data from patients with inconclusive diagnoses were excluded from these results. Fig 4, A, depicts the curves for peanut and sesame. The curves for pistachio, almond, and walnut, depicted in Fig 4, B, are more uncertain and require further validation because they are based on only approximately one third of the enrolled patients in the study.

Specific tree nuts display a significant amount of cross-reactivity. By using Spearman rank order correlation coefficients, the strength of an association can be measured. As the value approaches 1.0, the strength of the association increases. The correlation coefficients of specific IgE antibodies for all 324 patients are shown in Table IV. When considering all of the patients, specific IgE levels between most of the individual tree nuts were moderately correlated. For the tree nuts, the most notable correlations were between walnut and pecan (0.96), cashew

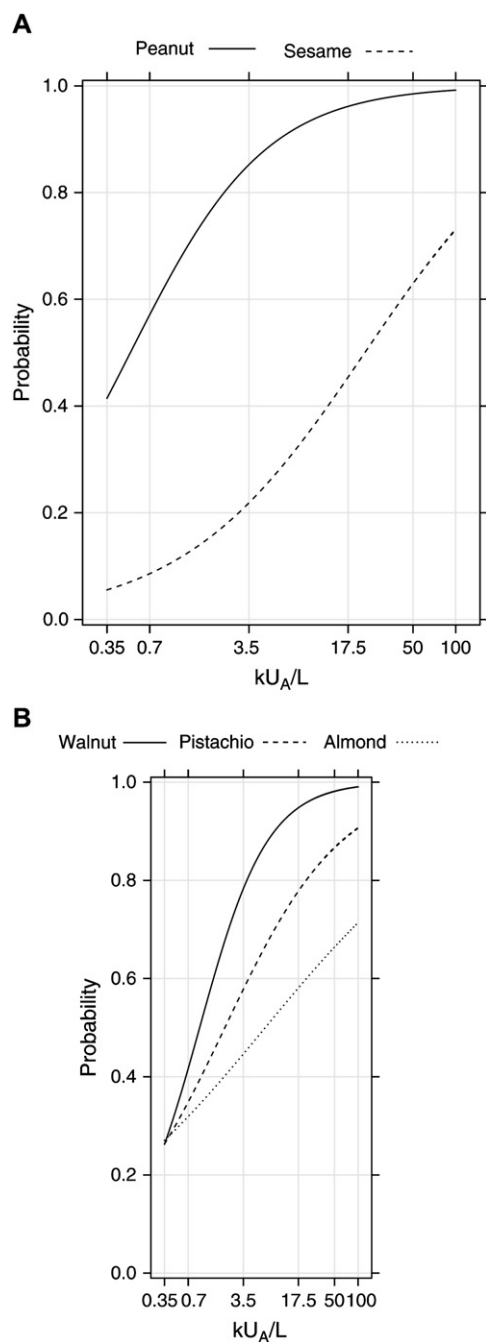


FIG 4. **A**, Fitted predicted probability curves of clinical reactivity in relation to allergen-specific IgE for peanut and sesame. **B**, Fitted predicted probability curves of clinical reactivity in relation to allergen-specific IgE for walnut, pistachio, and almond.

and pistachio (0.95), and almond and hazelnut (0.84). Peanut was not as highly correlated with tree nuts or seeds. The serum specific IgE levels between sesame and the tree nuts were moderately correlated. The same analysis was performed on other subgroups, including patients with a positive allergen-specific diagnosis to peanut and at least 1 tree nut and patients with a positive allergen-specific diagnosis to any tree nut but not to peanut. A similar pattern of correlation was noted between the IgE antibody levels in the subgroup that had allergen-specific diagnoses to peanut and

at least 1 tree nut. For the subgroup that was allergic to a tree nut but not to peanut, lower correlations were noted between certain nuts and sesame seed, as displayed in Table V. In this subgroup pecan retained a strong correlation to walnut, and pistachio retained a strong correlation with cashew.

DISCUSSION

Peanut and tree nut allergies are common, affecting more than 1% of the US population.^{2,3,21} Reactions to these foods are often severe¹⁸ and frequently occur on the first known ingestion of the food.^{6,20} These food allergies are typically lifelong, although there are small percentages of patients who do outgrow them.^{5,13} Less is known about seed hypersensitivity; however, the rate of sesame seed allergy seems to be increasing.¹¹ Reactions to sesame can be severe, and one study reported that tolerance develops in approximately 20% of those allergic to sesame.¹² Given the number of persons affected and the significant social and psychologic effect of living with food allergies and food avoidance,^{22,23} an improved understanding about the relationships among these foods is needed, and better diagnostic testing for food allergies is imperative.

The aims of this study were to learn more about the associations between the tree nuts and between tree nuts and peanut and to suggest diagnostic decision points for these foods. In previous work from our group, decision points based on 95% predicted probability of a diagnosed allergen-specific IgE-mediated reaction have been suggested for egg, milk, peanut, and fish.¹⁶ For the clinical practitioner, these decision points have helped to decrease the need for oral food challenges to aid in the diagnosis of IgE-mediated allergies to these foods. In our study we have acquired specific IgE levels with a 90% and 95% predicted probability of clinical reactivity for peanut and walnut. One should be aware that this does not automatically imply that these decision points will have exactly the same predicted probability of clinical reactivity when used in other patient populations. Apart from the uncertainty in the estimation of the decision points in the present study, there are a number of other factors that can influence their predictive ability, such as the type of population and the prevalence of disease in the situation in which the test is applied. With an obvious difference in the prevalence of disease, an appropriate shift of the curves should be considered (ie, a shift down for higher-prevalence situations and a shift up for lower-prevalence situations). Nevertheless, the suggested decision points should perform well at identifying disease in similar patient populations with a similar prevalence of food allergies (eg, a referral center for food allergy).

When looking at the performance characteristics of the allergen-specific IgE levels at the suggested decision points, sensitivities and negative predictive values are poor. Therefore patients with serum specific IgE levels of less than the diagnostic decision points might still have clinical reactivity to the food, and an oral challenge could be used for confirmation of their reactivity. The high specificities indicate that the tests perform well in those subjects without allergies, and the high positive predictive values indicate a high likelihood of disease in those with allergen-specific IgE levels of greater than the decision points. As an example based on the results, if a patient has a walnut-specific IgE level of greater than 18.5 kUA/L, the decision point with a 95% predicted probability in the study population, the patient has a very high probability of experiencing a reaction to walnut, if

TABLE IV. Correlations (r_s) among serum levels of peanut, individual tree nut, and individual seed-specific IgE in 324 patients with suspected peanut, tree nut, and/or seed allergy*

	Peanut	Hazelnut	Almond	Pecan	Cashew	Pistachio	Walnut	Sesame
Peanut	1.00	0.46	0.53	0.08	0.21	0.21	0.04	0.34
Hazelnut	0.46	1.00	0.84	0.62	0.70	0.72	0.57	0.79
Almond	0.53	0.84	1.00	0.46	0.64	0.65	0.40	0.73
Pecan	0.08	0.62	0.46	1.00	0.51	0.53	0.96	0.61
Cashew	0.20	0.70	0.64	0.51	1.00	0.95	0.45	0.61
Pistachio	0.21	0.73	0.65	0.53	0.95	1.00	0.48	0.65
Walnut	0.04	0.57	0.40	0.96	0.45	0.48	1.00	0.57
Sesame seed	0.34	0.79	0.73	0.61	0.61	0.65	0.57	1.00

*Correlation is weak if r_s is less than 0.5, moderate if r_s is 0.5 to 0.8, and strong if r_s is greater than 0.8.

TABLE V. Correlations (r_s) among serum levels of peanut, individual tree nut, and individual seed-specific IgE in 49 patients with suspected tree nut allergy who are not allergic to peanut

	Peanut	Hazelnut	Almond	Pecan	Cashew	Pistachio	Walnut	Sesame
Peanut	1.00	0.66	0.70	0.38	0.40	0.36	0.35	0.72
Hazel	0.66	1.00	0.71	0.62	0.55	0.51	0.58	0.71
Almond	0.70	0.71	1.00	0.38	0.48	0.45	0.38	0.69
Pecan	0.38	0.62	0.38	1.00	0.21	0.17	0.97	0.63
Cashew	0.40	0.55	0.48	0.21	1.00	0.98	0.21	0.42
Pistachio	0.36	0.51	0.45	0.17	0.98	1.00	0.16	0.38
Walnut	0.35	0.58	0.38	0.97	0.21	0.16	1.00	0.59
Sesame	0.72	0.71	0.69	0.63	0.42	0.38	0.59	1.00

*Correlation is weak if r_s is less than 0.5, moderate if r_s is 0.5 to 0.8, and strong if r_s is greater than 0.8.

ingested. However, given the low sensitivity of the test at this level, there will be a significant number of patients who will experience symptoms if they eat walnut and have a walnut-specific IgE level of less than 18.5 kUA/L. For patients who have never ingested the food and who have increased food-specific IgE levels that are less than the diagnostic decision point, clinical reactivity would need to be delineated by oral food challenges.

The predicted probability curves illustrate the probability of receiving a positive clinical diagnosis as a function of the specific IgE antibody level. The probability of receiving a positive clinical diagnosis increases with increasing specific IgE antibody levels. However, as depicted on the curves, even patients with undetectable serum specific IgE levels might be at risk for clinical reactivity, which is most apparent on the curve for peanut. The curves for almond, pistachio, and walnut require further validation because the majority of the patients included in the study were unsure whether they were allergic or tolerant to these foods. As a result, each of these curves was based on only approximately one third of the enrolled patients in the study. Apart from the limited number of patients, it can also be questioned whether the prevalence of reactivity to almond, pistachio, and walnut in the patients with a diagnosis also reflects the unknown prevalence in the patients with an inconclusive diagnosis.

Our investigation confirmed cross-reactivity between certain tree nut pairs, specifically cashew-pistachio and walnut-pecan. Strong associations were not present between the specific IgE levels of peanut and the tree nuts or the seeds. Despite this finding, most patients with peanut allergy are sensitized to tree nuts, and most patients with tree nut allergy are sensitized to peanut. Peanut-specific IgE antibodies have been shown to cross-react with the tree nut allergens of pecan, almond, Brazil nut, and hazelnut when using an inhibition ELISA technique.^{24,25}

Furthermore, by using a stripped basophil activation assay, *in vitro* cross-reactivity of peanut-specific IgE antibodies with almond and Brazil nut has been demonstrated.²⁶ These findings might correlate with the high degree of tree nut sensitization in patients with peanut allergy.

In our cohort 34% of patients with peanut allergy were found to be allergic to at least 1 tree nut. This finding is consistent with previous reports that indicate rates of coallergy to be between 28% and 50%.¹⁸⁻²⁰ When considering patients with a convincing history of tree nut allergy, an enhanced prevalence of hazelnut and cashew nut allergies was noted in peanut-tolerant patients (as shown in Fig 3, B).

An important limitation of this study, as well as others,¹⁸⁻²⁰ is that the diagnoses are based on self-reported convincing histories of reaction and, for ethical and practical considerations, not on double-blind, placebo-controlled food challenges. Without performing double-blind, placebo-controlled food challenges, clinical reactivity to the foods has not been confirmed. The lack of confirmed clinical reactivity impairs the ability to corroborate the decision points and precludes a final conclusion with respect to the relationships between peanut allergy and allergy to the tree nuts and seeds. Additionally, the group sizes of patients allergic to each of the individual tree nuts and seeds are relatively small. More patients will need to be studied in each group to substantiate the predictability of the probability curves and the suggested decision points and to confirm the rates of coallergy between peanut and the tree nuts. Finally, it is important for clinicians to use these food-specific IgE levels in conjunction with a thorough clinical history. Making diagnoses based on IgE testing alone will lead to overly restrictive and potentially unhealthy diets.

The suggested decision points based on a 95% predicted probability for peanut and walnut are similar to the decision

points previously reported by our group for peanut.^{16,17} Our results are also supported by an observational study of 1000 children and adults with peanut and tree nut allergy conducted by Clark and Ewan,²⁷ which suggested the utility of using 15 kUA/L as a diagnostic decision point for the diagnosis of peanut and tree nut allergy. Of the individuals in their study, only 5% of their population with serum specific IgE levels of greater than 15 kUA/L tolerated the nut, illustrating the usefulness of this cutoff in predicting symptomatic allergy.

Although it is common practice to recommend avoidance of all tree nuts for individuals with peanut or tree nut allergy, our data will assist the practicing allergist in deciding which patient is at risk for an allergic reaction. Awareness of the tree nut allergies that occur more or less commonly with peanut allergy is also valuable information that will complement patient education and anticipatory guidance. The improved understanding about an individual's food allergies might decrease some of the psychological burden that occurs for patients with food hypersensitivities.

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Clinical implications: Understanding the relationships between peanut, tree nuts, and seeds is crucial for the clinician treating patients with food allergy.

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