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Clinical factors associated with peanut allergy in a high-risk infant cohort

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Abstract

Background: Prognostication of peanut allergy (PNA) is relevant for early interventions. We aimed to determine baseline parameters associated with the development of PNA in 3- to 15-month-olds with likely egg and/or milk allergy, and/or moderate to severe atopic dermatitis (AD) and a positive egg/milk skin prick test (SPT), but no known PNA.

Methods: The primary endpoint was PNA [confirmed/convincing diagnosis or last classified as serologic PNA (<2 years, ≥ 5 kUA/L, otherwise ≥ 14 kUA/L, peanut IgE)] among 511 participants (median follow-up, 7.3 years). Associations were explored with univariate logistic regression; factors with $P < 0.15$ were analyzed by stepwise multiple logistic regression, using data stratified by PNA status and randomly assigned to development and validation datasets.

Results: 205/511 (40.1%) had PNA. Univariate factors associated with PNA ($P < 0.01$) included increased AD severity, larger egg and peanut SPT, greater egg, milk, peanut, Ara h1-h3 IgE, higher peanut IgG and IgG4, and increased pregnancy peanut consumption. P -values were between 0.01 and 0.05 for younger age, non-white race, lack of breastfeeding, and increased lactation peanut consumption. Using a development dataset, the multivariate model identified younger age at enrollment, greater peanut and Ara h2 IgE, and lack of breastfeeding as prognosticators. The final model predicted 79% in the development and 75% in the validation dataset (AUC = 0.83 for both). Models using stricter or less strict PNA criteria both found Ara h2 as predictive. **Conclusions:** Key factors associated with PNA in this high-risk population included lack of breastfeeding, age, and greater Ara h2 and peanut-specific IgE, which can be used to prognosticate outcomes.

KEYWORDS

IgE, natural history, peanut allergy, skin prick test

1 | INTRODUCTION

Peanut allergy affects ~2% of Americans ≤ 18 years of age,^{1,2} and studies suggest that the prevalence of peanut allergy has been increasing.³ It is the most common cause of severe and fatal food-induced anaphylactic reactions in the United States.^{4,5} The only approved management strategy for peanut allergy remains avoidance and emergency management of accidental ingestions, which markedly affects the quality of life of patients and caregivers.⁶ An uncontrolled trial of low-dose peanut (300 mg peanut protein) oral immunotherapy in peanut-allergic children 9–36 months of age resulted in 4-week sustained unresponsiveness in about 80% of children and enabled them to introduce peanut into their diets ad libitum.⁷ These results suggest that early oral immunotherapy may disrupt peanut allergy and enhance outcomes, perhaps due to the plasticity of the young developing immune system. Given this result, the identification of infants likely to develop persistent peanut allergy may be beneficial.

The identification of infants at risk of peanut allergy is also important for targeting prevention. The Learning Early About Peanut (LEAP) study⁸ targeted infants with severe eczema and/or egg allergy, and 17.2% randomized to avoiding peanut developed the allergy. Peanut allergy was reduced by 81% in those randomized to early introduction. Guidelines have substantially reiterated testing children in the LEAP-defined high-risk group⁹ although testing is resource-intensive and controversial.^{10,11} There could be a benefit for improved prognostication in infants already displaying features of high risk to develop peanut allergy. Both studies highlighted above underscore the potential benefit of identifying young children at high risk for developing life-long peanut allergy so that appropriate preventative or therapeutic measures can be initiated.

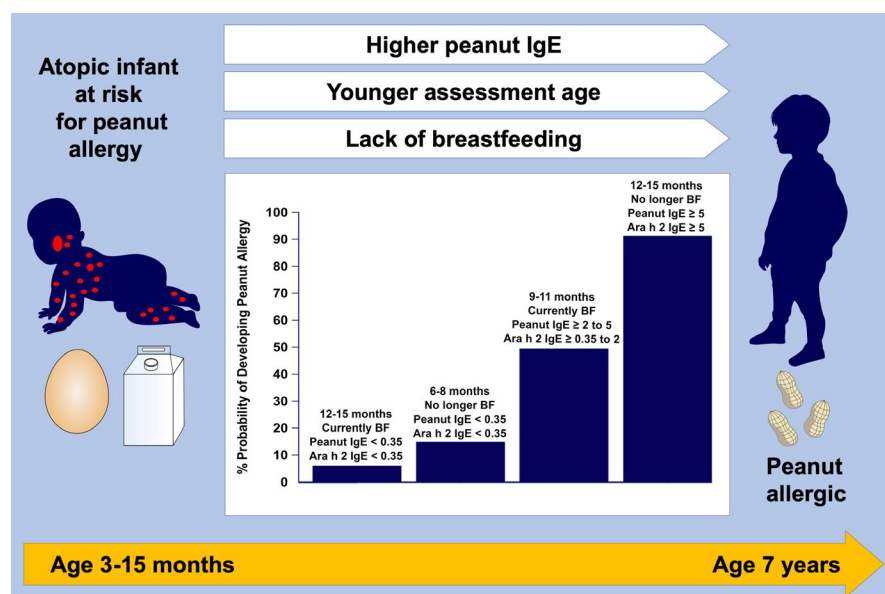
The Consortium for Food Allergy Research (CoFAR) enrolled infants without previously known peanut allergy at high risk to develop peanut allergy, in a multicenter observational study to address

the immunologic, genetic, and environmental factors that affect the natural course of food allergy.¹² The infants were enrolled with milk or egg allergy and/or with moderate to severe atopic dermatitis (AD) because these characteristics have been considered risk factors to develop peanut allergy.^{13–15} We previously reported the natural course of resolution of milk and egg allergy in this cohort^{16–18} and identified a number of prognostic markers that could be used to estimate resolution rates using baseline characteristics. The primary aim of the current analysis is to assess variables similar to those evaluated for the course of milk and egg allergy, namely baseline demographic, clinical, and serum/skin test parameters associated with the development of peanut allergy in this cohort. The identification of markers of prognosis could reveal potential prevention strategies and also provide early identification of infants who are in most need of interventions to prevent peanut allergy. This study describes potential markers toward these aims.

2 | METHODS

2.1 | Subjects and enrollment criteria

Participant characteristics and study enrollment procedures were previously reported.^{12,19,20} Briefly, this is an observational study of infants in the Consortium for Food Allergy Research observational study (COFAR2) enrolled with likely egg or milk allergy who were not yet diagnosed with a likely peanut allergy, recruited at ages 3–15 months, and enrolled at 5 US sites (New York, NY, Baltimore, MD, Little Rock, AR, Denver, CO, Durham, NC). Infants fulfilled at least one of the following 2 criteria: (1) convincing allergic reaction to milk and/or egg with a positive prick skin test (SPT) to the trigger food(s), and/or (2) moderate to severe AD and a positive SPT to milk and/or egg. AD severity was scored according to the criteria of Rajke and Langeland.²¹ Out of the 511 children included in the analysis, 202 (39.5%) were enrolled based on the atopic dermatitis



GRAPHICAL ABSTRACT

In high-risk infants (eg, moderate to severe eczema and egg/milk sensitization or likely egg/milk allergy), parameters associated with the development of peanut allergy were identified. Multivariate models identified younger age at initial assessment, higher peanut IgE and Ara h2 IgE levels, and lack of breastfeeding (BF) as significant associated factors. Models were constructed to predict risk of peanut allergy based on these variables.

criteria, 91 (17.8%) through the food allergy criteria, and 218 (42.7%) through both criteria. As the primary objective of the observational study was to characterize risk factors for the development of peanut allergy among a high-risk cohort, infants with clinical evidence of peanut allergy or known peanut IgE above 5 kU/L ($n = 104$) were excluded from enrollment as they were unable to be prospectively evaluated for the development of peanut allergy. In-person clinical and immunological evaluations were scheduled at enrollment, 6 months, 1 year, and then yearly, with telephone contacts between each visit. A Data Safety Monitoring Board (DSMB) convened by the Division of Allergy, Immunology and Transplantation of the National Institute of Allergy and Infectious Diseases, and local Institutional Review Boards approved study procedures, written consents were obtained, and interim data monitoring was performed.

2.2 | Definition of peanut allergy

The primary endpoint of the study was peanut allergy diagnosed at any time during follow-up. As an observational study, diagnoses were made at each study visit (at three visits in the first year and

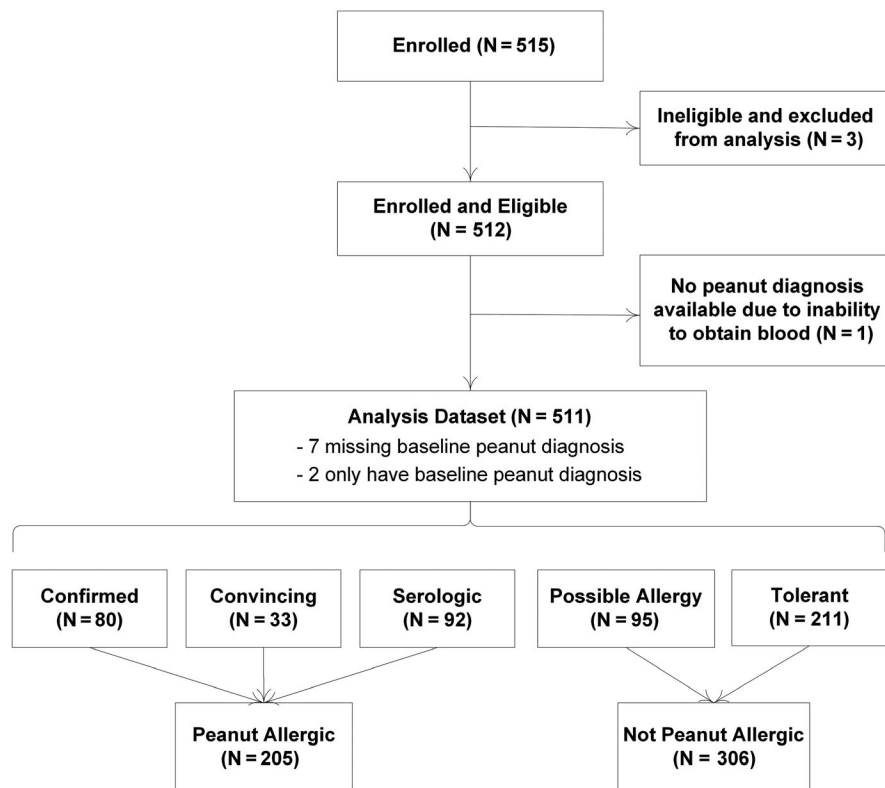
then annually) based on prespecified criteria (Table 1).¹² If clinically indicated, participants were offered oral food challenges (OFCs); however, OFCs were not a required study procedure due to the observational nature of the study. For analysis, participants were categorized into a final peanut allergy status based on diagnoses across all visits accounting for clinical or historical data including results of formal OFCs, home ingestion of peanut, or peanut-specific IgE testing. Final peanut allergy status was defined in mutually exclusive categories comprising a peanut-allergic group with three subgroups (confirmed, convincing, and serologic) reflecting the means of diagnosis as explained below, and a not peanut-allergic group with two subgroups (possible allergy [as discussed below includes potential, not sensitized and never ingested, and non-IgE subcategories] and tolerant), as shown in Figure 1 and Table 1. The confirmed category includes participants who at some point during the study failed a formal OFC to peanut and had sensitization to peanut or participants who had a convincing reaction and highly diagnostic peanut-specific serum IgE.²²⁻²⁴ The convincing category includes participants who at any point in the study had a convincing history of a peanut reaction and sensitization to

TABLE 1 Peanut diagnostic category definitions^a

Diagnostic category	Description	Definition
1	Confirmed IgE-mediated reaction	- Oral food challenge positive and sensitization to peanut (peanut IgE ≥ 0.35 kU_A/L or peanut skin prick test ≥ 3 mm more than the saline control) and/or - Convincing reaction plus a highly predictive peanut IgE test as defined below Convincing reaction: At least 1 of the following acute symptoms within an hour of isolated peanut ingestion: - Skin with hives and/or angioedema - Respiratory symptoms with trouble breathing, wheezing, and throat tightness - Gastrointestinal with vomiting occurring within 1 h of ingestion Highly predictive (>95%) peanut IgE test result: - Child <2 y old: ≥ 5 kU_A/L - Child age 2 y or older: ≥ 14 kU_A/L
2	Convincing, but not confirmed IgE-mediated reaction	- Convincing reaction as defined above with sensitization demonstrated by a positive serologic test (≥ 0.35 kU_A/L but less than highly predictive levels as defined above) and/or positive skin prick test (≥ 3 mm more than saline control) - History of flare of atopic dermatitis upon peanut ingestion and peanut IgE > 95% predictive level as defined above
3	Serological diagnosis	Individual has a peanut IgE level that is highly predictive of a clinical reaction as defined above, but has no known exposure to peanut
4	Potential allergy	- Individual may not have ingested food and has an indeterminate test result (sensitized but not serologic diagnosis), but not yet challenged to peanut - Individual has a convincing history but peanut IgE is <0.35 kU_A/L and peanut SPT <3 mm - Flare of atopic dermatitis and sensitization to peanut (but peanut IgE not in diagnostic range)
5	Not allergic-sensitized	Peanut tolerant but detectable peanut IgE antibody (sensitized, peanut IgE ≥ 0.35 kU _A /L or peanut SPT ≥ 3 mm)
6	Not allergic-not sensitized	Peanut tolerant but no evidence of peanut IgE antibody
7	Not sensitized-never ingested	Individual tested negative for peanut IgE antibody and has not ingested peanut (does not include exposure to peanut in breast milk)
8	Non-IgE food allergy	Individual has a positive oral food challenge, but not sensitized (peanut IgE < 0.35 kU _A /L and peanut SPT < 3 mm)

^aIn this paper, peanut allergy includes categories 1, 2, and 3 above, and not peanut allergy includes the remaining categories. The subcategory of possible peanut allergy includes categories 4, 7, and 8 above.

FIGURE 1 Participant disposition



peanut as evidenced by positive peanut-specific serum IgE (but not a level considered highly diagnostic, ie, below the cutoff levels shown above) and/or SPT, or participants who reported a flare of AD upon peanut ingestion and had highly diagnostic peanut-specific serum IgE (delayed flares or flares without highly predictive IgE to peanut were not included). The serologic category includes participants who had no known exposure to peanut but had standard peanut-specific serum IgE highly diagnostic of clinical reactivity at their last assessment. The possible allergy category includes participants who fulfilled any of three prespecified categories including of potential allergy, not sensitized but never ingested peanut, and non-IgE-mediated allergy. The tolerant category includes participants with or without evidence of sensitization who were able to consume peanut and had never otherwise had a confirmed/convincing peanut allergy diagnosis during the study.

Sensitivity analyses were conducted using four alternate definitions of peanut allergic and not peanut allergic with more and less strict definitions of allergy (Table S1). Briefly, alternate criteria to define peanut allergic vs. not peanut allergic included (1) confirmed or convincing vs. all other categories, (2) confirmed or convincing vs. tolerant, (3) confirmed, convincing, or serologic vs. tolerant, and (4) confirmed or serologic vs. all other categories.

2.3 | Oral food challenges

Physician-supervised OFCs were offered at clinician discretion and family preference guided by the protocol under the following circumstances: (a) There was no recent (past 6 months) reaction to peanut, (b) current test results (skin test/serum IgE) indicated approximately

a 50% or better chance of tolerance (peanut IgE < 5 kU_A/L if no past history, <2 kU_A/L if positive history)²² and skin tests wheal <10 mm.^{25,26} After 5 years in the study, OFCs were offered without requiring the aforementioned test results. The food challenges were generally performed without masking, and ingestion of a meal size amount (8-10 g) without symptoms was considered "passing".

2.4 | Skin prick tests and serum IgE

Skin Prick Tests were performed using the GreerPick® and Greer peanut (F171) extract (Lenoir, NC) with participants avoiding antihistamines for at least 5 half-lives of the specific agent. Tests were performed on the infant's back, and at 15 minutes, the wheal was outlined in pen and transferred by tape to paper. The size of the longest diameter and its longest perpendicular was averaged. The final SPT wheal size was determined after subtraction of the saline control. Tests were considered reliable if the wheal of the negative control (50% glycerin-saline) was 3 mm or smaller and wheal size of the histamine control was at least 3 mm larger than the wheal size of the negative control. The concentration of specific IgE antibody to peanut, Ara h1, Ara h2, Ara h3, and Ara h8 was measured from plasma at a single central laboratory using the Phadia ImmunoCAP® system (Uppsala, Sweden) and reported in kU_A/L.

2.5 | Statistical methods

Logistic regression was used to explore the association between peanut allergy diagnosis and baseline risk factors.²⁷ A univariate logistic regression with peanut allergy as the outcome was performed

with each risk factor in the model one at a time; factors with likelihood ratio test *P*-values of 0.15 or less were included in a stepwise multiple logistic regression analysis. Prior to performing the stepwise regression, the data were stratified by peanut allergy status and then divided at random with two-thirds put into a development dataset and one-third into a validation dataset. The model selection with stepwise regression was performed using the development dataset and the final logistic regression model and then run using the validation dataset to assess model fit. Interactions among the key risk factors in the stepwise regression were considered and if not significant were not included in the final model building. Models were summarized using standard classification measures [AUC, negative predictive value (NPV), positive predictive value (PPV), sensitivity, specificity, Brier score]. A significance level of 0.05 was used, and no adjustments were made for multiple comparisons. Additional statistical methods are included in the Appendix S1 associated with this manuscript.

3 | RESULTS

3.1 | Demographic characteristics

The demographic characteristics of the study participants have been previously published.¹² There were 1297 participants who were screened, and 782 of them were not enrolled (104 had peanut allergy exclusion, 288 did not have a milk or egg allergy, 120 were over the age limit, 101 had other miscellaneous exclusions, and 169 declined to participate). A total of 515 children were enrolled between July 2006 and March 2008; three participants were subsequently excluded due to ineligibility (prior peanut allergy, inadequate skin test reactivity, and mild AD without clinical allergy), and one subject had no peanut diagnosis information available due to inability to obtain blood, leaving 511 for the current analyses (Figure 1). Table 2 summarizes participant demographics. The median age at enrollment was 9.9 months (range, 3.1 to 15.0 months) and the median length of follow-up was 7.3 years (IQR, 6.0 to 8.1 years) with final study follow-up occurring in August 2015. The cohort included 67.5% males, 82% with moderate to severe AD, 74.2% white, 15.3% Black or African American, 8.4% Asian, 2.2% other, and 6.7% Hispanic/Latino. There were a total of 123 participants (24.1%) with OFCs to peanut, with 32 of them (26.0%) having a failing result at their last OFC. The remainder of the diagnoses were based upon the criteria described previously (Table 1).

3.2 | Peanut allergy diagnostic outcomes

Figure 1 describes participant disposition. Per enrollment criteria, none of the participants had a diagnosis of confirmed or convincing peanut allergy at study entry and initial diagnoses were primarily potential peanut allergy (67.5%) as shown in Table 2. Of the 511 analyzed, 205 (40.1%) participants were categorized as peanut-allergic and 306 (59.9%) participants as not peanut-allergic (Figure 1, Table 2). Of the 113 combined subjects with either confirmed (*n* = 80)

or convincing (*n* = 33) peanut allergy after baseline, 12 (10.6%) were consuming peanut at the end of the study (Table S3). Table S4 shows a cross-tabulation of peanut diagnostic category at each visit by final diagnostic categories

3.3 | Baseline peanut allergy risk factors

Table 3 and Table S2 show baseline risk factors according to peanut allergy status for skin test and serologic results to peanut, milk/egg baseline allergic diagnosis, infant diet, breastfeeding, maternal peanut consumption, and presence of peanut in the household. As noted in Table 3, *P*-values (not corrected for multiple comparisons) from a univariate logistic regression comparing allergic to not allergic participants were <0.01 for increased AD severity (moderate/severe vs. none/mild), greater egg and peanut skin prick test, greater egg, milk and peanut IgE levels, greater peanut component test levels (Ara h1, Ara h2, and Ara h3), greater peanut IgG and IgG4, and increased peanut consumption during pregnancy; *P*-values were between 0.01 and 0.05 for younger age, non-white race, lack of breastfeeding, and increased peanut consumption during lactation. Results according to additional peanut allergy diagnostic definitions (Table S1) are described below.

3.4 | Multivariate model identifying baseline risk factors for peanut allergy

A multivariable logistic regression model was constructed. Table 4 shows the risk factor probabilities and odds ratios of the final model for both the development (data used to develop the multivariate model) and the validation (data used to validate the model) datasets (frequencies of these factors are shown in Table S5). The final model included age group at the time of enrollment, Ara h2 level, breastfeeding status, and peanut IgE level. Risk factor probabilities and odds ratios from the univariate model for factors with a likelihood ratio test *P*-values less than or equal to 0.05 that were not included in the final multivariate model are shown in Table 5. A mathematical model was constructed to prognosticate outcomes (Table S6). The characteristics of the final model are shown in Table 6, showing that the model correctly predicts 79% of the participants in the development dataset and 75% of participants in the validation dataset. The ROC curve for the final model using the developmental and validation datasets is shown in Figure 2.

3.5 | Risk models based on alternative diagnostic definitions

As described above in Methods, alternative definitions of peanut allergy with stricter or less strict characteristics and with a resulting variation in the number of participants included in the model were evaluated. Tables S7 and S8 show the same analysis as Tables 4 and 6 using the alternative diagnostic definitions. The sensitivity analysis of peanut-allergic groups produced very similar models with Ara h2 uniformly prognosticative of future peanut allergy. Peanut

TABLE 2 Demographics by peanut allergy status

	Peanut allergic			Not peanut allergic		
	Confirmed (N = 80)	Convincing ^b (N = 33)	Serologic (N = 92)	Possible Allergy ^c (N = 95)	Tolerant ^d (N = 211)	Total (N = 511)
Gender—n (%)						
Male	53 (66.3)	20 (60.6)	71 (77.2)	57 (60.0)	144 (68.2)	345 (67.5)
Female	27 (33.8)	13 (39.4)	21 (22.8)	38 (40.0)	67 (31.8)	166 (32.5)
Age at enrollment (Mo)—n	80	33	92	95	211	511
Mean (SD)	9.8 (3.1)	9.9 (3.1)	9.3 (3.2)	10.0 (2.8)	10.2 (3.1)	9.9 (3.1)
Median (IQR)	9.8 (7.1, 12.1)	10.7 (7.6, 12.3)	9.2 (6.7, 11.7)	9.7 (8.4, 12.2)	10.5 (8.0, 12.5)	9.9 (7.6, 12.2)
Min, Max	4.2, 15.0	4.1, 14.9	3.6, 15.0	3.2, 14.9	3.1, 15.0	3.1, 15.0
Race—n (%)						
White	61 (76.3)	21 (63.6)	56 (60.9)	65 (68.4)	176 (83.4)	379 (74.2)
Black/African American	11 (13.8)	8 (24.2)	18 (19.6)	16 (16.8)	25 (11.8)	78 (15.3)
Asian	6 (7.5)	3 (9.1)	17 (18.5)	9 (9.5)	8 (3.8)	43 (8.4)
Other	2 (2.5)	1 (3.0)	1 (1.1)	5 (5.3)	2 (0.9)	11 (2.2)
Follow-up time (Y)—n	80	33	92	95	211	511
Mean (SD)	7.5 (1.1)	6.8 (2.3)	6.8 (2.1)	5.8 (2.0)	6.8 (1.7)	6.7 (1.9)
Median (IQR)	7.8 (7.1, 8.3)	8.1 (5.9, 8.5)	7.5 (6.6, 8.1)	6.2 (4.5, 7.5)	7.3 (6.1, 8.0)	7.3 (6.0, 8.1)
Min, Max	2.6, 9.1	0.6, 8.9	0.0, 9.0	0.0, 8.8	0.6, 9.1	0.0, 9.1
Last oral food challenge ^e —n (%)						
Passed peanut OFC	3 (3.8)	4 (12.1)	0 (0.0)	0 (0.0)	84 (39.8)	91 (17.8)
Failed peanut OFC	32 (40.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	32 (6.3)
No peanut OFC	45 (56.3)	29 (87.9)	92 (100.0)	95 (100.0)	127 (60.2)	388 (75.9)
Baseline peanut diagnosis—n (%)						
Unknown	1 (1.3)	2 (6.1)	1 (1.1)	2 (2.1)	1 (0.5)	7 (1.4)
Serologic	30 (37.5)	11 (33.3)	57 (62.0)	24 (25.3)	12 (5.7)	134 (26.2)
Possible Allegy ^c	40 (50.0)	16 (48.5)	34 (37.0)	69 (72.6)	186 (88.2)	345 (67.5)
Not allergic	9 (11.3)	4 (12.1)	0 (0.0)	0 (0.0)	12 (5.7)	25 (4.9)
Last peanut diagnosis—n (%)						
Confirmed	68 (85.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	68 (13.3)
Convincing	5 (6.3)	25 (75.8)	0 (0.0)	0 (0.0)	0 (0.0)	30 (5.9)
Serologic	0 (0.0)	0 (0.0)	92 (100.0)	0 (0.0)	0 (0.0)	92 (18.0)
Possible Allegy ^c	0 (0.0)	3 (9.1)	0 (0.0)	95 (100.0)	0 (0.0)	98 (19.2)
Not allergic	7 (8.8)	5 (15.2)	0 (0.0)	0 (0.0)	211 (100.0)	223 (43.6)

^aThe peanut-allergic group is defined as having confirmed or convincing peanut allergy at any visit or serologic peanut allergy at the last study visit; all other participants were in the not peanut-allergic group.

^bIncludes participants who ever had a convincing diagnosis but never had a confirmed diagnosis and whose last diagnosis was not serologic.

^cIncludes diagnoses of potential allergy as well as not sensitized-never ingested and non-IgE food allergy.

^dThirty-five participants ever not allergic were not included if they were also ever confirmed (n = 22) or ever convincing (n = 13).

^eEight participants had previously failed an OFC prior to their final OFC; of these, 6 passed their last OFC and 2 failed it, one of them having previously failed an OFC twice.

IgE and age at enrollment also appear to be important risk factors. Alternative definition 1 had the poorest fit (lowest AUC) compared with the other three definitions. The primary definition and alternative definitions 2, 3, and 4 successfully prognosticated 79%, 80%, 80%, and 79%, respectively, using the development dataset compared with 73% for alternative definition 1. The positive predictive value (using the development dataset) for alternative definition 1

was only 41% compared with 78%, 80%, 88%, and 71% for the primary definition and alternative definitions 2, 3, and 4, respectively. A model considering only those with oral food challenge-proven diagnoses included 35 cases, limiting the ability to identify associations. However, in this analysis, baseline Ara h2 was still highly significant ($P = 0.0005$), but age, breastfeeding, and peanut IgE were no longer significant; AUC for this model was 0.74. This model successfully

TABLE 3 baseline risk factors by peanut allergy status

	Peanut allergic			Not peanut allergic		
	Confirmed (N = 80)	Convincing ^a (N = 33)	Serologic (N = 92)	Possible allergy ^b (N = 95)	Tolerant ^c (N = 211)	Total (N = 511)
Peanut IgE ^d (kU _A /L)—n	79	30	91	93	210	503
Mean (SD)	10.08 (17.31)	14.28 (24.87)	25.34 (33.06)	6.71 (17.14)	1.90 (6.79)	9.05 (20.58)
Median (IQR)	3.09 (0.63, 11.52)	3.94 (0.33, 8.94)	10.36 (1.46, 30.43)	0.80 (0.05, 5.33)	0.17 (0.05, 0.93)	0.87 (0.05, 5.92)
Min, Max	0.05, 86.93	0.05, 94.54	0.05, 101.0	0.05, 101.0	0.05, 65.14	0.05, 101.0
Ara h1 IgE ^d (kU _A /L)—n	76	28	89	89	194	476
Mean (SD)	2.27 (5.15)	6.32 (20.31)	6.31 (16.01)	2.06 (7.26)	0.35 (1.56)	2.44 (9.56)
Median (IQR)	0.44 (0.05, 1.80)	0.16 (0.05, 3.16)	0.89 (0.05, 4.95)	0.05 (0.05, 0.81)	0.05 (0.05, 0.05)	0.05 (0.05, 0.89)
Min, Max	0.05, 33.00	0.05, 101.0	0.05, 101.0	0.05, 55.30	0.05, 19.00	0.05, 101.0
Ara h2 IgE ^d (kU _A /L)—n	76	28	89	89	194	476
Mean (SD)	6.50 (13.25)	10.37 (21.07)	13.29 (24.89)	3.17 (13.26)	0.96 (7.85)	5.12 (15.73)
Median (IQR)	0.47 (0.05, 6.59)	1.55 (0.05, 9.27)	0.71 (0.05, 15.80)	0.05 (0.05, 0.31)	0.05 (0.05, 0.05)	0.05 (0.05, 1.06)
Min, Max	0.05, 73.10	0.05, 88.10	0.05, 101.0	0.05, 101.0	0.05, 91.90	0.05, 101.0
Skin prick test ^e (mm)—n	80	33	92	95	211	511
Mean (SD)	6.72 (5.40)	6.45 (5.32)	6.80 (5.70)	4.20 (4.58)	2.30 (3.45)	4.42 (4.98)
Median (IQR)	6.00 (2.50, 10.50)	5.50 (2.00, 12.00)	6.50 (2.25, 11.25)	3.00 (0.00, 7.50)	0.00 (0.00, 4.00)	3.00 (0.00, 7.50)
Min, Max	−2.00, 18.50	0.00, 18.00	−2.50, 22.00	−3.00, 16.00	−3.00, 13.50	−3.00, 22.00
Breastfed—n (%)						
Never	11 (13.8)	9 (27.3)	19 (20.7)	12 (12.6)	22 (10.4)	73 (14.3)
Yes, currently	26 (32.5)	9 (27.3)	24 (26.1)	37 (38.9)	81 (38.4)	177 (34.6)
Yes, but no longer	43 (53.8)	15 (45.5)	49 (53.3)	46 (48.4)	108 (51.2)	261 (51.1)
Milk Allergic—n (%)	36 (45.0)	15 (45.5)	47 (51.1)	49 (51.6)	97 (46.0)	244 (47.7)
Egg allergic—n (%)	27 (33.8)	12 (36.4)	18 (19.6)	19 (20.0)	64 (30.3)	140 (27.4)
Atopic dermatitis—n (%)						
None	4 (5.0)	0 (0.0)	1 (1.1)	3 (3.2)	33 (15.6)	41 (8.0)
Mild	6 (7.5)	3 (9.1)	5 (5.4)	6 (6.3)	30 (14.2)	50 (9.8)
Moderate	47 (58.8)	18 (54.5)	50 (54.3)	47 (49.5)	96 (45.5)	258 (50.5)
Severe	23 (28.8)	12 (36.4)	36 (39.1)	39 (41.1)	52 (24.6)	162 (31.7)
Peanut consumption during pregnancy—n (%)						
Unknown	2 (2.5)	0	1 (1.1)	2 (2.1)	2 (0.9)	7 (1.4)
<2x per wk	38 (47.5)	19 (57.6)	45 (48.9)	55 (57.9)	133 (63.0)	290 (56.8)

(Continues)

TABLE 4 Odds ratios and confidence intervals for factors in the final model^a

Baseline risk factor	Category	Univariate model		Multivariate model			
		Complete dataset		Development dataset		Validation dataset	
		Odds ratio (95% CI)	Wald chi-square P-value	Odds ratio (95% CI)	Wald chi-square P-value	Odds ratio (95% CI)	Wald chi-square P-value
Age group	3-5 mo	–	–	–	–	–	–
	6-8 mo	0.68 (0.37, 1.23)	0.20	0.20 (0.08, 0.53)	0.001	0.92 (0.23, 3.61)	0.90
	9-11 mo	0.44 (0.25, 0.79)	0.006	0.22 (0.09, 0.55)	0.001	0.14 (0.03, 0.59)	0.007
	12-15 mo	0.52 (0.29, 0.95)	0.032	0.18 (0.07, 0.46)	0.0003	0.30 (0.07, 1.32)	0.11
Breastfed	Never	–	–	–	–	–	–
	Yes, currently	0.44 (0.25, 0.76)	0.003	0.36 (0.15, 0.87)	0.024	0.23 (0.06, 0.82)	0.024
	Yes, but no longer breastfeeding	0.61 (0.36, 1.02)	0.06	0.90 (0.41, 1.98)	0.79	0.18 (0.05, 0.64)	0.009
Peanut IgE	<0.35	–	–	–	–	–	–
	≥0.35-2	2.33 (1.35, 4.02)	0.002	2.89 (1.32, 6.35)	0.008	1.16 (0.38, 3.60)	0.79
	≥2-5	4.07 (2.18, 7.61)	<0.0001	3.84 (1.55, 9.54)	0.004	1.68 (0.41, 6.90)	0.47
	≥5	12.50 (7.42, 21.06)	<0.0001	4.10 (1.68, 9.98)	0.002	7.84 (1.89, 32.42)	0.004
Ara h2 IgE	<0.35	–	–	–	–	–	–
	≥0.35-2	4.44 (2.18, 9.07)	<0.0001	3.30 (1.26, 8.66)	0.015	6.33 (1.33, 30.09)	0.020
	≥2-5	4.48 (2.09, 9.60)	0.0001	4.11 (1.40, 12.08)	0.010	1.65 (0.32, 8.59)	0.55
	≥5	16.70 (8.43, 33.11)	<0.0001	16.16 (4.93, 52.91)	<0.0001	1.75 (0.36, 8.52)	0.49

^aThe peanut-allergic group is defined as having confirmed or convincing peanut allergy at any visit or serologic peanut allergy at the last study visit; all other participants were in the not peanut-allergic group.

in this cohort, a cohort that was preselected for risk factors associated with developing peanut allergy (which likely explains why AD severity and positive tests to milk/egg are not included in the final model). While still far from perfect, this model correctly prognosticated peanut allergy in 79.4% in the development dataset and 74.8% in the validation dataset. These data, if validated, could help to identify from among infants who already exhibit some risk factors (for example, moderate to severe AD), those most likely to benefit from treatment or prevention strategies. Importantly, these results are pertinent only to the high-risk group evaluated in this study, not to the general infant population. Our sample does not include “low-risk” infants (those without atopic dermatitis or food allergy), and we do not endorse testing/screening those not at high risk. We also assessed alternative classifications using more or less strict definitions of peanut allergy, with these analyses revealing similar results and Ara h2 levels being most predictive of future peanut allergy, and total peanut IgE and age at enrollment also remaining as important

risk factors. Alternative definition 1 had a worse fit likely due to serologic diagnoses, which are known to be highly predictive of peanut allergy, being treated as not peanut allergic, thereby reducing the ability of the model selection process to identify appropriate risk factors.

These data are most important when considered in relation to the LEAP study and current recommendations for the possible prevention of peanut allergy.^{8,9} Of note, 40.1% of our cohort had peanut allergy (37.2% at their final evaluation) and had a high rate of peanut sensitization at enrollment,¹² higher than LEAP,³⁰ and the rate of peanut allergy was higher than the avoidance group in LEAP (17.2%), suggesting that the criteria we used at study enrollment are another tenable one to identify high-risk infants for prevention strategies. While our cohort and the LEAP cohort are not identical, with inclusion in LEAP being driven primarily by moderate to severe eczema rather than likely milk or egg allergy, there is considerable overlap between the

TABLE 5 Odds ratios and confidence intervals from univariate model for significant factors^a Not in the final model^b

Baseline risk factor	Category	Odds ratio (95% CI)	Wald chi-square P-value
Predominant race	White	–	–
	Black/African American	1.58 (0.96, 2.58)	0.07
	Asian	2.67 (1.40, 5.10)	0.003
	Other	1.00 (0.29, 3.47)	1.00
Atopic dermatitis	None/mild	–	–
	Moderate/severe	3.01 (1.75, 5.17)	<0.0001
Ara h1 IgE	<0.35	–	–
	≥0.35-2	3.68 (2.23, 6.06)	<0.0001
	≥2-5	4.13 (2.02, 8.44)	0.0001
	≥5	11.83 (5.29, 26.46)	<0.0001
Ara h3 IgE	<0.35	–	–
	≥0.35-2	2.28 (1.35, 3.85)	0.002
	≥2-5	12.15 (3.51, 42.03)	<0.0001
	≥5	12.15 (3.51, 42.03)	<0.0001
Peanut IgG	<5	–	–
	≥5-14	1.54 (1.00, 2.38)	0.05
	≥14	6.83 (4.09, 11.40)	<0.0001
Peanut IgG4	<0.35	–	–
	≥0.35-2	2.82 (1.69, 4.69)	<0.0001
	≥2-5	7.42 (1.56, 35.42)	0.012
	≥5	1.86 (0.12, 29.89)	0.66
Peanut SPT	<3	–	–
	≥3-5	1.69 (0.98, 2.90)	0.06
	≥5-10	3.96 (2.43, 6.45)	<0.0001
	≥10	7.09 (4.12, 12.20)	<0.0001
Milk IgE	<5	–	–
	≥5-14	1.69 (0.97, 2.93)	0.06
	≥14	3.17 (1.89, 5.31)	<0.0001
Egg IgE	<0.35	–	–
	≥0.35-2	1.93 (1.09, 3.43)	0.025
	≥2-5	2.87 (1.55, 5.31)	0.0008
	≥5	5.48 (3.24, 9.27)	<0.0001
Egg SPT	<3	–	–
	≥3	2.74 (1.47, 5.09)	0.001
Peanut consumption during pregnancy	<2x/wk	–	–
	≥2x/wk	1.62 (1.13, 2.32)	0.009
Peanut consumption during breastfeeding	<2x/wk or never breastfed	–	–
	≥2x/wk	1.60 (1.07, 2.40)	0.022

^aSignificant factors had a likelihood ratio test P-value of ≤0.05.^bThe peanut-allergic group is defined as having confirmed or convincing peanut allergy at any visit or serologic peanut allergy at the last study visit; all other participants were in the not peanut-allergic group.

study populations. Most importantly, given that this study was primarily designed to study the risk factors for the development of peanut allergy, we can now use these data to better inform families and clinicians about the infants for whom preventative

measures are most likely to be indicated. The risk factors that we have identified, including skin test or serologic evidence of early peanut sensitization, as well as a diagnosis of likely egg allergy, are completely consistent with those risk factors proposed in the

TABLE 6 Characteristics of the final model

	Development dataset	Validation dataset
Area under the ROC curve (AUC)	0.83	0.83
Brier score	0.16	0.16
Sensitivity	69.5	66.1
Specificity	86.3	80.6
Positive predictive value (PPV)	77.8	69.5
Negative predictive value (NPV)	80.4	78.1
% Successfully predicted (Allergic and Not allergic) ^a	79.4	74.8

^aCorrectly predicted categorically as follows: developmental dataset: confirmed = 57.7%, convincing = 73.7%, serologic = 78.3%, possible allergy = 76.2%, tolerant = 90.8%. Validation dataset: confirmed = 54.2%, convincing = 77.8%, serologic = 72.4%, possible allergy = 56.7%, tolerant = 92.1%.

guidelines for the prevention of peanut allergy. Milk sensitization was not named a specific risk factor in recent PNA prevention guidelines;⁹ in this cohort, elevated milk-specific IgE was a risk factor for PNA (although it did not survive in multivariate analysis). We also identified an association between younger age at enrollment and a higher risk of current or future peanut allergy. While the reasons for this are not clear, we propose that more severely affected infants were simply more likely to be referred for care at an earlier age, as noted in LEAP and proposed as an explanation in that study.³¹ Alternatively, exclusion of infants with known peanut allergy from the study may have reduced the enrollment of higher risk older infants.

The strengths of this study include the large sample size, the duration of follow-up, and the sequential measurement of possible peanut allergy through history, oral food challenges, and skin and serologic testing. We were also able to utilize banked samples to measure peanut component results in most subjects using assays that were not available at the time of study initiation, demonstrating the prognostic value of Ara h2 levels even in infancy. The primary weakness of the study is the absence of scheduled OFCs (ideally double-blind, placebo-controlled OFCs, to peanut in all subjects). While the protocol recommended criteria for peanut OFCs, ethical concerns prevented us from performing challenges for those children deemed extremely likely to have peanut allergy in an observational study. The criteria used to designate serologic peanut allergy are based on IgE levels from prior studies, and the analysis is conservative in characterizing those with levels below high predictive values and without clinical exposure as not allergic. Other weaknesses include recall bias for the maternal feeding history, and possible issues with generalizability because this is a US population.

In conclusion, we identified key risk factors associated with the development of peanut allergy in this high-risk cohort, specifically including lack of breastfeeding and greater Ara h2 and peanut-specific

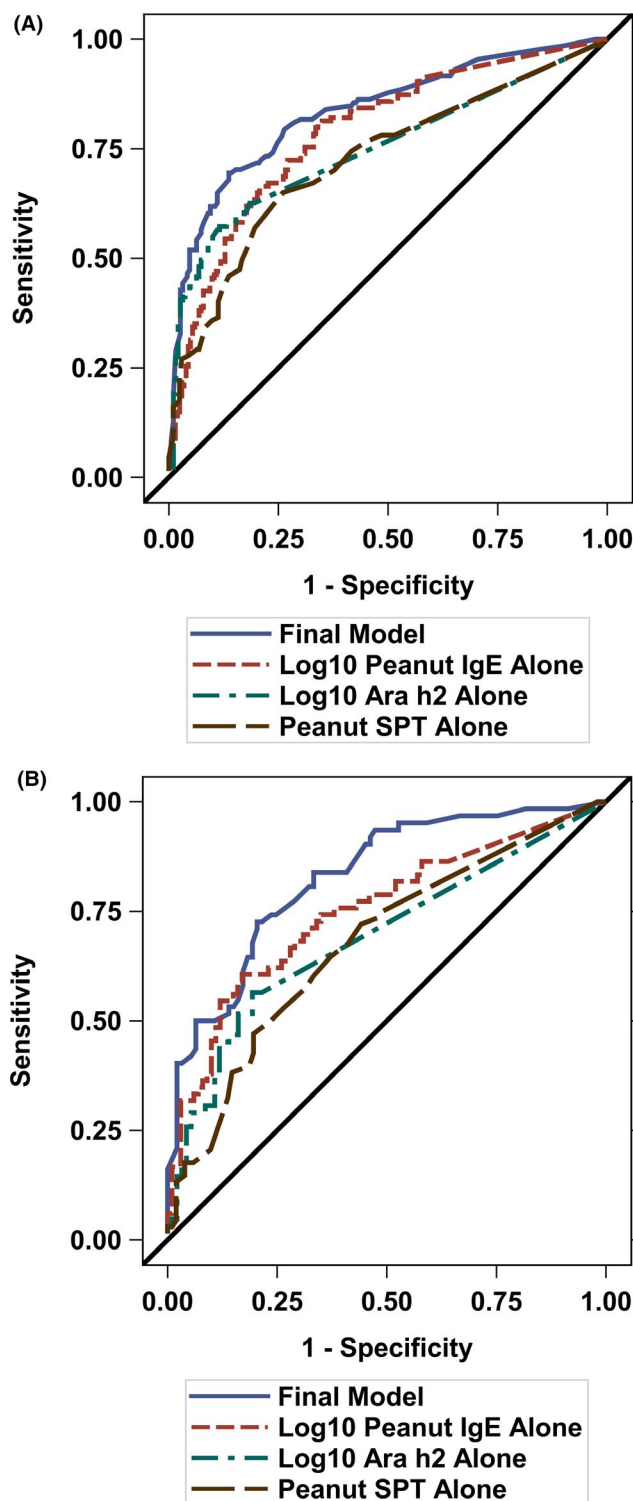


FIGURE 2 ROC curve for the logistic regression model for developing peanut allergy (primary definition) for the final multivariate model as well as the univariate models of log 10 peanut IgE, log 10 Ara h2 IgE, and peanut SPT using (A) the development dataset (AUC: final model = 0.83, log 10 peanut IgE alone = 0.79, log 10 Ara h2 IgE = 0.75, peanut SPT = 0.72) and (B) the validation dataset (AUC: final model = 0.83, log 10 peanut IgE alone = 0.75, log 10 Ara h2 IgE = 0.69, peanut SPT = 0.68) [Colour figure can be viewed at wileyonlinelibrary.com]

IgE levels. These specific data may be used to calculate risk, although the results must be considered preliminary and this approach needs validation in other cohorts prior to clinical use. Importantly, the data also suggest beneficial protective effects of breastfeeding in general. Given that 40% of our cohort developed peanut allergy, we suggest that prevention strategies, such as early introduction of peanut, could reasonably be applied to infants with our cohort's inclusion criteria.

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CONFLICT OF INTEREST

Dr. Wood reports grants from Astellas, grants from DBV, grants from Aimmune, grants from Regeneron, grants from NIAID, outside the submitted work. Dr. Dawson reports grants from DAIT/NIAID/NIH during the conduct of the study. Ms. Henning reports grants from DAIT/NIAID/NIH, during the conduct of the study. Dr. Jones reports grants from NIH-NIAID, during the conduct of the study; personal fees from FARE-Food Allergy Research and Education, personal fees from Aimmune herapeutics, grants from Aimmune Therapeutics, grants from DBV Technologies, grants from Astellas, Inc., grants from FARE, grants from NIH/NIAID, personal fees from EMMES Corporation, grants from Sanofi, Inc., grants from Regeneron, Inc., outside the submitted work. Dr. Lindblad reports grants from DAIT/NIAID/NIH during the conduct of the study. Dr. Burks reports personal fees from Aimmune Therapeutics, Inc., personal fees from Astella Pharma Global Development, personal fees from Consortia TX, Inc., personal fees from DBV Technologies, personal fees from Intromune Therapeutics, personal fees from Protia Therapeutics, personal fees from N-Fold, LLC, personal fees from Aravax, personal fees from Genetech, personal fees from Hycor Biomedical, grants from NIH, grants from Johns Hopkins/NIH, grants from NIH, grants from NIH, grants from FARE, grants from Wallace Research Foundation, grants from NIH, grants from NIH, grants from PRA Health Sciences, Inc., other from Allertein stock, other from Mastcell Pharmaceuticals, other from UpToDate royalties, outside the submitted work; In addition, Dr. Burks has a patent US #7879977 with

royalties paid, a patent US #6835824 with royalties paid, a patent US #6486311 with royalties paid, a patent US #6441142 with royalties paid, a patent US #5973121 with royalties paid, and a patent US #5558869 with royalties paid.

AUTHOR CONTRIBUTIONS

All authors have contributed in a manner to justify inclusion as authors.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Table S1. Peanut Allergic Group Definitions

Definition	Peanut Allergic	Not Peanut Allergic
Primary	Diagnostic categories 1 or 2 at any visit, or category 3 at last visit	All other participants not defined as peanut allergic
Alternate Definition 1	Diagnostic categories 1 or 2 at any visit	All other participants not defined as peanut allergic
Alternate Definition 2	Diagnostic categories 1 or 2 at any visit	Diagnostic categories 5 or 6 at any visit (and never diagnostic categories 1 or 2)
Alternate Definition 3	Diagnostic categories 1 or 2 at any visit, or category 3 at last visit	Diagnostic categories 5 or 6 at any visit (and never diagnostic categories 1 or 2)
Alternate Definition 4	Diagnostic category 1 at any visit, or category 3 at last visit	All other participants not defined as peanut allergic

Table S2. Baseline Risk Factors by Peanut Allergy Status

	Peanut Allergic¹ (N=205)	Not Peanut Allergic² (N=306)	Total (N=511)
Peanut IgE³ (kU_A/L) – n	200	303	503
Mean (SD)	17.65 (27.45)	3.37 (11.24)	9.05 (20.58)
Median (IQR)	5.11 (0.83, 19.32)	0.25 (0.05, 1.74)	0.87 (0.05, 5.92)
Min, Max	0.05, 101.0	0.05, 101.0	0.05, 101.0
Ara h1 IgE³ (kU_A/L) – n	193	283	476
Mean (SD)	4.72 (13.78)	0.89 (4.33)	2.44 (9.56)
Median (IQR)	0.47 (0.05, 3.03)	0.05 (0.05, 0.19)	0.05 (0.05, 0.89)
Min, Max	0.05, 101.0	0.05, 55.30	0.05, 101.0
Ara h2 IgE³ (kU_A/L) – n	193	283	476
Mean (SD)	10.19 (20.61)	1.66 (9.91)	5.12 (15.73)
Median (IQR)	0.72 (0.05, 9.34)	0.05 (0.05, 0.05)	0.05 (0.05, 1.06)
Min, Max	0.05, 101.0	0.05, 101.0	0.05, 101.0
Skin Prick Test⁴ (mm) – n	205	306	511
Mean (SD)	6.71 (5.50)	2.89 (3.93)	4.42 (4.98)
Median (IQR)	6.00 (2.50, 11.00)	1.00 (0.00, 4.50)	3.00 (0.00, 7.50)
Min, Max	-2.50, 22.00	-3.00, 16.00	-3.00, 22.00
Breastfed - n (%)			
Never	39 (19.0)	34 (11.1)	73 (14.3)
Yes, currently	59 (28.8)	118 (38.6)	177 (34.6)
Yes, but no longer	107 (52.2)	154 (50.3)	261 (51.1)
Milk Allergic - n (%)	98 (47.8)	146 (47.7)	244 (47.7)
Egg Allergic - n (%)	57 (27.8)	83 (27.1)	140 (27.4)
Atopic Dermatitis - n (%)			
None	5 (2.4)	36 (11.8)	41 (8.0)
Mild	14 (6.8)	36 (11.8)	50 (9.8)
Moderate	115 (56.1)	143 (46.7)	258 (50.5)
Severe	71 (34.6)	91 (29.7)	162 (31.7)
Peanut Consumption During Pregnancy - n (%)			
Unknown	3 (1.5)	4 (1.3)	7 (1.4)
<2x per week	102 (49.8)	188 (61.4)	290 (56.8)
>=2x per week	100 (48.8)	114 (37.3)	214 (41.9)
Peanut Consumption During Breastfeeding - n (%)			
Unknown	2 (1.0)	5 (1.6)	7 (1.4)
<2x per week or never breastfed	140 (68.3)	235 (76.8)	375 (73.4)
>=2x per week	63 (30.7)	66 (21.6)	129 (25.2)
Peanut Present in House During Breastfeeding - n (%)	146 (71.2)	231 (75.5)	377 (73.8)

Note: ¹Had confirmed or convincing peanut allergy at any visit or serologic peanut allergy at the last study visit; all others in the not peanut allergic group.

²Includes diagnoses of tolerant, possible peanut allergy (potential allergy, not sensitized-never ingested, and non-IgE food allergy).

³IgE values <0.01 were set to 0.05 kU_A/L and those >100 were set to 101 kU_A/L because they were outside the assay limits of detection.

⁴Skin prick test values were calculated by subtracting the size of the saline wheal from the peanut wheal; when the saline wheal is larger than the peanut wheal, negative values occur.

Table S3. Peanut Allergy Resolution Among Subjects with Ever Confirmed/Convincing Peanut Allergy

	Peanut Allergy Status				Total	
	Confirmed		Convincing			
	N	%	N	%	N	%
Total Subjects Ever Confirmed/Convincing	80	100.0	33	100.0	113	100.0
Resolved Peanut Allergy	7	8.8	5	15.2	12	10.6
Did Not Resolve Peanut Allergy	73	91.3	28	84.8	101	89.4

Table S4. Baseline Peanut Diagnosis by Last Known Peanut Diagnosis*

		Last Known Peanut Diagnosis											
		Confirmed		Convincing		Serologic		Possible Allergy ¹		Tolerant		Total	
		N	%	N	%	N	%	N	%	N	%	N	%
Visit	Peanut Allergy Diagnosis												
Baseline	Confirmed	0	0	0	0	0	0	0	0	0	0	0	0
	Convincing	0	0	0	0	0	0	0	0	0	0	0	0
	Serologic	23	17.2	15	11.2	57	42.5	24	17.9	15	11.2	134	100.0
	Possible Allergy	37	10.7	9	2.6	34	9.9	72	20.9	193	55.9	345	100.0
	Tolerant	7	28.0	4	16.0	0	0.0	0	0.0	14	56.0	25	100.0
Year 1	Confirmed	8	66.7	4	33.3	0	0.0	0	0.0	0	0.0	12	100.0
	Convincing	2	22.2	4	44.4	0	0.0	0	0.0	3	33.3	9	100.0
	Serologic	19	16.8	5	4.4	64	56.6	17	15.0	8	7.1	113	100.0
	Possible Allergy	31	10.1	15	4.9	23	7.5	75	24.4	164	53.2	308	100.0
	Tolerant	7	15.2	1	2.2	0	0.0	1	2.2	37	80.4	46	100.0
Year 2	Confirmed	13	100.0	0	0.0	0	0.0	0	0.0	0	0.0	13	100.0
	Convincing	5	31.3	9	56.3	0	0.0	0	0.0	2	12.5	16	100.0
	Serologic	13	16.0	2	2.5	57	70.4	7	8.6	2	2.5	81	100.0
	Possible Allergy	25	8.8	13	4.6	25	8.8	77	27.0	145	50.9	285	100.0
	Tolerant	7	10.4	1	1.5	0	0.0	1	1.5	58	86.6	67	100.0
Year 3	Confirmed	16	94.1	0	0.0	0	0.0	0	0.0	1	5.9	17	100.0
	Convincing	8	34.8	12	52.2	0	0.0	2	8.7	1	4.3	23	100.0
	Serologic	14	16.5	3	3.5	58	68.2	8	9.4	2	2.4	85	100.0
	Possible Allergy	19	9.3	8	3.9	20	9.8	74	36.1	84	41.0	205	100.0
	Tolerant	4	3.7	2	1.9	0	0.0	1	0.9	101	93.5	108	100.0
Year 4	Confirmed	27	90.0	1	3.3	0	0.0	0	0.0	2	6.7	30	100.0
	Convincing	9	36.0	11	44.0	0	0.0	2	8.0	3	12.0	25	100.0
	Serologic	10	12.3	2	2.5	64	79.0	4	4.9	1	1.2	81	100.0
	Possible Allergy	16	9.9	8	4.9	16	9.9	80	49.4	42	25.9	162	100.0
	Tolerant	2	1.3	2	1.3	0	0.0	1	0.7	146	96.7	151	100.0
Year 5	Confirmed	35	92.1	0	0.0	0	0.0	0	0.0	3	7.9	38	100.0
	Convincing	8	38.1	10	47.6	0	0.0	1	4.8	2	9.5	21	100.0
	Serologic	5	7.5	1	1.5	56	83.6	5	7.5	0	0.0	67	100.0
	Possible Allergy	10	13.2	7	9.2	5	6.6	34	44.7	20	26.3	76	100.0
	Tolerant	3	2.3	1	0.8	0	0.0	1	0.8	127	96.2	132	100.0
Year 6	Confirmed	39	100.0	0	0.0	0	0.0	0	0.0	0	0.0	39	100.0
	Convincing	8	33.3	13	54.2	0	0.0	1	4.2	2	8.3	24	100.0
	Serologic	3	4.6	1	1.5	60	92.3	1	1.5	0	0.0	65	100.0

		Last Known Peanut Diagnosis											
		Confirmed		Convincing		Serologic		Possible Allergy ¹		Tolerant		Total	
		N	%	N	%	N	%	N	%	N	%	N	%
Year 7	Possible Allergy	7	11.3	4	6.5	3	4.8	40	64.5	8	12.9	62	100.0
	Tolerant	2	1.4	0	0.0	0	0.0	0	0.0	139	98.6	141	100.0
	Confirmed	43	95.6	1	2.2	0	0.0	0	0.0	1	2.2	45	100.0
	Convincing	5	26.3	12	63.2	0	0.0	0	0.0	2	10.5	19	100.0
	Serologic	2	3.4	1	1.7	54	91.5	1	1.7	1	1.7	59	100.0
Year 8	Possible Allergy	4	9.3	2	4.7	1	2.3	35	81.4	1	2.3	43	100.0
	Tolerant	1	0.9	0	0.0	0	0.0	0	0.0	116	99.1	117	100.0
	Confirmed	25	96.2	1	3.8	0	0.0	0	0.0	0	0.0	26	100.0
	Convincing	4	26.7	11	73.3	0	0.0	0	0.0	0	0.0	15	100.0
	Serologic	0	0.0	0	0.0	39	100.0	0	0.0	0	0.0	39	100.0
Year 9	Possible Allergy	3	13.6	0	0.0	0	0.0	18	81.8	1	4.5	22	100.0
	Tolerant	1	1.3	0	0.0	0	0.0	0	0.0	79	98.8	80	100.0
	Confirmed	5	100.0	0	0.0	0	0.0	0	0.0	0	0.0	5	100.0
	Convincing	1	33.3	2	66.7	0	0.0	0	0.0	0	0.0	3	100.0
	Serologic	0	0.0	0	0.0	4	100.0	0	0.0	0	0.0	4	100.0
		0	0.0	0	0.0	0	0.0	2	100.0	0	0.0	2	100.0
		0	0.0	0	0.0	0	0.0	0	0.0	7	100.0	7	100.0

* The last known peanut diagnosis is the peanut diagnostic category at the last study visit. Overall, 10.6% resolved peanut allergy. The ages (yrs) at which allergy resolution were recorded were: 2 at age 3, 2 at age 4, 1 at age 5, 2 at age 7, 4 at age 8, and 1 at age 9. There were 13 subjects who were tolerant at baseline but later developed a confirmed/convincing peanut allergy. The approximate age at which these subjects developed their peanut allergy (yrs) was as follows: six at age 1, three at age 3, two at age 4, one at age 8, and one at age 9. ¹Includes categories of potential, not-sensitized, never ingested and non-IgE allergy.

Table S5. Frequency of Factors in Final Model in Development and Validation Datasets

	Peanut Allergy Status																	
	Allergic						Not Allergic						Total Participants					
	Development		Validation		All		Development		Validation		All		Development		Validation		All	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total Participants	137	100.0	68	100.0	205	100.0	204	100.0	102	100.0	306	100.0	341	100.0	170	100.0	511	100.0
Age (months)																		
3-5 months	27	19.7	8	11.8	35	17.1	20	9.8	10	9.8	30	9.8	47	13.8	18	10.6	65	12.7
6-8 months	24	17.5	32	47.1	56	27.3	52	25.5	19	18.6	71	23.2	76	22.3	51	30.0	127	24.9
9-11 months	45	32.8	16	23.5	61	29.8	69	33.8	49	48.0	118	38.6	114	33.4	65	38.2	179	35.0
12-15 months	41	29.9	12	17.6	53	25.9	63	30.9	24	23.5	87	28.4	104	30.5	36	21.2	140	27.4
Breastfed																		
Never	25	18.2	14	20.6	39	19.0	25	12.3	9	8.8	34	11.1	50	14.7	23	13.5	73	14.3
Yes, currently	34	24.8	25	36.8	59	28.8	78	38.2	40	39.2	118	38.6	112	32.8	65	38.2	177	34.6
Yes, but no longer breastfeeding	78	56.9	29	42.6	107	52.2	101	49.5	53	52.0	154	50.3	179	52.5	82	48.2	261	51.1
Baseline peanut IgE (kU_A/L)																		
Missing	3	2.2	2	2.9	5	2.4	1	0.5	2	2.0	3	1.0	4	1.2	4	2.4	8	1.6
<0.35	21	15.3	14	20.6	35	17.1	114	55.9	49	48.0	163	53.3	135	39.6	63	37.1	198	38.7
>=0.35-2	24	17.5	11	16.2	35	17.1	45	22.1	25	24.5	70	22.9	69	20.2	36	21.2	105	20.5
>=2-5	22	16.1	6	8.8	28	13.7	18	8.8	14	13.7	32	10.5	40	11.7	20	11.8	60	11.7
>=5	67	48.9	35	51.5	102	49.8	26	12.7	12	11.8	38	12.4	93	27.3	47	27.6	140	27.4
Baseline ara h2 IgE (kU_A/L)																		
Missing	6	4.4	6	8.8	12	5.9	14	6.9	9	8.8	23	7.5	20	5.9	15	8.8	35	6.8
<0.35	56	40.9	31	45.6	87	42.4	168	82.4	78	76.5	246	80.4	224	65.7	109	64.1	333	65.2
>=0.35-2	15	10.9	7	10.3	22	10.7	10	4.9	4	3.9	14	4.6	25	7.3	11	6.5	36	7.0
>=2-5	13	9.5	6	8.8	19	9.3	7	3.4	5	4.9	12	3.9	20	5.9	11	6.5	31	6.1
>=5	47	34.3	18	26.5	65	31.7	5	2.5	6	5.9	11	3.6	52	15.2	24	14.1	76	14.9

Table S6. Probability of Developing Peanut Allergy Calculator*

Variable	Variable Category	Model Coefficient
Intercept	NA	-0.0565
Age at Enrollment	3-5 mos	0
	6-8 mos	-1.5964
	9-12 mos	-1.5007
	12-15 mos	-1.7003
Breastfeeding	Never	0
	Yes, currently	-1.0117
	Yes, no longer	-0.1048
Baseline Peanut IgE (kU _A /L)	<0.35	0
	>=0.35 to 2	1.0626
	>=2 to 5	1.3462
	>= 5	1.4102
Baseline Ara h2 IgE (kU _A /L)	<0.35	0
	>=0.35 to 2	1.1933
	>=2 to 5	1.4128
	>= 5	2.7825

* To calculate the probability for an individual, add together the model coefficients for the intercept and for the category that correspond to this individual for the 4 variables in the model; this sum is called X. The percent probability of developing peanut allergy for this individual is $e^X/(1+e^X) * 100$.

Table S7. Odds Ratios and Confidence Intervals for Factors in the Final Model by Peanut Allergy Definition

Alternative Peanut Allergy Definition	Baseline Risk Factor	Category	Univariate Model		Multivariate Model			
			Complete Dataset		Development Dataset		Validation Dataset	
			Odds Ratio (95% CI)	Wald Chi- square P- Value	Odds Ratio (95% CI)	Wald Chi- square P- Value	Odds Ratio (95% CI)	Wald Chi- square P- Value
Definition 1	Ara h2 IgE	<0.35	--	--	--	--	--	--
		>=0.35-2	4.99 (2.41, 10.33)	< 0.0001	4.99 (2.41, 10.33)	< 0.0001	7.52 (2.04, 27.76)	0.05
		>=2-5	3.94 (1.79, 8.66)	0.0006	3.94 (1.79, 8.66)	0.0006	2.35 (0.56, 9.86)	0.72
		>=5	4.07 (2.33, 7.09)	< 0.0001	4.07 (2.33, 7.09)	< 0.0001	3.76 (1.40, 10.12)	0.49
Definition 2	Atopic Dermatitis	None/Mild	--	--	--	--	--	--
		Moderate/Severe	3.27 (1.71, 6.26)	0.0003	2.48 (1.02, 6.06)	0.046	3.00 (0.59, 15.18)	0.18

Alternative Peanut Allergy Definition	Baseline Risk Factor	Category	Univariate Model		Multivariate Model			
			Complete Dataset		Development Dataset		Validation Dataset	
			Odds Ratio (95% CI)	Wald Chi- square P- Value	Odds Ratio (95% CI)	Wald Chi- square P- Value	Odds Ratio (95% CI)	Wald Chi- square P- Value
Definition 3	Log10 Ara h2 IgE		4.15 (2.86, 6.02)	< 0.0001	4.06 (2.56, 6.43)	< 0.0001	3.67 (1.94, 6.97)	< 0.0001
	Age group	3-5 months	--	--	--	--	--	--
		6-8 months	0.67 (0.35, 1.30)	0.24	0.17 (0.06, 0.51)	0.001	2.67 (0.54, 13.25)	0.23
		9-11 months	0.47 (0.25, 0.89)	0.020	0.26 (0.09, 0.72)	0.010	0.36 (0.09, 1.49)	0.16
		12-15 months	0.51 (0.27, 0.99)	0.045	0.24 (0.08, 0.70)	0.009	0.52 (0.11, 2.52)	0.42
	Historical/baseline Atopic Dermatitis	None	--	--	--	--	--	--
		Mild	3.08 (0.99, 9.58)	0.05	2.58 (0.51, 13.03)	0.25	3.57 (0.21, 60.66)	0.38
		Moderate	7.91 (2.97, 21.04)	< 0.0001	5.21 (1.33, 20.38)	0.018	6.86 (0.64, 73.09)	0.11
		Severe	9.01 (3.29, 24.65)	< 0.0001	2.05 (0.48, 8.69)	0.33	9.68 (0.83, 112.4)	0.07
	Log10 Peanut IgE		3.66 (2.83, 4.75)	< 0.0001	2.25 (1.45, 3.49)	0.0003	2.14 (1.12, 4.07)	0.021
Definition 4	Log10 Ara h2 IgE		4.11 (2.93, 5.76)	< 0.0001	2.78 (1.63, 4.71)	0.0002	1.86 (0.90, 3.81)	0.09
	Age group	3-5 months	--	--	--	--	--	--
		6-8 months	0.78 (0.43, 1.43)	0.43	0.28 (0.11, 0.69)	0.006	1.47 (0.39, 5.50)	0.56
		9-11 months	0.44 (0.24, 0.79)	0.006	0.26 (0.11, 0.62)	0.002	0.20 (0.05, 0.76)	0.018
		12-15 months	0.50 (0.27, 0.92)	0.025	0.25 (0.11, 0.61)	0.002	0.31 (0.08, 1.26)	0.10
	Log10 Peanut IgE		2.70 (2.18, 3.36)	< 0.0001	2.18 (1.50, 3.18)	< 0.0001	2.32 (1.35, 3.98)	0.002
	Log10 Ara h2 IgE		2.27 (1.86, 2.79)	< 0.0001	1.67 (1.17, 2.39)	0.005	1.00 (0.61, 1.65)	0.99

Table S8. Characteristics of the Final Model by Peanut Allergy Definition

Alternative Peanut Allergy Definition		Development Dataset	Validation Dataset
Definition 1	Area Under the ROC Curve (AUC)	0.67	0.67
	Brier Score	0.16	0.15
	Sensitivity	56.3	18.2
	Specificity	77.2	95.9
	Positive Predictive Value (PPV)	41.2	54.5
	Negative Predictive Value (NPV)	86.2	81.3
	% Successfully Predicted (Allergic & Non-allergic)	72.6	79.4
Definition 2	Area Under the ROC Curve (AUC)	0.79	0.79
	Brier Score	0.16	0.16
	Sensitivity	56.3	51.5
	Specificity	92.4	92.1
	Positive Predictive Value (PPV)	80.0	77.3
	Negative Predictive Value (NPV)	79.6	78.4
	% Successfully Predicted (Allergic & Non-allergic)	79.7	78.1
Definition 3	Area Under the ROC Curve (AUC)	0.87	0.85
	Brier Score	0.14	0.15
	Sensitivity	68.7	69.4
	Specificity	90.8	92.1
	Positive Predictive Value (PPV)	88.2	89.6
	Negative Predictive Value (NPV)	74.4	75.3
	% Successfully Predicted (Allergic & Non-allergic)	79.8	80.8
Definition 4	Area Under the ROC Curve (AUC)	0.80	0.80
	Brier Score	0.16	0.16
	Sensitivity	67.0	64.2
	Specificity	85.6	86.3
	Positive Predictive Value (PPV)	71.4	70.8
	Negative Predictive Value (NPV)	82.9	82.2
	% Successfully Predicted (Allergic & Non-allergic)	79.1	78.7

Risk Factors Associated with Peanut Allergy in a High Risk Infant Cohort

SUPPLEMENTARY MATERIAL

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SUPPLEMENTAL METHODS FOR ONLINE REPOSITORY

Logistic Regression Analysis Methods

Logistic regression was used to explore the association between peanut allergy diagnosis and baseline risk factors. Continuous factors were categorized for this initial analysis. A univariate logistic regression with peanut allergy as the outcome was performed with each risk factor in the model one at a time. Risk factors with likelihood

ratio test p-values of 0.15 or less unadjusted for multiple comparisons were included in a stepwise multiple logistic regression analysis where a p-value of 0.15 was required to enter the model and a p-value of 0.05 was required to stay in the model. For risk factors such as peanut IgE that had been categorized in several different ways, the categorization with the lowest value of AIC was used in the stepwise multiple regression.

The data were divided at random where two-thirds were put into a development dataset and one-third were put into a validation dataset. The random selection was stratified by 3 groups: 1) participants who ever had confirmed or convincing peanut allergy 2) participants who never had confirmed or convincing peanut allergy but were ever diagnosed as not allergic 3) all other participants.

The model selection described below was performed using the development dataset.

The stepwise multiple regression was done in two ways: 1) only categorical variables were included such that any continuous variables such as IgE were included using the best categorization identified by the lowest AIC as described above, and 2) the log₁₀ value for all continuous immunoglobulin variables as well as the value for any SPT variables were included. The AUC, AIC and Brier score were compared for these models. The model with the highest AUC, lowest AIC, and lowest Brier score (or had 2 out of these 3) was selected.

Once the final model was identified, a logistic regression with just the risk factors in the final model was performed. To be considered to have a good fit, a model should have an AUC > 80% and a Hosmer-Lemeshow goodness-of-fit p-value > 0.05.

The Youden Index for the final model selected using the development dataset was used to determine the cut point for the predicted probability to identify which participants would develop peanut allergy. The proportion of correctly identified participants was calculated as well as the Sensitivity, Specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV).

A logistic regression was then performed using the final model with the validation dataset. The Youden Index cut point calculated using the development dataset was used with the validation dataset and the proportion of correctly identified participants was calculated.