How to diagnose food allergy

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Purpose of review
To assess the recent studies that focus on specific immunoglobulin E (sIgE) testing and basophil activation test (BAT) for diagnosing IgE-mediated food allergies.

Recent findings
The sIgE to allergen extract or component can predict reactivity to food. The cutoff value based on the positive predictive value (PPV) of sIgE can be considered whenever deciding whether oral food challenge (OFC) is required to diagnose hen's egg, cow's milk, wheat, peanut, and cashew nut allergy. However, PPV varies depending on the patients' background, OFC methodology, challenge foods, and assay methodology. Component-resolved diagnostics (CRD) has been used for food allergy diagnosis. Ovomucoid and omega-5 gliadin are good diagnostic markers for heated egg and wheat allergy. More recently, CRD of peanut, tree nuts, and seed have been investigated. Ara h 2 showed the best diagnostic accuracy for peanut allergy; other storage proteins, such as Jug r 1 for walnut, Ana o 3 for cashew nut, Ses i 1 for sesame, and Fag e 3 for buckwheat, are also better markers than allergen extracts. Some studies suggested that BAT has superior specificity than skin prick test and sIgE testing.

Summary
The sIgE testing and BAT can improve diagnostic accuracy. CRD provides additional information that can help determine whether OFCs should be performed to diagnose food allergy.

Keywords
antigen-specific IgE, basophil activation test, component-resolved diagnostics, food allergy, oral food challenge

INTRODUCTION

Food allergy is defined as an adverse health effect arising from a specific immune response that occurs reproducibly upon exposure to a given food [1]. Food allergies are classified based on antigen-specific immunological mechanisms after exposure to a given food. The most common mechanism of food allergy is immunoglobulin (Ig) E-mediated reactions, such as urticaria, anaphylaxis, oral allergy syndrome, and food-dependent exercise-induced anaphylaxis [1].

The diagnostic approach for IgE-mediated food allergy is based on the combination of clinical history and the presence of specific IgE (sIgE) antibodies (Fig. 1) [2]. Key points in history taking are suspected foods and their intakes, reproducibility of symptom, details of symptoms, other causative conditions (exercise, medication, etc.), and present food ingested [3]. Sensitization to a food allergen can be confirmed with sIgE testing, in-vitro test [serum antigen-sIgE test or basophil activation test (BAT)], or an in-vivo test [skin prick test (SPT)] [1,2]. The presence of sIgE antibodies indicates sensitization to the suspected foods, but such foods are not always the proven food allergen that causes allergic reaction because of a few reasons. One of the reasons can be explained by the cross reactivity of allergen, and the other would be acquisition of tolerance to food allergies during infancy. An oral food challenge (OFC) is the most accurate test to diagnose food allergy. However, it requires resources and trained medical staff and has the risk of developing allergic reactions including anaphylaxis. Therefore, conducting an OFC is safe or therefore, safety is a concern while conducting an OFC.

The sIgE testing available for general practice varies between countries. Previous studies showed that the accuracy of diagnosing food allergy using these tests varies between studies [4]. Measurements

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KEY POINTS

- In hen's egg, cow's milk, wheat, peanut, and cashew nut allergies, the cutoff value of sIgE can be used for predicting food allergies but these values vary between studies.
- CRD can improve diagnostic accuracy. Allergen components to storage protein, such as Ara h 2 for peanut, Jug r 1 for walnut, Ana o 3 for cashew nut, Cor a 14 for hazelnut, Ses i 1 for sesame, and Fag e 3 for buckwheat, are associated with the development of food allergies.
- Although BAT has better specificity than other IgE testing, it is not currently performed by standardized procedures. Thus, further studies are needed to assess its importance in clinical practice.

of sIgE to allergen extracts have been used for many years, and many studies have been published. Recently, some studies showed that the decision point based on positive predictive value (PPV) can help assess the reactivity to foods [5–9], and component-resolved diagnosis (CRD) can improve the accuracy of diagnosing food allergy [10]. Moreover, BAT is increasingly used in clinical practices. Therefore, the results of these tests must be considered to determine whether an OFC is required to diagnose food allergy or not.

This review covers an overview diagnosis of IgE-mediated food allergy with a focus on the recent advances of serum sIgE testing and BAT.

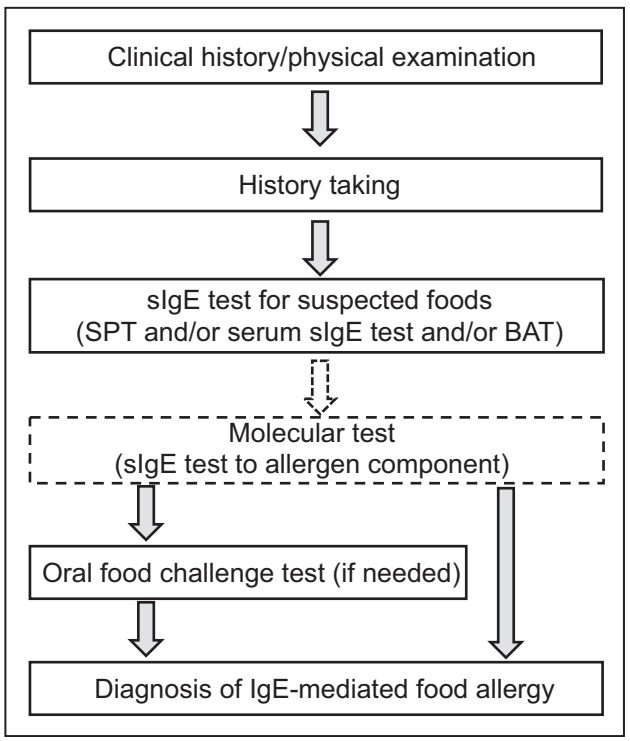

FIGURE 1. Flow chart showing the process of diagnosing food allergies. The diagnostic approach for IgE-mediated food allergy is based on the combination of clinical history and/or physical examination, and the presence of sIgE antibodies. If food allergy is not diagnosed using these information, OFC is required. BAT, basophil activation test; SPT, skin prick test.

POSITIVE PREDICTIVE VALUE OF SPECIFIC IMMUNOGLOBULIN E FOR THE DIAGNOSIS OF FOOD ALLERGY

Previous reports indicated that the cutoff value of a 95% PPV can be useful in diagnosing food allergies, especially in patients with a recent history of an immediate-type allergic reaction [11–13]. Table 1 presents a summary of the PPVs from recent studies based on the sIgE value for the diagnosis of food allergy [5–9,14,15]. The PPV varied widely in different studies. These differences are related to several factors such as patients' history of immediate reaction, challenge food, target doses, and rate of food allergy [6,14,16].

Additionally, several assays for measuring serum sIgE antibodies are used in clinical practice. Some studies showed discrepancies in the results obtained by different methodologies [17]. A study of egg allergy in early childhood demonstrated that a correlation was observed between the values of egg-sIgE and ovomucoid-sIgE antibodies detected in Siemens IMMULITE 3gAllergy (3gAllergy) and ImmunoCAP systems [6]. However, the two assay methods showed different cutoff values. Recently, Sato *et al.* [5] reported similar results, and they showed that the predictive decision points for hen's egg, cow's milk, and wheat allergy were different between the two assay methods (Table 1 and Fig. 2). These results indicate that clinicians should be careful during assessment when extrapolating cutoff values from published studies into clinical practice.

Several studies investigated the PPVs of sIgE to allergen extracts and allergen components [7,8▪▪,15]. Results showed that sIgE to allergen components is a better predictor of wheat and peanut allergy than those of allergen extracts [7,15]. Recently, Lange *et al.* [8▪▪] reported the probability for a positive cashew challenge by cashew sIgE and Ana o 3-sIgE. The 95% PPV for positive cashew challenge was estimated for Ana o 3 sIgE at 2.0 kU/l, whereas that of cashew sIgE was not estimated. Several allergen component sIgE tests, which are available for clinical practice, can be used to improve the accuracy of diagnosing food allergy.

Table 1. Summary of positive predictive values by specific immunoglobulin E value: recent studies

	Age (year)	Subjects (*n*)	Challenge food	Target dose	Allergen	Assay method	90% PPV	Reference number
Hen's egg	3.6	257	Scrambled egg	One whole egg	Egg white	ImmunoCAP	NE	[5]
						3gAllergy	466.1 IU_A/l	
	1.9	433	Heated egg white powder	1 year: half of egg 2–5 years: 1 whole egg	Egg white	ImmunoCAP	NE	[6]
						3gAllergy	1 year: NE 2–5 y: 355 IU_A/l	
					Ovomucoid	ImmunoCAP	1 year: NE 2–5 y: 50.0 kU/l	
						3gAllergy	1 year: NE 2–5 y: 211 IU_A/l	
Cow's milk	1.8	499	Heated milk or yogurt	25 ml of heated milk or 48 g of yogurt	Milk	ImmunoCAP	27.7 kU/l	[5]
						3gAllergy	53.1 IU_A/l	
	6.0	217	Heated milk	3 ml of heated milk	Milk	ImmunoCAP	NE	[14]
Wheat	1.1	626	Boiled udon noodle	15–100 g of udon noodle	Wheat	ImmunoCAP	NE	[5]
						3gAllergy	50.6 IU_A/l	
	2.3	331	-	-	Omega 5 gliadin	ImmunoCAP	Less than 1 year: 2.2 kU/l Greater than 2 year: 3.5 kU/l	[15]
Peanut	6	165	Peanut	-	Peanut	ImmunoCAP	NE	[7]
					Ara h 2	ImmunoCAP	12 kU/l	
	Tolerant: 4.3 Allergic: 4.8	210	Peanut	4.443 g	Ara h 2	ImmunoCAP	14.4 kU/l	[9]
Cashew nut	Tolerant: 6.7 Allergic: 3.8	61	Cashew	25.55 g	Cashew nut	ImmunoCAP	10.9 kU/l	[8▪▪]
					Ana o 3	ImmunoCAP	1.3 kU/l	

NE, not estimated; PPV, positive predictive value.

MOLECULAR ALLERGY DIAGNOSTICS

Common IgE assay method uses allergen extracts. Allergen extracts contain a complex mixture of allergen components. sIgE testing to allergen components can be performed using singleplex IgE antibody assay and multiplex IgE antibody assay in microarrays. CRD or molecular-based allergy can help explain the cross-reactivity between allergens and improve the accuracy of diagnosing food allergy (Tables 2 and 3) [6,8▪▪,9,18–31].

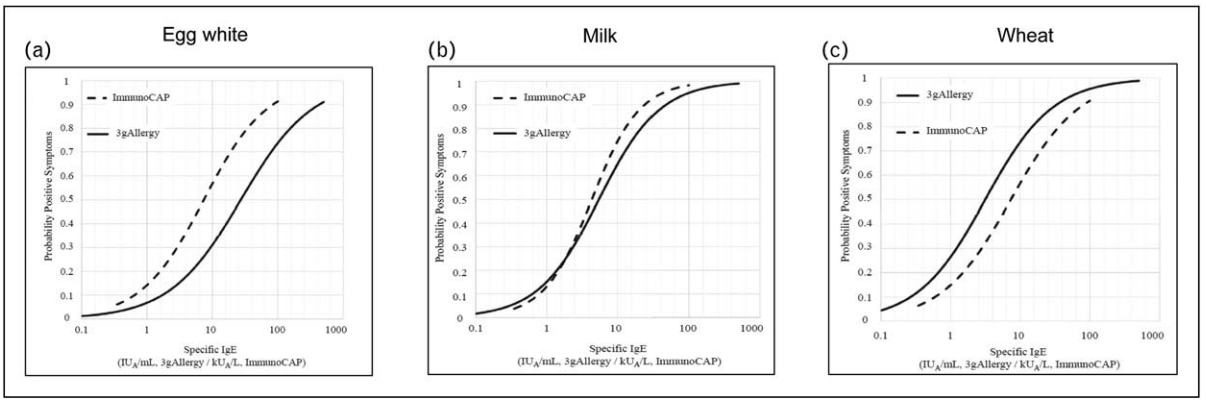

FIGURE 2. Comparison of probability curves between 3gAllergy and ImmunoCAP assays. A comparison of the probability curves of (a) egg white ($n = 436$), (b) milk ($n = 497$), and (c) wheat-specific IgE ($n = 626$) are shown. A logistic regression model was used to evaluate the sIgE values necessary to predict the probability of inducing symptoms. Black line indicates ImmunoCAP assay, whereas black dot line indicates 3gAllergy assay. Reproduced with permission from [5].

Table 2. Diagnostic accuracy of specific immunoglobulin E to allergen components: recent studies

Antigen	Component to food allergens	Results	Reference number
Hen's egg	Gal d 1 (ovomucoid)	Ovomucoid was a good predictor of cooked egg allergy than egg white allergy, but not a good predictor of raw egg allergy.	[6]
		Ovomucoid was the best marker to distinguish between allergy to raw eggs only and allergy to raw and cooked egg.	[18]
	Gal d 2 (ovalbumin)	Ovalbumin was the best marker of raw and cooked egg allergies.	[18]
Cow's milk	Bos d 8 (casein)	Casein was associated with baked milk allergy.	[19]
Wheat	Tri a 19 (omega-5 gliadin)	These wheat components were associated with positive and severity of wheat OFC.	[20]
	Gliadin		
	HMW-glutenin		
	LMW-glutenin		

Hen's egg

Major hen's egg allergens include ovomucoid (Gal d 1), ovalbumin (Gal d 2), conalbumin (Gal d 3), lysozyme (Gal d 4), and livetin (Gad d 5) (Table 2) [2]. Ovomucoid is the most immunodominant allergen based on the OFC result [32]. It is stable against heat and digestion by proteinases. Recent systematic review indicated that ovomucoid showed the highest diagnostic accuracy for hen's egg allergy [33]. Furthermore, previous studies showed that ovomucoid-sIgE is a better predictor of cooked egg allergy than egg white-sIgE [32,34]. A similar result with different patient characteristics was reported by Benhamou Senouf *et al.* [18], indicating that ovalbumin was the best test to diagnose raw and cooked egg allergy. Another egg study showed that ovomucoid was not a better predictor of raw egg allergy than egg white [6]. For hen's egg allergy, the best predictive marker is different between raw and cooked egg allergy.

Cow's milk

Major cow's milk allergens are casein (Bos d 8), beta-lactoglobulin (Bos d 5), and alphalactoglobulin (Bos d 4; Table 2) [5]. The proteins present in cow's milk are found in human breast milk, except beta-lactoglobulin. Casein is very resistant to heat, whereas beta-lactoglobulin and alphalactoglobulin are more sensitive to heat than casein. More than 50% of cow's milk allergic patients are sensitized to these allergens, and multiple allergens are immunodominant. Previous studies showed that casein was related to cow's milk allergy [35,36], and it is a good marker for clinical reactivity to extensively heated baked milk [19]. A recent systematic review of CRD

Table 3. Diagnostic accuracy of specific immunoglobulin E (sIgE) to allergen components: recent studies

Antigen	Component to food allergens	Results	Ref. No
Peanut	Ara h 2	Ara h 2 was a predictive marker of peanut allergy.	[9]
		Ara h 2 showed the best diagnostic accuracy.	[21]
	Ara h 2 and 6	Ara h 2 and Ara h 6 were the best diagnostic markers of severe reaction to peanut.	[22]
Soy	Gly m 8	Gly m 8 was a predictive marker of soybean allergy.	[23]
Cashew nut	Ana o 3	sIgE to Ana o 3 was a valuable tool for the diagnosis of cashew allergy.	[8▪▪]
Walnut	Jug r 1	sIgE to Jug r 1 has additional value to crude extract testing in children.	[24▪]
		sIgE to Jug r 1 did not improve the diagnostic accuracy in adults.	[25▪]
Hazelnut	Cor a 9 and 14	Cor a 9 and Cor a 14 were associated with clinical hazelnut allergy.	[26]
		Cor a 9 and Cor a 14 were diagnostic markers of a more severe hazelnut allergy.	[27]
	Cor a 14	Cor a 14 was a predictive marker of hazelnut allergy.	[9,28]
Sesame	Ses i 1	Sensitization to Ses i 1 is strongly associated with clinical sesame allergy.	[29]
Buckwheat	Fag e 3	Sensitization to Fag e 3 improved the diagnostic accuracy of buckwheat allergy.	[30]

Table 4. Allergen components

	LTP	2S albumin	7S globulin	11S globulin	PR-10	Profilin	Oleosins
Peanut	Ara h 9 Ara h 16 Ara h 17	Ara h 2 Ara h 6 Ara h 7	Ara h 1	Ara h 3	Ara h 8	Ara h 5	Ara h 10 Ara h 11 Ara h 14 Ara h 15
Soy	Gly m 1	Gly m 8	Gly m 5	Gly m 6	Gly m 4	Gly m 3	
Cashew nut		Ana o 3	Ana o 1	Ana o 2		Ana o Profilin	
Walnut	Jug r 3	Jug r 1 Jug n 1	Jug r 2 Jug n 2	Jug r 4	Jug r 5	Jug r 7	
Hazelnut	Cor a 8	Cor a 14	Cor a 11	Cor a 9	Cor a 1	Cor a 2	Cor a 12 Cor a 13
Almond	Pur du 3			Pur du 6		Pur du 4	
Sesame		Ses i 1 Ses i 2	Ses i 3	Ses i 6 Ses i 7			Ses i 4 Ses i 5
Buckwheat		Fag e 2	Fag e 3	Fag e 1			

showed that casein has the highest diagnostic accuracy for cow's milk allergy [33].

Wheat

Major wheat allergens are glutens, which can be subdivided into gliadins and glutenins (Table 2). Omega-5-gliadin (Tri a 19) is one of the gliadins; it is useful for the diagnosis of wheat-dependent exercise-induced anaphylaxis [37,38]. Nilsson *et al.* [20] showed that omega-5-gliadin was associated with positive and severity of wheat OFC. This result is similar to a study conducted in the Japanese population [15]. However, studies conducted in the American and German populations indicated that mega-5-gliadin levels did not correlate with the outcomes of patients with wheat allergy [39]. Moreover, a recent study on IgE binding to wheat protein showed that challenge-proven wheat allergy and tolerant ones had a similar pattern of IgE binding to wheat protein [40]. Therefore, the results of omega-5 gliadin in the prediction of wheat allergy may be influenced by geographic region.

Peanut

Currently, 17 peanut allergens have been identified (Tables 3 and 4). Ara h 2 is one of the storage proteins and immunodominant peanut allergens [41]. Sensitization to nonspecific lipid-transfer proteins (nsLTP; Ara h 9, 16, and 17), Bet v 1 homologs (Ara h 8), and profilins (Ara h 5) are caused by cross-reactions [2]. Two systematic reviews indicated that Ara h 2 (2S albumin)-sIgE showed the best diagnostic accuracy of peanut allergy [21,33], whereas Ara h 8 and Ara h 9 showed a poor diagnostic accuracy [21]. A study published by Beyer *et al.* [9] showed similar results, and Ara h 2 sIgE obtained a 95% PPV for positive peanut OFC. However, the PPV range is most likely because of the variations in patients' background and geographic location. Recently, Kukkonen *et al.* [22] showed that co-sensitization to Ara h 2 and Ara h 6 was the best marker of severe reactions at low dose during peanut OFC. Therefore, CRD is very helpful in assessing peanut allergy.

Soybean

The most important soybean allergens are Gly m 5 (7S Globulin), Gly m 6 (11S Globulin), and Gly m 8 (2S albumin; Tables 3 and 4). Gly m 5 and 6 predicted systemic allergic reactions to soy more than Gly m 4 (Bet v 1 homolog) [42], and Gly m 8 was a good marker of soybean allergy in children [43] and adults [44]. More recently, Gly m 8 is equally sensitive to SPT, soy extract, and other soy components, but more specific for predicting clinical reactivity [23]. Hence, Gly m 4 can cause anaphylaxis after consumption of soy milk [45].

Tree nut and seed

The most important hazelnut allergens are the seed storage proteins, Cor a 9 (11S globulin) and Cor a 14 (2S albumin), and the cross-reactive proteins, Cor a 8 (LTP) and Cor a 1 (PR-10; Tables 3 and 4). Although hazelnut extract has a poor predictive value for clinical reactivity because of cross-reactivity with birch pollen, Cor a 9 and 14 can be useful for predicting clinical reactivity to hazelnut [26,27]. Previous studies indicated that Cor a 14 was superior to Cor a 9 in predicting challenge-proven hazelnut allergy [28,39]. These differences were because of the

patients' background. A recent systematic review showed that Cor a 14 showed the best diagnostic accuracy for hazelnut allergy [33].

Regarding walnut and cashew nut, 2S albumin as one of storage protein is the most important allergen to predict reactivity to each nut. For walnut, the most important walnut allergens are Jug r 1 (2S albumin), Jug r 2 (7S globurin), and Jug r 3 (LTP) [2]. Jug r 1 sIgE was recently identified as an important complement in the diagnosis of walnut allergy in children and youth because of its improved clinical specificity to walnut extract compared with IgE [24▪]. However, there was no improvement in the diagnostic accuracy of Jug r 1 in adults [25▪]. This discrepancy seems to indicate an age-related association. Cashew nut 2S albumin, Ana o 3, was highly predictive of cashew and pistachio allergy [31]. More recently, Lange *et al.* [8▪▪] published that Ana o 3 was distinguished better among cashew nut allergic and tolerant children than cashew-sIgE, and a 95% probability was estimated at 2.0 kU/l for Ana o 3.

In other seed protein, Maruyama *et al.* investigated that sesame and buckwheat allergen components were associated with reactivity to each food. The sIgE to Ses i 1 (2S albumin) was strongly associated with sesame allergy [29], and Fag e 3 (7S globulin)-sIgE could improve the diagnostic accuracy for buckwheat allergy compared with sIgE [30].

Shrimp

Tropomyosin is the one of the major allergens in shellfish allergy [2]. A recent study demonstrated that Pen m 1 (tropomyosin) and Pen m 4 (sarcoplasmic calcium-binding protein) sensitization were associated with shrimp allergy [46]. In a systematic review of CRD, Pen a 1, Lit v 1 (tropomyosin), and Lit v 4 (sarcoplasmic calcium-binding protein) were investigated. Lit v 1 showed the best diagnostic accuracy for shrimp allergy [33].

BASOPHIL ACTIVATION TEST

The BAT is a functional assay that measures the response of basophils in whole blood to detect the ability of sIgE. It can assess not only the sIgE value but also the IgE epitope specificity, affinity, and clonality [47]. BAT measures the expression of activation markers, such as CD63 or CD203c, after a flow-cytometric allergen stimulation test [48]. Various methods of reporting results, such as stimulation index (SI), percentage positive basophil, and CD-sens, have been used in different studies [49].

Previous studies showed that BAT with allergen extracts or allergen components can potentially improve its diagnostic accuracy (Table 5) [50–57]. BAT has superior specificity and comparable sensitivity to diagnose food allergy than SPT or sIgE testing. In a peanut allergy study reported by Santos *et al.*, BAT can improve diagnostic accuracy over the use of SPT and sIgE and can reduce the number of OFC required for accurate diagnosis [51]. More recent peanut study indicated that BAT sensitivity was associated with the threshold of allergic reaction to peanut, and BAT reactivity is associated with the severity of allergic reaction to peanut [50].

Table 5. Diagnostic accuracy of basophil activation test

Antigen	Food allergens	Results	Reference number
Peanut	Peanut extract	BAT sensitivity was associated with threshold, and BAT reactivity reflected the severity of allergic response to peanuts.	[50]
		Mean %CD63 showed the best diagnostic accuracy.	[51]
	Peanut extract	Patients with a positive OFC had significantly higher CD-sens values to peanut and Ara h 2 than those with a negative OFC.	[52]
	Ara h 2		
Hazelnut	Hazelnut extract	Cutoff value of CD-sens value showed 100% sensitivity and 97% specificity.	[53]
Hen's egg	Egg white extract	Cutoff value of SI CD203c showed 74% sensitivity and 62% specificity.	[54]
	Ovomucoid	Cutoff value of SI CD203c showed 80% sensitivity and 73% specificity.	
	Ovalbumin	Cutoff value of %CD63 showed 77% sensitivity and 100% specificity.	[55]
Cow's milk	Milk extract	Cutoff value of %CD63 showed 91% sensitivity and 90% specificity.	[56]
	Milk extract	SI CD203c to milk extract showed the best diagnostic accuracy.	[54]
	Casein		
Wheat	Wheat extract	%CD203c to omega 5 gliadin showed the best diagnostic accuracy.	[57]
	Omega-5 gliadin		

CD-sens is defined as the inverted value for LC50, as the lowest allergen concentration giving 50% of maximum %CD63 upregulation of the dose–response curve, multiplied by 100. BAT, basophil activation test; SI, stimulation index.

Several studies have shown that BAT with single allergen components can improve the diagnostic accuracy for food allergy, but further research studies are needed. Additionally, patients who were considered as nonresponders required other IgE testing or OFC to diagnose food allergy.

CONCLUSION

The cutoff value of sIgE can predict reactivity to causative foods and reduced the OFC required to diagnose food allergy. Recent studies indicated that CRD can improve diagnostic accuracy and predict severity of symptoms. BAT provides additional information that can be used in diagnosing food allergies, but further studies using standardized procedures are needed in order to establish this as an acceptable method in clinical practice. A combination of these tests would show high diagnostic accuracy and reduce the number of OFCs.

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Conflicts of interest

M.E. has received research support from the Practical Research Project for Allergic Disease and Immunology from Japan Agency for Medical Research and Development (17ek0410019h0003). M.E. is on the DBV technologies Scientific Advisory Board. The rest of the authors declare that they have no relevant conflicts.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Boyce JA, Assa'ad A, Burks AW, *et al.* Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. J Allergy Clin Immunol 2010; 126(6 Suppl): S1–S58.
2. Matricardi PM, Kleine-Tebbe J, Hoffmann HJ, *et al.* EAACI molecular allergology user's guide. Pediatr Allergy Immunol 2016; 27(Suppl 23):1–250.
3. Ebisawa M, Ito K, Fujisawa T. Committee for Japanese Pediatric Guideline for Food Allergy TJSoPA, Clinical Immunology TJSoA: Japanese guidelines for food allergy 2007. Allergol Int 2017; 66:248–264.
4. Santos AF, Brough HA. Making the most of in vitro tests to diagnose food allergy. J Allergy Clin Immunol Pract 2017; 5:237–248.
5. Sato S, Ogura K, Takahashi K, *et al.* Usefulness of antigen-specific IgE probability curves derived from the 3gAllergy assay in diagnosing egg, cow's milk, and wheat allergies. Allergol Int 2017; 66:296–301.
6. Furuya K, Nagao M, Sato Y, *et al.* Predictive values of egg-specific IgE by two commonly used assay systems for the diagnosis of egg allergy in young children: a prospective multicenter study. Allergy 2016; 71:1435–1443.
7. Ebisawa M, Moverare R, Sato S, *et al.* The predictive relationship between peanut- and Ara h 2-specific serum IgE concentrations and peanut allergy. J Allergy Clin Immunol Pract 2015; 3:131.e1–132.e1.
8. ■■ Lange L, Lasota L, Finger A, *et al.* Ana o 3-specific IgE is a good predictor for clinically relevant cashew allergy in children. Allergy 2017; 72:598–603.

This study describes Ana o 3-sIgE is better predictor than cashew-sIgE with an area under the curve of 0.94 vs. 0.78 in receiver operating curves. It might decrease number of oral food challenges superfluous.

9. Beyer K, Grabenhenrich L, Hartl M, *et al.* Predictive values of component-specific IgE for the outcome of peanut and hazelnut food challenges in children. Allergy 2015; 70:90–98.
10. Borres MP, Maruyama N, Sato S, Ebisawa M. Recent advances in component resolved diagnosis in food allergy. Allergol Int 2016; 65:378–387.
11. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. J Allergy Clin Immunol 2001; 107:891–896.
12. Komata T, Soderstrom L, Borres MP, *et al.* The predictive relationship of food-specific serum IgE concentrations to challenge outcomes for egg and milk varies by patient age. J Allergy Clin Immunol 2007; 119:1272–1274.
13. Komata T, Soderstrom L, Borres MP, *et al.* Usefulness of wheat and soybean specific IgE antibody titers for the diagnosis of food allergy. Allergol Int 2009; 58:599–603.
14. Yanagida N, Minoura T, Kitaoka S, Ebisawa M. A three-level stepwise oral food challenge for egg, milk, and wheat allergy. J Allergy Clin Immunol Pract 2017; 6:658–660.e10.
15. Ebisawa M, Shibata R, Sato S, *et al.* Clinical utility of IgE antibodies to omega-5 gliadin in the diagnosis of wheat allergy: a pediatric multicenter challenge study. Int Arch Allergy Immunol 2012; 158:71–76.
16. Yanagida N, Sato S, Takahashi K, *et al.* Reactions of Buckwheat-hypersensitive patients during oral food challenge are rare, but often anaphylactic. Int Arch Allergy Immunol 2017; 172:116–122.
17. Wang J, Godbold JH, Sampson HA. Correlation of serum allergy (IgE) tests performed by different assay systems. J Allergy Clin Immunol 2008; 121:1219–1224.
18. Benhamou Senouf AH, Borres MP, Eigenmann PA. Native and denatured egg white protein IgE tests discriminate hen's egg allergic from egg-tolerant children. Pediatr Allergy Immunol 2015; 26:12–17.
19. Caubet JC, Nowak-Wegrzyn A, Moshier E, *et al.* Utility of casein-specific IgE levels in predicting reactivity to baked milk. J Allergy Clin Immunol 2013; 131:222.e1–224.e4.
20. Nilsson N, Sjolander S, Baar A, *et al.* Wheat allergy in children evaluated with challenge and IgE antibodies to wheat components. Pediatr Allergy Immunol 2015; 26:119–125.
21. Klemans RJ, van Os-Medendorp H, Blankestijn M, *et al.* Diagnostic accuracy of specific IgE to components in diagnosing peanut allergy: a systematic review. Clin Exp Allergy 2015; 45:720–730.
22. Kukkonen AK, Pelkonen AS, Makinen-Kiljunen S, *et al.* Ara h 2 and Ara 6 are the best predictors of severe peanut allergy: a double-blind placebo-controlled study. Allergy 2015; 70:1239–1245.
23. Kattan JD, Sampson HA. Clinical reactivity to soy is best identified by component testing to Gly m 8. J Allergy Clin Immunol Pract 2015; 3:970.e1–972.e1.
24. ■ Sato S, Yamamoto M, Yanagida N, *et al.* Jug r 1 sensitization is important in walnut-allergic children and youth. J Allergy Clin Immunol Pract 2017; 5:1784.e1–1786.e1.

This study describes Jug r 1-sIgE has better clinical specificity than walnut-sIgE with an area under the curve of 0.843 vs. 0.792 in receiver operating curves, and it might be an important complement in diagnosis of walnut allergy in children and youth.

25. ■ Blankestijn MA, Blom WM, Otten HG, *et al.* Specific IgE to Jug r 1 has no additional value compared with extract-based testing in diagnosing walnut allergy in adults. J Allergy Clin Immunol 2017; 139:688–690; e684.

This study describes that regarding diagnosis of walnut allergy in adults, IgE testing to Jug r 1 had no additional value compared with walnut-sIgE with an area under the curve of 0.78 vs. 0.79 in receiver operating curves. This result is different from a study by Sato *et al.* It might be important for clinician in diagnosis of walnut allergy.

26. Kattan JD, Sicherer SH, Sampson HA. Clinical reactivity to hazelnut may be better identified by component testing than traditional testing methods. J Allergy Clin Immunol Pract 2014; 2:633.e1–634.e1.
27. Masthoff LJ, Mattsson L, Zuidmeer-Jongejan L, *et al.* Sensitization to Cor a 9 and Cor a 14 is highly specific for a hazelnut allergy with objective symptoms in Dutch children and adults. J Allergy Clin Immunol 2013; 132:393–399.
28. Eller E, Mortz CG, Bindslev-Jensen C. Cor a 14 is the superior serological marker for hazelnut allergy in children, independent of concomitant peanut allergy. Allergy 2016; 71:556–562.
29. Maruyama N, Nakagawa T, Ito K, *et al.* Measurement of specific IgE antibodies to Ses i 1 improves the diagnosis of sesame allergy. Clin Exp Allergy 2016; 46:163–171.
30. Maruyama N, Sato S, Yanagida N, *et al.* Clinical utility of recombinant allergen components in diagnosing buckwheat allergy. J Allergy Clin Immunol Pract 2016; 4:322.e3–323.e3.

31. Savvatianos S, Konstantinopoulos AP, Borga A, *et al.* Sensitization to cashew nut 2S albumin, Ana o 3, is highly predictive of cashew and pistachio allergy in Greek children. J Allergy Clin Immunol 2015; 136:192–194.

32. Ando H, Moverare R, Kondo Y, *et al.* Utility of ovomucoid-specific IgE concentrations in predicting symptomatic egg allergy. J Allergy Clin Immunol 2008; 122:583–588.

33. Flores Kim J, McCleary N, Nwaru BI, *et al.* Diagnostic accuracy, risk assessment, and cost-effectiveness of component-resolved diagnostics for food allergy: a systematic review. Allergy 2018; doi: 10.1111/all.13399. [Epub ahead of print] Review.

34. Haneda Y, Kando N, Yasui M, *et al.* Ovomucoids IgE is a better marker than egg white-specific IgE to diagnose boiled egg allergy. J Allergy Clin Immunol 2012; 129:1681–1682.

35. Ito K, Futamura M, Moverare R, *et al.* The usefulness of casein-specific IgE and IgG4 antibodies in cow's milk allergic children. Clin Mol Allergy 2012; 10:1.

36. D'Urbano LE, Pellegrino K, Artesani MC, *et al.* Performance of a component-based allergen-microarray in the diagnosis of cow's milk and hen's egg allergy. Clin Exp Allergy 2010; 40:1561–1570.

37. Matsuo H, Dahlstrom J, Tanaka A, *et al.* Sensitivity and specificity of recombinant omega-5 gliadin-specific IgE measurement for the diagnosis of wheat-dependent exercise-induced anaphylaxis. Allergy 2008; 63:233–236.

38. Morita E, Matsuo H, Chinuki Y, *et al.* Food-dependent exercise-induced anaphylaxis -importance of omega-5 gliadin and HMW-glutenin as causative antigens for wheat-dependent exercise-induced anaphylaxis. Allergol Int 2009; 58:493–498.

39. Beyer K, Chung D, Schulz G, *et al.* The role of wheat omega-5 gliadin IgE antibodies as a diagnostic tool for wheat allergy in childhood. J Allergy Clin Immunol 2008; 122:419–421.

40. Sievers S, Rawel HM, Ringel KP, *et al.* Wheat protein recognition pattern in tolerant and allergic children. Pediatr Allergy Immunol 2016; 27: 147–155.

41. Koppelman SJ, Wensing M, Ertmann M, *et al.* Relevance of Ara h1, Ara h2 and Ara h3 in peanut-allergic patients, as determined by immunoglobulin E Western blotting, basophil-histamine release and intracutaneous testing: Ara h2 is the most important peanut allergen. Clin Exp Allergy 2004; 34:583–590.

42. Ito K, Sjolander S, Sato S, *et al.* IgE to Gly m 5 and Gly m 6 is associated with severe allergic reactions to soybean in Japanese children. J Allergy Clin Immunol 2011; 128:673–675.

43. Ebisawa M, Brostedt P, Sjolander S, *et al.* Gly m 2S albumin is a major allergen with a high diagnostic value in soybean-allergic children. J Allergy Clin Immunol 2013; 132:976.e1–978.e5.

44. Klemans RJ, Knol EF, Michelsen-Huisman A, *et al.* Components in soy allergy diagnostics: Gly m 2S albumin has the best diagnostic value in adults. Allergy 2013; 68:1396–1402.

45. Fukutomi Y, Sjolander S, Nakazawa T, *et al.* Clinical relevance of IgE to recombinant Gly m 4 in the diagnosis of adult soybean allergy. J Allergy Clin Immunol 2012; 129:860.e3–863.e3.

46. Pascal M, Grishina G, Yang AC, *et al.* Molecular Diagnosis of Shrimp Allergy: Efficiency of Several Allergens to Predict Clinical Reactivity. J Allergy Clin Immunol Pract 2015; 3:521.e10–529.e10.

47. Christensen LH, Holm J, Lund G, *et al.* Several distinct properties of the IgE repertoire determine effector cell degranulation in response to allergen challenge. J Allergy Clin Immunol 2008; 122:298–304.

48. Boumiza R, Monneret G, Forissier MF, *et al.* Marked improvement of the basophil activation test by detecting CD203c instead of CD63. Clin Exp Allergy 2003; 33:259–265.

49. Hoffmann HJ, Santos AF, Mayorga C, *et al.* The clinical utility of basophil activation testing in diagnosis and monitoring of allergic disease. Allergy 2015; 70:1393–1405.

50. Santos AF, Du Toit G, Douiri A, *et al.* Distinct parameters of the basophil activation test reflect the severity and threshold of allergic reactions to peanut. J Allergy Clin Immunol 2015; 135:179–186.

51. Santos AF, Douiri A, Becares N, *et al.* Basophil activation test discriminates between allergy and tolerance in peanut-sensitized children. J Allergy Clin Immunol 2014; 134:645–652.

52. Glaumann S, Nopp A, Johansson SG, *et al.* Basophil allergen threshold sensitivity, CD-sens, IgE-sensitization and DBPCFC in peanut-sensitized children. Allergy 2012; 67:242–247.

53. Brandstrom J, Nopp A, Johansson SG, *et al.* Basophil allergen threshold sensitivity and component-resolved diagnostics improve hazelnut allergy diagnosis. Clin Exp Allergy 2015; 45:1412–1418.

54. Sato S, Tachimoto H, Shukuya A, *et al.* Basophil activation marker CD203c is useful in the diagnosis of hen's egg and cow's milk allergies in children. Int Arch Allergy Immunol 2010; 152(Suppl 1):54–61.

55. Ocmant A, Mulier S, Hanssens L, *et al.* Basophil activation tests for the diagnosis of food allergy in children. Clin Exp Allergy 2009; 39: 1234–1245.

56. Rubio A, Vivinus-Nebot M, Bourrier T, *et al.* Benefit of the basophil activation test in deciding when to reintroduce cow's milk in allergic children. Allergy 2011; 66:92–100.

57. Tokuda R, Nagao M, Hiraguchi Y, *et al.* Antigen-induced expression of CD203c on basophils predicts IgE-mediated wheat allergy. Allergol Int 2009; 58:193–199.