

Real world use of peanut component testing among children in the Chicago metropolitan area

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ABSTRACT

Background: Peanut component tests (PCT) have become important in the evaluation of peanut allergy. There remains a paucity of research across the United States in investigating the utility of PCT in clinical practice in conjunction with current standards of care.

Objective: The primary aims were to evaluate the performance and sensitization patterns of PCT in clinical practice when first available at our institution.

Methods: We performed a retrospective chart review of 184 children with PCT and oral food challenge (OFC) results between 2012 and 2017. Simple logistic regression models assessed the associations between PCT and OFC outcomes. Receiver operator characteristic curves were constructed, and a predicted probability curve was derived for Ara h 2.

Results: The median (interquartile range [IQR]) age at OFC was 4 years (2–7 years), and 111 patients (60%) were boys. Ara h 2 was the most commonly sensitized PCT. Sixty-one patients (33%) reacted at OFC. Ara h 2 specific immunoglobulin E (sIgE) ≥ 0.35 kU_A/L was associated with increased odds of reacting at OFC (odds ratio 5.91 95% confidence interval, 2.93–11.89; $p < 0.001$); however, 19 patients (37%) positive for Ara h 2 did not react. Ara h 2 sIgE of 0.49 kU_A/L and 4.58 kU_A/L were associated with 50% and 90% probability, respectively, of reacting at OFC. Among those sensitized only to Ara h 8 or 9 ($n = 21$), 86% had no reaction. There was no statistically significant association with polysensitization to Ara h 1, 2, and 3, and peanut OFC outcome.

Conclusion: Although the Ara h 2 sIgE value was associated with clinical reactivity, a significant proportion of the patients sensitized to Ara h 2 tolerated peanut. OFC remains an important tool in the evaluation of peanut allergy.

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Peanut is one of the most common food allergens in children.^{1–3} Evaluation of suspected peanut allergy uses skin-prick testing (SPT) and quantification of whole peanut specific immunoglobulin E (sIgE). However, these tests lack specificity and can fail to distinguish patients with sensitization versus allergy.^{4–6} Peanut component testing (PCT) can also be used to predict clinical reactivity to peanut.^{7,8} Sensitization to Ara h 2 correlates with systemic allergic reactions and

is more specific than whole-peanut sIgE.^{4,8–10} Patients with monosensitization to Ara h 8, a Bet v 1-homolog, are frequently tolerant of peanut.^{11,12} Assessment of PCT in clinical practice has typically been an adjunctive test, and oral food challenges (OFC) are often still performed to distinguish between sensitization and allergy.^{13–15}

Although there has been increased PCT research, study methodologies vary, along with differing sensitization patterns, by geographic region and age.^{16–20} The utility of PCT in younger children, especially those < 2 years of age, has not been widely studied.²¹ Most studies that investigated the predictive value of PCT with direct comparison to OFC were conducted in research settings outside of the United States.^{22–27} Although guidelines for a peanut allergy diagnosis now recommend routine measurement of Ara h 2, there remains a paucity of research that is investigating PCT utility in routine clinical practice before introduction of these practice parameters.²⁸ The primary aims of this pragmatic study were to evaluate PCT in predicting OFC outcomes and to characterize sensitization patterns.

METHODS

Study Design

We conducted a retrospective chart review of 184 children who underwent open, unblinded peanut OFC

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at Ann and Robert H. Lurie Children's Hospital of Chicago between January 2012 and August 2017. All children with at least one PCT result (Ara h 1, 2, 3, 8, or 9) before peanut OFC were included. Decisions about ordering PCT and conducting OFC were based on the treating clinician's discretion, which reflected standard practice at the time. There were no exclusion criteria. PCT was performed by using ImmunoCAP (ThermoFisher Scientific, Waltham, MA). At the time of the study, Ara h 6 testing was not available at our institution. For most patients, whole-peanut sIgE was ordered at the same time as PCT. The lower and upper limits of detection of sIgE were $<0.1 \text{ kU}_A/\text{L}$ and $>100 \text{ kU}_A/\text{L}$, respectively. For primary analyses, we considered patients with sIgE of $\geq 0.35 \text{ kU}_A/\text{L}$ to have a positive result. The Lurie Children's institutional review board determined the study exempt, with waiver of consent granted.

Demographics, medical and family history, and whole-peanut sIgE values, and SPT (widest diameter wheal in mm), PCT, and peanut OFC results were extracted by chart review. The decision to pursue OFC was determined by the treating allergist to establish peanut allergy diagnosis or development of tolerance. The peanut OFC outcome was binary: reaction versus no reaction. A positive OFC result was determined by documentation of the following signs and symptoms: cutaneous (urticaria, pruritus, rash, erythema), upper respiratory (sneezing, congestion, rhinorrhea), lower respiratory (wheezing, cough), gastrointestinal (oral pruritus, abdominal pain and/or cramping, emesis, diarrhea), or cardiovascular (hypotension, change in mental status). For patients who reacted to peanut OFC, details about the signs and/or symptoms listed above were used to calculate a numeric modified Bock/PRACTALL (Practical Allergy, a joint effort of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma and Immunology that aims to synchronize the European and American approaches to allergy care.) score (range, 0–33), which served as a quantitative measure for severity, with higher scores signifying more severe reactions.^{29,30}

Statistical Analysis

Descriptive statistics summarized all key variables overall and by OFC outcome. PCT sensitization patterns were evaluated by age and sex. Simple logistic regression models considered associations between PCT results and binary OFC outcomes (reaction or no reaction). The Firth penalized likelihood ratio was used in logistic regression models due to a small sample size.³¹ Receiver operator characteristic curve analyses for whole-peanut sIgE and PCT were performed. The Youden index was used to identify optimal cut points for PCT. A predicted probability curve for Ara

h 2 was also constructed. Models that considered continuous variables included all the patients with detectable sIgE levels ($\geq 0.1 \text{ kU}_A/\text{L}$).

Secondary logistic regression models assessed for associations between demographic and clinical characteristics and OFC outcome. The associations between PCT and OFC were stratified by reason for avoidance (preventative or never consumed versus previous reaction) and by age (patient ages < 2 years versus ≥ 2 years). The Spearman correlation coefficients assessed associations between PCT and severity of reaction (defined by Bock/PRACTALL score). Because of the retrospective design, all patients who met inclusion and exclusion criteria within the study period were included. All analyses assumed a two-sided type 1 error rate of 0.05. Analyses were performed by using SAS software (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

Of 451 children with results of PCT during our study time frame, 184 also underwent peanut OFC. Most of these patients were boys (60%) and white (66%). The median (interquartile range [IQR]) age at peanut OFC was 4 years (2–7 years) (range, <1 –20 years). More than half of the patients ($n = 97$ [53%]) had never consumed peanut and were avoiding peanut based on positive testing results and/or family preference. The median (IQR) whole-peanut sIgE value and peanut SPT wheal size were $0.73 \text{ kU}_A/\text{L}$ (0.26 – $1.88 \text{ kU}_A/\text{L}$) and 6.0 mm (4.0 – 8.0 mm), respectively. Approximately half of the patients (49%) in our study reported a history of an additional food allergy. A full summary of the patient characteristics is presented in Table 1. Sixty-one children (33%) reacted to peanut challenge. Thirty-five patients had mild reactions, and 22 had severe anaphylactic reactions that required treatment with intramuscular epinephrine (4 patients did not have enough clinical data documented to accurately classify severity of reaction). The median (IQR) Bock/PRACTALL score for those who reacted to peanut OFC was 4.0 (2.5–6).

Sensitization Patterns

Ara h 2 was the most commonly sensitized peanut component among all the children ($n = 51$ [27.7%]), followed by Ara h 1 ($n = 29$ [15.8%]) and Ara h 8 ($n = 21$ [11.4%]). Monosensitization to Ara h 8 or 9 was documented in 21 patients (11.4%) and was uncommon in children < 3 years of age ($n = 1$). Approximately half of the patients (91 [49.5%]) who underwent peanut OFC had Ara h 1, 2, 3, 8, and 9 levels $< 0.35 \text{ kU}_A/\text{L}$. Complete PCT sensitization profiles by age and sex are presented in Table 2.

Table 1 Summary of demographic and clinical characteristics of total cohort (N = 184)

Parameter	Result
Demographics	
Sex, n (%)	
Boys	111 (60.3)
Girls	73 (39.7)
Race, n (%)	
White	122 (66.3)
Black	15 (8.2)
Other	45 (24.5)
Missing	2 (1.1)
Age at OFC, median (IQR), y	4.0 (2.0–7.0)
Medical history	
Total peanut sIgE value kU _A /L, median (IQR),	0.73 (0.26–1.88)
SPT wheal size, median (IQR), mm	6.0 (4.0–8.0)
Avoidance, n (%)	
Never consumed	97 (52.7)
Previous reaction	84 (45.7)
Missing data	3 (1.6)
History of accidental peanut ingestion with reaction, n (%)	
No	124 (67.4)
Yes	59 (32.1)
Missing data	1 (0.5)
History of additional food allergies, n (%)	
No or sensitization only	94 (51.1)
True allergy, with history of reaction	90 (48.9)
Patient history, n (%)	
Allergic rhinitis	64 (34.8)
Asthma	35 (19.0)
Atopic dermatitis	92 (50.0)

OFC = Oral food challenge; IQR = interquartile range; sIgE = specific immunoglobulin E; SPT = skin-prick test.

Univariable Associations with OFC Outcomes

Of the 51 patients with Ara h 2 values ≥ 0.35 kU_A/L, 32 (63%) reacted to peanut OFC, whereas 19 (37%) did not react (odds ratio [OR] 5.91 [95% confidence interval {CI}, 2.93–11.89]; $p < 0.001$). When an Ara h 2 value of ≥ 0.1 kU_A/L was considered, 43 (51%) had reacted, whereas 42 (49%) had not reacted. In contrast, the patients with positive sIgE results to other components (Ara h 1, 3, 8, or 9) did not have increased odds of reacting at OFC. Similarly, there was no significant association when polysensitization to Ara h 1, 2, and 3 was compared with the peanut OFC outcome. The patients with sIgE values < 0.35 kU_A/L to all components were more likely to tolerate peanut (OR 0.50

[95% CI, 0.26–0.93]; $p = 0.028$). Among patients mono-sensitized to Ara h 8 or 9, 86% had no reaction, but this finding was not statistically significant (OR 0.34 [95% CI, 0.1–1.15]; $p = 0.082$). A full summary of OFC outcomes by sensitization pattern is presented in Table 3. There were no associations between age, race, sex, or other atopic diagnoses and the peanut OFC outcome. A history of accidental peanut exposure and reaction ($n = 59$) was associated with increased odds of reacting (OR 2.08 [95% CI, 1.09–3.96]; $p = 0.027$). The patients with negative SPT results ($n = 21$) had decreased odds of reacting; however, this trend did not reach statistical significance.

Stratified Analyses

We noted no meaningful differences in effect sizes stratified by reason for avoidance. When stratified by age, patients at least 2 years of age and with Ara h 2 values ≥ 0.35 kU_A/L had increased odds of reacting to OFC (OR 6.85 [95% CI, 3.07–15.29]; $p < 0.001$) compared with those with Ara h 2 values < 0.35 kU_A/L. This association persisted but was attenuated in the patients < 2 years of age (OR 3.55 [95% CI, 0.8–15.69]; $p = 0.095$). There were no significant correlations between PCT and reaction severity.

Diagnostic Accuracy of PCT Results

The receiver operator characteristic curves assessed the performance of whole-peanut sIgE and PCT (Fig. 1). Ara h 2 performed best with the area under the curve of 0.750. The predicted probability of an OFC reaction at various levels of Ara h 2 and whole-peanut sIgE is depicted in Fig. 2. The median (IQR) for Ara h 2 for patients who did not react to OFC was 0.29 (0.10–0.45) compared with 1.04 (0.35–1.96) for those patients who did react (Table 3). Ara h 2 sIgE values of 0.49 kU_A/L and 4.58 kU_A/L were associated with 50% and 90% predicted probability, respectively, of reacting at OFC (Table 4). The whole-peanut sIgE value of 6.6 kU_A/L was associated with a 50% predicted probability of reacting at OFC. The best cut point for the Ara h 2 sIgE value was identified by the Youden index as 0.3 kU_A/L, with a corresponding sensitivity of 57% and specificity of 84% (Table 4).

DISCUSSION

Our study represents a large real-world investigation of PCT and peanut OFC outcomes in a cohort of U.S. children. During the study time frame (2012–2017), there was limited guidance about the use of PCT in clinical settings. Our study provides an overview of the potential value of PCT in clinical practice compared with standard testing methods for peanut allergy. Overall, our results support previous studies that higher levels of Ara h 2 correlate with increased

Table 2 Peanut component test sensitization patterns by patient age and sex (N = 184)

Component	Total Patients, n (%)	Age at Component Testing, n (%)						Sex, n (%)	
		0–3 y (n = 73)	>3–6 y (n = 46)	>6–9 y (n = 30)	>9–12 y (n = 17)	>12–15 y (n = 11)	>15–20 y (n = 7)	Boys (n = 111)	Girls (n = 73)
Ara h1*	29 (15.8)	10 (13.7)	8 (17.4)	6 (20.0)	2 (11.8)	0 (0.0)	3 (42.9)	21 (18.9)	8 (11.0)
Ara h2*	51 (27.7)	25 (34.3)	10 (21.7)	9 (30.0)	3 (17.7)	1 (9.1)	3 (42.9)	32 (28.8)	19 (26.0)
Ara h3*	13 (7.1)	4 (5.5)	4 (8.7)	0 (0.0)	2 (11.8)	1 (9.1)	2 (28.6)	7 (6.3)	6 (8.2)
Ara h8*	21 (11.4)	1 (1.4)	3 (6.5)	7 (23.3)	3 (17.7)	2 (18.2)	5 (71.4)	17 (15.3)	4 (5.5)
Ara h9*	16 (8.7)	1 (1.4)	7 (15.2)	4 (13.3)	2 (11.8)	1 (9.1)	1 (14.3)	11 (9.9)	5 (6.9)
Ara h1, 2, and 3*	4 (2.2)	0 (0.0)	1 (2.2)	0 (0.0)	1 (5.9)	0 (0.0)	2 (28.6)	3 (2.7)	1 (1.4)
Ara h8 or 9*	21 (11.4)	1 (1.4)	6 (13.0)	5 (16.7)	4 (23.5)	3 (27.3)	2 (28.6)	16 (14.4)	5 (6.9)
Ara h1-9#	91 (49.5)	39 (53.4)	23 (50.0)	14 (46.7)	8 (47.1)	6 (54.6)	1 (14.3)	52 (46.9)	39 (53.4)

*sIgE ≥ 0.35 kU_A/L.

#sIgE <0.35 kU_A/L.

odds of clinical reactivity to peanut.^{25–27,32,33} However, we found that more than one-third of our study population with an Ara h 2 level ≥ 0.35 kU_A/L did not react to peanut.

Clinicians often rely on estimates of likelihood of passing OFC when deciding to offer challenges. To date, there have been limited published data about the predicted probability of passing OFC based on PCT. In

Table 3 Univariable logistic regression models of sensitization to individual peanut component testing results*

sIgE Values per Component	OFC Outcome, n (%)		OR (95% CI)	p
	No Reaction (n = 123)	Reaction (n = 61)		
Ara h1				
<0.35 kU _A /L	107 (69.0)	48 (31.0)	Reference	0.148
≥ 0.35 kU _A /L	16 (55.2)	13 (44.8)	1.81 (0.81, 4.06)	
Ara h2				
<0.35 kU _A /L	104 (78.2)	29 (21.8)	Reference	<0.001
≥ 0.35 kU _A /L	19 (37.3)	32 (62.8)	5.91 (2.93, 11.89)	
Ara h3				
<0.35 kU _A /L	114 (66.7)	57 (33.3)	Reference	0.925
≥ 0.35 kU _A /L	9 (69.2)	4 (30.8)	0.94 (0.28, 3.15)	
Ara h8				
<0.35 kU _A /L	109 (66.9)	54 (33.1)	Reference	0.938
≥ 0.35 kU _A /L	14 (66.7)	7 (33.3)	1.04 (0.40, 2.71)	
Ara h9				
<0.35 kU _A /L	111 (66.1)	57 (33.9)	Reference	0.542
≥ 0.35 kU _A /L	12 (75.0)	4 (25.0)	0.70 (0.22, 2.22)	
Ara h1, 2, and 3 ≥ 0.35 kU _A /L				
No	122 (67.8)	58 (32.2)	Reference	0.15
Yes	1 (25.0)	3 (75.0)	4.88 (0.56, 42.37)	
Ara h8 or 9 ≥ 0.35 kU _A /L and Ara h1, 2, and 3 < 0.35 kU _A /L				
No	105 (64.4)	58 (35.6)	Reference	0.082
Yes	18 (85.7)	3 (14.3)	0.34 (0.10, 1.15)	
Ara h1-9 < 0.35 kU _A /L				
No	55 (59.1)	38 (40.9)	Reference	0.028
Yes	68 (74.7)	23 (25.3)	0.50 (0.26, 0.93)	

OFC = Oral food challenge; OR = odds ratio; CI = confidence interval. P values indicate a difference in OFC reaction (no reaction vs reaction) associated with the peanut component test value.

*The model was performed with the Firth penalized likelihood ratio.

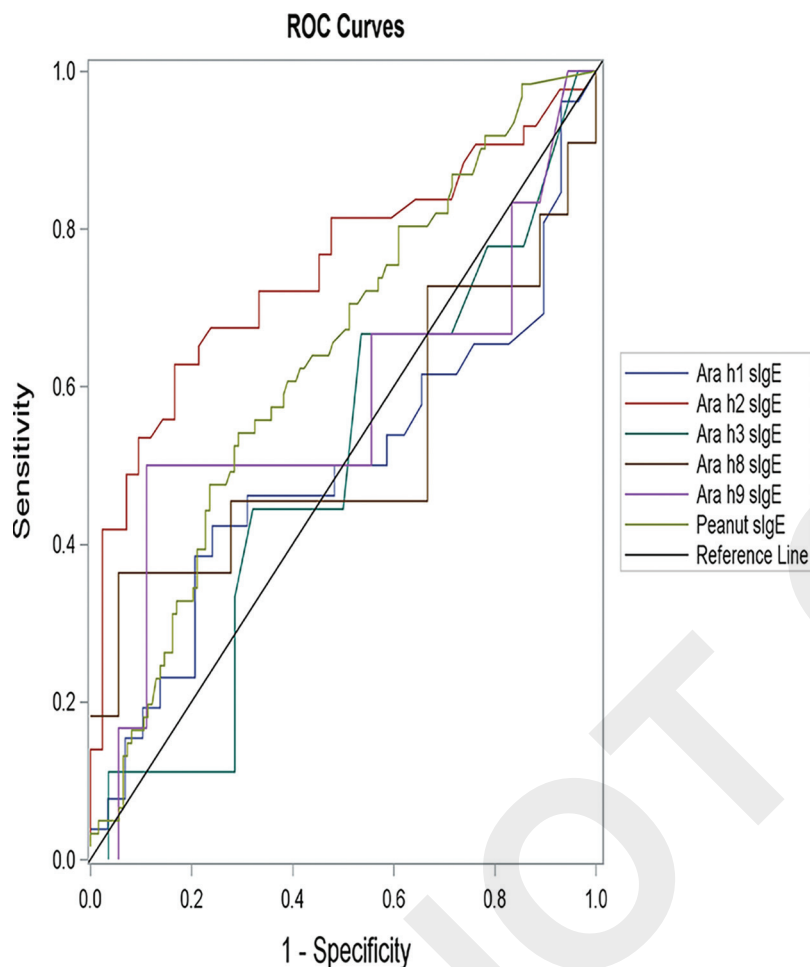


Figure 1. The diagnostic utility of specific immunoglobulin E (sIgE) to whole peanut and individual peanut components.

a prospective study that investigated PCT and OFC outcomes in German children, Ara h 2 sIgE levels of 0.7 kU_A/L and 14.4 kU_A/L represented 50% and 90% probability, respectively, of reacting at peanut OFC.²⁴ A study of Australian children showed that Ara h 2 sIgE levels of 0.35 kU_A/L and 1.0 kU_A/L were associated with 72% and 83% probability of OFC reaction, respectively.²² Our study also again demonstrates that some children with positive Ara h 2 sIgE levels can tolerate peanut.

Less is known about the utility of PCT in infants and children. Few studies of PCT and OFC outcomes in U. S. children have been published.^{21,25} In a study of infants at high risk of peanut allergy, Ara h 2 was found to be the best predictor of peanut OFC ($n = 57$) when compared with peanut SPT wheal size (excluding infants with a peanut SPT wheal ≥ 8 mm) and whole-peanut sIgE value.²¹ In comparison, our study demonstrated that sensitization to Ara h 2 was not a good predictor of OFC reaction in infants, but this may, in part, be due to our smaller sample size of children ages < 2 years ($n = 36$). Additional prospective studies with larger numbers of infants and toddlers that investigated PCT and OFC outcomes are needed

to further elucidate any potential differences in the application of PCT to this age group, especially because more peanut OFCs are conducted after introduction of the Learning Early About Peanut (LEAP) guidelines.^{34,35}

We also investigated PCT sensitization patterns as predictors of peanut OFC outcome. Compared with Ara h 2, no other PCT or sensitization patterns accurately predicted peanut OFC. In an Australian cohort, polysensitization to Ara h 1, 2, and 3 predicted peanut OFC outcome,²² but we did not find the same results. This may be due to the small numbers of children in our study with polysensitization to Ara h 1, 2, and 3, or differences in patient populations (United States versus Australia). We also found that most children (86%) sensitized only to Ara h 8 or 9 did not to react to peanut OFC, but these results did not reach statistical significance, likely due to the small number of patients with monosensitization to Ara h 8 or 9 ($n = 21$). Our findings may also be due to differing sensitization patterns in children because Ara h 8 and 9 sensitization increases with age.^{16,18–20} In addition, increased rates of sensitization to Ara h 8 have been documented in northeastern United States, and the Mediterranean

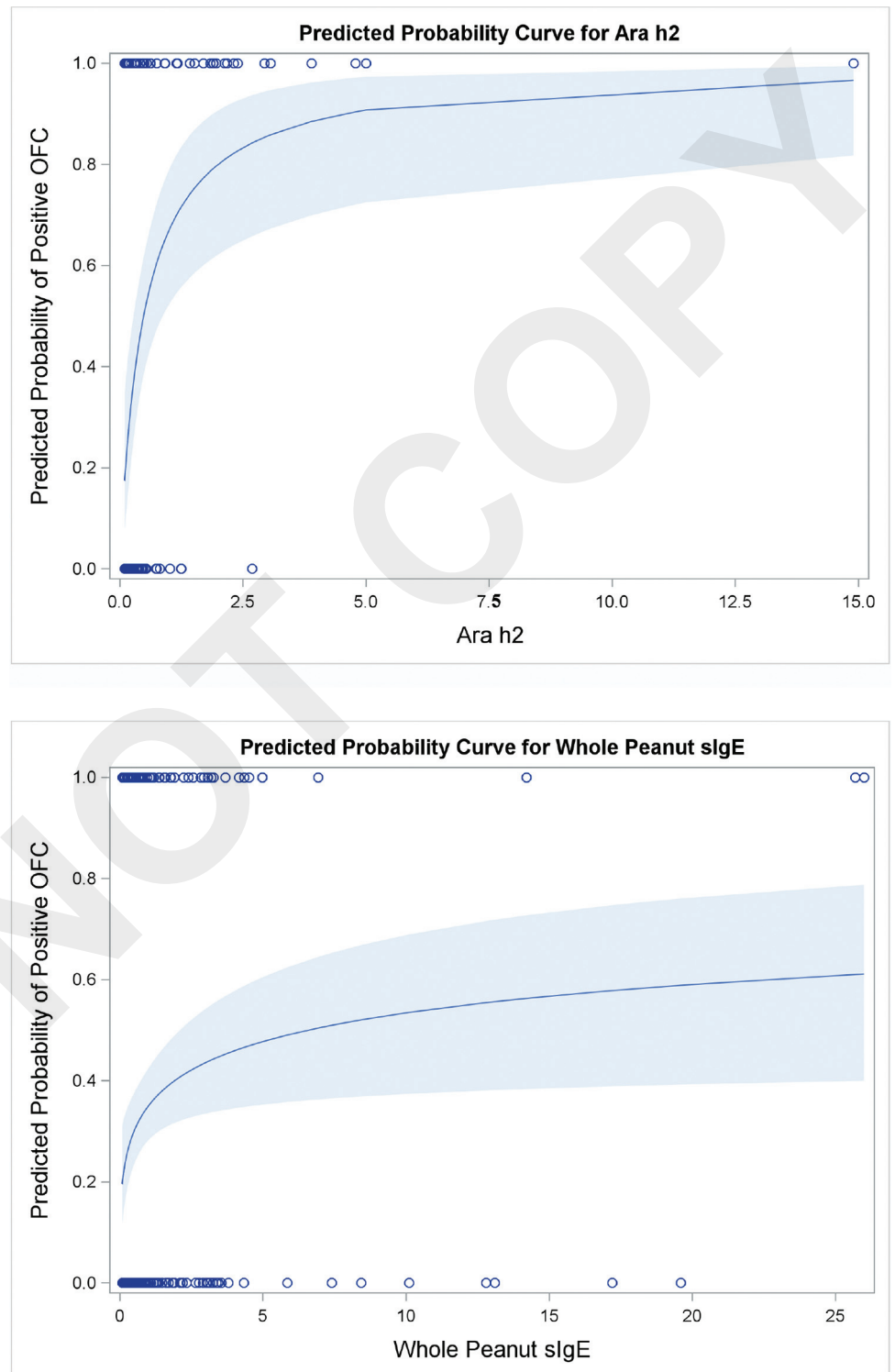


Figure 2. A predicted probability curve for peanut oral food challenge (OFC) failing for Ara h 2 and whole peanut specific immunoglobulin E (sIgE).

regions have been shown to have increased rates of sensitization to Ara h 9.^{16,18,19} Variations in PCT sensitization by age and geographic region limit generalizability. However, results of our study suggest that U.S. clinicians may recommend peanut OFC to patients with monosensitization to Ara h 8 or 9 given our observed trend toward tolerance.

Our study did not include measurement of Ara h 6 sIgE values. Ara h 2 and 6 are homologous structures with significant cross-reactivity.³⁶ Some proponents suggest that the measurement of both Ara h 2 and 6 can improve the diagnostic accuracy of PCT.^{37,38} However, Hemmings *et al.*³⁹ demonstrated that Ara h 2 sIgE was the dominant allergen in a cohort of U.K.

Table 4 Probability for positive peanut OFC at given sIgE levels

Ara h2 sIgE	Predicted Probability of Reaction at Peanut OFC, % (95% CI)
0.49 kU _A /L	50 (38–62)
4.58 kU _A /L	90 (72–97)
9.82 kU _A /L	95 (79–99)

OFC = Oral food challenge; sIgE = specific immunoglobulin E; CI = confidence interval.

children, with measurement of Ara h 6 rarely needed to diagnose peanut allergy. Further studies that investigate the utility of measuring both Ara h 2 and 6 in predicting OFC outcome will help to identify the utility of these components.

We recognize that selection bias occurred because we performed a retrospective chart review at a single center. In addition, partial verification bias is a limitation of studies that investigate diagnostic testing in food allergy.⁴⁰ This bias occurred in our study as demonstrated by a low median whole-peanut sIgE level and high percentage of patients with negative PCT results who underwent challenge. Current published guidelines⁴¹ suggest that clinicians consider peanut OFC for patients with and without a history of reaction with whole-peanut sIgE levels of ≤ 2 kU_A/L and ≤ 5 kU_A/L, respectively. Based on these recommendations, it is likely that most patients with high peanut sIgE levels and PCT were not offered OFC, and, similarly, patients who had low peanut sIgE levels and PCT may have introduced peanut at home without OFC.

We also noted that a high number of patients in our study with negative PCT results ($n = 23$ [25%]) still reacted at OFC. We suspected that some of these positive OFCs were likely false positives and may have benefited from blinded food challenges. Although we did include the presence of atopic dermatitis as a covariate in our study, we did not have data about the severity or level of atopic dermatitis control, which also may have influenced decisions about testing and offering OFC. Despite these limitations, our study represents typical clinical practice and demonstrates that measurement of Ara h 2 provides additional value for clinicians practicing within current standards of care.

CONCLUSION

Our retrospective study of the real-world use of PCT confirmed that pediatric patients sensitized to Ara h 2 were more likely to react to peanut OFC, but we found that more than one-third of the patients sensitized to

Ara h 2 were peanut tolerant. Measurement of other PCT and patterns of sensitization were not accurate predictors of a peanut OFC outcome. We suggest that clinicians in the United States consider offering peanut OFC to patients with detectable Ara h 2 sIgE levels up to 0.5 kU_A/L, given an ~50% probability of these patients reacting to OFC. Our study adds to the growing body of literature that demonstrates that Ara h 2 sIgE is more accurate than whole-peanut sIgE values and should be measured routinely in clinical practice.

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