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IgE Testing Can Predict Food Allergy Status in Patients with Moderate-Severe Atopic Dermatitis

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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} AD is frequently associated with other atopic diseases.^{5, 6} Up to two-thirds of AD patients are sensitized to food antigens, and 15–40% 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

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Conflict of Interest

M.P. Borres and J. Jones are employees of Thermo Fisher Scientific (Uppsala, Sweden). P.A. Frischmeyer-Guerrero 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.

associated with symptoms upon ingestion. This frequently leads to unnecessary food avoidance, which can not only have 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, there is great interest in identifying strategies that will improve the accuracy of food allergy diagnosis among patients with AD. While 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) have also 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-severe AD.

Methods

Study Population

Subjects 2–20 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 five 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 (e.g. hives with erythema and/or angioedema, persistent cough, wheezing, vomiting, hypotension) within approximately 30–60 minutes of eating the food along with positive sIgE testing. Subjects who tolerated baked milk and/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 due to 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 where the sIgE test was positive ($>0.10 \text{ kU}_A/\text{L}$). Total serum IgE was measured on all subjects by ImmunoCAP. All samples where the IgE level was above the limit of detection ($>100 \text{ kU}_A/\text{L}$ for sIgE and component IgE; $>5000 \text{ kU/L}$ 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 non-allergic 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 non-allergic subject. MW also equals the area under the curve (AUC) of the receiver operating curve (ROC) of sensitivity against 1-specificity when $\text{MW} > 0.5$, and $1 - \text{MW} = \text{AUC}$ when $\text{MW} < 0.5$.

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. While 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 where 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 two-sided and p-values less than 0.05 were considered statistically significant. No adjustments were made for multiple comparisons, and while it is always appropriate to interpret such results cautiously, 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

78 subjects (65% male) with a median age of 10.7 years were enrolled (Table 1). 43.6% of the subjects were Caucasian, 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 median total IgE 5338 kU/L (Table 1).

Ninety-one percent of subjects were sensitized ($sIgE > 0.10 \text{ kU}_A/L$) to at least one of the five 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 one 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 as 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 one of the five foods, and 23%, 5.1 %, and 1.3% to two, three, and four foods, respectively. There was no difference in age, gender, ethnicity, race, or coexistent allergic disease between those allergic to at least one food and those nonallergic to all five foods (Table 1). Subjects who had egg allergy were more likely to be allergic to other foods, including milk ($p=0.0042$), peanut ($p=0.0005$), and wheat ($p=0.0205$; Supplemental Table 1). Of the 21 subjects allergic to egg, all but one had an allergy to another food.

The severity of AD, as assessed by SCORAD, was not different between subjects allergic versus tolerant to any of the five foods (Supplemental Fig 1; Tables 2–4; Supplemental Tables 2, 3) or between those allergic to at least one of the five foods and those tolerant to all 5 foods (Table 1). Although median total serum IgE levels were higher among subjects allergic versus nonallergic to each of the five foods, the difference did not reach statistical significance, except for peanut where levels were higher in those with peanut allergy (Supplemental Fig 1; Tables 2–4; Supplemental Tables 2, 3). Total IgE was also increased in subjects allergic to at least one of the foods compared to those tolerant to all five foods (Table 1).

Ability of food- and component-specific IgE levels to discriminate allergic status

As shown in Tables 2–4, Supplemental Figs 2–6, and Supplemental Tables 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 to 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 milk tolerant (n=54) subjects (Supplemental Fig 2, Table 2). Egg-allergic subjects (n=21) had high amounts of Gal d1 and Gal d2 IgE but not Gal d3 IgE. On the other hand, 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 (Supplemental Fig 3, Table 3). While levels of IgE to peanut and its components Ara h1, Ara h2, and Ara h3 were higher among peanut allergic (n=19) versus nonallergic (n=34) subjects, the difference was greatest for Ara h2, and this component dominated the IgE response to peanut in the allergic group (Supplemental Fig 4, Table 4). On the other hand, 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, there was a trend ($p=0.0543$) towards higher levels of Tri a19 IgE in the wheat allergic (n=4) compared to nonallergic (n=74) group, while levels of Tri a14 IgE were not different (Supplemental Fig 5, Supplemental Table 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 (Supplemental Fig 6, Supplemental Table 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 Mann-Whitney parameters (MW). 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 one, indicating higher levels in milk allergic versus tolerant patients with little overlap in IgE levels between the groups ($p<0.00001$ for all; Supplemental Fig 2; Table 2). The MW for Bos d6 IgE (0.70; $p=0.0104$) 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 ($p=0.0252$), 0.25 for Bos d5 and Bos d6 ($p=0.0011$ for both), and 0.36 for Bos d4 ($p=0.0726$; Supplemental Fig 2; 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 ($p<0.0001$ for all), while the MW for Gal d3 (0.63) IgE was not statistically significant (Supplemental Fig 3; Table 3). The MW parameter for the ratio of Gal d1 to egg IgE (0.63; $p=0.0872$) suggested a positive association with egg allergy, while the ratio of Gal d3 to egg IgE (0.35; $p=0.0500$) suggested a positive association with

tolerance. The MW for the ratio of Gal d2/egg IgE (0.54) was not statistically significant (Supplemental Fig 3; Table 3).

The highest MW parameter for peanut was for Ara h2 IgE (MW 0.97, $p < 0.00001$), indicating a strong association between high Ara h2 IgE and the presence of peanut allergy (Supplemental Fig 4; Table 4). MW estimates for peanut (MW 0.92, $p < 0.00001$), Ara h1 (MW 0.89, $p < 0.00001$), and Ara h3 (MW 0.89, $p < 0.00001$) IgE also indicated an association with peanut allergy, while 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; $p = 0.00004$) or Ara h1/peanut IgE (MW 0.70; $p = 0.0279$) also demonstrated a strong association with peanut allergy, while the ratio of Ara h8 IgE/peanut IgE indicated an association with tolerance (MW 0.30; $p = 0.0243$). 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 ($p = 0.0543$) and reached significance when the ratio of Tri a19/total IgE was considered (MW 0.83; $p = 0.0236$; Supplemental Fig 5; Supplemental Table 2). None of the MW parameters for soy indicated statistically significant relationships between IgE levels and allergy status (Supplemental Fig 6; Supplemental Table 3).

Calculating the ratio of sIgE, or each of the component IgEs, to total IgE minimally changed the MW compared to each of these parameters alone for all foods tested (Tables 2–4, Supplemental Figs 2–6, and Supplemental Tables 2 and 3).

The pattern of IgE reactivity to milk, egg, and peanut, as well as the components for each of these foods in relation to sIgE, for individual subjects is shown in Supplemental Figs 7–9.

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 a 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).

Logistic curves demonstrating the probability of allergy at a given sIgE level are shown in Supplemental Fig 10.

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 step-wise fashion could improve their predictive capacity, using a pre-specified 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). 51/52 subjects with milk IgE < 26.1 kU_A/L were not allergic to milk. Among those with milk IgE > 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 to only 2/5 whose ratio was less than 0.5.

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

While the pre-specified 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 < 10 kU_A/L, only 2 have allergy. Among the 6 with Ara h2 IgE ≥ 10 kU_A/L but with Ara h8 IgE/peanut IgE > 0.09, half have allergy. And, among the 14 with Ara h2 IgE ≥ 10 kU_A/L but Ara h8 IgE/peanut IgE < 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-severe AD were sensitized to at least one of the five most common food allergens, and 51% reported acute clinical reactivity to at least one of these foods. Specific IgE levels, particularly to milk, egg, and peanut, were significantly higher in subjects allergic versus 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.

AD patients are known to be more likely to exhibit false positive testing for food allergy. In a study of infants with mild-moderate AD, 15.9% developed at least one food allergy over a 6-year period. Although baseline sIgE levels were significantly higher among infants who developed food allergy compared to those who didn't, 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. Importantly, there were no significant differences in eczema severity 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 one year of age (median age 7.3 months), while 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 due to 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-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-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, the majority of 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, while Gal d3 IgE predominated in those subjects who were tolerant to egg. The presence of egg allergy also appeared to be a 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-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 due 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 revealed 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, the vast majority of 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 due to 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 while 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 due to 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-severe AD and elevated total IgE levels.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AD	atopic dermatitis
sIgE	food-specific IgE
OFC	oral food challenge
PPV	positive predictive value
SCORAD	severity of atopic dermatitis index score
MW	Mann-Whitney estimate
NPV	negative predictive value
CI	confidence interval
AUC	area under the curve

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

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) *	10.7 (7.9 – 14.4)	10.5 (5.7 – 14.6)	10.7 (8.2 – 14.3)
SCORAD *	45 (31 – 56)	42 (31 – 60)	46 (34 – 53)
Total IgE (kU/L) *	5338 (1938 – 14416)	8430 (3946 – 19095) [‡]	3323 (1076 – 9140) [‡]
Asthma N (%)	55 (71%)	40 (75%)	25 (66%)
AR N (%)	71 (91%)	37 (93%)	34 (89%)
EoE N (%)	3 (4%)	3 (8%)	0 (0%)
Ethnicity (Hispanic) N (%)	3 (4%)	1 (3%)	2 (5%)
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%)

* median (25th-75th percentile)

[‡]Total IgE significantly different between Allergic and Nonallergic groups; p=0.0165

AR: Allergic Rhinitis

EoE: Eosinophilic Esophagitis

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

		Non-Allergic (N=54)	Allergic (N=20)	Mann-Whitney	Wilcoxon Test p-value
	SCORAD	47 (34–57)	42 (31–57)	0.46 (0.32–0.61)	0.6090
	Total IgE	4816(1474–14012)	8430 (4052–19204)	0.60 (0.45–0.73)	0.1907
	Milk IgE	1.1 (0.3–4.7)	127.5 (69.7–642)	0.97 (0.88–0.99)	<0.00001
	Bos d4	0.4 (0.1–1.4)	42.8 (14.1–74.1)	0.92 (0.80–0.97)	<0.00001
	Bos d5	0.5 (0.2–1.4)	45.9 (6.2–66.7)	0.90 (0.78–0.95)	<0.00001
	Bos d6	0.3 (0.1–2.6)	1.4 (0.3–29.4)	0.70 (0.55–0.81)	0.0104
	Bos d8	0.6 (0.1–2.1)	130 (41.9–581)	0.94 (0.83–0.98)	<0.00001
	Milk IgE	2.10 (0.75–6.54)	351.63 (168.96–573.75)	0.96 (0.87–0.99)	<0.00001
	Bos d4	0.57 (0.23–1.52)	48.80 (27.56–112.10)	0.92 (0.81–0.97)	<0.00001
Ratio to Total IgE (x 10 ⁴)	Bos d5	0.77 (0.31–2.04)	41.84 (19.79–112.39)	0.89 (0.77–0.95)	<0.00001
	Bos d6	0.71 (0.25–1.97)	3.99 (0.33–19.83)	0.67 (0.52–0.79)	0.0252
	Bos d8	0.69 (0.35–3.57)	318.98 (111.03–427.98)	0.94 (0.83–0.98)	<0.00001
	Bos d4	0.434 (0.113–0.624)	0.175 (0.096–0.398)	0.36 (0.24–0.51)	0.0726
Ratio to Milk IgE	Bos d5	0.602 (0.215–0.795)	0.114 (0.066–0.369)	0.25 (0.14–0.39)	0.0011
	Bos d6	0.602 (0.115–0.970)	0.007 (0.000–0.128)	0.25 (0.15–0.40)	0.0012
	Bos d8	0.448 (0.236–0.853)	0.856 (0.688–0.931)	0.67 (0.52–0.79)	0.0289

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

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

		Non-Allergic (N=53)	Allergic (N=21)	Mann-Whitney	Wilcoxon Test p-value
	SCORAD	47 (36–56)	35 (29–57)	0.43 (0.30–0.58)	0.3747
	Total IgE	4857 (1960–13637)	6160 (1930–17284)	0.54 (0.40–0.68)	0.5731
	Egg IgE	1.3 (0.4–6.4)	38.5 (10.1–81.1)	0.86 (0.74–0.93)	<0.00001
	Gal d1	0.4 (0.1–1.9)	20.9 (5.6–76.9)	0.88 (0.76–0.94)	<0.00001
	Gal d2	0.5 (0.2–3.1)	31.3 (3.7–62.4)	0.86 (0.74–0.93)	<0.00001
	Gal d3	0.2 (<0.1–0.6)	0.6 (0.2–7.7)	0.63 (0.48–0.75)	0.0812
	Egg IgE	2.15 (0.69–12.20)	35.09 (20.22–322.55)	0.89 (0.77–0.95)	<0.00001
Ratio to Total IgE (x 10 ⁴)	Gal d1	0.48 (0.13–2.66)	26.15 (13.68–124.84)	0.90 (0.79–0.96)	<0.00001
	Gal d2	0.98 (0.32–3.19)	31.95 (11.35–150.65)	0.91 (0.79–0.96)	<0.00001
	Gal d3	0.26 (0.00–0.89)	0.73 (0.29–8.74)	0.66 (0.51–0.78)	0.0351
	Gal d1	0.359 (0.118–0.767)	0.553 (0.322–0.999)	0.63 (0.48–0.76)	0.0872
Ratio to Egg IgE	Gal d2	0.687 (0.278–0.974)	0.730 (0.380–0.956)	0.54 (0.39–0.68)	0.6218
	Gal d3	0.210 (0.020–0.483)	0.053 (0.001–0.158)	0.35 (0.23–0.50)	0.0500

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

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

		Non-Allergic (N=34)	Allergic (N=19)	Mann-Whitney	Wilcoxon Test p-value
	SCORAD	47 (35–54)	43 (30–61)	0.50 (0.35–0.66)	0.9778
	Total IgE	3467 (564–9046)	9082 (4440–15077)	0.69 (0.53–0.81)	0.0242
	PN IgE	4.5 (0.4–17.8)	91.9 (49.1–469)	0.92 (0.79–0.97)	<0.00001
	Ara h1	0.1 (<0.1–0.3)	10.1 (2.4–55.7)	0.90 (0.76–0.95)	<0.00001
	Ara h2	0.3 (<0.1–0.7)	67.1 (23.1–213.5)	0.97 (0.86–0.99)	<0.00001
	Ara h3	0.2 (<0.1–0.5)	6.2 (0.6–19.4)	0.89 (0.75–0.95)	<0.00001
	Ara h8	0.4 (<0.1–15.7)	0.8 (0.3–14.6)	0.61 (0.45–0.75)	0.1785
	Ara h9	0.2 (<0.1–1.6)	0.9 (0.4–2.1)	0.66 (0.50–0.79)	0.0499
	PN IgE	6.07 (0.25–17.33)	158.13 (23.81–574.77)	0.90 (0.76–0.96)	<0.00001
	Ara h1	0.12 (0.00–0.51)	15.51 (1.79–62.59)	0.88 (0.75–0.95)	<0.00001
	Ara h2	0.26 (0.00–1.19)	111.65 (15.03–216.22)	0.95 (0.83–0.98)	<0.00001
	Ara h3	0.18 (0.00–0.54)	4.73 (1.28–23.37)	0.90 (0.77–0.96)	<0.00001
	Ara h8	0.81 (0.00–20.81)	0.81 (0.43–10.93)	0.59 (0.42–0.73)	0.3085
	Ara h9	0.31 (0.00–1.75)	0.78 (0.35–2.70)	0.65 (0.49–0.78)	0.0702
	Ara h1	0.027 (0.000–0.111)	0.098 (0.019–0.227)	0.696 (0.52–0.82)	0.0279
	Ara h2	0.079 (0.023–0.243)	0.553 (0.361–0.729)	0.864 (0.71–0.94)	0.00004
	Ara h3	0.028 (0.005–0.061)	0.033 (0.014–0.076)	0.583 (0.41–0.73)	0.3549
	Ara h8	0.261 (0.097–3.521)	0.024 (0.001–0.074)	0.299 (0.17–0.47)	0.0243
	Ara h9	0.060 (0.006–0.414)	0.008 (0.001–0.048)	0.353 (0.21–0.53)	0.0992

Total gE 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: Sensitivity Maximum of + Specificity
IgE	42.8 (23.2–116.7) [‡]	100	27.4
Sensitivity	0.850	0.550	0.950
Specificity	0.963	0.982	0.944
PPV [*]	0.835	0.917	0.864
NPV [*]	0.932	0.855	0.981

[‡]from Logistic Model, Bootstrap-based 95% CI

^{*} Model based PPV and NPV

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) [‡]	100	16.7
Sensitivity	0.619	0.238	0.714
Specificity	0.905	0.981	0.906
PPV [*]	0.709	0.833	0.750
NPV [*]	0.847	0.765	0.889

[‡]from Logistic Model, Bootstrap-based 95% CI

^{*} Model 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) [‡]	100	35.600
	Sensitivity	0.737	0.421	0.790
	Specificity	0.941	1	0.941
	PPV [*]	0.830	1	0.882
	NPV [*]	0.846	0.756	0.889
Ara h2	IgE	10.9 (4.6–24.5) [‡]	100	5.450
	Sensitivity	0.895	0.316	0.947
	Specificity	0.912	1	0.882
	PPV [*]	0.859	1	0.818
	NPV [*]	0.924	0.723	0.968

[‡]from Logistic Model, Bootstrap-based 95% CI

^{*}Model based PPV and NPV