

Allergen Component Testing in the Diagnosis of Food Allergy

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Abstract IgE-mediated food allergies are an important public health problem, affecting 5 % of adults and 8 % of children, with numerous studies indicating that the prevalence is increasing. Food allergic reactions can range in severity from mild to severe and life threatening. Accurate diagnosis of food allergy is necessary not only to provide appropriate and potentially life-saving preventive measures but also to prevent unwarranted dietary restrictions. The diagnosis of food allergy has traditionally been based on clinical history and food specific IgE (sIgE) testing, including skin prick testing (SPT), serum tests, or both. These tests tend to be extremely sensitive, but positive test results to foods that are tolerated are common. Studies of allergen component-resolved diagnostics (CRD) show that adjuvant use of this modality may provide a more accurate assessment in the diagnosis of food allergy, though the reported benefits are questionable for a number of major allergens. Furthermore, diagnostic cutoff values have been difficult to determine for allergens where component testing has been demonstrated to be beneficial.

Keywords Food allergy · Diagnosis · Skin prick testing · Food specific IgE · Sensitivity · Specificity · Oral food challenge · Component-resolved diagnostics · Microarray

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Introduction

An expert panel of the National Institute of Allergy and Infectious Diseases has defined food allergy as an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food [1]. Upon ingestion of an allergen, symptoms of an IgE-mediated reaction can vary from a mild reaction, with symptoms such as localized urticaria or tingling of the lips, to a severe reaction, including life-threatening anaphylaxis. Food allergy likely affects nearly 5 % of adults and 8 % of children, and the prevalence has been increasing in recent decades [2–4]. The prevalence of self-reported allergy is higher, approximately 12 to 13 % [5••], and the disparity between perceived and confirmed food allergy accentuates the need for accurate diagnostics. Making the correct diagnosis of a food allergy is necessary to provide appropriate and potentially life-saving preventive measures as well as to prevent unwarranted dietary restrictions.

The diagnosis of an IgE-mediated food allergy is typically made using a detailed clinical history and physical exam, skin prick testing (SPT), and serum food specific IgE (sIgE) levels. Unfortunately, these tests have several limitations. In order to effectively capture the population at risk, these tests are sensitive but often not highly specific. Also, a positive SPT or sIgE may help predict the likelihood of clinical reactivity but does not predict reaction severity [1]. When the diagnosis of a food allergy is unclear, an oral food challenge (OFC) may be performed. The double-blind placebo-controlled food challenge (DBPCFC) is the gold standard test for diagnosing food allergy, but due to the time and labor-intensive nature of this test, open food challenges are typically performed in the clinical setting. While the open OFC is a highly specific test and is easier to administer than DBPCFC, it also requires significant time and resources, and can potentially result in severe allergic

reactions. Clearly, there is still room for improvement in the evaluation of food allergy prior to OFC.

Allergen component-resolve diagnostics (CRD) have attracted a lot of attention in the field of food allergy in recent years, with the hope that they may offer a more accurate assessment [2]. Numerous studies on a variety of major allergens have demonstrated improved specificity of allergy testing using CRD. CRD uses allergenic proteins from rDNA technology or purification from natural sources to identify reactivity to recombinant allergenic proteins rather than whole allergens [6]. Evaluating IgE binding to specific proteins within a food may provide additional diagnostic information about risk, tolerance, and potentially even the natural course of disease. Here, we review the current state of CRD in a number of common food allergens.

Milk Allergy

Cow's milk (CM) allergy affects approximately 2–3 % of young children, and although the majority of children will outgrow this allergy, it will persist into school age and beyond in a majority of patients [7]. Investigations into the usefulness of CRD for the diagnosis of CM allergy have had conflicting results. In an early investigation examining the use of CRD for CM allergy, Ott et al. [8] evaluated a component-based microarray with respect to the outcome of OFC in suspected CM allergy. Protein microarrays allow sIgE against multiple specific proteins to be detected using small amounts of sera. They reported that testing for sIgE to individual CM components was comparable, but not superior, to standard testing to CM extract in differentiating clinically reactive from sensitized but tolerant subjects [8].

These results differed from those of later studies. D'Urbano et al. [9] evaluated 58 children with suspected CM allergy by SPT, sIgE (ImmunoCAP and microarray), and OFC. IgE reactivity to casein (Bos d 8), the major protein in CM [10], was found to have higher positive predictive value (PPV) and negative predictive value (NPV) in the diagnosis of CM allergy when compared with standard sIgE testing. They concluded that the use of the 95 % clinical decision point (CDP) for Bos d 8 (>0.60 Immunosolid phase allergen chip (ISAC) standard units (ISU)), which resulted in a PPV of 96 % and an NPV of 78 %, could decrease the need for OFC [9]. However, for those with Bos d 8 levels lower than the 95 % CDP, a high number of false negatives were observed, suggesting that an OFC should still be performed in these patients. In a study by Ito et al. [11], investigators measured serum sIgE to CM extract and CM components in 83 children with suspected CM allergy, 61 diagnosed as allergic and 23 as non-allergic based on results of an open OFC or a convincing history. The CM allergic group showed higher levels of CM, Bos d 8, and beta-lactoglobulin (Bos d 5) sIgE than the non-allergic group. Bos d 8 showed the best discriminating performance with a cutoff

value of 6.6 kU/L being 100 % specific for allergy, with a sensitivity of 72 %.

Among children with CM allergy, approximately 75 % tolerate extensively heated CM [12]. This has led to studies assessing the utility of CRD to predict tolerance to baked milk. Caubet et al. [13] examined 225 children with CM allergy and determined that the Bos d 8 sIgE (area under receiver operating characteristic curve (AUC) 0.81) was a more accurate predictor than the CM sIgE (AUC 0.77) in determining tolerance to baked milk. All patients with undetectable levels of sIgE to Bos d 8 ($n=25$, 11.1 %) tolerated baked milk. A Bos d 8 sIgE of 4.95 kU/L was 74 % sensitive and 77 % specific with a NPV of 89 % and PPV of 54 % for baked milk reactivity, whereas a CM sIgE of 9.97 kU/L was 62 % sensitive and 85 % specific with a NPV of 86 % and PPV of 60 %. The authors suggest that the use of the cutoff decision points for sIgE levels to Bos d 8 could identify the optimal candidates for baked milk OFCs. Casein is likely the best component for predicting tolerance to baked milk because it retains its allergenicity after extensive heating, unlike whey (Bos d 4) proteins, which have low heat stability [10, 14].

Overall, the data is conflicting as to whether or not CRD, specifically the use of sIgE to Bos d 8, is better than traditional sIgE to CM in predicting allergy or tolerance to CM. Recent studies do indicate a potential role for the use of Bos d 8 sIgE levels in predicting tolerance to baked milk.

Egg Allergy

Allergy to hen's egg (HE) is the second most common allergy in infants and young children [15]. Similar to children with CM allergy, a significant portion of children with HE allergy will outgrow their allergy [15]. In a second arm of the previously mentioned study by D'Urbano et al. [9], 46 children with severe and/or immediate reactions to HE were evaluated, and sIgE levels to several components were determined, including ovomucoid (Gal d 1), ovalbumin (Gal d 2), ovotransferrin (Gal d 3), lysozyme (Gal d 4), and conalbumin (Gal d 5). The 95 % CDP (>0.86 ISU) for Gal d 1 yielded a PPV of 94 % and NPV of 79 %, while the HE sIgE 95 % CDP (>25.3 kU/L) yielded a PPV of 86 % and a NPV of 59 %. Similar to the results in the CM arm, the protein component sIgE, in this case to Gal d 1, resulted in a high number of false negatives indicating the need for OFC in patients with values below the 95 % CDP. In light of the increased cost and limited availability of microarray, the authors proposed using the 95 % CDP for Gal d 1 as a second level assay to decrease the number of OFCs needed to be performed as well as to reduce the risk of serious reactions during OFC.

The majority of children with HE allergy will tolerate extensively heated or baked egg [16]. There have been several investigations evaluating the utility of microarray sIgE testing

in determining heated versus raw egg allergy. In a study by Alessandri et al. [17], 68 children referred for suspected HE allergy underwent DBPCFCs with boiled and raw egg. These outcomes were compared with SPT to boiled and raw egg, total IgE, sIgE to egg white detected using ImmunoCAP, and sIgE to HE allergens available on the ISAC 103 microarray (Gal d 1, Gal d 2, Gal d 3, and Gal d 5). Gal d 1-negative children (sIgE=0 kU/L) showed a high frequency of tolerance (94 %) to boiled egg, while 20 of 21 (95 %) Gal d 1-positive subjects reacted to raw egg. Gal d 1 sIgE performance results showed 84 % sensitivity and 90 % specificity versus boiled egg DBPCFC. Thus, the sIgE to Gal d 1 could be helpful in determining which patients should undergo OFC to boiled egg. The other HE components were not able to discriminate patients' response to HE OFC.

In Japan, Ando et al. [18] evaluated 108 children with suspected HE allergy. All participants underwent DBPCFCs with raw and heated egg. Thirty-eight patients had reactions to raw and heated egg, 29 patients reacted to only raw egg white, and 41 patients were tolerant. The outcomes of the challenges were compared to the sIgE levels to egg white and components by ImmunoCAP. Receiver operating characteristic analysis showed that the sIgE to egg white was more useful in the diagnosis of allergy to raw egg white, while sIgE to Gal d 1 was superior in the diagnosis of allergy to heated egg. The optimal cutoff point for reactivity to raw egg white was found to be at an egg white sIgE of 2.82 kU/L, which resulted in a sensitivity of 81 % and a specificity of 85 %, compared to a Gal d 1 sIgE of 2.26 kU/L, which resulted in a sensitivity of 73 % and specificity of 83 %. The optimal cutoff point for reactivity to heated egg was found to be a Gal d 1 sIgE of 4.40 kU/L, which resulted in a sensitivity of 76 % and a specificity of 81 %, compared to an egg white sIgE of 7.38 kU/L, which resulted in a sensitivity of 66 % and specificity of 79 %.

A study by Lemon-Mule et al. [16] also indicated a correlation between Gal d 1 sIgE levels and reactivity to baked egg. In this study of 117 children, higher sIgE levels to Gal d 1 were found in children reactive to baked egg (baked with wheat flour in a form of a muffin or a waffle) compared with patients tolerant to baked egg and lightly cooked egg (e.g., French toast). Interestingly, a Gal d 1 sIgE level of 50 kU/L was found to be more than 90 % predictive of heated egg reactivity. The authors postulated that this high level may be due to decreased solubility of Gal d 1 when egg was mixed with wheat flour, suggesting that ovomucoid forms complexes with gluten, leading to aggregation and insolubilization, and potentially decreased digestibility. Unlike the previous studies, in a retrospective study of 169 patients who underwent Gal d 1 sIgE testing over an 18-month period at a US hospital, Bartnikas et al. [19] were unable to confirm the superiority of sIgE testing to Gal d 1 compared to egg white SPT or sIgE testing in predicting outcomes of baked egg challenges.

Though Gal d 1 levels may be more indicative of baked egg tolerance compared to traditional testing methods, there are significant differences in the methodology, egg preparation, and patient populations studied to date. Further investigations will be needed to evaluate the benefit of CRD in the evaluation of HE allergy.

Soy Allergy

Soybean allergy is one of the most commonly reported food allergies, affecting about 0.4 % of young children in the USA [5•, 20]. A majority of those with soy allergy will become tolerant, making reassessment and retesting an important part of managing this allergy [2, 20]. It is often difficult to make the diagnosis of soy allergy as testing is complicated by a high rate of false positives on routine IgE testing. Several studies have identified a dissociation between high levels of sIgE to soy proteins and low rates of clinical symptoms [21, 22].

In a Japanese study of 74 children (ages 0.16–16.3 years), Ito et al. [23] investigated the clinical utility of measuring sIgE antibodies to eight allergens, including soy extract, Gly m 4, Gly m 5, and Gly m 6. In this study, subjects were labeled as symptomatic ($n=33$) based on challenge outcomes or clinical history. The remaining subjects ($n=41$) were sensitized to soybean but did not demonstrate clinical reactivity, as demonstrated by OFC or a history of daily ingestion of soybean products. The sIgE levels to soybean, Gly m 5, and Gly m 6 were elevated in all but one of the subjects in the non-symptomatic group. The sIgE levels to Gly m 5 and soybean, but not Gly m 6, were significantly higher in the symptomatic group than the non-symptomatic group. The authors did not find a benefit in the measurement of Gly m 5 levels, however, as the soybean sIgE provided the best differentiation between the symptomatic and non-symptomatic groups.

The soy storage protein Gly m 2S albumin (Gly m 8) has recently been evaluated in studies in the Netherlands and Japan in the diagnosis of soy allergy. Gly m 8 has a conserved three-dimensional structure and high stability to the gastrointestinal environment and heat processing [24]. In a Dutch study, Klemans et al. [25] examined 46 adult patients with suspected soy allergy, 35 diagnosed as soy allergy based on challenge (19) or history (16), and 11 diagnosed as tolerant by OFC. Specific IgE levels to soy extract, Gly m 4, Gly m 5, Gly m 6, and Gly m 8 were measured. They reported that the Gly m 8 sIgE had the greatest accuracy in the diagnosis of soy allergy among the available soy components (AUC 0.79), but that the diagnostic value of Gly m 8 was comparable to SPT and sIgE to soy extract (AUC 0.76 and 0.77, respectively). In a study from Japan, Ebisawa et al. [24] examined the utility of soy component testing in 55 children (ages 0.6–10.3 years), 19 of whom were symptomatic and 36 who were non-symptomatic on ingestion of soy. The authors reported

that Gly m 8 sIgE levels were significantly higher in the symptomatic group than in the non-symptomatic group ($P=0.0024$), while sIgE to Gly m 5 and Gly m 6 were not. They concluded that Gly m 8 is a major allergen in Japanese children with soy allergy.

Soy allergy can also be birch pollen related. The soy component Gly m 4 is a birch pollen Bet v 1 homolog, and this component has been evaluated in a number of studies examining soy components, with mixed results. While some studies have reported that elevated Gly m 4 sIgE levels correlate with clinical reactivity [26, 27], other studies have not found this to be true [24, 25]. Interestingly, in the study by Klemans et al. mentioned above [25], it was reported that subjects who only reacted to soy milk, but tolerated other forms of soy, had significantly higher sIgE levels to Gly m 4.

CRD may hold the potential of providing a more specific method of evaluating soy allergy, though the studies are conflicting and likely reflect differences in study methods and populations used. Recently, Gly m 8 has shown promise in the evaluation of soy allergy, though further studies will be needed to elucidate the value of this component in different populations.

Peanut Allergy

Peanut (PN) allergy is one of the most common food allergies and the prevalence is increasing. In the USA alone, the prevalence has grown from 0.4 % in 1997 to 1.4 % in 2008 to more than 2 % in 2010 [4, 28]. Although about 20 % of PN allergic children will outgrow this allergy, the majority of patients have life-long disease [29]. The diagnosis of PN allergy results in tremendous life changes and significant anxiety for those affected [30, 31]. While sensitization to PN is common, with somewhere between 8 and 12 % of the general public showing sensitivity on either SPT or PN sIgE testing, the majority of these people are not allergic [30]. The largest study demonstrating this finding was a cohort of 933 children in the UK followed from birth to age 8 years. It was found that 11.8 % of subjects were PN sensitized at 8 years of age. An OFC was performed on all children with a PN sIgE ≤ 15 kU/L and SPT ≤ 8 mm who did not have a convincing history of a recent allergic reaction to PN. The results demonstrated the high rate of false positives occurring with SPT and sIgE testing to PN, with only 22.4 % of sensitized children having clinical PN allergy [32].

There has been extensive investigation into the relationship of specific PN protein components and clinical reactivity. Among the known components, Ara h 2 has been shown in multiple studies to be the most important predictor of clinical reactivity, though Ara h 1, 3, and 6 have also been associated with severe reactions [32–37]. Ara h 9 has been correlated with mild to severe symptoms in Mediterranean patients

[30, 38]. In addition, some studies have indicated that binding to multiple PN epitopes may be a better indicator of clinical reactivity [39, 40].

In contrast to other PN components, isolated sensitization to Ara h 8 (a Bet v 1 homolog) is associated with no or very mild symptoms on OFC [41]. Asarnoj et al. [41] evaluated 144 children monosensitized to Ara h 8 (≥ 0.35 kU/L, <0.35 kU/L to Ara h 1, Ara h 2, and Ara h 3) for clinical reactivity to PN. In this cohort, 129 children could tolerate PN, 14 experienced only transient mild oral symptoms, and 1 boy experienced lip swelling, stomach cramping, and objective tiredness. The patient with more severe symptoms showed an increase in PN sIgE from 1.5 to 8.8 kU/L and a detectable Ara h 6 sIgE at 0.45 kU/L. The results indicate that isolated sensitization to Ara h 8 demonstrates tolerance to PN in a majority of cases.

Koppleman et al. [37] were the first to demonstrate the significance of Ara h 2 in the diagnosis of PN allergy. In a cohort of 32 adult patients with convincing history of PN allergy, 26 patients were found to have serum recognition of Ara h 2. In this study, an Ara h 2 sIgE level of 0.55 kU/L was found to be 93 % sensitive and 100 % specific for PN allergy. Several additional studies, mostly in children, have found Ara h 2 to be the PN component most strongly associated with clinical reactivity, with higher levels of Ara h 2 sIgE correlating to a greater likelihood of clinical allergy [32–36].

In a large Australian study, Dang et al. [35] evaluated 411 infants (11–15 months of age) identified as PN sensitive based on a detectable SPT wheal. Of those infants, 274 had a negative OFC while 137 demonstrated reactivity. An additional 140 non-sensitized patients, confirmed by OFC to be non-PN allergic, were included as controls. Ara h 2 testing was performed on 100 randomly selected PN allergic and 100 tolerant patients (58 sensitized and 42 non-sensitized). Whole PN sIgE was also performed. Compared to sIgE to whole PN, the sIgE to Ara h 2 was more accurate in determining clinical reactivity. An Ara h 2 sIgE level of 0.46 kU/L was determined to be 95 % specific and 73 % sensitive, whereas a PN sIgE of 6.2 kU/L provided 95 % specificity but only 44 % sensitivity. At 15 kU/L, the PN sIgE has 95 % PPV and 98 % specificity but the sensitivity drops to 26 %. An Ara h 2 sIgE level of 1.19 kU/L was found to be a more accurate predictor of clinical reactivity, providing 98 % specificity and 60 % sensitivity.

In a recently published prospective multicenter study in Germany of 210 children with suspected PN allergy, 43 % were found to be clinically reactive upon OFC [42]. In this study, the sIgE to Ara h 2 was again confirmed to better discriminate PN allergic from tolerant patients than traditional testing. The sensitivity of the Ara h 2 sIgE was 86 % at 0.35 kU/L, with a specificity of 86 %. A 90 % probability for a positive PN challenge was estimated for an Ara h 2 sIgE at 14.4 kU/L and 95 % probability at 42.2 kU/L.

Despite the consistent finding of Ara h 2 as the best predictor, no universal sIgE level has been established as predictive of clinical reactivity [30•]. It has been suggested that the range of cutoffs proposed may be due to variations in geographic location and patient selection criteria [38]. In an attempt to identify a diagnostic cutoff value with utility in clinical practice, Keet et al. [43] retrospectively applied previously suggested Ara h 2 sIgE cutoff values of 0.23, 0.3, 0.35, and 2 kU/L, to patients with suspected PN allergy who had undergone OFCs. They reported that between 21 and 36 % of patients in their cohort would have been misclassified using any of these suggested cutoffs. They concluded that although the predictive ability is clearly improved over traditional PN sIgE testing, the use of Ara h 2 sIgE values was not a replacement for OFC, as many patients would be misclassified [43].

CRD appears to be most effective when used in conjunction with traditional testing. In the previously mentioned Australian study, Dang et al. [35] evaluated a stepwise approach to the diagnosis of PN allergy including component testing. Using diagnostic values of PN sIgE >15 or <0.35 kU/L, PST >8 mm or <3 mm, or Ara h 2 sIgE >1.0 kU/L or <0.10 kU/L, 95 of the 200 patients would have required OFC using the PN sIgE alone, 50 of 200 using SPT alone, and 44 of 200 using the Ara h 2 sIgE alone. A stepped approach of adding the Ara h 2 sIgE to PN sIgE would have decreased the need for OFC from 95 to 32 (approximately 66 %), and adding Ara h 2 to SPT would have decreased the need for OFC from 50 to 21 (approximately 58 %).

It has been well established that PN component testing can be helpful in the evaluation of some patients with suspected PN allergy. In a review of advances in the diagnosis of PN allergy, Sicherer et al. [30•] suggested a number of factors that make component testing more or less likely to be informative (Table 1). Factors that made it more likely that CRD would be informative included a history of mild reaction or no reaction history to PN, being sensitized to birch, older age, and having a PN sIgE level between 0.35 and 15 kU/L.

Hazelnut Allergy

Hazelnut allergy is more prevalent in adults than children [44, 45], though in birch endemic areas, children often have more severe symptoms, while adults tend to have mild oral symptoms [46–48]. Cor a 1 is a heat labile protein homologous to birch pollen Bet v 1 [49]. Since 2007, ImmunoCAP hazelnut testing has been supplemented with Cor a 1 to increase the test's sensitivity for birch-related allergy to hazelnut. Unfortunately, this has made it almost impossible to distinguish between those who are clinically reactive to hazelnut and those who are tolerant among patients with birch pollen allergy. Several studies from birch endemic regions of Europe have associated Cor a 1 sensitization with tolerance or only mild oral allergy symptoms [46, 49, 50]. In contrast, Cor a 8, a lipid transfer protein, Cor a 9, an 11S globulin, and Cor a 14, a 2S albumin, have been associated with more severe symptoms [46, 49, 50, 51•, 52]. Interestingly, while studies of Mediterranean populations have found Cor a 8 to be linked to more severe symptoms, sensitization to this component has not been found to be of great importance in predicting clinical reactivity to hazelnut in studies from other regions [50, 51•, 52].

Recent studies in the USA and Europe have demonstrated an important role for Cor a 9 and Cor a 14 in predicting clinical reactivity to hazelnut. A Dutch study by Masthoff et al. [51•] compared 40 children and 15 adults with objective symptoms on DBPCFC and 24 adults with a history of convincing objective symptoms with hazelnut ingestion to 41 children and 41 adults with no or subjective symptoms on DBPCFC. Specific IgE levels to hazelnut extract and individual components were analyzed by ImmunoCAP. The sIgE levels to hazelnut extract were significantly higher in children with objective symptoms than those with no or subjective symptoms. Sensitization to Cor a 9, Cor a 14, or both was strongly associated with having objective symptoms with ingestion of hazelnut. In children, sIgE levels to Cor a 9 of ≥ 1 kU/L or Cor a 14 of ≥ 5 kU/L, and, in adults, sIgE levels to Cor a 9 of ≥ 1 kU/L or Cor a 14 of ≥ 1 kU/L had a specificity of >90 % and accounted for 83 % of children and 44 % of adults with hazelnut allergy with objective symptoms. In a US

Table 1 Considerations in obtaining peanut component tests

Factors that make component testing <i>LESS</i> likely to be informative	Factors that make component testing <i>more</i> likely to be informative
A recent convincing clinical reaction	Mild reactions or no reaction history
A remote significant clinical reaction in a patient with PN-IgE ≥ 15	Remote clinical reaction with development of birch sensitization over time
PN-IgE >25 or <0.35 kU/L	PN-IgE 0.35–15 kU/L
Lack of birch sensitization	Birch sensitization
Younger children	Older persons

Reproduced with permission from [30•] (p. 9)

cohort, Kattan et al. [53] reported similar findings among 13 patients clinically reactive to hazelnut and 29 patients who were clinically non-reactive. They found that a sIgE result ≥ 2.0 kU/L for Cor a 9 or ≥ 1.0 kU/L for Cor a 14 had a sensitivity of 92 % and specificity of 93 % for clinical reactivity.

In a recent German multicenter study, Beyer et al. [42] evaluated 143 children with suspected hazelnut allergy. All children underwent an OFC to hazelnut, and sIgE to whole hazelnut and Cor a 1, Cor a 8, Cor a 9, and Cor a 14 were analyzed. With an AUC of 0.89, Cor a 14 sIgE was found to distinguish between allergic and tolerant children better than whole hazelnut sIgE (AUC 0.71, $p < .001$). The AUC for Cor a 9 was 0.80. A Cor a 14 level of 0.35 kU/L was found to reach a sensitivity of 85 % and a specificity of 81 %, with a 90 % probability of reaction found at 47.8 kU/L. The authors note, however, that the results might be different in other geographical locations.

Hazelnut component testing to Cor a 9 and Cor a 14 has demonstrated improved utility in differentiating patients with birch pollen sensitization who are not clinically reactive or have mild oral symptoms from those more likely to have severe allergic reactions. These tests show much greater specificity than traditional SPT and sIgE to hazelnut extract, though it is difficult to determine diagnostic cutoff values as predictive sIgE levels vary among the different studies.

Conclusion

CRD are becoming more widely available and offer the potential of increasing the accuracy of allergy diagnosis. For foods such as peanut and hazelnut, there are clear associations between sensitization to specific protein components and increased risk of clinical allergy, which may help distinguish patients who are likely tolerant and thus good candidates for OFC from those who have a high risk for clinical reactivity and should maintain strict food allergen avoidance. While CRD can be helpful in the evaluation of possible food allergy to peanut or hazelnut, diagnostic cutoff values have been difficult to determine. For other major allergens, such as cow's milk, hen's egg, and soy, reports on the utility of CRD demonstrate potential benefits, though results have been mixed. Further studies are necessary to better elucidate the role of CRD in the diagnosis of these food allergies and to determine how sensitization to specific components varies among subjects of different ages and in different geographic regions. At this time, CRD has been demonstrated to be helpful in some instances as a supplement to current diagnostic tests, but OFC remains the gold standard in the diagnosis of food allergy.

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Compliance with Ethics Guidelines

Conflict of Interest The authors declare that they have no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of major importance

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