



IgE testing can predict food allergy status in patients with moderate to severe atopic dermatitis



Pamela A. Frischmeyer-Guerrerio, MD, PhD^{*}; Marjohn Rasooly, MSN[†];
Wenjuan Gu, MS[‡]; Samara Levin, BA^{*}; Rekha D. Jhamnani, MD^{*};
Joshua D. Milner, MD^{*}; Kelly Stone, MD, PhD^{*}; Anthony L. Guerrerio, MD, PhD[‡];
Joseph Jones, MS[§]; Magnus P. Borres, MD[¶]; Erica Brittain, PhD^{||}

^{*} Laboratory of Allergic Diseases, NIAID, NIH, Bethesda, Maryland

[†] Clinical Research Directorate/Clinical Monitoring Research Program, Leidos Biomedical Research, Inc., NCI Campus, Frederick, Maryland

[‡] Department of Pediatrics, Johns Hopkins School of Medicine, Baltimore, Maryland

[§] ImmunoDiagnostics Branch, Thermo Fisher Scientific, Phadia US Inc., Portage, Michigan

[¶] Department of Maternal and Child Health, Uppsala University, Uppsala, Sweden

^{||} Biostatistics Research Branch, DCR, NIH, Bethesda, Maryland

ARTICLE INFO

Article history:

Received for publication November 6, 2018.

Received in revised form December 26, 2018.

Accepted for publication January 2, 2019.

ABSTRACT

Background: Diagnosing food allergy in patients with atopic dermatitis (AD) is complicated by their high rate of asymptomatic sensitization to foods, which can lead to misdiagnosis and unnecessary food avoidance. **Objective:** We sought to determine whether food-specific (sIgE) or component immunoglobulin (Ig) E levels could predict allergic status in patients with moderate to severe AD and elevated total IgE.

Methods: Seventy-eight children (median age, 10.7 years) with moderate to severe AD were assessed for a history of clinical reactivity to milk, egg, peanut, wheat, and soy. The IgE levels for each food and its components were determined by ImmunoCAP. The level and pattern of IgE reactivity to each food and its components, and their ratio to total IgE, were compared between subjects who were allergic and tolerant to each food.

Results: Ninety-one percent of subjects were sensitized, and 51% reported allergic reactivity to at least 1 of the 5 most common food allergens. Allergy to milk, egg, and peanut were most common, and IgE levels to each of these foods were significantly higher in the allergic group. Component IgEs most associated with milk, egg, and peanut allergy were Bos d8, Gal d1, and Ara h2, respectively. The ratio of sIgE to total IgE offered no advantage to sIgE alone in predicting allergy.

Conclusion: Specific IgE levels and the pattern of IgE reactivity to food components can distinguish AD subjects allergic vs tolerant to the major food allergens and may therefore be helpful in guiding the clinical management of these patients.

Published by Elsevier Inc. on behalf of the American College of Allergy, Asthma & Immunology.

Reprints: Pamela A. Frischmeyer-Guerrerio, MD, PhD, Building 10, Room 11N240B, MSC 1889, 10 Center Drive, Bethesda, MD 20892; E-mail: pamela.guerrerio@nih.gov.

Disclosures: M.P. Borres and J. Jones are employees of Thermo Fisher Scientific (Uppsala, Sweden). P.A. Frischmeyer-Guerrerio has received material from Thermo Fisher to perform the IgE analyses in this project. The other authors have indicated they have no potential conflicts of interest to disclose.

Funding Sources: This research was supported by the Intramural Research Program of the National Institute of Allergy and Infectious Diseases, NIH. This project was funded in part with federal funds from NCI, NIH under Contract No. HHSN261200800001E (to W.G.). The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

<https://doi.org/10.1016/j.anai.2019.01.001>

1081-1206/Published by Elsevier Inc. on behalf of the American College of Allergy, Asthma & Immunology.

Introduction

Atopic dermatitis (AD) is the most common chronic inflammatory disease of the skin in pediatric populations, affecting up to 20% of children in industrialized countries.^{1–4} Atopic dermatitis is frequently associated with other atopic diseases.^{5,6} Up to two thirds of AD patients are sensitized to food antigens, and 15% to 40% have clinical food allergy.^{7–11} Children with severe and persistent AD are at highest risk for having coexistent food allergy.^{5,12,13}

Food-specific IgE (sIgE) testing has been reported to have limited diagnostic utility in AD patients.^{11,14,15} This has been attributed to the high levels of total serum IgE common in these patients, which can lead to false-positive testing, detecting sensitizations to foods not associated with symptoms on ingestion. This

frequently leads to unnecessary food avoidance, which can have not only adverse nutritional consequences but also a profound negative impact on quality of life. Decision points of sIgE levels for some of the most common food allergens, including milk (32 kU_A/L), egg (7 kU_A/L), and peanut (15 kU_A/L), have been defined where there is a greater than 95% probability of reacting to the food during an oral food challenge (OFC).^{16–19} However, in a cohort of 125 AD patients, no patient with a sIgE level below these 95% positive predictive values (PPV) for milk, egg, or peanut failed an OFC, suggesting that sIgE testing may not be reliable in predicting food allergy in AD populations.¹⁵

Given these challenges, great interest has been expressed in identifying strategies that will improve the accuracy of food allergy diagnosis among patients with AD. Although OFCs are the gold standard for establishing a diagnosis, these procedures are time-consuming, require specially trained personnel, and carry an inherent risk of inducing a severe allergic reaction. Some but not all studies have suggested that the ratio of sIgE to total IgE is a better predictor of OFC outcomes than sIgE levels alone.^{20–22} Other studies have found that component testing, where IgE to individual allergens is measured, may be more accurate in diagnosing food allergy than conventional IgE testing to natural extracts, which consist of a complex mixture of proteins.^{23–38} The utility of component testing has been best studied with peanut, where IgE to Ara h2 has been shown to be the single best predictor of peanut allergy.^{23–28} High IgE levels to Gal d1 (ovomucoid) and Bos d8 (casein) also have been associated with more persistent allergy and reactivity to both heated and concentrated forms of egg and milk, respectively.^{29–38}

In this study, we sought to examine the utility of specific- and component-IgE testing in predicting food allergy among children with moderate to severe AD.

Methods

Study Population

Subjects 2 to 20 years of age with moderate to severe AD were enrolled in the Natural History of Atopic Dermatitis Protocol 10-I-0148 at the National Institutes of Health. This study was approved by the institutional review board, and subjects underwent informed consent and assent, where applicable. Subjects with AD secondary to a known genetic disorder were excluded from the study.

The severity of atopic dermatitis index score (SCORAD) was assessed on all subjects. The presence of food allergy to the 5 most common food allergens was determined by a detailed clinical history and review of clinical records. To be diagnosed with food allergy, subjects had to have objective symptoms (based on the PRACTALL guidelines³⁹) of a hypersensitivity reaction to the food (eg, hives with erythema or angioedema, persistent cough, wheezing, vomiting, hypotension) within approximately 30 to 60 minutes of eating the food along with positive sIgE testing. Subjects who tolerated baked milk or egg but clearly reacted to less extensively heated forms of the food were classified as allergic ($n = 3$ for milk and $n = 2$ for egg). Subjects were classified as nonallergic to the food if they were eating the food on a regular basis in their diet with no overt symptoms. Subjects whose reactivity to a food was unclear because they had never been exposed to the food and were avoiding it because of positive testing ($n = 4$ for milk, $n = 4$ for egg, $n = 3$ for soy, $n = 0$ for wheat, and $n = 25$ for peanut) were excluded from the analysis for that food.

Serologic Measurements

Serum from each subject was initially screened for sensitization to the most common food allergens with the fx5, a multiallergen ImmunoCAP assay that detects IgE antibodies to a mix of egg white,

milk, wheat, peanut, and soybean (Thermo Fisher, Uppsala, Sweden). If the fx5 test was positive, sIgE testing was performed for cow's milk, egg white, soybean, wheat, and peanut. Reflex ImmunoCAP component testing was then performed for each food in which the sIgE test was positive (>0.10 kU_A/L). Total serum IgE was measured on all subjects by ImmunoCAP. All samples in which the IgE level was above the limit of detection (>100 kU_A/L for sIgE and component IgE; >5000 kU/L for total IgE) were diluted and re-run to obtain more precise measurements.

Statistical Methods

Wilcoxon rank sum tests were used to compare SCORAD, IgE, sIgE, component IgE, and IgE ratios between allergic and nonallergic subjects for each food; box plots illustrate these relationships graphically. The corresponding Mann-Whitney (MW) parameters were estimated to reflect the strength and direction of the relationships. The MW estimate represents the probability that a random allergic subject has a higher value on the predictor than a random nonallergic subject. The MW also equals the area under the curve of the receiver operating curve of sensitivity against $1 - \text{specificity}$ when $MW > 0.5$, and $1 - MW = \text{area under the curve}$ when $MW < 0.5$.

Logistic regression was used to estimate thresholds of each univariate predictor associated with 50% probability of allergy. Bootstrap 95% confidence intervals based on this 50% threshold were computed. The negative predictive value (NPV) and positive predictive value (PPV) were computed using a model-based approach. The NPV is the mean logistic regression estimated probability of not having allergy across all individuals with values less than or equal to the reference value. Model-based estimates of PPV were computed likewise. A special approach was used for peanut NPV and PPV, because of the substantial missingness on peanut allergy status. Although the employed logistic estimates are derived from subjects with known allergy status to peanut, the NPV and PPV computations, which use these logistic estimates, included subjects with unknown peanut allergy status to reflect the distribution of predictor values in the full cohort.

Multivariate predictors were considered using classification trees to predict milk, egg, and peanut allergy. Before examining the data, we pre-specified an algorithm⁴⁰ to determine an optimum tree considering all IgE measures relevant to the respective food allergy including ratios. The algorithm applied cross-validation to find the misclassification rate as a function of the number of nodes. Then the optimal subtree with the previously determined optimal number of nodes was selected. For those foods in which this algorithm produced a split on only a single variable, the algorithm was modified with a 2:1 misclassification cost function, and where that failed, an ad hoc multivariate tree-like rule was postulated from direct examination of the data. Scatterplots illustrate the tree decision rules.

Tests were 2-sided, and P values less than .05 were considered statistically significant. No adjustments were made for multiple comparisons, and although interpreting such results cautiously is always appropriate, the concern about multiplicity is relatively muted in this context, given the large number of highly significant results.

Results

Prevalence of Food Sensitization and Allergy

Seventy-eight subjects (65% male) with a median age of 10.7 years were enrolled (Table 1). Of these subjects, 43.6% were white, 24.4% Asian, 14.1% multiracial, 12.8% African American, 1.3% American Indian/Alaska native, 1.3% Indian, and 1.3% unknown. Four percent were Hispanic. The median total SCORAD was 45, and the median total IgE was 5338 kU/L (Table 1).

Table 1

Characteristics of Study Participants Overall, Those Allergic to at Least One of the Five Most Common Food Allergens, and Those with No Known Allergies to Any of the Five Foods

	Overall	Allergic	Nonallergic
N	78	40	38
Male N (%)	51 (65%)	28 (70%)	23 (61%)
Age (years) ^a	10.7 (7.9–14.4)	10.5 (5.7–14.6)	10.7 (8.2–14.3)
SCORAD ^a	45 (31–56)	42 (31–60)	46 (34–53)
Total IgE (kU/L) ^a	5338 (1938–14,416)	8430 (3946–19,095) ^b	3323 (1076–9140) ^b
Asthma N (%)	55 (71%)	30 (75%)	25 (66%)
AR N (%)	71 (91%)	37 (93%)	34 (89%)
EoE N (%)	3 (4%)	3 (8%)	0 (0%)
Ethnicity	3 (4%)	1 (3%)	2 (5%)
(Hispanic) N (%)			
Race N (%)			
Caucasian	34 (44%)	20 (50%)	14 (37%)
Asian	19 (24%)	10 (25%)	9 (24%)
African American	10 (13%)	3 (8%)	7 (18%)
Multiracial	11 (14%)	7 (18%)	4 (11%)
American Indian/Alaska Native	1 (1%)	0 (0%)	1 (3%)
Indian	1 (1%)	0 (0%)	1 (3%)
Unknown	2 (2%)	0 (0%)	2 (6%)

Abbreviations: AR, allergic rhinitis; EoE, eosinophilic esophagitis.

^aMedian (25th–75th percentile).

^bTotal IgE significantly different between allergic and nonallergic groups; $P = .0165$.

Ninety-one percent of subjects were sensitized (sIgE > 0.10 kU_A/L) to at least 1 of the 5 most common food allergens (91% to milk, 90% to egg, 88% to peanut, 91% to wheat, and 87% to soy); 86% were sensitized to all 5 foods. We next assessed clinical reactivity, and 51% were allergic to at least 1 of the foods, including 26% to cow's milk, 27% to egg, 24% to peanut, 5% to wheat, and 6% to soy. Except for wheat, these percentages may be underestimates, because some subjects had never been exposed to the food and were therefore excluded from the analysis for that food (4 subjects for milk, 4 for egg, 25 for peanut, 0 for wheat, 3 for soy). Of the 78 subjects, 22% reported allergic reactivity to only 1 of the 5 foods, and 23%, 5.1%, and 1.3% to 2, 3, and 4 foods, respectively. No difference was seen in age, sex, ethnicity, race, or coexistent allergic disease between those allergic to at least 1 food and those nonallergic to all 5 foods (Table 1). Subjects who had egg allergy were more likely to be allergic to other foods, including milk ($P = .0042$), peanut ($P = .0005$), and wheat ($P = .0205$; eTable 1). Of the 21 subjects allergic to egg, all but 1 had an allergy to another food.

The severity of AD, as assessed by SCORAD, was not different between subjects allergic vs tolerant to any of the 5 foods

(Tables 2–4; eTables 2,3) or between those allergic to at least 1 of the 5 foods and those tolerant to all 5 foods (Table 1). Although median total serum IgE levels were higher among subjects allergic vs nonallergic to each of the 5 foods, the difference did not reach statistical significance, except for peanut, in which levels were higher in those with peanut allergy (Tables 2–4; eTables 2,3). Total IgE was also increased in subjects allergic to at least 1 of the foods compared with those tolerant to all 5 foods (Table 1).

Ability of Food- and Component-Specific IgE Levels to Discriminate Allergic Status

As shown in Tables 2 through 4, and eTables 2 and 3, levels of sIgE to milk, egg, peanut, and wheat (but not soy) were higher among AD subjects allergic to the food compared with those who were tolerant, and these differences were statistically significant. Component-specific IgEs for these foods also discriminated allergic status (except for soy).

The highest levels of component-specific IgE in milk-allergic subjects were directed against Bos d8, although all milk component IgEs were higher in milk-allergic ($n = 20$) than in milk-tolerant ($n = 54$) subjects (Table 2). Egg-allergic subjects ($n = 21$) had high amounts of Gal d1 and Gal d2 IgE but not Gal d3 IgE. Conversely, egg-tolerant subjects ($n = 53$) generally had low IgE to all 3 egg components, and levels were significantly below those in the allergic group for Gal d1 and Gal d2 (Table 3). Whereas levels of IgE to peanut and its components Ara h1, Ara h2, and Ara h3 were higher among peanut-allergic ($n = 19$) vs nonallergic ($n = 34$) subjects, the difference was greatest for Ara h2, and this component dominated the IgE response to peanut in the allergic group (Table 4). Conversely, IgE to Ara h8 and Ara h9 were generally low, and no significant differences were noted based on allergic status to peanut.

The frequency of allergy to wheat and soy in this cohort was relatively low; however, a trend was seen ($P = .0543$) toward higher levels of Tri a19 IgE in the wheat-allergic ($n = 4$) compared with nonallergic ($n = 74$) group, whereas levels of Tri a14 IgE were not different (eTable 2). No significant differences in either soy IgE or soy component (Gly m4, Gly m5, Gly m6, Gly m8) IgEs were detected between subjects allergic ($n = 5$) and tolerant ($n = 70$) to soy (eTable 3).

Utility of IgE Ratios in Determining Food Allergy Status

To compare the utility of specific or component-IgE values alone or as a ratio to total serum IgE or sIgE, respectively, we calculated

Table 2

Milk: Median (25th–75th percentile) and Mann-Whitney parameter (95% confidence interval) for SCORAD and levels of total, milk-specific, and milk component IgE and their ratios in subjects allergic or nonallergic to milk

		Nonallergic (n = 54)	Allergic (n = 20)	Mann-Whitney	Wilcoxon Test P-value
Ratio to Total IgE ($\times 10^4$)	SCORAD	47 (34–57)	42 (31–57)	0.46 (0.32–0.61)	.6090
	Total IgE	4816 (1474–14012)	8430 (4052–19204)	0.60 (0.45–0.73)	.1907
	Milk IgE	1.1 (0.3–4.7)	127.5 (69.7–642)	0.97 (0.88–0.99)	<.00001
	Bos d4	0.4 (0.1–1.4)	42.8 (14.1–74.1)	0.92 (0.80–0.97)	<.00001
	Bos d5	0.5 (0.2–1.4)	45.9 (6.2–66.7)	0.90 (0.78–0.95)	<.00001
	Bos d6	0.3 (0.1–2.6)	1.4 (0.3–29.4)	0.70 (0.55–0.81)	.0104
	Bos d8	0.6 (0.1–2.1)	130 (41.9–581)	0.94 (0.83–0.98)	<.00001
	Milk IgE	2.10 (0.75–6.54)	351.63 (168.96–573.75)	0.96 (0.87–0.99)	<.00001
	Bos d4	0.57 (0.23–1.52)	48.80 (27.56–112.10)	0.92 (0.81–0.97)	<.00001
	Bos d5	0.77 (0.31–2.04)	41.84 (19.79–112.39)	0.89 (0.77–0.95)	<.00001
Ratio to Milk IgE	Bos d6	0.71 (0.25–1.97)	3.99 (0.33–19.83)	0.67 (0.52–0.79)	.0252
	Bos d8	0.69 (0.35–3.57)	318.98 (111.03–427.98)	0.94 (0.83–0.98)	<.00001
	Bos d4	0.434 (0.113–0.624)	0.175 (0.096–0.398)	0.36 (0.24–0.51)	.0726
	Bos d5	0.602 (0.215–0.795)	0.114 (0.066–0.369)	0.25 (0.14–0.39)	.0011
	Bos d6	0.602 (0.115–0.970)	0.007 (0.000–0.128)	0.25 (0.15–0.40)	.0012
	Bos d8	0.448 (0.236–0.853)	0.856 (0.688–0.931)	0.67 (0.52–0.79)	.0289

Table 3
Egg: Median (25th–75th percentile) and Mann-Whitney parameter (95% confidence interval) for SCORAD and levels of total, egg-specific, and egg component IgE and their ratios in subjects allergic or nonallergic to egg

	Nonallergic (N = 53)	Allergic (N = 21)	Mann-Whitney	Wilcoxon test P value
SCORAD	47 (36–56)	35 (29–57)	0.43 (0.30–0.58)	.3747
Total IgE	4857 (1960–13637)	6160 (1930–17,284)	0.54 (0.40–0.68)	.5731
Egg IgE	1.3 (0.4–6.4)	38.5 (10.1–81.1)	0.86 (0.74–0.93)	<.00001
Gal d1	0.4 (0.1–1.9)	20.9 (5.6–76.9)	0.88 (0.76–0.94)	<.00001
Gal d2	0.5 (0.2–3.1)	31.3 (3.7–62.4)	0.86 (0.74–0.93)	<.00001
Gal d3	0.2 (<0.1–0.6)	0.6 (0.2–7.7)	0.63 (0.48–0.75)	.0812
Ratio to Total IgE ($\times 10^4$)				
Egg IgE	2.15 (0.69–12.20)	35.09 (20.22–322.55)	0.89 (0.77–0.95)	<.00001
Gal d1	0.48 (0.13–2.66)	26.15 (13.68–124.84)	0.90 (0.79–0.96)	<.00001
Gal d2	0.98 (0.32–3.19)	31.95 (11.35–150.65)	0.91 (0.79–0.96)	<.00001
Gal d3	0.26 (0.00–0.89)	0.73 (0.29–8.74)	0.66 (0.51–0.78)	.0351
Ratio to Egg IgE				
Gal d1	0.359 (0.118–0.767)	0.553 (0.322–0.999)	0.63 (0.48–0.76)	.0872
Gal d2	0.687 (0.278–0.974)	0.730 (0.380–0.956)	0.54 (0.39–0.68)	.6218
Gal d3	0.210 (0.020–0.483)	0.053 (0.001–0.158)	0.35 (0.23–0.50)	.0500

Total IgE measurements are kU/L; egg-specific and component IgE measurements are kU_A/L.

MW parameters. The MW describes the probability that a random allergic subject has a higher value than a random nonallergic subject. Therefore, MW values greater than 0.5 indicate a positive association with allergy, those less than 0.5 a positive association with tolerance, and those equal to 0.5 suggest no relationship between the value and allergic status.

With regard to milk, the MW for milk, Bos d4, Bos d5, and Bos d8 IgE all approached 1, indicating higher levels in milk-allergic vs tolerant patients with little overlap in IgE levels between the groups ($P < .00001$ for all; Table 2). The MW for Bos d6 IgE (0.70; $P = .0104$) also indicated a positive, albeit weaker, association with allergy. The ratio of component IgE to milk IgE revealed a MW parameter of 0.67 for Bos d8 ($P = .0252$), 0.25 for Bos d5 and Bos d6 ($P = .0011$ for both), and 0.36 for Bos d4 ($P = .0726$; Table 2), suggesting that a greater proportion of milk IgE is directed against Bos d8 in those subjects with milk allergy, and against Bos d4, d5, and d6 in those who are milk tolerant.

The MW for egg (0.86), Gal d1 (0.88), and Gal d2 (0.86) IgE indicated higher levels in egg-allergic subjects ($P < .0001$ for all), whereas the MW for Gal d3 (0.63) IgE was not statistically significant (Table 3). The MW parameter for the ratio of Gal d1 to egg IgE (0.63; $P = .0872$) suggested a positive association with egg allergy, while the ratio of Gal d3 to egg IgE (0.35; $P = .0500$) suggested a positive association with tolerance. The MW for the

ratio of Gal d2/egg IgE (0.54) was not statistically significant (Table 3).

The highest MW parameter for peanut was for Ara h2 IgE (MW 0.97, $P < .00001$), indicating a strong association between high Ara h2 IgE and the presence of peanut allergy (Table 4). The MW estimates for peanut (MW 0.92, $P < .00001$), Ara h1 (MW 0.89, $P < .00001$), and Ara h3 (MW 0.89, $P < .00001$) IgE also indicated an association with peanut allergy, whereas the MW parameters for Ara h8 and Ara h9 IgE alone did not indicate a significant relationship. The MW for the ratio of Ara h2 IgE/peanut IgE (MW 0.86; $P = .00004$) or Ara h1/peanut IgE (MW 0.70; $P = .0279$) also demonstrated a strong association with peanut allergy, whereas the ratio of Ara h8 IgE/peanut IgE indicated an association with tolerance (MW 0.30; $P = .0243$). The ratio of Ara h3 or Ara h9 IgE to peanut IgE was not significant. These data suggest that the dominant IgE response to peanut is against Ara h2 and Ara h1 in allergic subjects and against Ara h8 in tolerant subjects.

Regarding wheat, the MW for Tri a19 IgE (0.78) suggested higher levels in those with wheat allergy ($P = .0543$) and reached significance when the ratio of Tri a19/total IgE was considered (MW 0.83; $P = .0236$; eTable 2). None of the MW parameters for soy indicated statistically significant relationships between IgE levels and allergy status (eTable 3).

Table 4
Peanut: Median (25th–75th Percentile) and Mann-Whitney Parameter (95% Confidence Interval) for SCORAD and Levels of Total, Peanut (PN)-Specific, and Peanut Component IgE and Their Ratios in Subjects Allergic or Nonallergic to Peanut

	Nonallergic (N = 34)	Allergic (N = 19)	Mann-Whitney	Wilcoxon test P value
SCORAD	47 (35–54)	43 (30–61)	0.50 (0.35–0.66)	.9778
Total IgE	3467 (564–9046)	9082 (4440–15077)	0.69 (0.53–0.81)	.0242
PN IgE	4.5 (0.4–17.8)	91.9 (49.1–469)	0.92 (0.79–0.97)	<.00001
Ara h1	0.1 (<0.1–0.3)	10.1 (2.4–55.7)	0.90 (0.76–0.95)	<.00001
Ara h2	0.3 (<0.1–0.7)	67.1 (23.1–213.5)	0.97 (0.86–0.99)	<.00001
Ara h3	0.2 (<0.1–0.5)	6.2 (0.6–19.4)	0.89 (0.75–0.95)	<.00001
Ara h8	0.4 (<0.1–15.7)	0.8 (0.3–14.6)	0.61 (0.45–0.75)	.1785
Ara h9	0.2 (<0.1–1.6)	0.9 (0.4–2.1)	0.66 (0.50–0.79)	.0499
Ratio to Total IgE ($\times 10^4$)				
PN IgE	6.07 (0.25–17.33)	158.13 (23.81–574.77)	0.90 (0.76–0.96)	<.00001
Ara h1	0.12 (0.00–0.51)	15.51 (1.79–62.59)	0.88 (0.75–0.95)	<.00001
Ara h2	0.26 (0.00–1.19)	111.65 (15.03–216.22)	0.95 (0.83–0.98)	<.00001
Ara h3	0.18 (0.00–0.54)	4.73 (1.28–23.37)	0.90 (0.77–0.96)	<.00001
Ara h8	0.81 (0.00–20.81)	0.81 (0.43–10.93)	0.59 (0.42–0.73)	.3085
Ara h9	0.31 (0.00–1.75)	0.78 (0.35–2.70)	0.65 (0.49–0.78)	.0702
Ratio to Peanut IgE				
Ara h1	0.027 (0.000–0.111)	0.098 (0.019–0.227)	0.696 (0.52–0.82)	.0279
Ara h2	0.079 (0.023–0.243)	0.553 (0.361–0.729)	0.864 (0.71–0.94)	.00004
Ara h3	0.028 (0.005–0.061)	0.033 (0.014–0.076)	0.583 (0.41–0.73)	.3549
Ara h8	0.261 (0.097–3.521)	0.024 (0.001–0.074)	0.299 (0.17–0.47)	.0243
Ara h9	0.060 (0.006–0.414)	0.008 (0.001–0.048)	0.353 (0.21–0.53)	.0992

Total IgE measurements are kU/L; peanut-specific and component IgE measurements are kU_A/L.

Table 5
Milk: Sensitivity, Specificity, Positive (PPV) and Negative (NPV) Predictive Value for the Milk-Specific IgE Level (kU/L) Where the Probability of Being Allergic is 50% (Based on Logistic Model; 95% Confidence Interval), Milk-IgE Level ≥ 100 kU/L, and the Milk-IgE Level that Maximizes the Sum of Sensitivity and Specificity

Milk	Threshold: 50% from Logistic Model	Threshold: Milk-IgE ≥ 100	Threshold: Maximum of Sensitivity + Specificity
IgE	42.8 (23.2–116.7) ^a	100	27.4
Sensitivity	0.850	0.550	0.950
Specificity	0.963	0.982	0.944
PPV ^b	0.835	0.917	0.864
NPV ^b	0.932	0.855	0.981

^aFrom logistic model, bootstrap-based 95% CI.

^bModel-based PPV and NPV.

Calculating the ratio of sIgE, or each of the component IgEs, to total IgE minimally changed the MW compared with each of these parameters alone for all foods tested (Tables 2–4 and eTables 2 and 3).

Identification of Diagnostic Thresholds

Clinically, oral food challenges are generally recommended when a child has at least a 50% chance of passing the challenge. We therefore calculated sIgE levels that estimate a 50% likelihood of tolerating milk, egg, and peanut in our cohort. For milk, this decision point was 42.8 kU_A/L, which had a sensitivity of 0.850, specificity of 0.963, PPV of 0.835, and NPV of 0.932 (Table 5). For egg, the threshold level was 28.0 kU_A/L, which had a sensitivity of 0.619, specificity of 0.905, PPV of 0.709, and NPV of 0.847 (Table 6). For peanut, Ara h2 IgE was a better predictor of peanut allergy than peanut IgE levels. The decision point for Ara h2 IgE was 10.9 kU_A/L, which had a sensitivity of 0.842, specificity of 0.912, PPV of 0.859, and NPV of 0.924. A peanut IgE level of 36.4 kU_A/L had a sensitivity of 0.737, specificity of 0.941, PPV of 0.830, and NPV of 0.846 (Table 7).

Many of the subjects in our cohort had sIgE values above 100 kU_A/L, the upper limit of quantification for the ImmunoCAP. We therefore calculated the predictive probabilities for allergy to milk, egg, and peanut at an sIgE level of 100 kU_A/L or above. We also determined IgE decision points that maximized sensitivity and specificity for predicting allergy to these foods (Tables 5–7).

Decision Trees for Milk, Egg, and Peanut

As a proof of concept, we next asked whether the specific and component IgE tests used in a stepwise fashion could improve their predictive capacity, using a prespecified algorithm for forming classification trees. The algorithm produced a tree for milk, suggesting that milk IgE testing followed by IgE testing to Bos d8 may have added utility in predicting milk allergy in this cohort (Fig 1). Fifty-one of 52 subjects with milk IgE less than 26.1 kU_A/L were not allergic to milk. Among those with milk IgE greater than 26.1 kU_A/L, all 17 whose ratio of Bos d8 IgE/milk-specific IgE was greater than

0.5, were allergic to milk, compared with only 2 of 5 whose ratio was less than 0.5.

When the algorithm was refined such that misclassifying nonallergy was considered twice as bad as misclassifying allergy, this resulted in a 2-step classification for egg (Fig 1). Among those with egg IgE less than 16 kU_A/L, 6 of 54 had allergy to egg. However, among those with egg IgE greater than 16 kU_A/L: if the ratio of Gal d1 IgE/egg IgE was less than 0.14 kU_A/L, 1 in 4 had allergy; if the ratio was greater than 0.14 kU_A/L, 14 out of 16 had allergy.

Although the prespecified algorithm did not produce multiple variable thresholds for peanut, examination of the data suggests an exploratory tree. Among the 33 subjects with Ara h2 IgE less than 10 kU_A/L, only 2 have allergy. Among the 6 with Ara h2 IgE greater than 10 kU_A/L but with Ara h8 IgE/peanut IgE greater than 0.09, half have allergy. And, among the 14 with Ara h2 IgE greater than 10 kU_A/L but Ara h8 IgE/peanut IgE less than 0.09, all had allergy (Fig 1).

Discussion

The high rate of IgE-mediated food allergy in AD patients necessitates diagnostic strategies that can distinguish asymptomatic sensitization from clinical food allergy.^{5–11} In this study, 91% of children with moderate to severe AD were sensitized to at least 1 of the 5 most common food allergens, and 51% reported acute clinical reactivity to at least 1 of these foods. Specific IgE levels, particularly to milk, egg, and peanut, were significantly higher in subjects allergic vs tolerant to these foods, and IgE thresholds could be identified that effectively discriminated allergic status. Although ratios of specific to total IgE were not better at predicting allergy than sIgE values alone, component IgE testing had additional utility.

Atopic dermatitis patients are known to be more likely to exhibit false-positive testing for food allergy. In a study of infants with mild to moderate AD, 15.9% developed at least 1 food allergy over a 6-year period. Although baseline sIgE levels were significantly higher among infants who developed food allergy compared with those

Table 6
Egg: Sensitivity, Specificity, Positive (PPV), and Negative (NPV) Predictive Value for the Egg-Specific IgE Level (kU/L) Where the Probability of Being Allergic is 50% (Based on Logistic Model; 95% Confidence Interval), Egg-IgE Level ≥ 100 kU/L, and the Egg-IgE Level That Maximizes the Sum of Sensitivity and Specificity

Egg	Threshold: 50% from logistic model	Threshold: Egg-IgE ≥ 100	Threshold: Maximum of sensitivity + specificity
IgE	28.0 (11.4–103.8) ^a	100	16.7
Sensitivity	0.619	0.238	0.714
Specificity	0.905	0.981	0.906
PPV ^b	0.709	0.833	0.750
NPV ^b	0.847	0.765	0.889

^aFrom Logistic Model, Bootstrap-based 95% CI.

^bModel-based PPV and NPV.

Table 7
Peanut: Sensitivity, Specificity, Positive (PPV), and Negative (NPV) Predictive Value for the Peanut- or Ara h2-Specific IgE Level (kU/L) Where the Probability of Being Allergic Is 50% (Based on Logistic Model; 95% Confidence Interval), Peanut- or Ara h2-IgE Level ≥ 100 kU/L, and the Peanut- or Ara h2-IgE Level That Maximizes the Sum of Sensitivity and Specificity

		Threshold: 50% from logistic model	Threshold: peanut- or Ara h2-IgE ≥ 100	Threshold: maximum of sensitivity + specificity
Peanut	IgE	36.4 (19.8–66.7) ^a	100	35.600
	Sensitivity	0.737	0.421	0.790
	Specificity	0.941	1	0.941
	PPV ^b	0.830	1	0.882
	NPV ^b	0.846	0.756	0.889
Ara h2	IgE	10.9 (4.6–24.5) ^a	100	5.450
	Sensitivity	0.895	0.316	0.947
	Specificity	0.912	1	0.882
	PPV ^b	0.859	1	0.818
	NPV ^b	0.924	0.723	0.968

^aFrom logistic model, bootstrap-based 95% CI.

^bModel-based PPV and NPV.

who did not, the authors were unable to identify a threshold of sIgE that distinguished these groups. In contrast, we identified sIgE decision points for milk, egg, and peanut with high sensitivity, specificity, and predictive value that distinguished allergic status. No significant differences in eczema severity were found in those with and without allergy. One possible explanation for this discrepancy may be related to the difference in age between the cohorts studied. The prior study enrolled infants less than 1 year of age (median age, 7.3 months), whereas the median age in our study was 10.7 years. Although a study from National Jewish Health that enrolled older children (median age, 4 years) found that most AD patients avoiding foods because of positive testing had negative OFCs, participants whose sIgE values exceeded the 95% PPV values for milk, egg, and peanut were not challenged.¹⁵ Our results suggest that the sIgE values that strongly predict allergy in patients with moderate to severe AD are well above the commonly used values of 32 kU_A/L for milk, 7 kU_A/L for egg, and 15 kU_A/L for peanut.^{16–19} Indeed, we estimated that AD subjects with a milk IgE of 43 kU_A/L, egg IgE of 28 kU_A/L, and peanut IgE of 34 kU_A/L had at least a 50% chance of not being allergic to the food. Therefore, we propose that sIgE testing may have utility in predicting food allergy in patients with moderate to severe AD and high total serum IgE levels, although the decision points may be much higher than those that apply to a less atopic population. Of note, subjects in our study were selected with no bias for the presence or absence of food allergy.

Component testing is emerging as a promising approach that can improve the accuracy of food allergy diagnosis, particularly for peanut allergy where Ara h2 is a strong predictor of disease.^{23–28} High IgE levels to Gal d1 (ovomucoid) and Bos d8 (casein) have also been associated with more persistent allergy as well as reactivity to both heated and concentrated forms of egg and milk, respectively.^{29–38} We found that a significantly greater proportion of IgE to peanut in allergic subjects was directed against Ara h2 and Ara h1, both of which have been associated with severe reactions.^{24,25,41,42} In contrast, peanut IgE in nonallergic subjects was primarily specific for Ara h8, which is homologous to the birch pollen allergen Bet v1 and has been associated with no or only mild local symptoms.^{43,44} Likewise, most milk IgE was directed against Bos d8 in allergic children and against the heat-labile components Bos d4 (alpha-lactoglobulin) and Bos d5 (beta-lactoglobulin), as well as Bos d6 (bovine serum albumin) in those without milk allergy. Subjects with egg allergy tended to have a greater fraction of their egg IgE directed against Gal d1, whereas Gal d3 IgE predominated in those subjects who were tolerant to egg. The presence of egg allergy also appeared to be strongly associated with the

development of other food allergies, as has been observed in prior studies.^{45,46}

Consistent with prior studies of infants with AD, wheat and soy allergy were relatively rare in this cohort of patients with moderate to severe AD.¹¹ Despite this limitation, wheat and Tri a19 IgE levels, which has previously been associated with IgE-mediated wheat allergy, were higher among those with wheat allergy.^{47,48} However, neither soy IgE nor IgE to any of the soy components were significantly different between subjects with and without soy allergy, although this is perhaps in part attributable to the low number of patients with this allergy.

Given the high total serum IgE levels in this patient cohort, we hypothesized that the ratio of specific to total IgE may be better than sIgE levels alone in predicting food allergy. However, our data showed a positive association between both of these parameters and allergy to all foods studied (with the exception of soy), and the ratio of specific to total IgE did not provide added information that would further inform clinical decision making.

Our study has several important limitations. First, the diagnosis of food allergy was not confirmed by OFC. However, most allergic patients had sIgE levels well above the 95% PPVs commonly used in the United States, which raised ethical concerns about the safety of challenging these patients under current guidelines. Subjects whose allergic status was not clear because they had never eaten the food (avoiding it because of positive testing) were excluded from the analysis for that food, which may have skewed our results, particularly for peanut. The size of our cohort was relatively small, and although we were able to identify highly significant differences between those subjects with and without milk, egg, and peanut allergy, we had less power for wheat and soy.

Many children with AD are on overly restrictive diets that exclude foods they have either never eaten or once tolerated but now avoid because of positive sIgE testing. The care of these patients would be dramatically improved if decision points for specific or component IgEs could be identified that predict when a true food allergy is present. In contrast to prior studies in infants, this study in school-aged children suggests that sIgE testing for the common food allergens may be helpful in guiding OFCs in this difficult-to-diagnose population, and that component testing may have additional diagnostic value. Although additional studies that incorporate OFCs to confirm the diagnosis of food allergy are needed to identify more definitive threshold levels, our data suggest that practitioners should likely be more aggressive about offering OFCs in patients with moderate to severe AD and elevated total IgE levels.

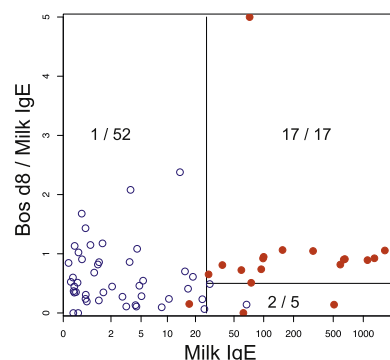
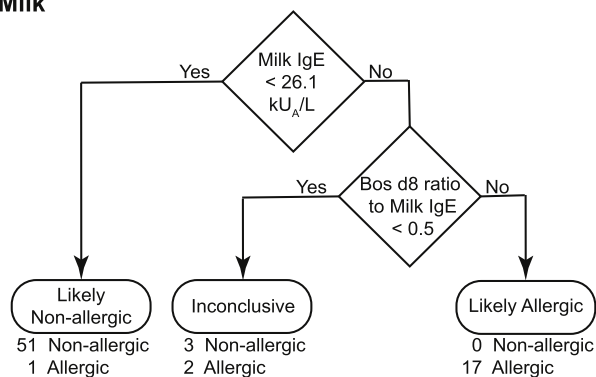
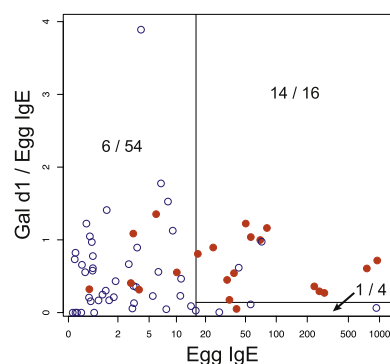
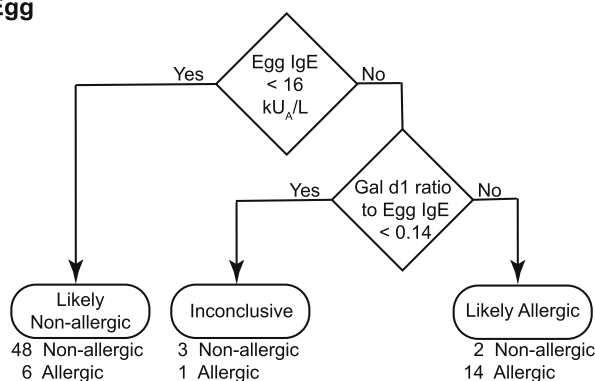
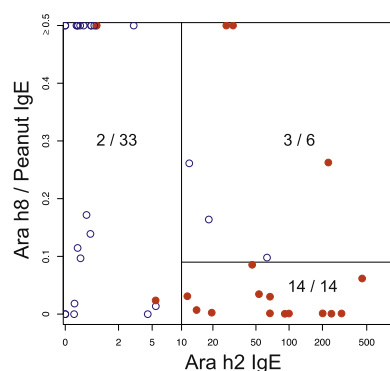
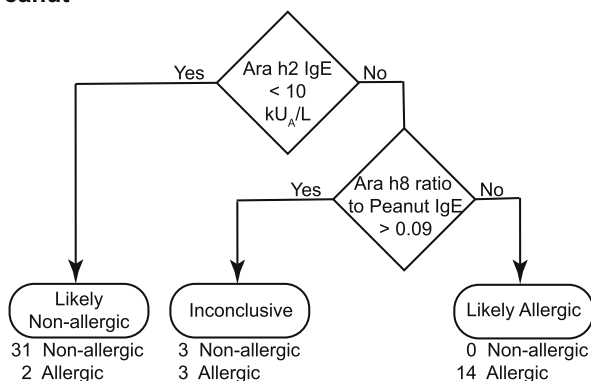
Milk**Egg****Peanut**

Figure 1. Decision trees and corresponding scatterplots for predicting milk, egg, and peanut allergy based on food specific- and component-IgE levels.

Supplementary Data

Supplemental figure accompanying this article can be found in the online version at <https://doi.org/10.1016/j.anai.2019.01.001>.

References

- Hanifin JM, Reed ML, Eczema P, Impact Working G. A population-based survey of eczema prevalence in the United States. *Dermatitis: Contact, Atopic, Occupational, Drug*. 2007;18:82–91.
- Flohr C, Mann J. New insights into the epidemiology of childhood atopic dermatitis. *Allergy*. 2014;69:3–16.
- Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. *Lancet*. 1998;351:1225–1232.
- Roduit C, Frei R, Loss G, et al. Development of atopic dermatitis according to age of onset and association with early-life exposures. *J Allergy Clin Immunol*. 2012;130:130–136.
- Tsakok T, Marrs T, Mohsin M, et al. Does atopic dermatitis cause food allergy? A systematic review. *J Allergy Clin Immunol*. 2016;137:1071–1078.
- Martin PE, Eckert JK, Koplin JJ, et al. Which infants with eczema are at risk of food allergy? Results from a population-based cohort. *Clin Exp Allergy*. 2015;45:255–264.
- Hill DJ, Hosking CS, de Benedictis FM, et al. Confirmation of the association between high levels of immunoglobulin E food sensitization and eczema in infancy: an international study. *Clin Exp Allergy*. 2008;38:161–168.
- de Benedictis FM, Franceschini F, Hill D, et al. The allergic sensitization in infants with atopic eczema from different countries. *Allergy*. 2009;64:295–303.

9. Burks AW, James JM, Hiegel A, et al. Atopic dermatitis and food hypersensitivity reactions. *J Pediatr*. 1998;132:132–136.
10. Gray CL, Levin ME, Zar HJ, et al. Food allergy in South African children with atopic dermatitis. *Pediatr Allergy Immunol*. 2014;25:572–579.
11. Spergel JM, Boguniewicz M, Schneider L, Hanifin JM, Paller AS, Eichenfield LF. Food allergy in infants with atopic dermatitis: limitations of food-specific IgE measurements. *Pediatrics*. 2015;136:e1530–1538.
12. Flohr C, Perkin M, Logan K, et al. Atopic dermatitis and disease severity are the main risk factors for food sensitization in exclusively breastfed infants. *J Invest Dermatol*. 2014;134:345–350.
13. Venkataraman D, Soto-Ramirez N, Kurukulaaratchy RJ, et al. Filaggrin loss-of-function mutations are associated with food allergy in childhood and adolescence. *J Allergy Clin Immunol*. 2014;134:876–882.
14. 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;372:803–813.
15. Fleischer DM, Bock SA, Spears GC, et al. Oral food challenges in children with a diagnosis of food allergy. *J Pediatr*. 2011;158:578–583.
16. Santos AF, Brough HA. Making the most of in vitro tests to diagnose food allergy. *J Allergy Clin Immunol Pract*. 2017;5:237–248.
17. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol*. 2001;107:891–896.
18. Sicherer SH, Morrow EH, Sampson HA. Dose-response in double-blind, placebo-controlled oral food challenges in children with atopic dermatitis. *J Allergy Clin Immunol*. 2000;105:582–586.
19. Perry TT, Matsui EC, Conover-Walker MK, Wood RA. Risk of oral food challenges. *J Allergy Clin Immunol*. 2004;114:1164–1168.
20. Federly TJ, Jones BL, Dai H, Dinakar C. Interpretation of food specific immunoglobulin E levels in the context of total IgE. *Ann Allergy Asthma Immunol*. 2013;111:20–24.
21. 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;137:1751–1760.
22. Gupta RS, Lau CH, Hamilton RG, Donnell A, Newhall KK. Predicting outcomes of oral food challenges by using the allergen-specific IgE-total IgE ratio. *J Allergy Clin Immunol Pract*. 2014;2:300–305.
23. Klemans RJ, Otte D, Knol M, et al. The diagnostic value of specific IgE to Ara h 2 to predict peanut allergy in children is comparable to a validated and updated diagnostic prediction model. *J Allergy Clin Immunol*. 2013;131:157–163.
24. Lieberman JA, Glaumann S, Batelson S, Borres MP, Sampson HA, Nilsson C. The utility of peanut components in the diagnosis of IgE-mediated peanut allergy among distinct populations. *J Allergy Clin Immunol Pract*. 2013;1:75–82.
25. Dang TD, Tang M, Choo S, et al. Increasing the accuracy of peanut allergy diagnosis by using Ara h 2. *J Allergy Clin Immunol*. 2012;129:1056–1063.
26. Santos AF, Douiri A, Becares N, et al. Basophil activation test discriminates between allergy and tolerance in peanut-sensitized children. *J Allergy Clin Immunol*. 2014;134:645–652.
27. 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;125:191–197.
28. Beyer K, Grabenhenrich L, Hartl M, et al. Predictive values of component-specific IgE for the outcome of peanut and hazelnut food challenges in children. *Allergy*. 2015;70:90–98.
29. Ito K, Futamura M, Moverare R, et al. The usefulness of casein-specific IgE and IgG4 antibodies in cow's milk allergic children. *Clin Mol Allergy*. 2012;10:1.
30. D'Urbano LE, Pellegrino K, Artesani MC, et al. Performance of a component-based allergen-microarray in the diagnosis of cow's milk and hen's egg allergy. *Clin Exp Allergy*. 2010;40:1561–1570.
31. Ohtani K, Sato S, Syukuya A, et al. Natural history of immediate-type hen's egg allergy in Japanese children. *Allergol Int*. 2016;65:153–157.
32. Ando H, Moverare R, Kondo Y, et al. Utility of ovomucoid-specific IgE concentrations in predicting symptomatic egg allergy. *J Allergy Clin Immunol*. 2008;122:583–588.
33. Benhamou Senouf AH, Borres MP, Eigenmann PA. Native and denatured egg white protein IgE tests discriminate hen's egg allergic from egg-tolerant children. *Pediatr Allergy Immunol*. 2015;26:12–17.
34. Boyano-Martinez T, Garcia-Ara C, Pedrosa M, Diaz-Pena JM, Quirce S. Accidental allergic reactions in children allergic to cow's milk proteins. *J Allergy Clin Immunol*. 2009;123:883–888.
35. Ahrens B, Lopes de Oliveira LC, Grabenhenrich L, et al. Individual cow's milk allergens as prognostic markers for tolerance development? *Clin Exp Allergy*. 2012;42:1630–1637.
36. Caubet JC, Nowak-Wegrzyn A, Moshier E, Godbold J, Wang J, Sampson HA. Utility of casein-specific IgE levels in predicting reactivity to baked milk. *J Allergy Clin Immunol*. 2013;131:222–224. e221–224.
37. Bernhisel-Broadbent J, Dintzis HM, Dintzis RZ, Sampson HA. Allergenicity and antigenicity of chicken egg ovomucoid (Gal d III) compared with ovalbumin (Gal d I) in children with egg allergy and in mice. *J Allergy Clin Immunol*. 1994;93:1047–1059.
38. Sicherer SH, Wood RA, Vickery BP, et al. The natural history of egg allergy in an observational cohort. *J Allergy Clin Immunol*. 2014;133:492–499.
39. Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. *J Allergy Clin Immunol*. 2012;130:1260–1274.
40. James G, Witten D, Hastie T, Tibshirani R. *An Introduction to Statistical Learning: With Applications*. In: R. New York: Springer; 2013.
41. Klemans RJ, van Os-Medendorp H, Blankestijn M, Bruijnzeel-Koomen CA, Knol EF, Knulst AC. Diagnostic accuracy of specific IgE to components in diagnosing peanut allergy: a systematic review. *Clin Exp Allergy*. 2015;45:720–730.
42. Klemans RJ, Broekman HC, Knol EF, et al. Ara h 2 is the best predictor for peanut allergy in adults. *J Allergy Clin Immunol Pract*. 2013;1:632–638. e631.
43. Sicherer SH, Wood RA. Advances in diagnosing peanut allergy. *The Journal of Allergy and Clinical Immunology In Practice*. 2013;1:1–13. quiz 14.
44. Asarnoj A, Nilsson C, Lidholm J, et al. Peanut component Ara h 8 sensitization and tolerance to peanut. *The Journal of Allergy and Clinical Immunology*. 2012;130:468–472.
45. Sampson HA. Clinical practice. Peanut allergy. *The New England Journal of Medicine*. 2002;346:1294–1299.
46. 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. *The Journal of Allergy and Clinical Immunology*. 2013;131:135–143. e131–112.
47. Nilsson N, Sjolander S, Baar A, et al. Wheat allergy in children evaluated with challenge and IgE antibodies to wheat components. *Pediatr Allergy Immunol*. 2015;26:119–125.
48. Ebisawa M, Shibata R, Sato S, Borres MP, Ito K. Clinical utility of IgE antibodies to omega-5 gliadin in the diagnosis of wheat allergy: a pediatric multicenter challenge study. *Int Arch Allergy Immunol*. 2012;158:71–76.

Supplementary Data

eTable 1

Number of Subjects with and without Milk, Peanut, Soy, and Wheat Allergy with or without Coexistent Egg Allergy

	Milk allergy		Peanut allergy		Soy allergy		Wheat allergy	
	No	Yes	No	Yes	No	Yes	No	Yes
Egg allergy								
No	43	9	32	9	50	2	53	0
Yes	8	10	2	9	17	3	18	3
Fisher's exact test <i>P</i> =	.0042		.0005		.1272		.0205	

eTable 2

Wheat: Median (25th-75th Percentile) and Mann-Whitney Parameter (95% Confidence Interval) for SCORAD and Levels of Total, Wheat-Specific, and Wheat Component IgE and Their Ratios in Subjects Allergic or Nonallergic to Wheat

		Nonallergic (N = 74)	Allergic (N = 4)	Mann-Whitney	Wilcoxon test <i>P</i> value
Ratio to Total IgE ($\times 10^4$)	SCORAD	45 (32-56)	30 (22-41)	0.32 (0.13-0.61)	.2386
	Total IgE	5338 (1988-14416)	6451 (1616-14448)	0.49 (0.24-0.74)	.9368
	Wheat IgE	5.8 (0.9-13.1)	463.5 (320.4-695)	0.93 (0.65-0.99)	.0042
	Tri a14	0.5 (<0.1-2)	28.74 (0.21-112.9)	0.61 (0.33-0.82)	.4853
	Tri a19	0.2 (<0.1-0.4)	5.3 (0.4-13.3)	0.78 (0.50-0.92)	.0543
	Wheat IgE	6.52 (2.93-16.15)	484.39 (365.53-1949.00)	0.97 (0.71-1.00)	.0016
	Tri a14	0.75 (0.00-3.07)	26.79 (1.09-67.24)	0.68 (0.40-0.87)	.2210
	Tri a19	0.18 (0.00-0.35)	3.27 (1.86-87.40)	0.83 (0.55-0.95)	.0236
	Tri a14	0.092 (0.023-0.377)	0.066 (0.013-0.140)	0.38 (0.17-0.66)	.4377
	Tri a19	0.023 (0.000-0.051)	0.019 (0.006-0.036)	0.49 (0.25-0.74)	.9694

Total IgE measurements are kU/L; wheat-specific and component IgE measurements are kU_A/L.

eTable 3

Soybean: Median (25th-75th Percentile) and Mann-Whitney Parameter (95% Confidence Interval) for SCORAD and Levels of Total, Soybean (Soy)-Specific, and Soybean Component IgE and Their Ratios in Subjects Allergic or Nonallergic to Soybean

		Nonallergic (N = 70)	Allergic (N = 5)	Mann-Whitney	Wilcoxon test P value
	SCORAD	44 (32-56)	57 (46-59)	0.64 (0.38-0.83)	.3179
	Total IgE	5148 (1663-14986)	7728 (4087-13851)	0.52 (0.29-0.75)	.8902
	Soy IgE	3 (0.7-11.6)	1.4 (1.1-5.2)	0.45 (0.23-0.69)	.6941
	Gly m4	0.6 (0.1-16)	2.1 (0.3-15.4)	0.57 (0.33-0.78)	.6152
	Gly m5	1 (<0.1-4.5)	0.5 (0.3-4)	0.53 (0.30-0.75)	.8223
	Gly m6	2.1 (0.1-10)	1.4 (0.5-6.3)	0.53 (0.29-0.75)	.8396
	Gly m8	0.5 (0.1-1.7)	0.3 (0.2-0.8)	0.43 (0.22-0.67)	.6026
Ratio to total IgE ($\times 10^4$)	Soy IgE	4.92 (1.57-14.64)	3.00 (1.48-29.12)	0.50 (0.27-0.73)	.9915
	Gly m4	0.66 (0.10-12.51)	2.69 (0.78-11.12)	0.59 (0.34-0.79)	.5211
	Gly m5	1.31 (0.05-4.47)	2.29 (0.32-13.37)	0.60 (0.35-0.80)	.4606
	Gly m6	2.29 (0.42-9.75)	3.62 (0.60-29.61)	0.59 (0.34-0.80)	.5021
	Gly m8	0.58 (0.20-1.65)	0.25 (0.21-0.65)	0.41 (0.21-0.66)	.5222
Ratio to soy IgE	Gly m4	0.256 (0.036-2.475)	1.825 (0.027-16.739)	0.56 (0.32-0.78)	.6623
	Gly m5	0.292 (0.146-0.717)	0.382 (0.261-0.761)	0.58 (0.34-0.79)	.5441
	Gly m6	0.665 (0.233-1.077)	1.017 (0.404-1.022)	0.60 (0.35-0.80)	.4821
	Gly m8	0.156 (0.057-0.304)	0.167 (0.071-0.216)	0.46 (0.24-0.70)	.7958

Total IgE measurements are kU/L; soybean-specific and component IgE measurements are kU_A/L.