

Component resolved diagnostics in peanut sensitized children with and without a history of clinical reaction

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ABSTRACT

Background: Serum Peanut-specific-IgE (PN-sIgE) and peanut-component-resolved-diagnostics (CRD) are often ordered simultaneously in the evaluation for peanut allergy. Results often guide the plans for peanut oral challenge. However, the clinical utility of CRD at different total PN-sIgE levels is unclear. A commonly used predefined CRD Ara h2 cutoff value in the literature predicting probability of peanut challenge outcomes is 0.35kUA/L.

Objective: To examine the utility of CRD in patients with and without a history of clinical reactivity to peanut (PN).

Methods: This was a retrospective chart review of 196 children with PN-sIgE and CRD testing, of which, 98 patients had a clinical history of an IgE-mediated reaction when exposed to PN and 98 did not. The Fisher's exact test was used to assess the relationship between CRD and PN-sIgE at different cutoff levels, McNemar test and Gwet's approach (AC1 statistic) were used to examine agreement between CRD and PN-sIgE, and logistic regression was used to assess differences in the findings between patients with and without reaction history.

Results: Ara h 1, 2, 3, or 9 (ARAH) levels ≤ 0.35 kUA/L were significantly associated with PN-sIgE levels < 2 kUA/L rather than ≥ 2 kUA/L ($p < 0.0001$). When the ARAH threshold was increased to 1 kUA/L and 2 kUA/L, these thresholds were still significantly associated with PN-sIgE levels of < 2 , < 5 , and < 14 kUA/L. These findings were not significantly different in patients with and without a history of clinical reactivity.

Conclusion: ARAH values correlated with PN-sIgE. Regardless of clinical history, ARAH levels are unlikely to be below 0.35, 1, or 2 kUA/L if the PN-sIgE level is > 2 kUA/L. Thus, if possible, practitioners should consider PN-sIgE rather than automatically ordering CRD with PN-sIgE every time. Laboratory procedures that allow automatically and reflexively adding CRD when the PN-sIgE level is ≤ 5 kUA/L can be helpful. However, further studies are needed in subjects with challenge-proven PN allergy.

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Peanut (PN) allergy is one of the most common food allergies, with a current prevalence of $\sim 2\%$ in the United States.¹ Studies have reported a tripling of PN allergy in the United States since the 1990s.^{2,3} However, only 20% of children with PN allergy develop natural tolerance.⁴ An accurate diagnosis is important to provide appropriate management, preserve quality of life, and prevent overdiagnosis. Skin testing, measurements of PN-specific immunoglobulin E (sIgE), and

PN components can be used to predict the likelihood of clinical reactivity. According to current guidelines, and based on earlier studies, a PN-sIgE level ≥ 14 kUA/L in children of all ages has a 95% positive predictive value of a reaction.^{5–7} In addition, the 50% negative predictive value of PN-sIgE has been reported as ≤ 2 kUA/L in patients with a history of reaction, and ≤ 5 kUA/L in patients with no history of reaction.⁷

In an effort to increase the diagnostic accuracy, molecular-based techniques, known as component resolved diagnostics (CRD) were introduced into clinical practice. In contrast to detecting all the IgE antibodies directed at the particular food, CRD measures IgE levels to some of the individual protein allergens within the food.⁸ Seventeen PN components (Ara h 1–17) have been identified, of which Ara h 1–9 have been associated with PN allergy in humans. However, only Ara h 1, 2, 3, 6, 8, and 9 are commercially available in most clinical situations. Although Ara h 1, 2, 3, 6, or 9 levels have been associated with the risk for systemic allergic reactions, the best predictor for clinical reactivity has been reported to be Ara h 2. Ara h 9 is a lipid transfer protein allergen in PN, which has been associated with systemic allergic reactions, in particular, in the Mediterranean area.

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In contrast, Ara h 8, characterized by low stability to roasting and digestion, is associated with oral allergy syndrome due to cross-reactivity to birch (Bet v1 sensitization).⁹ Ara h 8 is likely most helpful for identification of birch cross-reactivity, and the presence of Ara h 8 might lead a clinician to consider PN oral challenge at much different values than Ara h 1, 2, 3, 6, and 9, and, therefore, was not considered in our analysis. When this is suspected, clinicians would likely order CRD at higher PN-sIgE levels. At the time, CRD was performed in our study population, Ara h 6 was not commercially available, hence, not considered. The cutoff values for the CRD components Ara h 1, 2, 3, or 9 (ARAH) levels of ≤ 0.35 , ≤ 1 , and ≤ 2 kUA/L were determined based on cutoffs used in previous studies. A widely used CRD cutoff value in the literature, predicting probability of PN challenge outcomes, is 0.35kUA/L.^{10–14}

Current guidelines (Practice Parameters American Academy of Allergy, Asthma and Immunology,⁷ Summary Statement 24) advise against the routine use of CRD testing because its clinical utility has not been fully elucidated (strength of recommendation, weak; evidence, C). However, specific guidance on when to use CRD is not stated yet. Although CRD may be used in specific situations for assessment of Ara h 8 sensitization in patients with seasonal allergic rhinitis or oral allergy syndrome, the primary objective of this study was to evaluate correlations between the ARAH (PN components Ara h 1, 2, 3 and 9, regardless of Ara h 8) and total PN-sIgE values at different cutoff levels in patients with and without a history of an IgE-mediated reaction to PN, who were assessed by an allergist. This could help elucidate the clinical utility of CRD.

METHODS

Clinical Data

This study was a retrospective chart review of 196 patients, ages 0 to 17 years, who were seen by a group of allergists at an academic center for a food allergy evaluation. This was a subgroup analysis of a larger study of 360 children with PN, egg, and cow milk allergy who were evaluated between January 1, 2001, and May 31, 2016. The initial patient sample was identified through a commercial laboratory (Northwell Health Core Laboratories, New Hyde Park, New York) by performing a query of the records for a minimum of two immunoassays of the same food allergen, to cow milk, egg white, and PN, at separate office visits.

An additional query of the medical records was performed for the *International Classification of Diseases, Ninth Revision* (ICD-9)¹⁵ and *International Classification of Diseases, Tenth Revision* (ICD-10)¹⁶ codes for the following: cow milk, egg, and PN allergy (ICD-9 V15.01, ICD-10 Z91.010); food allergy (ICD-9 V15.05, ICD-10

Z91.018); adverse food reaction, initial encounter (ICD-9 995.7, ICD-10 T78.1XXA); and adverse food reaction, subsequent encounter (ICD-9 995.7, ICD-10 T78.1XXD). Laboratory test results, age, race, gender, and medical history were transcribed from the patient's medical record and entered directly into an encrypted data base (RedCap data base). Northwell Health (formerly known as North Shore Long Island Jewish Medical Center) Institutional Review Board approval was obtained.

Charts were reviewed for patients with total PN-sIgE and a CRD panel performed at the same time. All the patients included in the study were assessed and told by their allergist to avoid PN, and were prescribed epinephrine autoinjectors, due to the risk for an IgE-mediated potentially severe allergic reaction. The patients' medical history was reviewed for clinical history consistent with an IgE-mediated reaction within 2 hours of eating PN (such as a cutaneous reaction, including angioedema, gastrointestinal, or respiratory symptoms) as reported by patients and/or their guardian(s).¹⁷ The patients' atopy status, including allergic rhinitis and/or conjunctivitis, atopic dermatitis, and asthma as documented in the charts.

The patients were divided into two groups, which consisted of patients who had an IgE-mediated reaction to PN, and patients who were avoiding PN and had never been exposed to PN due to positive PN-sIgE. PN-sIgE levels were measured by our laboratory, with a lower limit of normal of <0.35 kUA/L and an upper limit of >100 kUA/L. The CRD/ARAH were quantified with a lower limit of normal of <0.10 kUA/L and upper detection limit of >100 kUA/L. Exclusion criteria were patients who were ≥ 18 years and patients who did not undergo PN-sIgE and CRD panel testing.

Statistical Analysis

We examined various combinations of a priori cutoff levels for the CRD and PN-sIgE levels; these were selected from the commonly used cutoff levels used by pediatric allergists and reported in the literature.^{10–13} Cutoff levels for ARAH (regardless of Ara h 8) were ≤ 0.35 , ≤ 1 , and ≤ 2 kUA/L, and for total PN-sIgE 2, 5, and 14 kUA/L. The Fisher's exact test was used to assess the relationship between CRD and PN-sIgE at different pairs of cutoff levels. The McNemar's test, as well as the Gwet's approach (AC1 statistic), was used to examine agreement between CRD and PN-sIgE for these pairs of cutoff levels. Logistic regression was applied to assess differences in the findings between patients with and without a history of clinical reactivity. To account for multiple comparisons, we used a Bonferroni-like adjustment by using $p < 0.01$ for

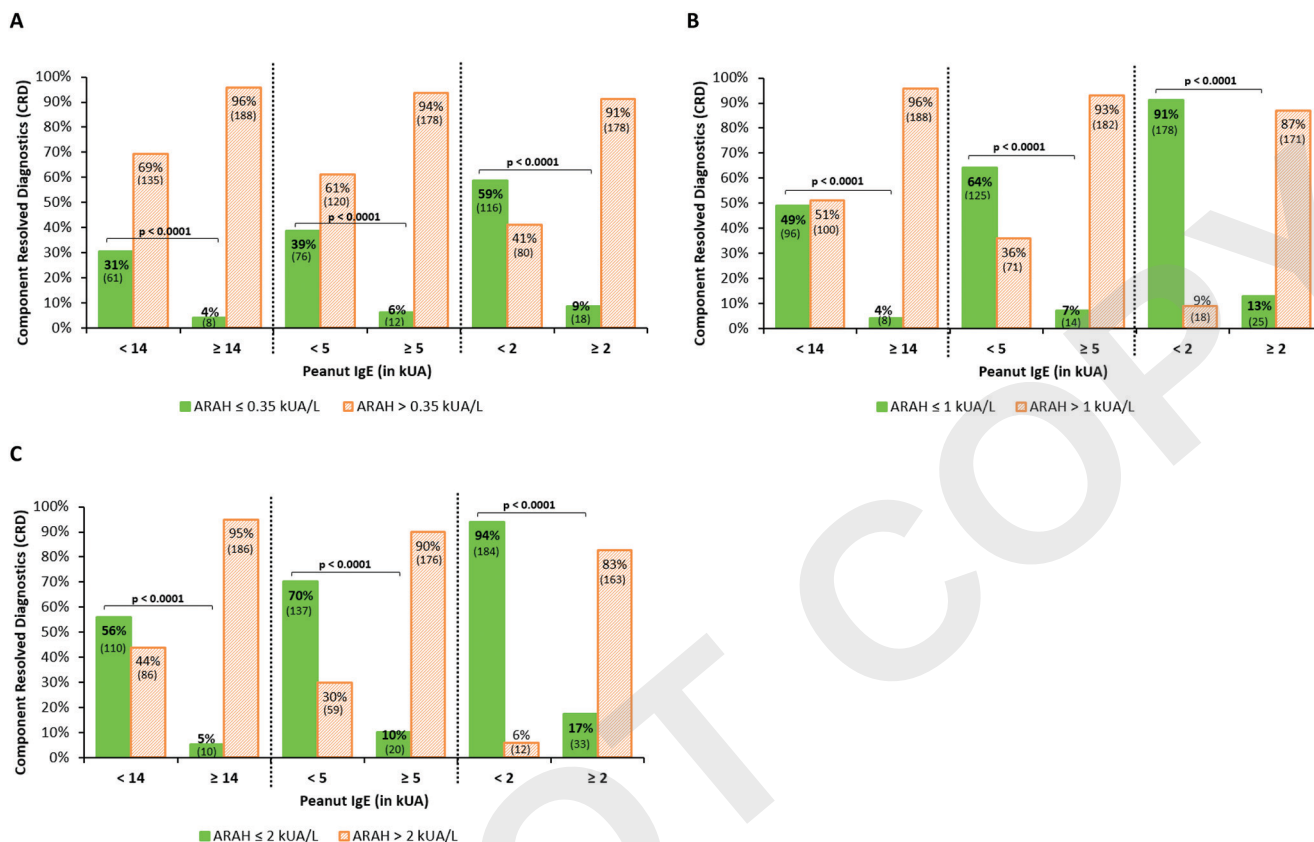


Figure 1. (A) ARAH (Ara h 1, 2, 3 or 9) values >0.35 and ≤0.35 kUA/L in 196 patients with peanut (PN) specific immunoglobulin E (sIgE) cutoffs of 2, 5, and 14 kUA/L. (B) ARAH (Ara h 1, 2, 3 or 9) >1 and ≤1 kUA/L in 196 patients with PN-sIgE cutoffs of 2, 5, and 14 kUA/L. (C) ARAH (Ara h 1, 2, 3 or 9) >2 and ≤2 kUA/L in 196 patients with PN-sIgE cutoffs of 2, 5, and 14 kUA/L.

significance. This was a retrospective study; the number of patients was not based on a formal power calculation. All analyses were carried out by using SAS v9.4 (SAS Institute, Cary, NC).

RESULTS

A total of 196 patients, who had been previously assessed by an allergist, told to strictly avoid PN, and were prescribed epinephrine autoinjectors, were identified. Half of the patients had a clinical history of an IgE-mediated reaction to PN and the other half had been avoiding PN due to positive PN-IgE values but had never ingested PN. Also, 64% of the patients were females, 36% were males, 65% had atopic dermatitis, 69% had allergic rhinitis and/or conjunctivitis, and 52% had asthma. The demographics for the two patient groups were not significantly different.

Among all 196 patients, there were significantly more patients with total PN-sIgE values <2 than ≥2 kUA/L (59% versus 9%, $p < 0.0001$) who were found to have ARAH values ≤0.35 kUA/L. This was also true when comparing total PN-sIgE levels <5 to ≥5 kUA/L (39% versus 6%, $p < 0.0001$), and <14 to ≥14 kUA/L

(31% versus 4%, $p < 0.0001$). These findings were not significantly different between the patients with and without a history of clinical reactivity ($p < 0.48$, $p < 0.84$, $p < 0.92$, respectively) (Fig. 1A). Even when higher ARAH levels are acceptable at 1 and 2 kUA/L, both are significantly more likely to be associated with total PN-sIgE levels of <2 than ≥2 kUA/L ($p < 0.0001$). These are also more likely to be associated with PN-sIgE levels <5 and <14 kUA/L ($p < 0.0001$) (Fig. 1, B and C, respectively).

DISCUSSION

Most clinicians consider ordering CRD when they suspect birch pollen, Bet v1, sensitization, and most clinicians would avoid diagnostic challenges when Ara h 2 sensitization is unacceptably high, but there is no clear guidance about when CRD is most helpful. This study looked into the relationship between the PN components Ara h 1, 2, 3, and 9, and total PN-sIgE at different cutoff levels in patients with and without a history of an IgE-mediated reaction to PN to help elucidate the clinical utility of CRD panels used to risk stratify patients with PN allergy for a

diagnostic oral challenge. Our study was not intended to assess the utility of CRD when a clinician plans on treating a patient with oral immunotherapy for PN. The cutoff values for the ARAH were determined based on cutoffs used in previous studies. A widely used CRD cutoff value in the literature, predicting probability of PN challenge outcomes, is 0.35 kUA/L.^{10–14}

In our study, not surprisingly, lower ARAH results correlated with lower total PN-sIgE levels in general. The patients with total PN-sIgE levels ≥ 2 kUA/L were significantly less likely to have ARAH, which includes Ara h 1, 2, 3, and 9 of ≤ 0.35 , ≤ 1 , or ≤ 2 kUA/L. If a clinician's goal ARAH level for an oral challenge is ≤ 0.35 kUA/L, which is a commonly used cutoff,^{10–14} then performing PN CRD when a total PN-sIgE level is >2 kUA/L is significantly less likely to be helpful for the majority of patients (91%).

In our study population, between 9 and 13% of all patients who had PN-sIgE >2 kUA/L had ARAH values between 0.35 and 1 kUA/L. Therefore, when looking at the data from a different approach, we considered the number of patients who would not be offered oral challenge by not doing CRD and, thereby, avoid PNs unnecessarily. When using the most conservative approach, if we assume that all patients who had ARAH values of <2 kUA/L would have passed a challenge and did not have CRD for anyone with PN-sIgE values >5 kUA/L, then, in our study population, 20 patients (10%), maximum, would be avoiding PN unnecessarily (Fig. 1C). However, a larger number of patients would have to undergo CRD unnecessarily. On the other end of the spectrum, if we assume any ARAH value >0.35 kUA/L will have a positive challenge, then any PN-sIgE value >2 kUA/L is unlikely to be helpful and is associated with 18 patients, 9%, unnecessarily avoiding PN (Fig. 1A).

The cutoff is a judgment call, with the receiver operating characteristic (ROC) curves balancing between sensitivity and specificity. This is in line with the accepted approach to determining risk assessment as per the Food Allergy Practice Parameters,⁷ which suggest a tiered approach to challenge thresholds PN-sIgE values of 2 kUA/L for those with a clinical history of reaction and 5 kUA/L for those without a history of reaction.⁷ Similarly, in balancing the unnecessary use of CRD with the unnecessary avoidance of PN, we suggest that performing CRD when PN-sIgE is >5 kUA/L is unlikely to be helpful if the goal is to proceed to an oral challenge. In patients suspected of having significant birch sensitization associated with high Ara h 8, practitioners would use their own judgment because high Ara h 8 numbers can also be associated with systemic oral allergy syndrome type reactions.

The strengths of this study were that the patients' food allergy diagnosis had been made by an allergist using history and sIgE testing. We were able to assess the impact of the clinical history on our study results because 50% of the study group had a history of an IgE-mediated reaction to PN and 50% did not, as previously assessed by an allergist. Study limitations are the overall small sample size, of 196 patients, and that no direct correlation with oral challenge was made in these patients because this was a retrospective study.

However, the correlation of CRD with oral challenge data has been established in the literature, as stated above.^{10–14} Although, we did not differentiate between the different ages within our study group (<18 years), age likely did not have a significant impact on our findings because Ara h 8 was excluded and the current accepted PN-sIgE levels are not age specific. Although one could argue that elevated Ara h 8 levels can lead to elevated PN-sIgE levels, we did not see that this affected our final analysis because these patients were still more likely to have elevated ARAH values. Another limitation was that this study did not include Ara h 6 in the analysis because it was not commercially available at the time.

CONCLUSION

The results of this study suggest that CRD values correlated with total PN-sIgE values. A commonly used predefined CRD cutoff value in the literature that predicts the probability of PN challenge outcomes is 0.35kUA/L.^{10–14} A two-tiered approach with initial total PN-sIgE testing and automatic CRD reflex testing on the same blood sample would be ideal instead of generalized CRD testing with every check of PN-sIgE levels. Larger studies that correlate challenge outcomes with diagnostic testing directly are needed to identify the optimal use of CRD in patients suspected to have PN allergy.

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