

Analysis of Oral Food Challenge Outcomes in IgE-Mediated Food Allergies to Almond in a Large Cohort



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What is already known about this topic? Almond IgE-mediated food allergy is often equated with other tree nuts, both in terms of diagnostic value of almond specific testing, as well as frequency and severity of clinical reactions.

What does this article add to our knowledge? Even with high levels of almond sensitization, true almond clinical reactivity is uncommon, with failure rates much lower than those of other nuts. When reactions occur, they are mostly mild.

How does this study impact current management guidelines? The majority of patients with almond sensitization (over 90%) will tolerate almond introduction. Some almond challenges may be safely conducted with higher patient-to-staff ratios or introduced at home, depending on almond specific testing.

BACKGROUND: Although almond specific IgE-mediated food allergies have traditionally been equated with other tree nut allergies, outcomes of oral food challenges to almond and the utility of clinical testing to predict IgE-mediated almond hypersensitivity are not well known.

OBJECTIVE: To describe almond oral challenge outcomes and assess the predictive value of clinical testing.

METHODS: A total of 603 almond challenges performed for 590 patients, aged 1 to 66 years, were analyzed from Massachusetts General Hospital allergy practices. Reactions were graded using the Niggemann and Beyer allergic reaction grading system and the Sampson 2006 National Institute of Allergy and Infectious Diseases anaphylaxis definition.

RESULTS: Almond challenges included 545 passes (92%), 15 (3%) indeterminates, and 30 (5%) failures, in contrast with 31% challenge failures for other foods. Most reactions were mild; 21 (4%) had grade 2/3 allergic symptoms, and 3 (0.5%) had anaphylaxis. Median almond specific IgE level was 0.89 kU/L (range, <0.35 to >100 kU/L), median skin prick test wheal diameter was 4.0 mm (range, 0-28 mm), and 475 subjects (81%) were sensitized to almond. Failure was associated with higher almond specific IgE level ($P < .001$), larger almond skin prick test wheal diameter ($P = .001$), higher peanut IgE level ($P = .003$), and a history of almond reaction ($P < .029$). Almond specific IgE level, almond skin prick test wheal diameter, and age at challenge combined demonstrated good predictive value for grade 2/3 allergic reactions by receiver-operating characteristic analysis (area under the curve, 0.83).

CONCLUSIONS: The proportion of failed almond challenges (5%) was low in contrast with other allergens, suggesting that some almond challenges may be safely conducted with higher patient-to-staff ratios or potentially introduced at home. Although reactions are usually uncommon and mild, anaphylaxis is possible with high almond sensitization. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:2359-68)

Key words: Oral food challenge; Almond allergy; Safety; Food allergy; Almond hypersensitivity

BACKGROUND

Almond was the most commonly consumed and produced tree nut in the United States in 2017.¹ Approximately 0.4% to 1.2% of the US population is allergic to tree nuts, and almond allergy is one of the most common tree nut allergens reported at 0.7% in the United States.²⁻⁴ Almond sensitization is common, with 71% of patients with birch allergy demonstrating cross-

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Abbreviations used*AUC*- Area under the curve*OFC*- Oral food challenge*ROC*- Receiver-operating characteristic*SPT*- Skin prick test

sensitization with almond (compared with 84% to hazelnut and 60% to peanut).⁵ The proportion of patients with peanut allergy who have concurrent almond sensitization is high, with 50% sensitized by skin prick testing to almonds.^{3,6} However, studies describing almond challenges show surprisingly low percentages of true clinical reactivity, with reactions generally ranging from 0% to 6% (Table I).⁸⁻¹⁰ Only 1 study by Andorf et al⁷ describing the outcome of 21 almond challenges showed a much higher proportion of failed challenges at 48%, and this study was distinct in its selection of highly sensitized individuals allergic to multiple foods. Even in this report, reactions were mostly mild, with none requiring epinephrine use. Interpretation of reactions is also confounded by the possibility of oral allergy syndrome to almond due to birch cross-reactivity, resulting in mild symptoms such as oral itch and a low risk of systemic reactivity.¹¹ Because of these factors and limited sample sizes, there is no available information regarding the predictive value of skin testing and serum specific IgE testing with regard to clinically relevant almond hypersensitivity.

Our main objectives were to use a large retrospective cohort of pediatric and adult subjects receiving oral food challenges (OFCs) to (1) determine the frequency and severity of reactions to almonds during OFCs and (2) assess the utility of clinical history, skin prick testing, and serum specific IgE testing to almond and other allergens in predicting clinically relevant almond allergy.

METHODS

Study population

All patients, pediatric and adult, who had been referred for an oral open food challenge for suspected almond allergy from 2009 to 2018 were included. The referral base consisted of 11 allergists from 2 main practice locations, Massachusetts General Hospital for Children - Food Allergy Center and Massachusetts General Hospital Allergy Associates. The decision to refer for challenge was determined on the basis of allergists' clinical judgment, and no guidelines were set regarding the criteria for challenge.

Study design

We conducted a retrospective cohort analysis of all patients undergoing an almond challenge. Provider documentation, nursing flowsheets, and symptom score sheets were reviewed to evaluate signs and symptoms of clinical hypersensitivity during OFCs. We also collected clinical history regarding reaction to almonds and peanuts, seasonal allergies, atopic dermatitis, and skin prick test (SPT) and IgE data on commonly cross-reactive allergens, including peanut, tree nuts (hazelnut, cashew, pistachio, walnut, pecan), and birch. This project was undertaken as a quality improvement initiative at Massachusetts General Hospital (Boston, Mass), and as such was not formally supervised by the Institutional Review Board per its policies.

Patient SPT and Immunocap IgE results were recorded from the closest date before their OFC (median, 6-7 months). Positive SPT results were defined as mean wheal diameter greater than or equal to 3 mm above that achieved with the saline control, and positive almond specific IgE levels were defined as levels more than 0.35 kU/L. Any IgE levels reported as more than 100 kU/L were analyzed as 100.1 kU/L and less than 0.35 kU/L as 0.34 kU/L. For any SPT or allergen specific IgE values that were documented as positive without details regarding the numeric value, the data were imputed as 3 mm for SPT. This imputation was done for 2 almond SPT, 15 peanut SPT, and 5 hazelnut SPT values.

Oral food challenges

OFCs were supervised by clinical allergists and nurse practitioners. The protocol involved graduated administration of a total of 6 g of almond protein (2 tablespoons of almond butter or 24 almonds divided into 5 doses of 1%, 3%, 10%, 30%, and 56%) every 10 to 15 minutes over the course of an hour, with 2 hours of observation following the administration of the final dose. Vitals and symptoms were documented every 15 minutes using a standardized flow sheet. If the in-office challenge was tolerated, patients or their caregivers were instructed to give 6 g of almond protein daily for 4 days to evaluate any subacute allergic reactions or intolerances.

Challenge outcomes were categorized as pass, fail, or indeterminate on the basis of the clinician's judgment. Failed challenges were generally defined as the patient displaying signs or symptoms of an IgE-mediated response during the observed challenge. A challenge was labeled as indeterminate if either (1) no evidence of IgE-mediated symptoms was present, but the patient was unable to consume the full amount of almond protein, or (2) the patient developed very mild symptoms that were difficult to confirm as IgE-mediated in origin. At the clinician's discretion, some patients with indeterminate challenges were offered the opportunity to introduce almond at home at the dose tolerated in the clinic. Patients who tolerated this home introduction were recategorized as passing their challenge. For patients who were challenged multiple times, repeat challenges were described separately and only the most recent challenge was included in the main analysis.

We noted variability in clinician interpretation of challenge outcomes, with some challenges being reported as failures with only mild subjective symptoms, whereas other clinicians described similar symptoms in patients and were able to successfully reintroduce almond. For these challenge failures, it was difficult to determine whether their reactions represented the early stages of a potentially life-threatening IgE-mediated reaction, oral allergy syndrome, non-IgE-mediated symptoms, or anxiety-triggered symptoms. To identify the subgroup of reactions that were more clearly potentially life-threatening IgE-mediated reactions, we retrospectively categorized reactions on the basis of Niggemann and Beyer classification system for grading allergic reactions.¹² We labeled all reactions that met criteria for grade 2 or grade 3 reactions (presence of urticaria, angioedema, generalized flushing, abdominal pain, vomiting, diarrhea, cough, wheeze, laryngeal symptoms, tachycardia, low blood pressure, or mental status changes) as "grade 2 or 3 Niggemann-Beyer reactions (grade 2/3 reactions)." Reactions that were grade 1 (isolated redness, local swelling [not angioedema], pruritus) were excluded from these analyses. All reactions that met criteria for anaphylaxis as defined by the 2006 Sampson National Institute of Allergy and Infectious Diseases guidelines were labeled as such. We reported outcomes for all 3 categories: clinician-determined challenge outcome, grade 2/3 reactions, and anaphylaxis.

TABLE I. Literature review of almond challenge outcomes

Study design	Almond diagnostics	Almond challenge outcomes
Andorf et al ⁷ • n = 165 patients with possible allergy to 2+ foods receiving 311 challenges	• Median SPT wheal diameter, 9.5 mm (range, 6-25 mm) • Median IgE level, 5.2 kU/L (range, 0.4-100 kU/L)	• 21 challenges to almond • 10 reactions = 52% pass • 48% with skin reaction, 0% with gastrointestinal reaction, 10% with respiratory symptoms, 0% received epinephrine
Couch et al ⁸ • n = 109 patients with tree nut allergy receiving 156 challenges	• Mean sIgE, 1.18 kU/L (median, 0 kU/L) • Mean SPT wheal diameter, 1.27 mm (median, 0 mm) • 42 with sIgE level of <2 kU/L • 6 with sIgE level of ≥2 kU/L • 37 with SPT wheal diameter of <3 mm • 11 with SPT wheal diameter of >3 mm	• 57 challenges to almond • 100% pass
Elizur et al ⁹ • n = 83 patients with peanut/tree nut allergy receiving 232 challenges	• 49 with SPT wheal diameter of >3 mm • Exact SPT wheal diameter and IgE level not specified	• 49 challenges to almond • 1 clinical reaction = 98% pass
Rodriguez et al ¹⁰ • n = 34 with suspected Rosaceae food allergy receiving 182 challenges • Performed SPT, IgE, and if positive, then OFC to all Rosaceae foods (apricot, almond, plum, strawberry, apple, peach, pear)	• 4 with reported almond clinical history • 18 with positive almond specific SPT wheal diameter or IgE level • Exact SPT wheal diameter and IgE level not specified	• 18 challenges to almond in individuals with sensitization • 1 clinical reaction = 94% pass • Only oral symptoms • Rate of clinical reactivity for those with positive SPT result (n = 15): 7% • Rate of clinical reactivity for those with positive IgE level (n = 6): 17%

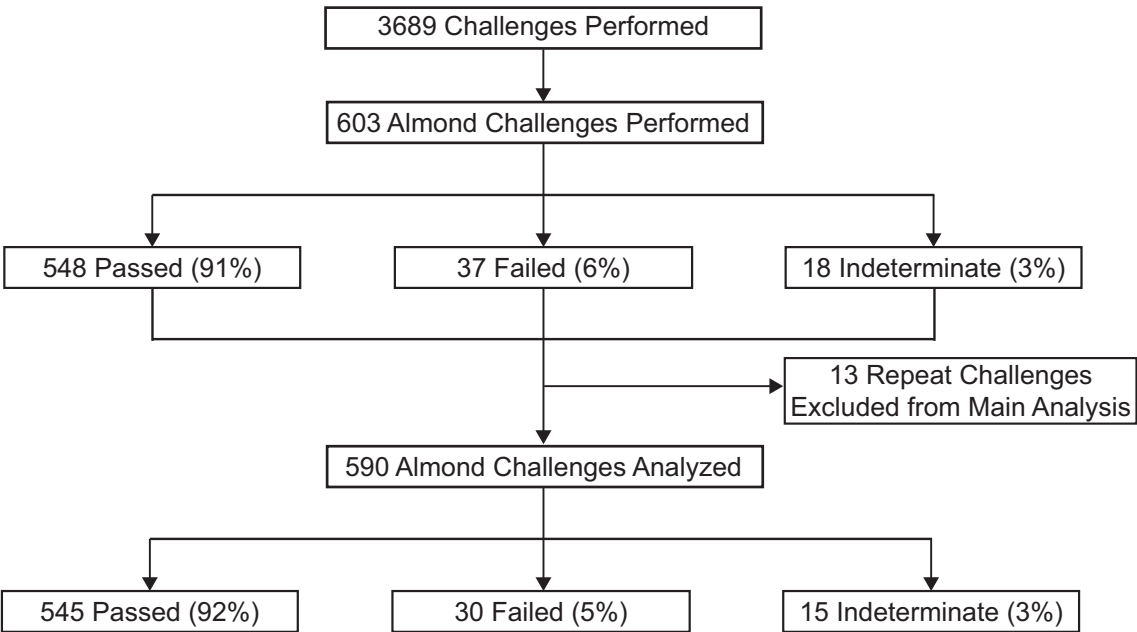


FIGURE 1. Consort diagram of study participants receiving an almond challenge: Eleven individuals had 13 repeat challenges performed to almond. In all cases, the latest challenge was selected for analysis and all 13 previous challenges were excluded. Ten of the 11 participants eventually went on to pass the final challenge.

TABLE II. Demographic and allergic clinical characteristics

Characteristic	n	Overall (n = 590)	Pass (n = 545)	Indeterminate (n = 15)	Fail (n = 30)	P
Demographic						
Female, n (%)	588	249 (42.3)	231 (42.5)	6 (40.0)	12 (40.0)	.995
Age at challenge (y), mean $\pm$ SD	590	10.2 $\pm$ 8.1	10.3 $\pm$ 8.0	10.9 $\pm$ 13.9	8.1 $\pm$ 6.4	.317
Race, n (%)	554					.220
White		461 (83.2)	428 (83.8)	13 (86.7)	20 (71.4)	
Asian		57 (10.3)	51 (10.0)	0 (0.0)	6 (21.4)	
Black or African American		7 (1.3)	7 (1.4)	0 (0.0)	0 (0.0)	
Other		29 (5.2)	25 (4.9)	2 (13.3)	2 (7.1)	
Hispanic/Latino, n (%)	482	26 (5.8)	24 (6)	0 (0.0)	2 (10.0)	.486
Allergic history						
Atopic dermatitis, n (%)	569	370 (65.0)	340 (64.9)	10 (66.7)	20 (66.7)	.972
Seasonal allergies, n (%)	570	348 (61.1)	321 (61.0)	8 (57.1)	19 (63.3)	.925
Positive birch testing, n (%)	259	194 (74.9)	182 (75.8)	5 (55.6)	7 (70.0)	.362
Total IgE, mean $\pm$ SD	451	633.2 $\pm$ 986.1	639.1 $\pm$ 1007.5	650.3 $\pm$ 824.7	521.5 $\pm$ 643.8	.85
Almond history						
Almond sIgE level, mean $\pm$ SD	570	3.5 $\pm$ 9.4	3.1 $\pm$ 7.7	3.4 $\pm$ 5.6	11.2 $\pm$ 23.7	<.001
Ratio of almond specific IgE:Total IgE level, mean $\pm$ SD	441	0.01 $\pm$ 0.03	0.04 $\pm$ 0.12	0.01 $\pm$ 0.01	0.01 $\pm$ 0.02	<.001
Almond SPT wheal diameter (mm), mean $\pm$ SD	570	4.0 $\pm$ 3.7	3.8 $\pm$ 3.6	3.6 $\pm$ 3.8	6.4 $\pm$ 5.6	.001
Previous almond reaction, n (%)	559	60 (10.7)	51 (9.8)	2 (14.3)	7 (25.9)	.029
Other allergic sensitization						
Peanut IgE level, mean $\pm$ SD*	503	27.9 $\pm$ 37.9	27.0 $\pm$ 37.3	14.9 $\pm$ 17.6	52.4 $\pm$ 49.2	.003
Peanut SPT wheal diameter (mm), mean $\pm$ SD	403	8.5 $\pm$ 6.8	8.4 $\pm$ 6.9	10.1 $\pm$ 5.0	10.2 $\pm$ 5.6	.462
Peanut allergy, n (%)	197	69 (35.0)	64 (35.6)	1 (20.0)	4 (33.3)	.766
Hazelnut IgE level, mean $\pm$ SD*	522	14.9 $\pm$ 24.9	14.6 $\pm$ 24.8	12.4 $\pm$ 20.4	21.7 $\pm$ 30.4	.369
Hazelnut SPT (mm), mean $\pm$ SD	500	4.3 $\pm$ 4.8	4.3 $\pm$ 4.9	4.2 $\pm$ 4.6	3.9 $\pm$ 4.1	.929
Pistachio IgE level, mean $\pm$ SD*	525	10.9 $\pm$ 21.2	10.7 $\pm$ 20.9	7.1 $\pm$ 13.4	15.7 $\pm$ 28.9	.420
Cashew IgE level, mean $\pm$ SD*	531	9.2 $\pm$ 19.5	9.1 $\pm$ 19.2	8.8 $\pm$ 16.2	12.5 $\pm$ 24.8	.677
Pecan IgE level, mean $\pm$ SD*	532	5.3 $\pm$ 13.6	5.0 $\pm$ 12.9	10.8 $\pm$ 23.5	8.6 $\pm$ 19.5	.131
Walnut IgE level, mean $\pm$ SD*	541	10.8 $\pm$ 23.4	10.3 $\pm$ 22.1	16.9 $\pm$ 35.5	17.4 $\pm$ 36.1	.203

sIgE, Specific IgE.

*Ratios of sIgEs to total IgE were not significantly different between groups.

Statistical analysis

We analyzed clinical and demographic variables, including clinical almond reactivity, serum specific IgE level measurements, total IgE level, and SPT results, using Fisher exact tests, chi-square tests, *t* tests, or ANOVA, where appropriate, with an alpha value of 0.05. We reported unadjusted and adjusted odds ratios with univariable and multivariable logistic regression to assess potential clinical predictors of challenge outcomes and used stepwise elimination based on Akaike information criterion to identify the variables most predictive of challenge outcome. We also conducted a sensitivity analysis including only those subjects who were sensitized to assess variables most strongly associated with challenge outcome. Receiver-operator characteristic (ROC) curve analysis was performed to assess the sensitivity and specificity of almond specific IgE and almond skin prick testing, and comparison of area under the curve (AUC) was conducted by DeLong's test (R packages ROCR_1.0-7, pROC_1.13.0). All analyses were conducted using R version 3.5.1. (R Foundation for Statistical Computing, Vienna, Austria).¹³

RESULTS

Study population and challenge outcomes

Of the 3689 challenges, 603 (16%) almond challenges were performed for 590 patients (Figure 1). The population was mostly pediatric, with 90% of subjects younger than 18 years, and was mostly white, with a slight male predominance (Table II). Allergic comorbidities were common, with 502 (85%) subjects having either atopic dermatitis or seasonal allergies, and high levels of birch sensitization (Table II). Most subjects, 475 (81%), had almond sensitization with either positive almond SPT result or almond specific IgE, and 304 (52%) had both positive SPT result and almond specific IgE. Median SPT wheal diameter was 4.0 mm (range, 0–28 mm), median IgE level was 0.89 kU/L (range, <0.35 to >100 kU/L), and 106 (18%) had high levels of sensitization with either almond specific IgE levels of greater than or equal to 15 kU/L or almond SPT wheal diameter of greater than or equal to 8 mm (Figure 2). Of the 60 subjects (11%) with self-reported history of previous reaction to

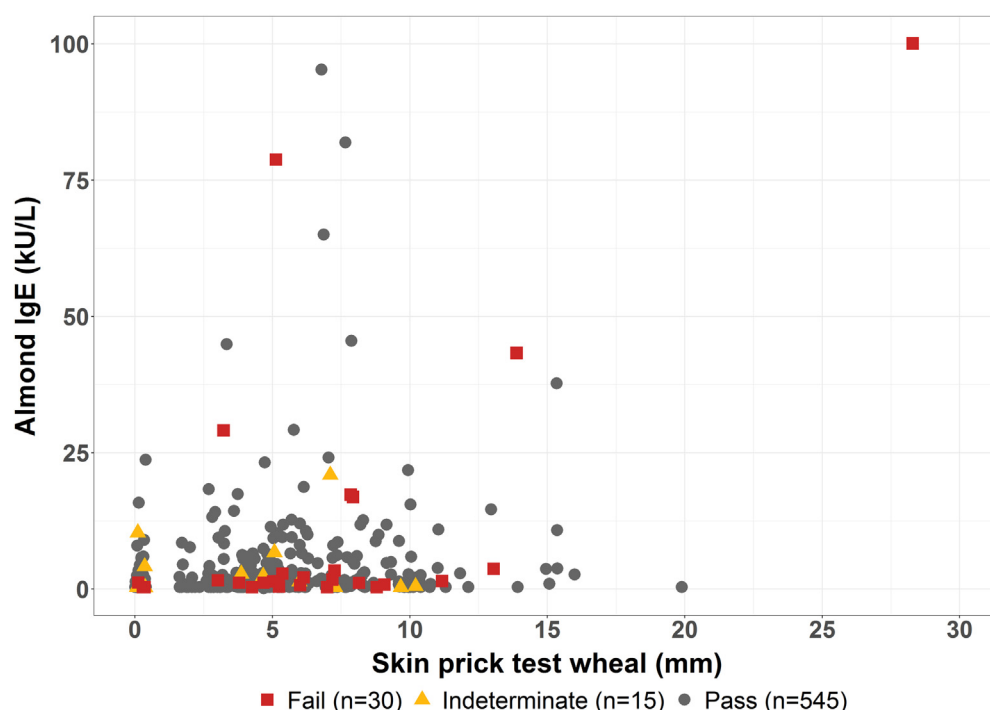


FIGURE 2. Almond specific IgE level vs almond SPT wheal diameter by challenge outcome. All specific IgE values of less than 0.35 kU/L were plotted as 0.34 kU/L, and all values of more than 100 kU/L were plotted as 100.1 kU/L.

almond, 7 were confirmed by previous challenge and 27 (45%) either reported or had challenge-proven objective symptoms (usually hives or local flushing). Of the 115 nonsensitized patients, at least 19 (2%) reported a history of almond reaction and all but 2 of these passed the almond challenge. Regarding the remainder of challenges performed on nonsensitized subjects without a history of reaction, clinicians reported conducting these challenges primarily to reduce parental or patient anxiety about introduction of almond or about future tree nut challenges.

Most patients tolerated the almond challenges, with 545 passed (92%), 30 failed (5%), and 15 indeterminate challenges (3%). In comparison, the proportion of failed outcomes for 1352 other challenges to common allergens was 31% (31% for peanut, 27% for tree nut, 34% for milk, 37% for baked milk, 16% for egg, and 47% for baked egg). Among the 30 failed challenges, 21 (4%) met the criteria for grade 2/3 allergic reactions and 3 (0.5%) were anaphylactic reactions.

Repeat challenges

Eleven subjects had multiple challenges to almond, comprising 24 challenges total (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). Ten patients initially had failed or indeterminate challenges and then eventually went on to pass the final challenge. The median time to rechallenge was 2.7 years (mean, 2.3 years). Most subjects had mild symptoms (oral itching, pruritus, nasal symptoms, urticaria). One subject (subject 5) had diffuse wheezing and then passed a challenge within the same year, and the original reaction was later attributed to uncontrolled asthma. Only 1 subject passed a challenge and then went on to fail a challenge (subject 9). During home introduction of almond following his initial

challenge, this patient experienced oral itching and eliminated almond from the diet. In the 2 years between the repeat challenges, the subject's almond SPT wheal diameter increased from 5 to 14 mm and almond specific IgE level increased from 0.42 to 43.3 kU/L. He had no history of allergic rhinitis symptoms and birch testing was not performed. On repeat challenge, the subject failed to develop perioral hives, oral itching, and mild abdominal pain.

Predictors of challenge outcome

Failure to pass the challenge was associated with larger almond specific SPT wheal diameter, higher almond specific IgE level, higher almond specific IgE level to total IgE level ratio, history of reaction to almond, and larger peanut specific IgE level (Table II). There was no association between challenge outcome and other nut sensitization (nut-specific SPT for peanut, and specific IgE level for pistachio, cashew, pecan, hazelnut, and walnut), total IgE level, atopic dermatitis, seasonal allergies, or birch sensitization. There was also no association between challenge outcome and the season in which the challenge was performed ($P = .12$). Despite the association of almond SPT and IgE level with challenge failure, the estimated 95% predicted probability of failing a challenge would be at an almond SPT response of 46 mm and almond specific IgE level of 174 kU/L, both well outside the range of our cohort for typically observed SPT IgE values (Figure 3, A and B). At the upper limits of the range of sensitization seen in our cohort, predicted probability of failing a challenge was 60% for SPT wheal diameter of 28 mm and 60% for IgE level of 100 kU/L. ROC analysis revealed that almond SPT (AUC, 0.66) and almond specific IgE (AUC, 0.61) individually, or combined (AUC, 0.67), were poor predictors of failed challenge outcome (Figure 3, C), consistent with the wide

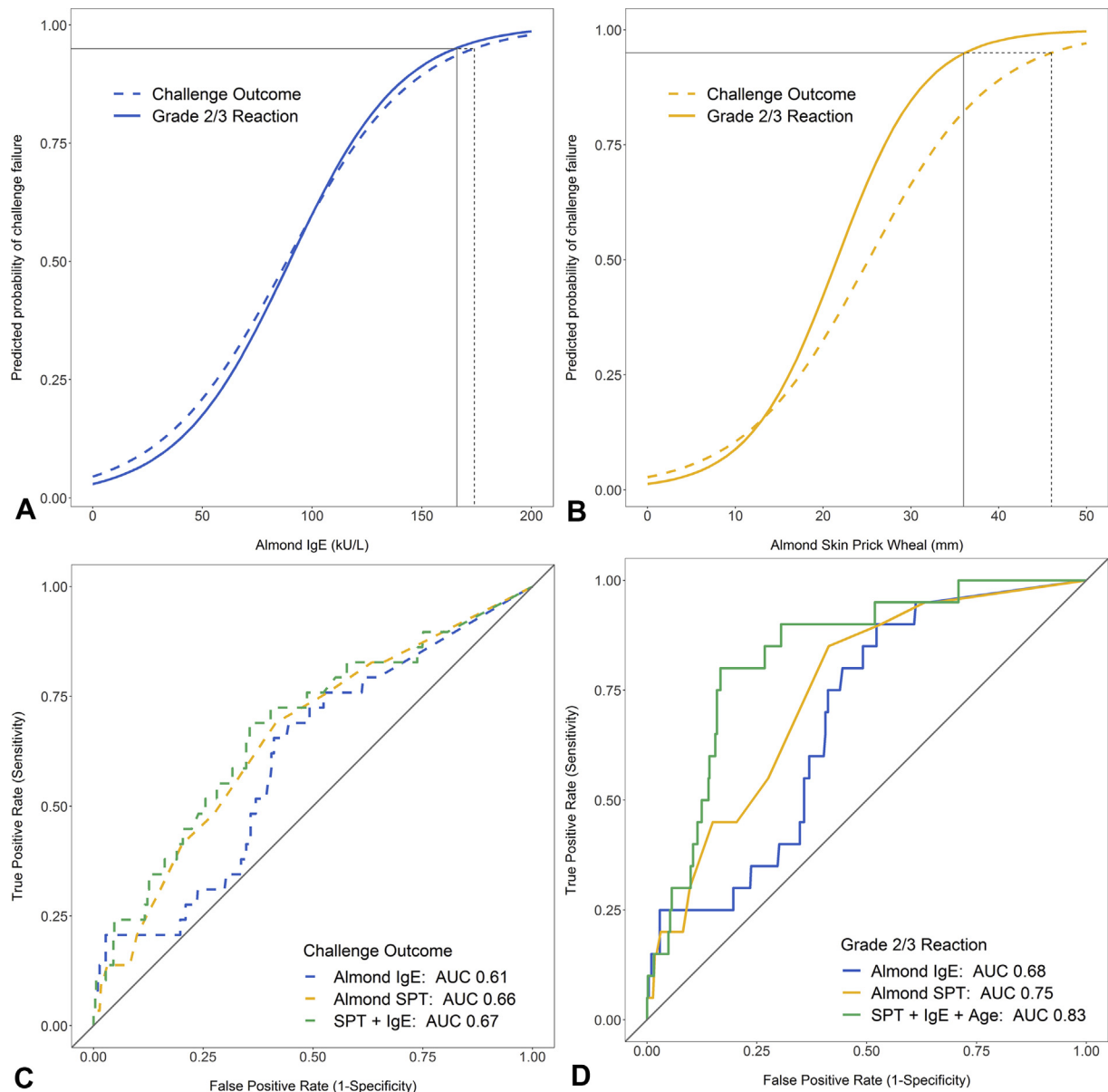


FIGURE 3. Predicted probabilities for almond specific IgE level (A) and almond SPT wheal diameter (B) and ROC analysis of almond SPT wheal diameter, almond specific IgE level, and age at challenge in predicting challenge outcome (C) and IgE-mediated reactions (D). Almond SPT wheal diameter of 46 mm and almond specific IgE level of 174 kU/L were associated with 95% predicted probability of failing a challenge (Figure 3, A and B, dashed black line). Almond SPT wheal diameter of 36 mm and almond specific IgE level of 166 kU/L were associated with 95% predicted probability of having a grade 2/3 allergic reaction during a challenge (Figure 3, A and B, solid line).

range of skin and serum sensitization among patients who passed challenges (Figure 2).

Narrowing the challenge outcome to grade 2/3 allergic reactions confirmed the association with higher almond sensitization and also revealed further associations with failed challenge outcome, including younger age at challenge and higher specific IgE levels to peanut, pecan, walnut, and pistachio (Table III). Using multivariable logistic regression, after adjusting for the other variables in the model, we found that younger age at challenge, increased almond SPT wheal diameter, and increased almond specific IgE level remained robust predictors of grade 2/3 allergic reactions (Table III). Sensitivity analysis removing any

nonsensitized patients showed similar findings on univariable logistic regression, with associations between grade 2/3 allergic reactions and age at challenge, almond specific IgE level, almond SPT wheal diameter, and peanut specific IgE level (see Table E2 in this article's Online Repository at www.jaci-inpractice.org). Almond SPT wheal diameter of 36 mm and almond specific IgE level of 166 kU/L were associated with 95% predicted probability of having a grade 2/3 allergic reaction during a challenge, once again outside of the range seen in our cohort (Figure 3, A and B). At the upper limits of the range of sensitization seen in our cohort, predicted probability of a grade 2/3 allergic reaction was 79% for SPT wheal diameter of 28 mm and 60% for IgE

TABLE III. Allergic clinical characteristics associated with grade 2/3 allergic reaction during almond challenge

Characteristic	No grade 2/3 symptoms (n = 569)	Grade 2/3 Niggemann-Beyer reaction (n = 21)	Unadjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
Demographic						
Age at challenge (y), mean ± SD	10.4 ± 8.2	6.1 ± 3.4	0.86 (0.77-0.97)	.01	0.85 (0.75-0.97)	.01
Almond history						
Almond specific IgE level, mean ± SD	3.1 ± 7.7	14.3 ± 27.3	1.51 (1.22-1.87)	<.001	1.25 (0.96-1.64)	.10
Almond SPT wheal diameter (mm), mean ± SD	3.8 ± 3.6	7.8 ± 5.8	2.75 (1.69-4.47)	<.001	2.57 (1.47-4.47)	<.001
Allergic sensitization						
Peanut IgE level, mean ± SD	26.9 ± 37.1	52.8 ± 49.3	1.16 (1.04-1.29)	.006	—	—
Pistachio IgE level, mean ± SD	10.5 ± 20.6	21.2 ± 32.5	1.17 (1.01-1.36)	.044	—	—
Pecan IgE level, mean ± SD	5.1 ± 13.2	12.0 ± 22.8	1.24 (1.01-1.52)	.048	—	—
Walnut IgE level, mean ± SD	10.4 ± 22.4	23.1 ± 41.0	1.16 (1.02-1.33)	.028	—	—

OR, Odds ratio.

ORs for specific IgE represent the increased odds for every 10-kU/L change in IgE level. ORs for SPT represent the increased odds for every 5-mm change in wheal diameter. Variables not meeting significance criteria were excluded from the table.

TABLE IV. Proportion of failed challenges by almond SPT size (A), almond specific IgE level (B), and age (C)

A.				
SPT Size (mm)	n (%)	Failed challenge	Grade 2/3 reaction	Anaphylactic reaction
0-2	203 (34)	3%	0.5%	0%
3-4	122 (21)	3%	2%	0%
5-6	124 (21)	7%	6%	1%
7-8	60 (10)	10%	5%	2%
>8	61 (10)	10%	10%	2%
B.				
Specific IgE level	n (%)	Failed challenge	Grade 2/3 reaction	Anaphylactic reaction
<0.35	195 (33)	3%	0.5%	0%
0.35-1.00	109 (18)	3%	3%	0%
1.01-2.00	86 (15)	12%	9%	1%
2.01-10.00	136 (23)	3%	2%	0%
>10.00	44 (7)	17%	14%	5%
C.				
Age at challenge (y)	n (%)	Failed challenge	Grade 2/3 reaction	Anaphylactic reaction
0-4	146 (25)	7%	6%	0%
5-9	203 (34)	6%	4%	1%
10-17	180 (31)	4%	2%	0%
18+	61 (10)	2%	0%	0%

level of 100 kU/L. Sensitivity and specificity of almond SPT wheal diameter and almond specific IgE level for grade 2/3 allergic reactions remain poor (see Table E3 in this article's Online Repository at www.jaci-inpractice.org). ROC analysis using grade 2/3 allergic reactions as an outcome demonstrated improved predictive ability of almond SPT wheal diameter (AUC, 0.75), and most of all the combination of almond SPT

wheal diameter, almond specific IgE level, and age at challenge (AUC, 0.83), which had significantly greater predictive value than SPT wheal diameter alone ($P = .008$) and almond specific IgE level alone ($P = .006$) (Figure 3, D).

On the basis of SPT, among subjects with almond SPT wheal diameter of 0 to 4 mm 3% had reactions (with 0.9% grade 2/3 reactions and 0% anaphylactic reactions), whereas among those with greater than 5 mm wheal diameter 8% had reactions (with 7% grade 2/3 reactions and 1% anaphylactic reactions) (Table IV). For almond specific IgE level of less than 1 kU/L, 3% reacted (with 1% grade 2/3 reactions and 0% anaphylactic reactions), and for almond IgE level of more than 1 kU/L 8% reacted (with 6% grade 2/3 reactions and 1% anaphylactic reactions).

Failed challenges

The failed reactions (Table V; see Table E4 in this article's Online Repository at www.jaci-inpractice.org) were mostly characterized by oral symptoms, 7 (23%), with 3 (10%) patients experiencing respiratory symptoms, 6 (20%) gastrointestinal symptoms, and 1 (3%) cardiovascular symptoms. Most challenge failures were treated with antihistamines, and for the anaphylactic reactions, 1 (3%) received only albuterol for uncontrolled asthma potentially independent of the oral challenge because they started the challenge with a brief transient wheeze (Table E4), and 2 (7%) received epinephrine for symptoms described in more detail below.

Many of the challenges that were categorized as failed challenges presented with only subjective symptoms. Of note, there was a trend of higher oral itching in those without grade 2/3 allergic symptoms versus those with grade 2/3 allergic symptoms (57% vs 14%; $P = .058$). Among the 475 sensitized patients, the proportion of failed challenges was 6%, whereas among the 115 nonsensitized patients, the proportion of failed challenges was 2.6% (3 subjects). Furthermore, the 3 subjects who failed challenges in the setting of negative almond SPT result and almond specific IgE developed only oral itch, without any other cutaneous, respiratory, or gastrointestinal symptoms.

TABLE V. Description of failed challenge reactions

Challenge outcomes	Overall (n = 30)	Grade 2/3 reaction (n = 21)	Anaphylactic reaction (n = 3)
Percent ingested, mean $\pm$ SD	37.0 $\pm$ 38.3	39.8 $\pm$ 41.8	57.0 $\pm$ 60.8
Reaction symptoms: Subjective, n (%)			
Oral itching	8 (27)	3 (14)	0 (0)
Pruritus	8 (27)	6 (29)	1 (33)
Nausea	2 (7)	2 (10)	0 (0)
Abdominal pain	3 (10)	3 (14)	1 (33)
Irritability	2 (7)	2 (10)	0 (0)
Dizziness	0 (0)	0 (0)	0 (0)
Reaction symptoms: Objective, n (%)			
Hives/angioedema	17 (57)	17 (81%)*	2 (67)
Nonurticarial rash	3 (10)	1 (5)	0 (0)
Flushing (local)	6 (20)	3 (14)	1 (33)
Flushing (generalized)	0 (0)	0 (0)	0 (0)
Nasal symptoms	12 (40)	10 (48)	3 (100)
Wheeze	2 (7)	2 (10)	2 (67)†
Laryngeal symptoms‡	1 (3)	1 (5)	0 (0)
Vomiting	3 (10)	3 (14)	1 (33)
Diarrhea	0 (0)	0 (0)	0 (0)
Tachycardia	1 (3)	1 (5)	1 (33)
Low blood pressure	0 (0)	0 (0)	0 (0)
Reaction treatment, n (%)			
Treatment given	21 (70)	14 (67)	3 (100)
Antihistamines	21 (70)	14 (67)	3 (100)
H ₂ blocker	3 (10)	3 (14)	2 (67)†
Steroid	2 (7)	2 (10)	2 (67)†
Albuterol	1 (3)	1 (5)	1 (33)
Epinephrine	2 (7)	2 (10)	2 (67)†

Symptom categories were derived from PRACTALL (Practical Allergy) guidelines and definitions of reactions.¹⁴

* $P < .001$.

† $P < .05$.

‡In this cohort, the 1 subject experiencing laryngeal symptoms had throat clearing.

Anaphylaxis cases

The first case of anaphylaxis was a 7-year-old female with atopic dermatitis, allergic rhinitis, asthma requiring controller medication, multiple food allergies (egg, peanut, and tree nut), and a history of food protein–induced allergic proctocolitis. She had never ingested almond. Her laboratory testing 5 years earlier showed total IgE level of 40 kU/L and almond specific IgE level of 4.26 kU/L and SPT wheal diameter of 11 mm. Seven months earlier, her total IgE level was 2104 kU/L, almond specific IgE level was greater than or equal to 100 kU/L, and SPT wheal diameter was 28 mm. During the challenge, the patient initially complained of transient mouth itch after the 1% dose, but eventually ingested 100% of the dose. One hour and 45 minutes later, she developed pruritus, hives, flushing, tachycardia, and objective and subjective gastrointestinal symptoms. She was given intramuscular epinephrine (0.15 mg [0.007 mg/kg]) and oral cetirizine. Shortly afterwards, she vomited and had progressive urticaria, and so she was treated with another 0.15 mg of epinephrine (total 0.014 mg/kg), oral steroid, and oral H₂ blocker. Her condition returned to baseline 2.5 hours after the initial administration of epinephrine.

The second case was a 5-year-old female with a history of mild persistent asthma and food allergies to egg and tree nuts. She had a history of hives and left eye and lip swelling at age 14 months

following ingestion of almonds and walnuts together. Her most recent almond SPT wheal diameter was 8 mm, total IgE level was 409 kU/L, and almond specific IgE level was 17.3 kU/L. During the challenge, she ingested 100% of the dose. Following the last dose, she developed increased congestion and diffuse wheezing. She was treated with one dose of intramuscular epinephrine (0.15 mg [0.009 mg/kg]), antihistamine, oral H₂ blocker, and oral steroid. Her wheezing resolved within 5 minutes of epinephrine administration. Common attributes of these 2 cases with anaphylaxis include ingestion of 100% of the dose, SPT wheal diameter greater than or equal to 8 mm, younger age, female sex, and persistent asthma, even though well controlled at the time of challenge.

DISCUSSION

This article describes the largest cohort of almond challenges in the literature to date. Almond is a particularly useful nut for reintroduction for several reasons. The prevalence of growth concerns in the food-allergic population¹⁵ indicates that for patients with concomitant milk allergy or growth concerns, supplementation of the diet with almond-based products, such as almond milk or almond butter, could be a useful alternative for improving nutrition in the food-allergic population. Almond-

based products are also often readily available without cross-contamination concerns. Finally, for families who are anxious about the challenge process, in our experience beginning with the almond challenge has been a useful way to reduce stress.

Most studies of almond challenge outcomes reported passage ranging from 94% to 100%, often with low sensitization levels and with uniformly mild reactions. In their description of 21 challenges to almond, Andorf et al⁷ challenged patients with median SPT wheal diameter of 9.5 mm and median almond specific IgE level of 5.2 kU/L and found a 52% of participants passed. However, even for this cohort, none of the patients required epinephrine. Our population spans a large range of sensitization, with 19% of patients having no almond sensitization and 18% of patients having either almond specific IgE level of greater than or equal to 15 kU/L or almond SPT wheal diameter of greater than or equal to 8 mm. In this diverse population, we demonstrated a similarly high percentage of passage of 92% compared with other studies, which contrasted with other common allergens such as peanuts, nonalmond tree nuts, milk, and egg.

Unlike for other tree nuts, almond specific SPT wheal diameter and specific IgE level serve as poor predictors of challenge outcome. Although almond specific SPT wheal diameter and specific IgE and history of reaction were significantly associated with challenge outcome, the sensitivity and specificity of these tests remain poor. In particular, the almond specific SPT wheal and specific IgE values associated with a 95% predicted probability of failing a challenge are unrealistically high and markedly different than the 15-kU/L cutoff commonly identified for peanut and other tree nuts,¹⁶⁻¹⁸ further illustrating the unreliability of almond specific testing in screening appropriate patients for challenge.

However, it appears that there are 2 distinct types of failed almond challenges, the first with more objective symptoms, which we termed grade 2/3 allergic reactions, and the second with mostly oral or very mild symptoms. This is supported by our finding that oral itching was less featured in reactions of subjects with grade 2/3 allergic symptoms, though oral itch as a symptom should not be used to rule out an IgE-mediated reaction. Unfortunately, because of limited data on birch sensitization, we were unable to statistically determine whether subjects without grade 2/3 allergic symptoms were experiencing symptoms consistent with oral allergy syndrome. However, we suspect that this subgroup may confound many of the previous analyses of the predictive value of almond skin and serum testing. To address the possible confounding nature of oral allergy syndrome reactions, we created the subgroup of "grade 2/3 allergic reactions." Here, we not only confirmed the association of failed challenges with increased almond specific IgE level, increased almond SPT wheal diameter, and increased peanut IgE level but also extended these findings to younger age at challenge and increased sensitization to other tree nuts, including hazelnut, walnut, pecan, and pistachio. We suspected that many of these associations were linked to the high correlations between tree nut and peanut IgE levels, and using multivariable logistic regression with stepwise model selection, we were able to narrow the predictors that remained associated with challenge failure even after adjusting for each other: almond SPT wheal diameter, almond specific IgE level, and age. We hypothesize that younger age is associated with the grade 2/3 allergic reactions, because children

being challenged at a younger age are less likely to have allergic rhinitis and therefore oral allergy syndrome. Using ROC analysis, almond SPT wheal diameter and almond specific IgE level individually remain limited in their sensitivity and specificity for even IgE-mediated reactions. However, the combination of all 3 factors shows relatively strong ability to predict potentially life-threatening IgE-mediated reactions. These findings, however, need to be replicated in equally large, well-characterized cohorts of almond challenges before being implemented as criteria for determining patients at risk for true IgE-mediated almond allergy.

Regarding safety, it should be noted that although almond challenges appear to be safer than those of other tree nuts, anaphylaxis can occur. As this cohort spanned 9 years of clinical practice, our physicians began referring more highly sensitized patients over time, which was reflected in statistically significantly higher proportions of failed almond challenges (data not shown). We began to see more anaphylactic reactions, including the 2 cases who received epinephrine. With only 2 subjects, we lack the statistical power to assess predictors of epinephrine use, but it should be noted that there appears to be a few commonalities including SPT wheal diameter of more than 8 mm, elevated almond specific IgE level (>17 kU/L), controller medication use for asthma, and larger quantity of almond ingested before symptom onset.

Given the access issues for OFCs, it has become essential to develop safe practices where we can increase the availability of food challenges for patients truly at risk for allergic reactions and anaphylaxis. Almond challenge pass rates are so high that some authors have discussed the possibility of challenging more aggressively.⁸ Potential strategies might include the following steps. First, all patients with negative almond specific SPT result and IgE level, even with a positive history, could have home introductions because 97% passed their challenge and the handful of failures we observed only had oral itch. Second, because the risk of anaphylactic reactions was 0% for those with SPT wheal diameter of less than 5 mm and IgE level of less than 1 kU/L, these data may support introducing almond at home for patients with low levels of sensitization, using gradual introduction methods that span 1 to 2 weeks. Third, the data certainly support challenging patients with higher levels of sensitization in outpatient clinics, because 80% to 90% of these patients will still pass an almond challenge. Fourth, given 92% of patients pass, clinics could increase the patient to provider ratio to challenging 4 subjects at a time and still maintain a 72% probability of all subjects passing (25% probability of only 1 patient reacting or having an indeterminate challenge and 3% chance of more than 1 patient doing so).

All these suggestions should be tempered by the limitations of this study. Our cohort represents various clinical practitioners with corresponding variability in referral, diagnostic, and management practice. However, this does improve the generalizability of our findings. Regarding the 18% of the cohort with very high levels of sensitization, sample sizes in the higher range of sensitization are lower, so final conclusions about the risk of challenging subjects with high levels of sensitization will require further study with larger sample sizes. Regarding the 19% of subjects who showed no sensitization, although a small proportion (3% of the cohort) were challenged because of history of reaction, our physicians reported that the remainder of challenges

were generally performed when parents had high levels of anxiety about introduction of almond at home. This supports the need for better education of families about the low risk of almond introduction. Furthermore, removal of these nonsensitized patients in our sensitivity analyses showed similar findings for predictors of challenge outcomes. Finally, in our efforts to identify the subjects who truly experienced potentially life-threatening IgE-mediated reactions, we acknowledge that the definition of the subgroup of “grade 2/3 allergic reactions” may have missed some of the potentially life-threatening reactions that were simply stopped before the development of objective and more severe systemic symptoms. However, we determined that the loss of a few subjects in the subgroup analysis allowed for a more accurate characterization of predictors of true potentially life-threatening IgE-mediated reactions.

In conclusion, examining 603 almond challenges, we have observed low rates of true clinical reactivity to almond, despite in some cases very high almond sensitization by both skin and serum testing. Most reactions were mild, though anaphylaxis to almond is possible and the 2 cases we observed both had high sensitization. Although the combination of almond SPT wheal diameter, almond specific IgE level, and age at challenge may prove useful in predicting which patients are truly at risk for developing almond allergy, these findings will need to be validated in other cohorts. We anticipate that by incorporating these findings into clinical practice, we can reduce the number of unnecessary almond challenges and improve access for food-allergic patients truly at risk for life-threatening reactions.

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TABLE E1. Characteristics of subjects requiring repeat almond challenges

Subject	Almond SPT wheal diameter (mm)/IgE level (kU/L)	Challenge 1 outcome/symptoms	Challenge 2 outcome/symptoms	Challenge 3 outcome/symptoms	Time interval (y)
1	SPT 6, IgE 29.2	Fail (oral itch, nasal symptoms, hives)	Pass	—	2.7
2	SPT 5, IgE 34.50	Fail (severe generalized pruritus, irritability)	Pass		4
	SPT 5, IgE 23.20				
3	SPT 5, IgE 8.74	Fail (throat itch, lip pruritus)	Pass		3.2
	SPT 10, IgE 1.13				
4	SPT 7, IgE 0.72	Fail (pruritus and flushing)	Pass		3.7
	SPT 0, IgE 0.34				
5	SPT 2, IgE 0.88	Fail (diffuse wheezing, later attributed to uncontrolled asthma)	Pass		0.4
	SPT 3, IgE 0.50				
6	SPT 5, IgE 0.90	Indeterminate (gagged and refused)	Pass		0.8
7	SPT 4, IgE 1.14	Pass (did not reintroduce because of intense abdominal pain hours later)	Pass		4.2
	SPT 4, IgE 2.89				
8	SPT 5, IgE 0.34	Pass (had eye swelling hours after challenge)	Pass		0.3
9	SPT 5, IgE 0.42	Pass (had difficulty with home introduction)	Fail (oral itch, 10-12 hives, abdominal pain)		2
	SPT 14, IgE 43.3				
10	SPT 0, IgE 0.34	Fail (few hives)	Indeterminate (fever, 1 hive)	Pass	3.7
	SPT 0, IgE 0.34				0.4
	SPT 4, IgE 0.43				
11	SPT 5, IgE 0.34	Fail (several hives)	Indeterminate (1 hive)	Pass	1.2
	SPT 0, IgE 0.44				3.3
	SPT 10, IgE 0.54				

TABLE E2. Sensitivity analysis of sensitized participants (n = 475): Allergic clinical characteristics associated with IgE-mediated reaction

Characteristic	Unadjusted OR (95% CI)	P
Demographic		
Age at challenge	0.86 (0.77-0.96)	.009
Almond history		
Almond specific IgE level	1.45 (1.18-1.8)	<.001
Almond SPT wheal diameter	2.48 (1.48-4.15)	<.001
Allergic sensitization		
Peanut IgE level	1.13 (1.02-1.26)	.02
Pistachio IgE level	1.13 (0.97-1.32)	.12
Pecan IgE level	1.19 (0.96-1.47)	.12
Walnut IgE level	1.13 (0.99-1.29)	.08

OR, Odds ratio.

ORs for specific IgE represent the increased odds for every 10-kU/L change in IgE level. ORs for SPT represent the increased odds for every 5-mm change in wheal diameter.

TABLE E3. Specificity and sensitivity of almond specific IgE and almond SPT for IgE-mediated reactions

Outcome	Test	Value	Sensitivity	Specificity	PPV	NPV	LR+	LR−
Challenge outcome	Almond SPT	7	1	0	0.05	1	1	0
		8	0.21	0.88	0.09	0.95	1.77	0.9
		9	0.21	0.94	0.17	0.95	3.61	0.84
		10	0.14	0.98	0.27	0.95	6.34	0.88
		11	0.14	0.99	0.36	0.95	9.97	0.87
		12	0.1	0.99	0.33	0.95	8.72	0.91
		14	0.07	0.99	0.29	0.95	6.98	0.94
		16	0.07	0.99	0.4	0.95	11.63	0.94
Grade 2/3 reaction	Almond SPT	4	1	0	0.04	1	1	0
		6	0.25	0.84	0.06	0.97	1.53	0.9
		7	0.25	0.94	0.14	0.97	4.29	0.8
		8	0.2	0.97	0.21	0.97	6.87	0.82
		9	0.15	0.98	0.21	0.97	7.02	0.87
		10	0.15	0.99	0.3	0.97	11.04	0.86
		12	0.15	0.99	0.38	0.97	15.45	0.86
		13	0.1	0.99	0.33	0.97	12.87	0.91
Challenge outcome	Almond IgE	0	1	0	0.05	1	1	0
		1	0.69	0.54	0.08	0.97	1.5	0.58
		2.25	0.31	0.71	0.06	0.95	1.08	0.97
		10	0.21	0.93	0.15	0.95	2.99	0.85
Grade 2/3 reaction	Almond IgE	0.25	1	0	0.04	1	1	0
		1.25	0.8	0.56	0.07	0.99	1.8	0.36
		2	0.4	0.68	0.05	0.97	1.25	0.88
		10	0.25	0.93	0.12	0.97	3.39	0.81
		15	0.25	0.97	0.23	0.97	7.57	0.78

LR−, Negative likelihood ratio; LR+, positive likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

TABLE E4. Details of failed challenge reactions and characterization: Niggemann-Beyer reaction severity: grade 1 (redness, swelling [not angioedema], or pruritus); grade 2 (urticaria, angioedema, generalized flushing, abdominal pain, vomiting, or diarrhea); grade 3 (cough, wheezing, stridor, tachycardia, decreased blood pressure, respiratory distress, shock, cardiac arrest)

S. no.	Niggemann-Beyer reaction severity	Sampson 2006	Symptoms reported	Treatment given
1	Grade 2	No	Pruritus, urticaria	Antihistamines
2	Grade 1	No	Throat pruritus	Antihistamines
3	Grade 1	No	Oral pruritus	Antihistamines
4	Grade 2	No	Nasal congestion, urticaria (with exercise)*	None
5	Grade 1	No	Oral sensitivity	Antihistamines
6	Grade 1	No	Oral itch, facial redness, nonurticarial rash	None
7	Grade 2	No	Urticaria, pruritus	None
8	Grade 1	No	Oral pruritus, facial redness	Antihistamines
9	Grade 1	No	Facial redness, pruritus, nasal congestion	Antihistamines
10	Grade 2	No	Oral discomfort, urticaria	Antihistamines
11	Grade 3	Anaphylaxis	Pruritus, flushing, urticaria, abdominal pain, vomiting, sneezing	Antihistamines, epinephrine, steroids, H ₂ blocker
12	Grade 3	Anaphylaxis†	Wheezing,† sneezing × 3	Antihistamines, albuterol
13	Grade 1	No	Palmar pruritus	Antihistamines
14	Grade 2	No	Urticaria, sneezing, nasal congestion	None
15	Grade 2	No	Urticaria, nasal congestion	Antihistamines
16	Grade 2	No	Oral pruritus, urticaria, mild abdominal pain	Antihistamines
17	Grade 1	No	Sneezing and nasal congestion	Antihistamines
18	Grade 2	No	Pruritus, urticaria	None
19	Grade 1	No	Taste aversion, refused to consume	None
20	Grade 2	No	Urticaria	Antihistamines
21	Grade 2	No	Urticaria, nonurticarial rash	Antihistamines
22	Grade 2	No	Vomiting, sneeze × 1	None
23	Grade 2	No	Sneezing, congestion, throat pruritus, throat clearing	None
24	Grade 2	No	Pruritus, urticaria	Antihistamines
25	Grade 2	No	Pruritus, urticaria	Antihistamines
26	Grade 3	Anaphylaxis	Nasal congestion, wheezing, urticaria	Antihistamines, epinephrine, steroids, H ₂ blocker
27	Grade 2	No	Urticaria, local flushing, mild lip angioedema, nasal congestion	Antihistamines
28	Grade 2	No	Oral itch, ear angioedema, local flushing, nasal congestion, mild abdominal pain	Antihistamines
29	Grade 2	No	Oral itch, vomiting	Antihistamines, H ₂ blocker
30	Grade 2	No	Urticaria	None

*Patient had nasal congestion during challenge, but during home introduction with exercise the next day, developed urticaria.

†Patient had transient wheeze and nasal congestion at baseline, then during the challenge had worsening wheeze and sneezed 3 times. Supervising clinician attributed symptoms to asthma exacerbation.

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