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REVIEW

Systematic review and meta-analyses on the accuracy of diagnostic tests for IgE-mediated food allergy

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Abstract

The European Academy of Allergy and Clinical Immunology (EAACI) is updating the Guidelines on Food Allergy Diagnosis. We aimed to undertake a systematic review of the literature with meta-analyses to assess the accuracy of diagnostic tests for IgE-mediated food allergy. We searched three databases (Cochrane CENTRAL (Trials), MEDLINE (OVID) and Embase (OVID)) for diagnostic test accuracy studies published between 1 October 2012 and 30 June 2021 according to a previously published protocol (CRD42021259186). We independently screened abstracts, extracted data from full texts and assessed risk of bias with QUADRAS 2 tool in duplicate. Meta-analyses were undertaken for food-test combinations for which three or more studies were available. A total of 149 studies comprising 24,489 patients met the inclusion criteria and they were generally heterogeneous. 60.4% of studies were in children ≤12 years of age, 54.3% were undertaken in Europe, ≥95% were conducted in a specialized paediatric or allergy clinical setting and all included oral food challenge in at least a percentage of enrolled patients, in 21.5% double-blind placebo-controlled food challenges. Skin prick test (SPT) with fresh cow's milk and raw egg had high sensitivity (90% and 94%) for milk and cooked egg allergies. Specific IgE (sIgE) to individual components had high specificity: Ara h 2-sIgE had 92%, Cor a 14-sIgE 95%, Ana o 3-sIgE 94%, casein-sIgE 93%, ovomucoid-sIgE 92/91% for the diagnosis of peanut, hazelnut, cashew, cow's milk and raw/cooked egg allergies, respectively. The basophil activation test (BAT) was highly specific for the diagnosis of peanut (90%) and sesame (93%)

Abbreviations: BAT, basophil activation test; BBEA, bead-based epitope assay; CM, cow's milk; CRD, component-resolved diagnosis; DBPCFC, double-blind placebo-controlled food challenge; EAACI, European Academy of Allergy and Clinical Immunology; FA, food allergy; HE, hen's egg; MA, Molecular Allergology; MAT, mast cell activation test; OFC, oral food challenge; PPV, positive predictive value; RCT, randomized control trial; SPP, skin prick to prick test; SPT, skin prick test; SR, systematic review.

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allergies. In conclusion, SPT and specific IgE to extracts had high sensitivity whereas specific IgE to components and BAT had high specificity to support the diagnosis of individual food allergies.

KEYWORDS
basophil activation test, component-resolved diagnostics, diagnosis, diagnostic tests, food allergy, IgE-mediated, sensitivity, skin prick test, specific IgE, specificity

1 | INTRODUCTION

The burden of food allergy (FA) remains a significant public health concern. There is ample evidence for the negative impact that FA can have on the quality of life of patients and their families, on the breadth and quality of social interactions, on the performance at school or work and on overall psychological well-being.[1-3] This is aggravated by the financial strain that FAs impose on families and individuals through the cost of allergen-free food, direct and indirect medical expenses, and missed work or school days.[4]

A recently published study documents a continued increase in the prevalence of FA in Europe. It estimates lifetime and point prevalence of self-reported FA to be 20% and 13%, respectively.[5] Considering both a clinical diagnosis of FA and a positive OFC, FAs have increased from 2.6% in the early 2000s to 3.5% in the period ranging from 2012 to 2021.[5] Currently, FA confirmed by oral food challenge (OFC) worldwide is estimated at 4%.[6] This has resulted in a growing demand for appropriate FA diagnosis, driving healthcare professionals to employ a wide range of allergy tests. However, not all these diagnostic tests are equally useful or appropriate to reach an accurate diagnosis of FA and while the OFC remains the reference standard, it is a costly and time-consuming procedure that may lead to life-threatening anaphylaxis.[7] For a highly sensitive test, a negative result effectively rules out the diagnosis of FA; for a highly specific test, a positive result rules in a FA diagnosis. Deeper understanding of diagnostic test accuracy could reduce the need for OFC and guide clinical practice.

Determining the optimal diagnostic cut-offs in single studies that are generalizable to other clinical settings poses a significant challenge. By combining and analysing data from multiple studies, we can overcome the limitations of individual studies and gain a more comprehensive understanding of the diagnostic performance of tests. Meta-analyses allow us to synthesize findings from various sources, enhancing the reliability and generalizability of the results. Thus, they play a crucial role in guiding clinical decision-making and improving diagnostic accuracy.

The European Academy of Allergy and Clinical Immunology (EAACI) is updating their guidelines on both the diagnosis and management of FA.[8,9] A systematic review (SR) of index tests is the most reliable form of evidence in the diagnostic field and enables clinicians and other healthcare professionals to make well-informed decisions.[10,11] To inform the EAACI guidelines on FA diagnosis, we undertook a SR and meta-analyses about the accuracy of index tests to support the diagnosis of IgE-mediated FA, following a previously registered and published protocol.[12]

This SR addresses the question: What is the diagnostic accuracy measured by the sensitivity and specificity of any index test for IgE-mediated FA to any food compared with the reference standard OFC (in at least a subset of patients) or previous clear history of immediate reaction to the food and evidence of IgE sensitization?

2 | METHODOLOGY

This SR was commissioned by EAACI and undertaken by an EAACI task force comprising methodologists, patient representatives, allergists, paediatricians, primary care doctors and other clinicians, psychologists, dieticians and other allied health representatives, from 23 countries, including Austria, Australia, Brazil, Canada, Denmark, France, Germany, Greece, Hong Kong, Italy, Ireland, Japan, the Netherlands, Poland, Russia, Romania, Spain, Singapore, South Africa, Switzerland, Turkey, UK and USA.

The methods are described in brief here, and a full review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO registration: CRD42021259186) and previously published.[12] We report our findings herein according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA).[13]

2.1 | Search strategy

The task force searched three databases (Cochrane CENTRAL (Trials), MEDLINE (OVID) and Embase (OVID)) for diagnostic test accuracy studies published between 1 October 2012 and 30 June 2021. Manuscripts preceding this date were evaluated previously in the EAACI SR on diagnostic tests.[8] A manual SR search was performed by the task force, and additional relevant references were found following suggestions from the EAACI expert panel group. For non-English language studies, a native speaker within the task force extracted and presented the relevant data for the group to reach a consensus on inclusion and assessment.

2.2 | Eligibility criteria

Studies were deemed eligible for the review if they included all the following:

- Population: Humans (irrespective of age) with suspected IgE-mediated allergy to any specific food.
- Intervention: Any index test.
- Comparator: IgE-mediated FA diagnosis determined by OFC using any method including open food challenge or double-blind placebo-controlled food challenge (DBPCFC) in at least a portion of study participants.
- Outcome: Sensitivity and specificity of the index test.

We excluded conference abstracts, editorials, correspondence, narrative reviews, qualitative studies, case reports and case series of less than 20 patients, as well as animal studies and studies in which allergies were defined based on sensitization tests alone without a history of clinical reaction following ingestion.

2.3 | Data collection

The reviewers screened titles, abstracts and reviewed full texts of potentially eligible records using Covidence systematic review software (Veritas Health Innovation). The data were extracted using standardized forms in duplicate by two reviewers independently. Any conflicts were resolved by a third reviewer and consensus of the task force core team (CR, IS, GdT, AFS). Where relevant information was missing from a study that was potentially eligible for the SR, the corresponding author of the respective study was contacted and inclusion of this study was contingent on completion of this information by email from the corresponding author.

2.4 | Data analysis

We evaluated the diagnostic accuracy for each index test for each individual food. The data were synthetized by tabulating the index test's true positives, true negatives, false positives and false negatives. For allergens with variable allergenic profiles resulting from extensive heating or cooking, separate analyses were conducted for each allergenic configuration. For hen's egg (HE) protein, the analyses were divided into baked HE, cooked (extensively heated) HE and raw HE. For cow's milk (CM), they were separated into baked milk and fresh milk.

Where three or more studies for a given combination of index test and food were available, a meta-analysis was performed with a generalized linear mixed model of the binomial family with a logit link. This approach was chosen to perform a random effect estimate of both sensitivity and specificity, accounting for their correlation, computing the pooled sensitivity and specificity and performing the summary receiver operating curves (ROC).[14] Briefly, every study contributed with its own contingency table for its specific cut-off value (i.e. true positive, true negative, false positive and false negative) were included in the model as a count. These analyses resulted in a bivariate random effect estimation of sensitivity and specificity along with heterogeneity assessed by *I*-squares defined according to Zhou and Dendukuri, 2014.[15] We defined tests with high accuracy as those which had a sensitivity or specificity of ≥90% with *I*-squares under 50%. Low sensitivity and specificity were considered for test performing under 75%.

We performed sensitivity and specificity analysis using the optimal cut-off reported by the individual studies, for example Youden's Index or other methods. To obtain the estimated cut-offs used for each meta-analysis, we reported the median and interquartile range of all cut-offs considered optimal by the different authors. Further analyses were performed and focused on the maximum values for sensitivity and specificity as reported by the authors of included studies.

Further analyses were undertaken with the pre-established 95% positive predictive value (PPV) cut-offs available in literature.[16] For skin prick tests (SPT), we used values of 8 mm for peanut[17] and CM and 7 mm for HE.[18] For sIgE, we used the following values: 15 kU_A/L for peanut,[17] CM and tree nuts, 7 kU_A/L for HE and 20 kU_A/L for fish.[19,20] We included only values which had been previously validated; thus, these were not available for all foods.[18,21,22,23]

A high sensitivity means that a negative test rules out the diagnosis (SnOUT) and a high specificity means that a positive test rules it in (SpIN). As the PPV is dependent on the prevalence of allergic disease in a specific population, we looked at the sensitivity and specificity of pooled data for these cut-offs and defined them as highly accurate if they reached a value ≥90%. Note that sensitivity and specificity are not affected by prevalence; thus, these measures reflect the discriminative ability intrinsic to the diagnostic tests.

In supplementary analyses, studies were stratified by test-specific threshold values, age of the participants (below 24 months, 24 months to 16 years and above 16 years) and by the country of origin. Where data on at least three different tests on the same food were available, a comparison was performed. To this end, the relative ratio of sensitivity and specificity was computed using an intercept only model.[24] Data for differences in subgroups were considered significant if there was a change in sensitivity or specificity over 7% (CI 95%) or they reached high diagnostic accuracy (over 90% of sensitivity or specificity for any given test).

To reduce heterogeneity in the meta-analyses, only index tests using the same characteristics were combined. For SPT, results are shown for studies using commercial extracts separate from those using skin prick to prick tests (SPP) with fresh foods. For sIgE testing, results from different platforms were used individually for meta-analyses (ImmunoCAP Specific IgE, ImmunoCAP™ ISAC, etc). Throughout the manuscript when talking about sIgE this refers to ImmunoCAP, if other methods were used for analysis, it is specified accordingly. The random effect bivariate meta-analysis was performed using the metadta function of the STATA software version 15.

2.5 | Assessment of risk of bias and quality of evidence

Data from included studies were reviewed for risk of bias assessment and applicability using the QUADAS-2 tool.[25] All

evaluations were performed independently by two different reviewers. Disagreements were resolved by a third reviewer and consensus of the task force core team (CR, IS, GdT, AS). The four key domains covering patient selection, index test, reference standard (OFC comparator), flow and timing were evaluated.

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE)[26,27] approach was used to assess heterogeneity and to evaluate the certainty of the body of evidence.[28-30] The task force reviewed studies about each intervention and created evidence profiles. The authors were not involved in decisions about topics where they had a potential conflict of interest. All taskforce members decided on the conclusions by consensus.

3 | RESULTS

3.1 | Summary of included studies

The systematic search identified 1494 unique records. A total of 149 studies[31-178] were included after application of our predefined eligibility criteria. Figure 1 illustrates the PRISMA meta-analyses flowchart for the study screening and selection process. This resulted in 24,489 subjects included in the analysis. The current SR includes representative data for 32 countries and all continents. The data principally originate from Europe (54.3%), Asia (19.9%) and America (13.9%). Only 13.4% of eligible data are derived from multicentre studies.

The studies evaluated were predominantly prospective (63.8%) including consecutive (51.0%) and randomized (6.7%) studies. Within the retrospective studies (34.2%), most were performed consecutively (30.2%). The studies included were mostly cross-sectional (59.1%) or cohort studies (35.6%). Only 5.4% were case controls. Most studies included subjects under 18 years of age (79.2%), most of which were in infants or children ≤12 years of age (60.4%). Studies exclusive on adults represented only 7.4%. The included studies were largely performed in an allergy or paediatric clinic setting (94.6%). All included studies used OFC as a reference standard in a proportion of patients, most of them in over 70% of the subjects included. Only 7.4% of studies explicitly stated OFCs were done in all subjects. Overall, 63.8% used open OFCs and 21.5% double-blind placebo-controlled food challenges (DBPCFC). The full summary of characteristics of the included studies is given in Table 1. Further information for individual studies is compiled in Table S1.

Nineteen different index tests were identified, most commonly sIgE (128 studies), Molecular Allergology (MA, 87 studies) and SPT (79 studies). Additional identified tests were SPP (15 studies), basophil activation test (BAT) (13 studies), mast cell activation test (MAT) (2 studies)[38,147] and bead-based epitope assay (BBEA).[157] Table S2 lists the identified index test studies. Note that individual studies may report on more than one diagnostic test. Evaluable

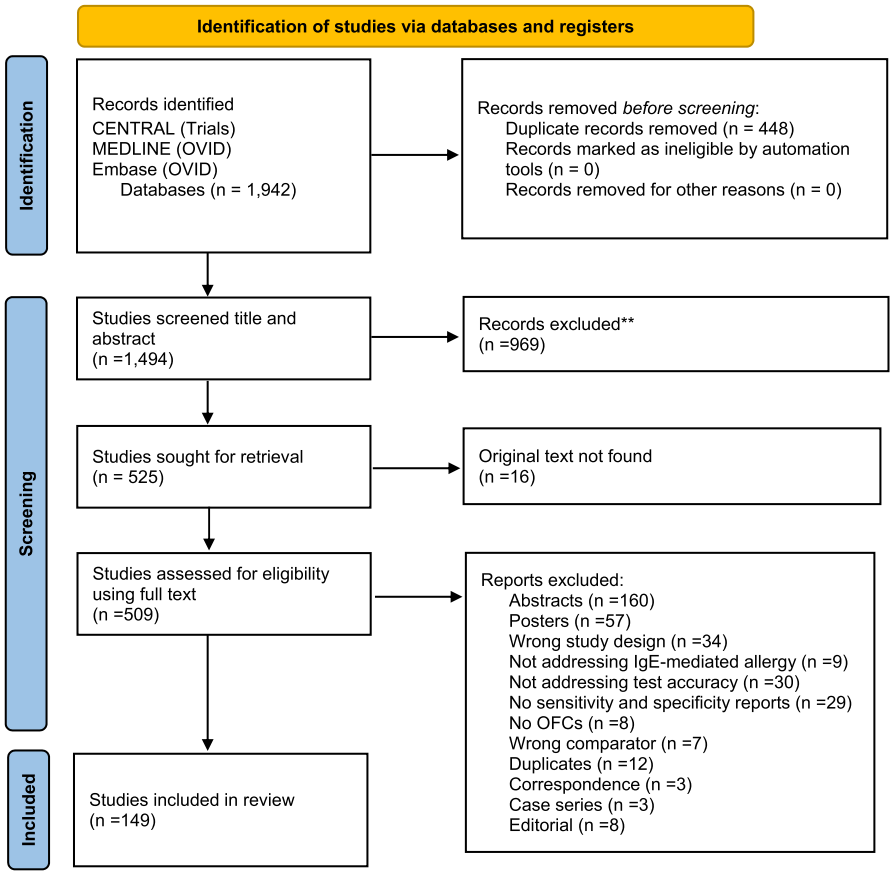

FIGURE 1 Flow chart of the identification and screening of studies to be included in the systematic literature review and meta-analyses of studies about the accuracy of diagnostic tests for IgE-mediated FA according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA). **No automatization tools used. From: Ref. [13].

data were available for 21 foods: mostly peanut (34.2%) followed by HE (25.5%), CM (18.1%), tree nuts (12.1%), wheat (10.7%), sesame (6.0%), and soy and shellfish (4.7%). All foods tested in the studies are listed in Table S3. The foods with three or more included publications per index test were peanut, CM, baked HE, extensively heated HE, raw HE, sesame, soy, walnut, hazelnut, cashew, almond, wheat and shrimp. Table 2 summarizes results for each food-test combination for which meta-analyses was possible.

3.2 | Risk of bias assessment

The selected studies were heterogeneous; the overall risk of bias assessment for the included studies is displayed in Figure 2. Within the patient selection domain, 43.6% of studies showed high risk, 31.5% low risk and 24.8% unclear risk of bias. This originates from studies that did not randomly select, consecutively enrol participants, use a case–control design or not report how exclusion was managed, highlighting the necessity to adhere to standardized procedures. For applicability, 96.0% of studies had low concerns that the included patients did not match the review question.

For the index test domain, 22.1% of studies showed high risk, 38.3% low risk and 36.9% unclear risk of bias. The most common reasons for assigning a high risk of bias were lack of blinding or failure to establish a threshold for the index tests before conducting the analysis. For applicability, 77.2% of studies had low concerns that the index test, its conduct or interpretation differed from the review question.

For the reference standard domain, 18.1% of studies showed high risk, 38.9% low risk and 43.0% unclear risk of bias. An increase in the risk of bias was seen in studies which included prior information of the reference standard test while performing the index test. For applicability, 88.6% of studies had low concerns that the target condition as defined by the reference standard does not match the review question.

For the flow and timing domain, 61.1% of studies showed high risk, 23.5% low risk and 15.4% unclear risk of bias. We considered studies to be of low risk of bias if all participants received the same reference standard within 6 months of having received the index test.

Table 3 shows the risk of bias assessment summary for each domain question, and Table S4 shows the individual risk of bias assessment per study.

3.3 | Peanut allergy

We included 51 studies[38,54,57,60,78,79,90,92,101,109,112,133,134,135,137,139,146,148,152,153,154,157,178] on the accuracy of diagnostic tests for peanut allergy. For meta-analyses, 20 studies of SPT-peanut[38,54,57,78,79,90,92,101,109,134,135,137,139,146,148,153,154,157,178] and 24 studies of sIgE-peanut[38,44,54,60,61,65,68,73,79,88,89,90,94,110,117,134,135,139,146,148,154,157,169,178] met the inclusion criteria.

Studies for SPT showed a pooled sensitivity of 84% and specificity of 86% at a 4 mm median cut-off (Table 2). We could not detect differences in accuracy of SPT to peanut in younger age groups (Table 4). There were differences in data obtained in different geographical regions. Most notably there was a high specificity for SPT to peanut in Australian studies (97%) but not in Asian studies (81% - Table 5). sIgE to peanut showed a pooled sensitivity of 81% and specificity 83% at a 4.3 kU_A/L cut-off. In children ≤2 years of age, sIgE-peanut shows an increase in accuracy with better sensitivity and high specificity of 94%. We also observed specificity of 93% for studies from Western Europe and Australia.

Twenty-seven[31,38,44,57,60,61,64,65,68,73,79,88,89,90,91,94,99,100,110,117,137,139,146,148,152,157] included studies employed MA. When applying optimal cut-offs, MA tests for peanut showed high specificity, 92% for Ara h 2-sIgE,[31,38,44,57,60,61,64,65,68,73,79,88,89,90,91,94,99,100,110,117,137,139,146,148,152,157] 93% for Ara h 3-sIgE[65,68,88,89,90,91,110,157] and 94% for Ara h 6-sIgE.[31,88,89,139] In studies using ISAC,[78,79,91,97] the performance of Ara h 2-sIgE was less heterogeneous with a specificity of 93% using the 0.3 cut-off. The specificity of Ara h 2-sIgE increased for adult subjects. Ara h 2-sIgE was highly accurate in Northern Europe and Australia with specificity of 97% in both regions. The specificity was lower for North American subjects at 89% and was lower even for Asia subjects at 75%. Data on Ara h 8-sIgE[68,88,89,90,110,117] and Ara h 9-sIgE[31,68,89,91] were highly heterogeneous. In general, sensitivity for MA in peanut allergy was lower than specificity. BAT to peanut was analysed in four studies[38,139,146,148] with pooled sensitivity of 84% and high specificity of 90%. These studies were less heterogeneous and had a lower risk of bias compared to other index test studies of peanut allergy (Figure 3A).

The maximum sensitivity and maximum specificity were ≥90% for SPT to peanut, sIgE to peanut, Ara h 2-sIgE and BAT to peanut (Tables S5 and S6).

3.4 | Hen's egg allergy

We included 35 studies[33,34,41,43,49,58,59,66,70,72,76,80,82,86,92,95,103,116,124,126,127,129,131,135,140,144,150,154,155,156,159,164,166,170,178] on the accuracy of diagnostic tests for HE allergy. For meta-analyses, tests were divided into raw, cooked and baked HE allergies.

For raw HE allergy, SPT to egg white[33,34,135,170] had a specificity of 80% compared to specificities of 96% for SPT to egg yolk[33,34,49] and 91% for SPT to ovalbumin.[34,49,170] Nine studies on sIgE to egg white (EW),[33,34,43,59,72,76,135,140,170] four on sIgE to egg yolk[33,34,76,140] and six on MA[34,43,59,72,76,140,170] met the inclusion criteria. EW-sIgE showed pooled sensitivity of 73% with a specificity of 88%. (Table 2) This increased to 95% for subjects ≤2 years of age (Table 4). Egg yolk-sIgE had low sensitivity and specificity. Ovomucoid-sIgE[34,43,59,72,76,170] showed high specificity of 91% with low sensitivity of 74% at a median cut-off 0.8 kU_A/L and ovalbumin-sIgE[34,43,59,76,140,170] did not reach appropriate accuracy with sensitivity of 78% and specificity of 79%.

TABLE 1 Characteristics of diagnostics test accuracy studies for IgE-mediated FA.

(A) Location						
	Europe	**Asia**	**America**	**Oceania**	**Middle East**	**Africa**
No. of articles	54.3% (*n* = 82)	19.9% (*n* = 30)	13.9% (*n* = 21)	6.0% (*n* = 9)	3.3% (*n* = 5)	2.6% (*n* = 4)
(B) Methodology						
	Retrospective		**Prospective**		**Retrospective and prospective**	
No. of articles	34.2% (*n* = 51) Consecutive 30.2% (*n* = 45)		63.8% (*n* = 94) Consecutive 51.0% (*n* = 76) Randomized 6.7% (*n* = 10)		2.0% (*n* = 3)	
(C) Study design						
	Cross-sectional		**Cohort**		**Case–control**	
No. of articles	59.1% (*n* = 88)		35.6% (*n* = 53)		5.4% (*n* = 8)	
(D) Age groups						
	Children (0 to 12 years old)		**Children and adolescents (up to 21 years old)**	**Adults**		**All ages**
No. of articles	60.4% (*n* = 90)		18.8% (*n* = 28)	7.4% (*n* = 11)		13.4% (*n* = 20)
(E) Reference standard						
	Open OFC		**DPFCFC**	**Single Blind**		**Mixed OFC's**
No. of articles	63.8% (*n* = 95)		21.5% (*n* = 32)	2.7% (*n* = 4)		12.1% (*n* = 18)

Note: Demographic characteristics of diagnostics test accuracy studies included for IgE-mediated FA.(A) Identifies the geographical regions the studies were done. Note that multicentric studies can have more than one region involved. (B) Methodologies (retrospective, prospective, consecutive and randomized) used in the diagnostic test accuracy studies included. (C) Study design used, including cross-sectional, cohort, case–control. (D) Age groups of participants involved in the diagnostic test accuracy studies. (E) Reference standard used in the studies, studies needed to have a proportion of patients who were tested against the gold-standard oral food challenge (OFC) or double blind placebo-controlled food challenge (DBPCFC).

For cooked HE allergy, 6 studies on SPT to EW,[33,80,82,116,155,166] 4 on SPP with raw EW,[33,80,124,166] 14 on sIgE to EW,[33,43,72,80,86,95,116,126,129,150,155,166,170] 7 on ovomucoid-sIgE[33,34,43,72,116,140,170] and 3 on ovalbumin-sIgE[33,43,170] met the inclusion criteria. SPP[33,80,124,166] was highly sensitive for cooked HE allergy diagnosis with pooled sensitivity of 94% and specificity of 66% at the 6 mm cut-off. SPT to EW[33,80,82,116,155,166] showed pooled sensitivity of 68% with a specificity of 77%. The sensitivity increased to 79% for subjects ≤2 years. sIgE to EW showed pooled sensitivity of 85% with a specificity of 73%, respectively. Ovomucoid-sIgE had a sensitivity of 74% with high specificity of 91% at the 0.8 kU_A/L cut-off. sIgG4 to HE had low sensitivity and low specificity in highly heterogenous studies. Studies for cooked HE allergy were less heterogeneous than those for raw or baked HE allergies.

For baked HE allergy, sIgE to EW[41,135,144] showed high specificity (94%) but very low sensitivity of 40% at the 8 kU_A/L cut-off with values ranging widely from 6 to 50 kU_A/L. The accuracy for SPT to EW[41,135,144,164] was low for baked HE allergy. There were insufficient data for meta-analyses on accuracy of CRD in baked HE allergy (Figure 3B).

For raw HE allergy, maximum sensitivity of ≥90% was not reached by analysed diagnostic tests. Maximum specificity was ≥90% for sIgE to EW, ovalbumin-sIgE and ovomucoid-sIgE. For cooked HE allergy, maximum sensitivity of ≥90% for SPP and maximum specificity was ≥90% for SPP and ovomucoid-sIgE. For baked HE, maximum specificity was ≥90% for SPT and sIgE to EW (Tables S5 and S6).

3.5 | Cow's milk allergy

We included 27 studies on accuracy of tests to support the diagnosis of CM allergy. Eleven studies for SPT to CM,[37,49,52,71,82,92,93,104,132,154,155,156,165,178] 5 for SPP using fresh CM[37,49,155,165,178] and 3 for SPT to casein[37,49,52,71] met the inclusion criteria for meta-analyses. SPT to CM and SPT to casein showed sensitivities of 52% and 64% and specificities of 80% and 87%, respectively. SPP showed a high sensitivity of 90% with specificity of 80% at the 4 mm cut-off (Table 2). CM-sIgE[37,51,52,71,92,93,95,104,132,141,150,154,155,165,176,178] showed pooled sensitivity of 82% with a high specificity of 92% at the 3.5 kU_A/L cut-off. MA also showed high specificity: casein-sIgE 93%[31,32,37,51,52,71,125,132,165] and alpha-lactalbumin-sIgE 92%[51,52,71,165] with sensitivities of 67% and 58% at 1.8 kU_A/L and 1.7 kU_A/L cut-offs, respectively. Studies of MA were less heterogeneous compared to SPT and sIgE to CM (Figure 3C). For CM allergy, maximum sensitivity was ≥90% for SPP and maximum specificity

TABLE 2 Estimates of the accuracy of diagnostic tests for IgE-mediated FA using reported optimal cut-off points.

Diagnostic test	Sensitivity (95% CI)	I^2 sensitivity (%)	Specificity (95% CI)	I^2 specificity (%)	Cut-off		Number of subjects included	References
					Median	IQ range		
Peanut								
SPT to peanut	0.84 (0.69; 0.92)	69.1	0.86 (0.79; 0.91)	54.7	4	3–8	2602	38,54,57,78,79,90,92,101,109,134,135,137,139,146,148,153,154,157,178
sIgE to peanut	0.81 (0.71; 0.88)	84.6	0.83 (0.71; 0.90)	80.6	4.3	0.35–10	3893	38,44,54,60,61,65,68,73,79,88,89,90,94,110,117,134,135,139,146,148,154,157,169,178
Ara h 1-sIgE	0.45 (0.36; 0.54)	67.4	0.89 (0.87; 0.92)	0.2	0.3	0.1–0.35	1212	65,68,88,89,90,91,110,157
Ara h 2-sIgE	0.82 (0.77; 0.86)	63	**0.92 (0.87; 0.95)**	61.6	0.44	0.3–1.3	2924	31,38,44,57,60,61,64,65,68,73,79,88,89,90,91,94,99,100,110,117,137,139,146,148,152,157
Ara h 2-sIgE (ISAC)	0.77 (0.64; 0.86)	17.8	**0.93 (0.66; 0.99)**	33.9	0.3	0.3	228	78,79,91,97
Ara h 3-sIgE	0.34 (0.20; 0.51)	86.8	**0.93 (0.88; 0.97)**	60.8	0.35	0.2–0.8	1269	65,68,88,89,90,91,110,157
Ara h 6-sIgE	0.87 (0.47; 0.98)	87.4	**0.94 (0.76; 0.99)**	72.1	0.4	0.1–0.9	648	31,88,89,139
Ara h 8-sIgE	0.22 (0.01; 0.87)	19.3	**0.99 (0.77; 1.00)**	2.3	0.67	0.1–65	1150	68,88,89,90,110,117
BAT to peanut	0.84 (0.76; 0.90)	13.8	**0.90 (0.83; 0.94)**	3.5	5.0	4.7–7.1	308	38,139,146,148
Raw egg								
SPT to egg white	0.78 (0.49; 0.93)	83.8	0.80 (0.55; 0.93)	84.1	6	4–10	880	33,34,135,170
SPT to egg yolk	0.41 (0.21; 0.64)	77.2	**0.96 (0.75; 0.99)**	59.3	7	6–11	335	33,34,49
SPT to ovalbumin	0.57 (0.10; 0.94)	92.4	**0.91 (0.59; 0.99)**	71.1	10	5–13	371	33,34,49
sIgE to egg white	0.73 (0.60; 0.83)	82.1	0.88 (0.75; 0.95)	75.4	1.7	0.5–3.2	1809	33,34,43,59,72,76,135,140,170
sIgE to egg yolk	0.57 (0.35; 0.77)	79.6	0.88 (0.74; 0.95)	66.9	0.4	0.1–1.5	473	33,34,76,140
Ovomucoid-sIgE	0.55 (0.40; 0.70)	84.2	**0.92 (0.83; 0.97)**	59	0.8	0.3–4.2	864	34,43,59,72,76,170
Ovalbumin-sIgE	0.78 (0.58; 0.90)	85	0.79 (0.62; 0.90)	75.9	1.0	0.3–3.2	995	34,43,59,76,140,170
Cooked egg								
SPT egg white	0.68 (0.37; 0.88)	82.2	0.77 (0.64; 0.86)	44	5	3–8	470	33,80,82,116,155,166
SPT raw egg white	**0.94 (0.76; 0.99)**	36.5	0.66 (0.51; 0.78)	38.9	6	4–10	196	33,80,124,166
sIgE egg white	0.85 (0.77; 0.90)	64.4	0.73 (0.63; 0.80)	65.3	3.5	1.7–5.5	1687	33,43,72,80,86,95,116,126,129,150,155,166,170
Ovomucoid-sIgE	0.74 (0.54; 0.87)	82.2	**0.91 (0.87; 0.93)**	10	0.8	0.35–3.7	866	33,34,43,72,116,140,170
Ovalbumin-sIgE	0.65 (0.43; 0.82)	80.2	**0.92 (0.83; 0.97)**	15	1.2	0.2–2.8	209	33,43,170
Baked egg								
SPT to egg white	0.23 (0.01; 0.92)	19.1	0.85 (0.49; 0.97)	90.1	11	9–11	1101	41,135,144,164
sIgE to egg white	0.40 (0.12; 0.77)	91.8	**0.94 (0.45; 1.00)**	61.6	8	6–50	915	41,135,144

(Continues)

TABLE 2 (Continued)

Diagnostic test	Sensitivity (95% CI)	I^2 sensitivity (%)	Specificity (95% CI)	I^2 specificity (%)	Cut-off		Number of subjects included	References
					Median	IQ range		
Cow's milk								
SPP to fresh cow's milk	0.90 (0.53; 0.94)	74.3	**0.80 (0.25; 1.00)**	18.5	4	3–9	458	37,49,155,165,178
SPT to cow's milk	0.52 (0.24; 0.79)	83.6	0.80 (0.65; 0.90)	77.3	4	3–8	1263	37,49,52,71,82,92,93,104,132,154,155,156,165,178
SPT to casein	0.64 (0.34; 0.85)	93	0.87 (0.54; 0.97)	77.9	4	3–6	406	37,49,52,71
sIgE to cow's milk	0.82 (0.59; 0.94)	76.3	**0.92 (0.80; 0.97)**	59.4	3.5	0.9–10.5	1965	37,51,52,71,92,93,95,104,132,141,150,154,155,165,176,178
Casein-sIgE	0.67 (0.53; 0.78)	76.1	**0.93 (0.85; 0.97)**	40.2	2.6	1.0–5.3	664	32,37,51,52,71,125,132,165
a-lactalbumin-sIgE	0.58 (0.52; 0.64)	2	**0.92 (0.77; 0.97)**	54.4	1.8	1.1–3.0	439	51,52,71,165
ß-lactoglobulin-sIgE	0.68 (0.53; 0.80)	78	0.89 (0.73; 0.96)	67.8	1.7	1.6–1.8	635	51,52,71,165
Hazelnut								
SPT to hazelnut	0.82 (0.68; 0.91)	74.6	0.78 (0.44; 0.94)	81.8	5	3–7	715	48,50,62,112,121,146,154
sIgE to hazelnut	0.79 (0.71; 0.85)	40.7	0.62 (0.38; 0.81)	89.7	2.34	0.6–6.3	858	44,48,50,62,85,120,121,146,154
Cor a 9-sIgE	0.69 (0.46; 0.85)	75.5	0.81 (0.73; 0.88)	41.9	0.83	0.35–1.4	474	44,47,48,50,62,64,68,120,121,146
Cor a 14-sIgE	0.73 (0.53; 0.87)	78.8	**0.95 (0.90; 0.98)**	45.3	0.64	0.35–3.5	464	44,47,48,50,62,64,68,120,121,146
Cashew								
SPT cashew	**0.93 (0.89; 0.96)**	16.5	**0.92 (0.82; 0.96)**	30.2	5	4–6	491	53,122,146,154
sIgE cashew	**0.94 (0.89; 0.97)**	13.2	0.64 (0.54; 0.74)	41.1	1.1	0.6–3.1	515	53,84,146,151,154
Ana o 3-sIgE	**0.96 (0.91; 0.98)**	0	**0.94 (0.88; 0.97)**	0	0.4	0.2–0.6	243	106,146,151
Walnut								
sIgE walnut	0.87 (0.60; 0.97)	85.5	0.82 (0.60; 0.93)	42.9	2.8	0.2–11.4	384	39,45,67,154,172
Jug r 1-sIgE	0.77 (0.58; 0.89)	44.6	**0.90 (0.78; 0.96)**	15.6	0.2	0.1–0.3	162	45,64,67
Almond								
sIgE almond	0.72 (0.62; 0.80)	0	**0.95 (0.43; 1.00)**	34.9	3.4	1.2–10.5	766	87,146,154,172
Sesame								
SPT sesame	0.70 (0.55; 0.82)	71.5	0.89 (0.76; 0.95)	45.6	8	4–10	713	35,74,135,143,145,146,154
sIgE sesame	0.70 (0.23; 0.95)	63.1	0.83 (0.26; 0.99)	10.4	7.5	0.9–50	723	74,118,135,143,145,146,154
BAT sesame	0.89 (0.80; 0.94)	0.3	**0.93 (0.76; 0.98)**	50	10.9	8.2–11. 6	207	35,74,146
Ses i 1-sIgE	0.77 (0.64; 0.86)	18.5	0.87 (0.77; 0.92)	0.1	2.0	0.3–4.0	164	74,118,143

TABLE 2 (Continued)

Diagnostic test	Sensitivity (95% CI)	I^2 sensitivity (%)	Specificity (95% CI)	I^2 specificity (%)	Cut-off		Number of subjects included	References
					Median	IQ range		
Soy								
SPT soy	0.47 (0.11; 0.87)	61.3	0.79 (0.63; 0.89)	30.4	3	2–6	150	63,98,156,178
sIgE Soy	0.73 (0.62; 0.82)	50.2	0.75 (0.44; 0.92)	81.9	3.0	0.1–8.7	338	98,119,149,178
Gly m 4-sIgE	0.61 (0.36; 0.81)	61.9	0.69 (0.30; 0.92)	66	0.2	0.1–17.6	152	63,98,119
Wheat								
SPT wheat	0.53 (0.23; 0.81)	80.6	0.72 (0.57; 0.84)	32.4	3	3–5	388	36,82,104,114,136,154,156,178
sIgE wheat	0.72 (0.54; 0.84)	81.3	0.79 (0.68; 0.86)	46.7	0.6	0.35–5.6	1285	32,36,55,56,77,104,114,128,130,136,150,154,158,178
w-5 gliadin-sIgE	0.79 (0.68; 0.88)	60	0.78 (0.66; 0.86)	40	0.3	0.1–0.6	347	32,56,77,128,130,136
Shrimp								
SPT shrimp	0.62 (0.44; 0.77)	0	**0.90 (0.31; 0.99)**	47.2	3	3–5	148	156,160,163,173
sIgE shrimp	**0.96 (0.42; 1.00)**	13.8	0.63 (0.46; 0.78)	41.6	1.2	0.5–3.1	182	160,163,171,173
Pen a 1-sIgE	0.62 (0.45; 0.76)	0	0.89 (0.75; 0.95)	0	1.1	0.6–4.4	78	163,171,173

Note: Estimates of the accuracy of diagnostic tests for IgE-mediated FA using optimal cut-off points. We performed sensitivity and specificity analysis using the optimal cut-off reported by the individual studies using Youden Index or those considered optimal by the authors. To obtain the estimated cut-offs used for each meta-analysis, we reported the median and interquartile range of all cut-offs considered optimal by the different authors. SPT, skin prick test; SPP, skin prick by prick test; BAT, basophil activation test. The results of SPT are expressed in mm, sIgE in kU_A/L and the basophil activation test in %CD63+ basophils. Results in bold refer to diagnostic tests which reached high sensitivity or specificity defined as ≥90%.

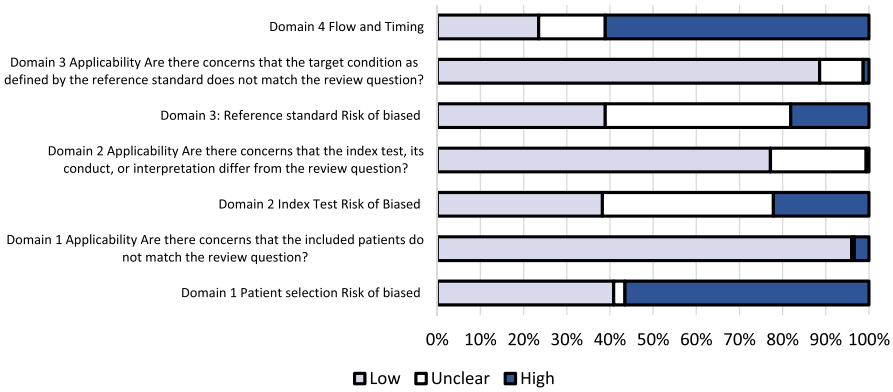

FIGURE 2 Summary of risk of bias assessment for index tests in diagnostic studies for IgE-mediated FA using the QUADRAS 2 tool.

TABLE 3 Risk of bias assessment per domain of diagnostic test accuracy studies in IgE-mediated FA ($n = 149$ studies).

Domains	Low risk of bias % ($n = 149$)	Unclear % ($n = 149$)	High risk of bias % ($n = 149$)
1: Patient selection	31.5% ($n = 47$)	24.8% ($n = 37$)	43.6% ($n = 65$)
Was a consecutive or random sample of patients enrolled?	89.3% ($n = 133$)	4% ($n = 6$)	6.7% ($n = 10$)
Was a case–control design avoided?	94.6% ($n = 141$)	0% ($n = 0$)	5.4% ($n = 8$)
Did the study avoid inappropriate exclusions?	55% ($n = 82$)	41.6% ($n = 62$)	3.4% ($n = 5$)
Could the selection of patients have introduced bias?	52.3% ($n = 78$)	7.4% ($n = 11$)	40.3% ($n = 60$)
Are there concerns that the included patients do not match the review question?	96% ($n = 143$)	0.7% ($n = 1$)	3.4% ($n = 5$)
2: Index Test	38.3% ($n = 57$)	39.6% ($n = 59$)	22.1% ($n = 33$)
Were the index test results interpreted without knowledge of the results of the reference standard?	59.1% ($n = 88$)	32.9% ($n = 49$)	8.1% ($n = 12$)
If a threshold was used, was it pre-specified?	77.2% ($n = 115$)	9.4% ($n = 14$)	13.4% ($n = 20$)
Could the conduct or interpretation of the index test have introduced bias?	47.7% ($n = 71$)	36.9% ($n = 55$)	15.4% ($n = 23$)
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	77.2% ($n = 115$)	22.1% ($n = 33$)	0.7% ($n = 1$)
3: Reference standard	38.9% ($n = 58$)	43% ($n = 64$)	18.1% ($n = 27$)
Is the reference standard likely to correctly classify the target condition?	99.3% ($n = 148$)	0.7% ($n = 1$)	0% ($n = 0$)
Were the reference standard results interpreted without knowledge of the results of the index test?	38.9% ($n = 58$)	41.6% ($n = 62$)	19.5% ($n = 29$)
Could the reference standard, its conduct, or its interpretation have introduced bias?	77.2% ($n = 115$)	2.7% ($n = 4$)	20.1% ($n = 30$)
Applicability: Are there concerns that the target condition as defined by the reference standard does not match the review question?	88.6% ($n = 132$)	10.1% ($n = 15$)	1.3% ($n = 2$)
4: Flow and timing	23.5% ($n = 35$)	15.4% ($n = 23$)	61.1% ($n = 91$)
Was there an appropriate interval between index test(s) and reference standard?	35.6% ($n = 53$)	46.3% ($n = 69$)	18.1% ($n = 27$)
Did all patients receive a reference standard?	61.7% ($n = 92$)	0% ($n = 0$)	38.3% ($n = 57$)
Did all patients receive the same reference standard?	77.9% ($n = 116$)	0.7% ($n = 1$)	21.5% ($n = 32$)
Were all patients included in the analysis?	67.1% ($n = 100$)	7.4% ($n = 11$)	25.5% ($n = 38$)
Could the patient flow have introduced bias?	49.7% ($n = 74$)	26.8% ($n = 40$)	23.5% ($n = 35$)

Note: Four domains were included according to QUADRAS 2 tool (24), patient selection, index test (SPT, SPP, sIgE, MA, BAT, etc.) reference standard (in this case OFC) and flow and timing of the study. Three applicability questions were also included.

Abbreviations: BAT, basophil activation test; MA, molec; OFC, oral food challenge; SPP, skin prick by prick test; SPT, skin prick test.

was ≥90% for SPT to casein, sIgE to CM and MA (Tables S5 and S6). We could not determine accuracy of index tests for CM allergy for different age groups or geographical regions.

For baked milk allergy, there were five studies available that met the inclusion criteria.[40,70,96,105,155] These studies were included in the systematic review, but no meta-analysis was performed because

TABLE 4 Stratified analyses by age groups.

Food/test	Age groups	Sensitivity (95% CI)	I^2sens (%)	Specificity (95% CI)	I^2spec (%)
Peanut allergy					
SPT to peanut	>2 & ≤16 years	83.0 (53.0; 96.0)	83.3	83.0 (74.0; 89.0)	44.4
	All ages	**94.0 (91.0; 96.0)**	0.0	**92.0 (83.0; 96.0)**	0.0
	≤16 years	77.0 (7.0; 99.0)	20.4	66.0 (50.0; 79.0)	32.5
	>2 years	**92.0 (83.0; 96.0)**	14.4	88.0 (73.0; 95.0)	53.1
sIgE to peanut	≤2 years	83.0 (22.0; 99.0)	80.1	**94.0 (80.0; 99.0)**	79.0
	>2 & ≤16 years	74.0 (56.0; 87.0)	88.4	83.0 (67.0; 92.0)	83.7
	All ages	79.0 (62.0; 89.0)	89.0	80.0 (52.0; 94.0)	81.8
	≤16 years	**92.0 (69.0; 98.0)**	51.5	57.0 (40.0; 71.0)	56.7
	>2 years	**90.0 (82.0; 95.0)**	25.2	65.0 (18.0; 94.0)	80.0
Ara h 2-sIgE	>2 & ≤16 years	82.0 (75.0; 87.0)	56.3	88.0 (79.0; 93.0)	47.2
	>16 years	74.0 (49.0; 89.0)	6.9	**100 (11.0; 100)**	87.4
	All ages	79.0 (71.0; 85.0)	46.2	**96.0 (83.0; 99.0)**	48.4
	≤16 years	70.0 (62.0; 77.0)	0.0	79.0 (71.0; 86.0)	0.0
	>2 years	84.0 (74.0; 91.0)	1.0	85.0 (58.0; 96.0)	46.7
Raw egg allergy					
sIgE to egg white	≤2 years	65.0 (22.0; 92.0)	90.0	**95.0 (74.0; 99.0)**	64.7
	≤16 years	82.0 (66.0; 91.0)	15.2	81.0 (68.0; 90.0)	18.6
Cooked egg allergy					
SPT to egg white	≤16 years	79.0 (33.0; 97.0)	74.3	81.0 (67.0; 89.0)	3.04
SPP to raw egg white	≤16 years	**98.0 (56.0; 100)**	17.8	64.0 (43.0; 81.0)	52.8
sIgE to egg white	>2 & ≤16 years	**90.0 (63.0; 98.0)**	45.6	72.0 (59.0; 83.0)	13.3
	≤16 years	84.0 (74.0; 91.0)	63.1	77.0 (73.0; 81.0)	11.2
Ovomucoid-sIgE	≤16 years	81.0 (65.0; 90.0)	62.4	**96.0 (88.0; 99.0)**	6.9
Cow's milk allergy					
SPT to cow's milk	≤16 years	57.0 (34.0; 78.0)	86.3	79.0 (68.0; 87.0)	74.6
sIgE to cow's milk	≤16 years	76.0 (46.0; 92.0)	82.4	**90.0 (75.0; 96.0)**	78.2
Casein-sIgE	≤16 years	66.0 (57.0; 74.0)	65.9	**92.0 (80.0; 97.0)**	56.1
ß-lactoglobulin-sIgE	≤16 years	58.0 (50.0; 66.0)	56.9	**91.0 (70.0; 98.0)**	69.0
Hazelnut allergy					
SPT to hazelnut	>2 & ≤16 years	88.0 (62.0; 97.0)	67.6	81.0 (70.0; 88.0)	37.9
	All ages	77.0 (65.0; 86.0)	73.2	78.0 (4.0; 100.0)	16.9
sIgE to hazelnut	>2 & ≤16 years	83.0 (73.0; 90.0)	17.3	74.0 (58.0; 85.0)	72.0
	All ages	75.0 (64.0; 83.0)	65.3	35.0 (7.00; 79.0)	91.0
Cor a 14-sIgE	>2 & ≤16 years	75.0 (54.0; 89.0)	80.1	**97.0 (82.0; 100)**	36.4
	All ages	57.0 (26.0; 83.0)	81.8	**94.0 (88.0; 97.0)**	6.6
Cashew nut allergy					
sIgE to cashew	>2 & ≤16 years	**93.0 (85.0; 97.0)**	18.6	65.0 (54.0; 75.0)	63.5
Sesame seed allergy					
SPT to sesame	All ages	61.0 (37.0; 80.0)	78.6	**91.0 (61.0; 98.0)**	32.8
Wheat allergy					
sIgE to wheat	≤16 years	81.0 (64.0; 92.0)	75.9	84.0 (70.0; 92.0)	62.0
w 5 gliadin-sIgE	≤16 years	85.0 (58.0; 96.0)	69.6	74.0 (54.0; 87.0)	49.6
Shrimp allergy					
sIgE to shrimp	>2 years	**99.0 (56.0; 100)**	7.8	68.0 (43.0; 86.0)	48.58

Note: Analyes were done according to the different age groups where three or more studies were available per age group, per food and per test. Optimal values were used as reported by the authors in each study. We divided them into four groups: ≤ 2 years of age, 2 to 16 years, ≥16 years and all ages. Some studies had more than one stratum; most studies were done in children over 2 years of age. This table shows the differences in diagnostic test sensitivity and specificity between the different age groups. Highlighted in bold are the diagnostic tests which have evidence of having high sensitivity or high specificity (defined as over 90%) in each age group.

Abbreviations: BAT, basophil activation test; sIgE, specific IgE; SPP, skin prick by prick test; SPT, skin prick test.

TABLE 5 Stratified analyses by geographical region.

Food/test	Region	Sensitivity (95% CI)	I^2sens (%)	Specificity (95% CI)	I^2spec (%)
Peanut allergy					
SPT to peanut	Asia	83.0 (54.0; 95.0)	55.3	81.0 (71.0; 88.0)	0.3
	Australia	50.0 (27.0; 73.0)	73.4	**97.0 (92.0; 99.0)**	0.3
	Northern Europe	**91.0 (83.0; 95.0)**	19.1	87.0 (84.0; 91.0)	5.3
sIgE to peanut	Asia	75.0 (34.0; 94.0)	86.1	80.0 (45.0; 95.0)	80.2
	Australia	80.0 (47.0; 95.0)	91.3	89.0 (75.0; 95.0)	63.8
	Northern Europe	77.0 (72.0; 82.0)	1.5	87.0 (80.0; 92.0)	5.7
	North America	**94.0 (89.0; 97.0**)	12.7	54.0 (21.0; 83.0)	91.7
	Western Europe	59.0 (38.0; 78.0)	92.6	**93.0 (83.0; 97.0)**	69.9
Ara h 2-sIgE	Asia	80.0 (68.0; 88.0)	0.19	79.0 (67.0; 87.0)	0.08
	Australia	86.0 (73.0; 93.0)	64.3	**97.0 (60.0; 100)**	42.7
	Northern Europe	88.0 (80.0; 93.0)	2.4	**99.0 (91.0; 100)**	1.5
	North America	85.0 (58.0; 96.0)	71.9	89.0 (66.0; 97.0)	82.1
	Western Europe	79.0 (69.0; 87.0)	83.1	**92.0 (81.0; 97.0)**	70.2
BAT to peanut	Northern Europe	88.0 (71.0; 96.0)	66.7	**92.0 (81.0; 97.0)**	30.6
Raw egg allergy					
SPT to egg white	Southern Europe	86.0 (64.0; 95.0)	66.9	73.0 (41.0; 91.0)	83.6
sIgE to egg white	Southern Europe	72.0 (37.0; 92.0)	82.6	87.0 (68.0; 95.0)	69.5
IgE to egg yolk	Southern Europe	56.0 (24.0; 84.0)	81.2	**91.0 (78.0; 97.0)**	53.8
Ovalbumin-sIgE	Southern Europe	80.0 (18.0; 99.0)	74.9	87.0 (62.0; 97.0)	69.7
Cooked egg allergy					
SPT to egg white	Southern Europe	83.0 (58.0; 95.0)	75.5	78.0 (67.0; 87.0)	3.8
SPT to raw egg white	Southern Europe	**91.0 (78.0; 97.0)**	30.5	70.0 (59.0; 80.0)	25.6
sIgE to egg white	Asia	82.0 (69.0; 90.0)	73.5	74.0 (67.0; 79.0)	40.6
	Southern Europe	86.0 (72.0; 94.0)	62.3	62.0 (36.0; 82.0)	82.4
Ovomucoid-sIgE	Southern Europe	64.0 (38.0; 83.0)	86.8	**94.0 (89.0; 97.0)**	0.0
Cow's milk allergy					
SPT to cow's milk	Asia	40.0 (17.0; 68.0)	77.7	74.0 (47.0; 90.0)	83.8
	Southern Europe	51.0 (4.00; 97.0)	21.8	82.0 (38.0; 97.0)	74.0
SPP to fresh cow's milk	Southern Europe	79.0 (43.0; 95.0)	75.6	**94.0 (39.0; 100)**	26.3
SPT to casein	Southern Europe	64.0 (26.0; 90.0)	93.5	**91.0 (53.0; 99.0)**	66.7
sIgE to cow's milk	Asia	56.0 (5.0; 97.0)	67.6	89.0 (52.0; 98.0)	80.9
	Southern Europe	89.0 (56.0; 98.0)	64.5	**96.0 (77.0; 99.0)**	43.2
Sesame seed allergy					
SPT to sesame	Middle East	74.0 (50.0; 89.0)	71.9	69.0 (50.0; 83.0)	6.7
Wheat allergy					
SPT to wheat	Asia	51.0 (34.0; 68.0)	44.5	66.0 (44.0; 83.0)	63.6
sIgE to wheat	Asia	75.0 (42.0; 93.0)	84.6	73.0 (59.0; 84.0)	58.9
	Northern Europe	71.0 (61.0; 79.0)	5.0	87.0 (69.0; 95.0)	21.3
w 5 gliadin-sIgE	Asia	75.0 (66.0; 82.0)	0.0	85.0 (74.0; 92.0)	0.0

Note: Analyses were done according to the different geographical regions where three or more studies were available per region, per food and per test. This table shows the differences in diagnostic test sensitivity and specificity between the different geographical locations. Geographical locations were divided between North, South and Western Europe, North America, Asia, Australia and Middle East. Not enough data were available for other geographical regions. Highlighted in bold are the diagnostic tests which have evidence of having high sensitivity or high specificity (defined as over 90%) in each specific region.

Abbreviations: BAT, basophil activation test; SPP, skin prick by prick test; SPT, skin prick test.

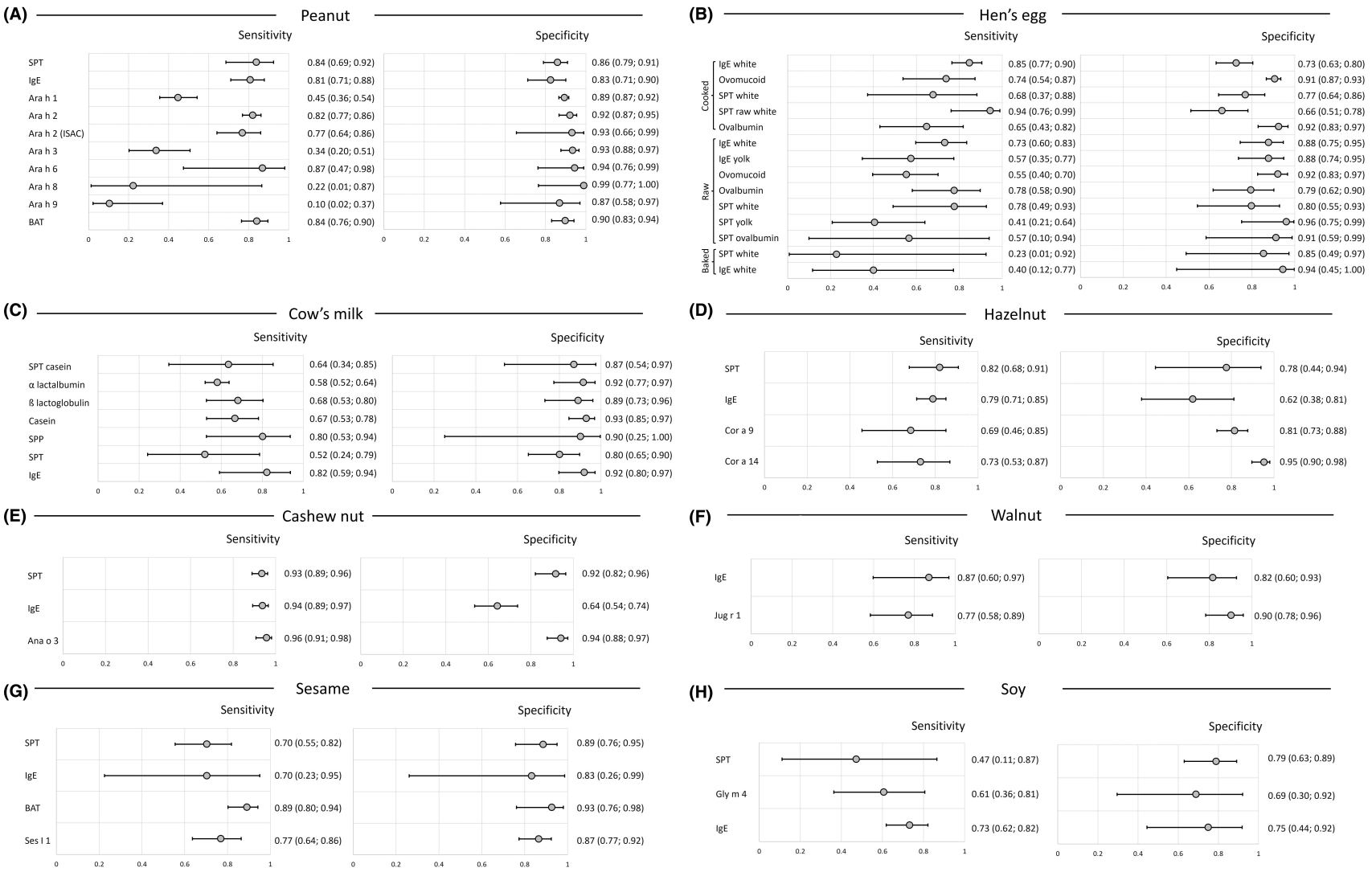

FIGURE 3 Forrest plots with sensitivity and specificity for the individual tests for the different foods (A: peanut, B: hen's egg, C: cow's milk, D: hazelnut, E: cashew nut, F: walnut G: sesame, H: soy, I: wheat, J: shrimp) For a test-food combination to be included in the meta-analyses, there needed to be a minimum of three studies. Data for hen's egg are showed separately for raw, cooked and baked egg allergies. Data for the cow's milk studies refer to fresh milk allergy.

three of these studies did not report diagnostic performance, namely sensitivity and specificity, for the index tests.

3.6 | Tree nut allergies

We included 18 studies on the accuracy of diagnostic tests for tree nut allergies. Seven studies for SPT,[48,50,62,68,112,121,146,154] eight for sIgE[44,48,50,62,68,85,120,121,146,154] and eight for MA met inclusion criteria for hazelnut allergy meta-analyses.[44,47,48,50,62,64,68,85,120,121,146] SPT to hazelnut and sIgE to hazelnut showed pooled sensitivities of 82% and 79% and pooled specificities of 78% and 62%, respectively (Table 2). The specificity increased to 73% in the 2–16-year age group for sIgE-to hazelnut (Table 3). Cor a 14-sIgE[44,47,48,50,62,64,68,120,121,146] showed pooled sensitivity of 73% and high specificity of 95% at the 0.64 kU_A/L cut-off. For the 2–16-year age group, Cor a 14 maintained high specificity of 97% (Figure 3D).

Four studies for SPT,[53,122,146,154] five for sIgE[53,84,146,151,154] and three for MA[106,146,151] met inclusion criteria for cashew nut allergy meta-analyses. SPT to cashew showed high sensitivity of 93% and high specificity of 92% at the 5 mm cut-off. sIgE to cashew showed high sensitivity of 94% with a pooled specificity of 64% at the 1.1 kU_A/L cut-off. Ana o 3-sIgE showed high sensitivity of 96% and high specificity 94% at the 0.4 kU_A/L cut-off (Figure 3E).

Four studies for sIgE-walnut[39,45,67,154,172] met inclusion criteria for meta-analyses showing a pooled sensitivity of 87% and 82% specificity. For Jug r 1-sIgE, sensitivity was higher at 90% for a median cut-off 0.2 kU_A/L[45,64,67] (Figure 3F). Four studies for sIgE to almond[87,146,154,172] met inclusion criteria for meta-analyses, with a pooled sensitivity of 72% and 95% specificity at a median cut of 3.4 kU_A/L. Hazelnut and walnut allergies' studies were heterogeneous regarding co-sensitizations, comorbidities and age of subjects. Studies for cashew and almond allergies were less heterogeneous than those for hazelnut and walnut allergies.

For hazelnut allergy, the maximum sensitivity was ≥90% using hazelnut-sIgE. The maximum specificity was ≥90% for hazelnut SPT and Cor a 14-sIgE. For cashew nut allergy, maximum sensitivity was ≥90% and maximum specificity was ≥90% for SPT to cashew, sIgE to cashew and Ana o 3-sIgE. For walnut allergy, maximum specificity was ≥90% for Jug r 1-sIgE. For almond allergy, maximum sensitivity and specificity were ≥90% for almond-sIgE (Tables S5 and S6).

3.7 | Sesame seed allergy

We included nine studies on accuracy of diagnostic tests for sesame allergy. Seven studies for SPT,[35,74,135,143,145,146,154] seven for sesame-sIgE,[74,118,135,143,145,146,154] three for Ses i 1-sIgE[74,118,143] and three for BAT[35,74,146] met inclusion criteria for sesame allergy meta-analyses. SPT to sesame and sIgE to sesame showed pooled sensitivity of 70% each with a specificity of 89% and 83%, respectively (Figure 3G).

Sensitivity increased in the 2–16-year age group for sIgE to sesame to 94% (Table 4). For studies done in the Middle East, specificity of SPT to sesame decreased to 69% (Table 5). For MA, Ses i 1-sIgE had a sensitivity of 77% with a specificity of 87%. BAT to sesame showed pooled sensitivity of 89% with a high specificity of 93% (Table 2) at a 10% cut-off. Studies on SPT to sesame and sIgE to sesame were more heterogeneous than those for BAT to sesame.

The maximum sensitivity was ≥90% for BAT to sesame, and the maximum specificity was ≥90% for sIgE to sesame, BAT to sesame and SPT to sesame (Tables S5 and S6).

3.8 | Soy allergy

Three studies for SPT[63,98,156,178] met the inclusion criteria for soy allergy meta-analyses, with pooled sensitivity of 47% and specificity of 79% (Table 2). IgE to soy[98,119,149,178] and Gly m 4[63,98,119] had sensitivities of 73% and 61% with specificities of 75% and 69%, respectively. For SPT to soy, the maximum specificity was ≥90% (Tables S5 and S6; Figure 3H).

3.9 | Wheat allergy

We included 16 studies on accuracy of diagnostic tests for wheat allergy. For meta-analyses, there were 5 studies of SPT to wheat,[36,82,104,114,136,154,156,178] 10 of sIgE to wheat[32,36,55,56,77,104,114,128,130,136,150,154,158,178] and 6 of ω-5 gliadin-sIgE[32,56,77,128,130,136] with pooled sensitivities of 53%, 72% and 79% and specificities of 72%, 79% and 78%, respectively (Table 2 and Figure 3I). For sIgE-wheat and ω-5 gliadin-sIgE, sensitivity increased for subjects ≤16 years of age (Table 4). The maximum sensitivity was ≥90% for wheat-sIgE, and the maximum specificity was ≥90% for ω-5 gliadin-sIgE (Tables S5 and S6).

3.10 | Fish and shellfish allergies

We included two studies on fish and seven on shellfish allergies. Most studies focused on shrimp allergy, three studies of SPT to shrimp,[156,160,163,173] four of shrimp-sIgE[160,163,171,173] and three of MA using Pen m 1-sIgE[163,171,173] met inclusion criteria for shrimp allergy meta-analyses. SPT to shrimp had pooled sensitivity of 62% with specificity of 90% at the median 3 mm cut-off. sIgE-shrimp showed high sensitivity of 96% with a pooled specificity of 63% at a median cut of 1.2 kU_A/L. Pen m 1-sIgE had a sensitivity of 62% and specificity of 89% (Table 2 and Figure 3J). The maximum sensitivity was ≥90% for shrimp-sIgE. The maximum specificity of ≥90% was for SPT to shrimp (Table S5). There were insufficient data for meta-analyses on other fish or shellfish allergies.

3.10.1 | Comparison of tests to support the diagnosis of specific food allergies

To further evaluate the different diagnostic tests, we compared them against each other for each FA. Table 6 shows the statistically significant comparisons of tests by food. For the diagnosis of peanut allergy, SPT to peanut has a higher relative sensitivity and relative specificity compared to the sIgE to peanut. Ara h 2-sIgE measured using ImmunoCAP shows a higher relative specificity compared to sIgE to peanut. When different techniques are used to measure sIgE to Ara h 2, Ara h 2-sIgE measured by ImmunoCAP has a higher relative specificity than Ara h 2-sIgE measured using ISAC. The relative sensitivity of Ara h 2-sIgE is higher than that of BAT to peanut.

For the diagnosis of cooked HE allergy, sIgE had a higher relative sensitivity than SPT to egg white, SPP to raw egg white and ovomucoid-sIgE. Ovomucoid-sIgE performed better than ovalbumin-sIgE. For CM allergy diagnosis, SPP to fresh CM had higher relative sensitivity and specificity than SPT using cow's milk commercial extracts and higher sensitivity than sIgE to CM. sIgE to casein performed better than SPT to CM. For the diagnosis of hazelnut allergy, sIgE and SPT show higher relative sensitivity than Cor a 14-sIgE and can help in ruling out allergy to hazelnut. Cor a 14-sIgE has a higher specificity than Cor a 9-sIgE and can be used to rule in allergic disease. sIgE to wheat and shrimp, respectively, had a higher sensitivity and so will be more useful to rule out allergy while w-5 gliadin-sIgE and Pen m 1-sIgE had higher relative specificity and could be used to rule in wheat and shrimp allergies, respectively.

3.10.2 | Stratified analyses by pre-defined thresholds

We evaluated the sensitivity and specificity of individual tests at cut-off values commonly used as 95% PPV cut-offs. For peanut allergy, peanut SPT ≥8 mm, sIgE peanut ≥15 kU_A/L and Ara h 2-sIgE ≥ 0.35 kU_A/L were all highly specific (≥90%) with results at or over those values ruling in FA. For HE allergy (both raw and cooked HE allergies), ovomucoid-sIgE ≥0.35 kU_A/L was highly specific (≥90%) and when above the cut-off rules in HE allergy. For CMA, SPT ≥8 mm was highly specific (≥90%). We were unable to calculate sensitivity and specificity for sIgE CM ≥15 kU_A/L as the bivariate binomial model failed to converge due to over dispersed parameter along with limited number of studies. Cor a 14-sIgE was highly specific for hazelnut allergy and with values ≥0.35 kU_A/L can rule in hazelnut allergy. More information is available in Table 7.

3.10.3 | Stratified analyses by age groups

We performed a sub-analysis using different age groups to assess the performance of diagnostic tests at different ages. Table 4 and Figure 4 show more details. For patients ≤2 years old, sIgE to peanut was more specific (94%) than for other age groups; thus in toddlers, a positive sIgE can help rule in peanut allergy. Ara h 2-sIgE was specific for all age groups but especially for those ≥16 years old where a positive result can accurately rule in peanut allergy. sIgE to egg white was more specific in ≤2 years olds (95%) compared to ≤16 years olds where it only had 81% specificity for the diagnosis of raw HE allergy. For CM allergy, sIgE to CM and Casein-sIgE had higher specificity (≥90%) in the ≤16 year olds compared to SPT to CM.

3.10.4 | Stratified analyses by geographical region

sIgE to peanut was highly sensitive in North America (94%) but presented lower sensitivities in Asia (75%), Australia (80%), Northern Europe (77%) and Western Europe (59%). Ara h 2-sIgE was highly specific in Australia (97%), Northern Europe (99%) and Western Europe (92%) but lower in Asian populations (79%). For the diagnosis of CMA, SPT and sIgE had a lower performance in Asian populations; and a lower specificity in Asia (74% and 89%) compared to Southern Europe (82% and 96%). For wheat allergy, diagnostic accuracy of wheat-sIgE was also lower in Asia with a specificity of 73% versus 87% in Northern Europe. Overall, diagnostic tests showed variability according to geographical regions, and more details can be seen in Table 5 and Figure 5.

A summary of the diagnostic tests and its accuracy is shown in Table 8.

4 | DISCUSSION

4.1 | Summary of the evidence

This SR of 149 diagnostic accuracy studies comprising 24,489 patients with suspected IgE-mediated FA shows that many IgE sensitization tests to suspected food triggers can support the diagnosis of IgE-mediated FA. Our findings favour the use of SPT and sIgE testing in clinical settings in the diagnosis of FA, especially for peanut, HE, CM, hazelnut and cashew nut allergies for which there is more evidence and their diagnostic accuracy is higher. Their high sensitivity means a negative test is useful for ruling out FA. Conversely, SPT and sIgE are less accurate in supporting the diagnosis of sesame, soy, wheat and shrimp allergies with moderate certainty of evidence. High certainty of evidence for the diagnostic accuracy of MA for ruling in FA due to high specificity is demonstrated for IgE to several allergen components, namely Ara h 2 in peanut, Cor a 14 in hazelnut and Ana o 3 in cashew. Ovomucoid-sIgE can support the diagnosis of raw and cooked HE allergies while casein-sIgE can support diagnosis of CM allergy; however, the accuracy of IgE to these allergen components is not superior to IgE to the allergen extracts. Current diagnostic tests (SPT, specific IgE to extracts or components) do not accurately reflect a subject's ability to tolerate baked milk or baked egg, as there is limited evidence on test accuracy for baked HE and baked CM allergies. There is high certainty of evidence for the ability of BAT to support the diagnosis of peanut and sesame seed allergies,

TABLE 6 Comparison of sensitivity and specificity of tests to support the diagnosis of specific food allergies.

FA	Diagnostic Test	Sens (95% CI)	Rel sens (95% CI)	Spec (95% CI)	Rel Spec (95% CI)
Peanut allergy	SPT peanut	92.0 (83.0; 96.0)	**1.02 (1.00; 1.05)**	78.0 (63.0; 89.0)	**1.19 (1.06; 1.34)**
	*sIgE peanut	90.0 (79.0; 95.0)		66.0 (48.0; 80.0)	
	Ara h 2-sIgE	88.0 (82.0; 93.0)	1.03 (0.98; 1.08)	82.0 (72.0; 89.0)	**1.12 (1.02; 1.22)**
	*SPT peanut	86.0 (78.0; 92.0)		73.0 (60.0; 83.0)	
	Ara h 2-sIgE	87.0 (80.0; 91.0)	1.01 (0.98; 1.04)	84.0 (73.0; 91.0)	**1.37 (1.16; 1.61)**
	*sIgE peanut	86.0 (78.0; 91.0)		62.0 (45.0; 76.0)	
	SPT peanut	89.0 (78.0; 95.0)	**2.42 (1.36; 4.33)**	80.0 (68.0; 88.0)	0.92 (0.85; 1.00)
	*Ara h 2-sIgE (ISAC)	79.0 (55.0; 92.0)		79.0 (71.0; 86.0)	
	Ara h 2-sIgE (ISAC)	83.0 (73.0; 90.0)	1.08 (0.94; 1.22)	65.0 (56.0; 73.0)	**0.79 (0.69; 0.91)**
	*Ara h 2-sIgE	77.0 (65.0; 86.0)		82.0 (73.0; 88.0)	
	Ara h 2-sIgE	83.0 (77.0; 88.0)	**1.15 (1.01; 1.32)**	92.0 (77.0; 97.0)	1.05 (0.93; 1.19)
	*BAT peanut	72.0 (62.0; 80.0)		87.0 (66.0; 96.0)	
Hazelnut allergy	sIgE hazelnut	79.0 (59.0; 91.0)	**1.23 (1.03; 1.47)**	65.0 (23.0; 92.0)	0.66 (0.36; 1.23)
	*Cor a 14-sIgE	64.0 (41.0; 83.0)		99.0 (91.0; 100)	
	SPT hazelnut	74.0 (58.0; 86.0)	**1.15 (1.01; 1.31)**	74.0 (45.0; 91.0)	0.77 (0.57; 1.02)
	*Cor a 14-sIgE	64.0 (48.0; 78.0)		97.0 (90.0; 99.0)	
	Cor a 14-sIgE	71.0 (44.0; 88.0)	1.15 (0.97; 1.37)	94.0 (89.0; 97.0)	**1.12 (1.04; 1.20)**
	*Cor a 9-sIgE	62.0 (35.0; 83.0)		84.0 (76.0; 90.0)	
Sesame seed allergy	sIgE sesame	98.0 (80.0; 100)	1.08 (0.90; 1.28)	20.0 (10.0; 37.0)	**0.30 (0.18; 0.50)**
	*Ses i 1-sIgE	92.0 (46.0; 99.0)		67.0 (46.0; 83.0)	
Cooked egg allergy	sIgE egg white	81.0 (71.0; 88.0)	**1.30 (1.04; 1.59)**	73.0 (61.0; 82.0)	0.88 (0.78; 1.00)
	*SPT egg white	63.0 (46.0; 77.0)		82.0 (70.0; 90.0)	
	Ovomucoid-sIgE	82.0 (73.0; 89.0)	1.03 (0.97; 1.10)	82.0 (73.0; 88.0)	**1.10 (1.02; 1.19)**
	*sIgE egg white	79.0 (70.0; 86.0)		74.0 (64.0; 82.0)	
	sIgE egg white	82.0 (73.0; 88.0)	**1.19 (1.05; 1.37)**	73.0 (61.0; 82.0)	0.88 (0.77; 1.00)
	*Ovalbumin-sIgE	68.0 (55.0; 80.0)		83.0 (69.0; 91.0)	
	Ovomucoid-sIgE	82.0 (63.0; 92.0)	**1.47 (1.10; 2.00)**	82.0 (63.0; 92.0)	0.94 (0.85; 1.05)
	*Ovalbumin-sIgE	56.0 (31.0; 77.0)		87.0 (69.0; 95.0)	
	sIgE egg white	81.0 (72.0; 88.0)	**1.37 (1.09; 1.72)**	77.0 (64.0; 86.0)	1.03 (0.88; 1.22)
	*SPP raw egg white	59.0 (43.0; 74.0)		74.0 (56.0; 86.0)	
Raw egg allergy	SPT egg white	84.0 (65.0; 94.0)	**1.45 (1.08; 1.94)**	79.0 (59.0; 91.0)	0.97 (0.82; 1.15)
	*Ovomucoid-sIgE	58.0 (37.0; 77.0)		82.0 (64.0; 92.0)	
Cow's milk allergy	Casein-sIgE	72.0 (59.0; 82.0)	**1.18 (1.05; 1.32)**	89.0 (69.0; 97.0)	1.01 (0.94; 1.08)
	*β-Lactoglobulin-sIgE	61.0 (47.0; 73.0)		89.0 (68.0; 96.0)	
	α-Lactoglobulin-sIgE	75.0 (58.0; 86.0)	**1.22 (1.04; 1.43)**	81.0 (58.0; 93.0)	0.93 (0.81; 1.06)
	*sIgE cow's milk	61.0 (42.0; 77.0)		88.0 (72.0; 95.0)	
	sIgE cow's milk	74.0 (59.0; 85.0)	**1.16 (1.02; 1.31)**	88.0 (74.0; 95.0)	1.05 (0.95; 1.17)
	*β-Lactoglobulin-sIgE	64.0 (46.0; 79.0)		83.0 (65.0; 93.0)	
	Casein-sIgE	47.0 (24.0; 71.0)	0.99 (0.79; 1.23)	93.0 (83.0; 97.0)	**1.27 (1.04; 1.54)**
	*SPT cow's milk	47.0 (25.0; 71.0)		73.0 (53.0; 87.0)	
	SPP fresh cow's milk	89.0 (73.0; 96.0)	**1.88 (1.25; 2.84)**	53.0 (24.0; 80.0)	**0.67 (0.47; 0.96)**
	*SPT cow's milk	47.0 (26.0; 70.0)		79.0 (52.0; 93.0)	
	SPP fresh cow's milk	88.0 (79.0; 94.0)	**1.29 (1.09; 1.53)**	61.0 (29.0; 86.0)	0.71 (0.50; 1.00)
	*sIgE cow's milk	68.0 (57.0; 78.0)		86.0 (62.0; 96.0)	

TABLE 6 (Continued)

FA	Diagnostic Test	Sens (95% CI)	Rel sens (95% CI)	Spec (95% CI)	Rel Spec (95% CI)
Wheat	sIgE wheat	83.0 (64.0; 93.0)	**1.92 (1.16; 3.23)**	61.0 (42.0; 77.0)	0.93 (0.70; 1.22)
	*SPT wheat	43.0 (20.0; 70.0)		66.0 (43.0; 83.0)	
	sIgE wheat	87.0 (78.0; 93.0)	1.08 (0.99; 1.16)	51.0 (34.0; 68.0)	**0.65 (0.50; 0.83)**
	*w-5 gliadin-sIgE	81.0 (70.0; 89.0)		79.0 (65.0; 89.0)	
Seafood	sIgE shrimp	97.0 (83.0; 100)	**1.54 (1.12; 2.08)**	64.0 (38.0; 84.0)	**0.71 (0.51; 0.99)**
	*Pen a 1-sIgE	64.0 (43.0; 80.0)		90.0 (71.0; 97.0)	

Note: Statistically significant comparisons of tests by FA (* reference category is the test on the second line—reported by FA). Only main comparisons are shown in the table based on optimal cut-off as per Table 2. Statistically relevant results are highlighted in bold.

Abbreviations: BAT, basophil activation test; sIgE, specific IgE; SPP, skin prick by prick test; SPT, skin prick test.

particularly in cases where the clinical history and results of other diagnostic tests are inconclusive. BAT had very good diagnostic performance; however, currently, it is not widely available in clinical practice and the interpretation of BAT results can be complex and require expert knowledge.

It is important to note that the accuracy of these diagnostic tests may vary depending on the individual being tested and the specific allergen being evaluated. Diagnostic tests should always be interpreted in the context of the patient's pre-test probabilities (likelihood of having an FA before being tested) which is influenced by the medical history, comorbidities and presenting symptoms. There is also inherent variability in the diagnostic methods employed, particularly in the case of SPTs, namely the specific technique, individual performing the test, reagents and equipment used can potentially impact the outcomes. There can also be variability within subjects with the site of testing, time of day, temperature, exercise prior to testing, etc. To ensure comprehensive coverage in our analysis, we included studies utilizing a range of commercial extracts. It is important to consider that including studies which used different SPT reagents or methods may have influenced the results.[179] These variations become particularly significant when dealing with allergens that lack standardization, such as fish[180] and shellfish.[181] Due to limited data available, we were unable to conduct a thorough meta-analyses on some food allergies, such as LTP-related FA, fish or shellfish allergies. For allergy tests not included in the SR, there is insufficient evidence on the accuracy of that test for diagnosing IgE-mediated FA and no conclusions can be made on the certainty of evidence for its use in clinical practice.

4.2 | Comparison with previous research

A previous SR on diagnostic test accuracy[8] included only studies where at least 50% of subjects had a DBPCFC as reference standard. While this approach may potentially increase the rigour of the studies included, it may also exclude evidence from various geographical regions and clinical settings where the logistics of a DBPCFC are not feasible or practical and may exclude a subset of patients seen in allergy clinic who do not have an indication or do not accept to undergo an OFC (e.g. highly sensitized subjects or patients with a recent history of reaction to the culprit food). As the objective of the current systematic review is to inform clinical recommendations, we chose to include index tests validated with other OFC techniques, namely open OFCs which are widely used in clinical practice and reliable in most clinical cases. We considered merging the studies included in the previous SR in this SR as an update and a way to increase the number of studies; however, we decided not to include older studies as methodologies have changed and available diagnostic tools have higher quality and diversity compared to those used prior to 2012.

4.3 | Strengths and limitations

This SR was based on an ambitious, open and inclusive protocol, which aimed to include studies using any test to support the diagnosis of any FA. This way we captured all available evidence beyond the commonly used tests and the most common food allergies. However, we were limited by the number of studies available to do meta-analyses and by the quality of the available evidence. For instance, randomized controlled trials (RCTs) are considered the highest level of evidence for evaluating the effectiveness of diagnostic strategies; however, none of the studies found by our SR followed this methodology. It is important to note that RCTs may not always be feasible or practical for evaluating diagnostic strategies, especially if the strategy is already in widespread use as is the case for SPT, sIgE and MA. In such instances, observational studies may be used to evaluate diagnostic tests. Evidence from our SR met these criteria and included cross-sectional and cohort study designs. Although we included eight case–control studies, these were judged as having high risk of bias and did not contribute to the certainty of evidence. Another limitation of our SR is that OFC was used as a comparator only in a portion of the study population. Not all subjects included in the analysis had FA confirmed or excluded by OFC as some studies allowed for a portion of the participants to be included based on clinical diagnosis of FA, that is based on history and sensitization tests. However, including studies where all patients underwent OFC has its own limitations as well, as noted above.

The heterogeneity of studies was a major obstacle for our SR complicating meaningful comparisons across studies. We found

TABLE 7 Stratified analyses of diagnostic performance by predefined cut-offs.

FA/test	Cut-off values	Sensitivity (95% CI)	I^2sens (%)	Specificity (95% CI)	I^2spec (%)	Subjects included	References
Peanut allergy							
SPT to peanut	≥8 mm	68.0 (42.0; 86.0)	85.2	**94.0 (85.0; 98.0)**	28.6	1086	38,99,134,135,154
sIgE to peanut	≥15 kU_A/L	28.0 (16.0; 45.0)	84.1	**98.0 (96.0; 99.0)**	25.6	872	88,134,169
Ara h 2-sIgE	≥0.35 kU_A/L	83.0 (78.0; 87.0)	54.5	**93.0 (87.0; 96.0)**	58.7	1994	38,44,61,64,65,68,73,79,88,89,91,99,110,117,137,139,146,148,152
Raw egg allergy							
Ovomucoid-sIgE	≥0.35 kU_A/L	56.0 (37.0; 73.0)	88.8	**91.0 (80.0; 96.0)**	69.5	827	34,59,72,76,170
Ovalbumin-sIgE	≥0.35 kU_A/L	76.0 (51.0; 91.0)	84.9	82.0 (62.0; 93.0)	71.9	546	34,43,76,140,170
Cooked egg allergy							
SPT to egg white	≥7 mm	45.0 (14.0; 81.0)	84.9	68.0 (55.0; 79.0)	33.7	323	33,80
sIgE egg white	≥7 kU_A/L	74.0 (64.0; 82.0)	14.1	70.0 (61.0; 78.0)	6.8	573	72,80,129
Ovomucoid-sIgE	≥0.35 kU_A/L	76.0 (53.0; 90.0)	82.3	**90.0 (85.0; 93.0)**	10.2	827	34,59,72,76,170
Cow's milk allergy							
SPT to cow's milk	≥8 mm	28.0 (1.00; 96.0)	18.3	**94.0 (23.0; 100)**	5.0	497	49,82,93,154
IgE to cow's milk	≥15 kUA/L	Not estimable[a]					
Hazelnut allergy							
Cor a 14-sIgE	≥0.35 kU_A/L	74.0 (51.0; 89.0)	82.1	**95.0 (89.0; 98.0)**	47.8	726	44,47,48,50,62,69,120,146
Sesame seed allergy							
SPT to sesame	≥8 mm	76.0 (59.0; 88.0)	72.6	89.0 (64.0; 97.0)	52.7	269	35,74,134,154
Wheat allergy							
w 5 gliadin-sIgE	≥0.35 kU_A/L	73.0 (64.0; 81.0)	23.6	81.0 (71.0; 88.0)	16.7	236	32,56,128

Note: Analysis undertaken according to specific cut-offs which have been predefined in the literature. For skin prick test (SPT), we used values of 8 mm for peanut (17) and cow's milk allergies and 7 mm for hen's egg allergy (16, 18). For sIgE, we used the following values: 15 kU_A/L for peanut (17), cow's milk and tree nut allergies and 7 kU_A/L for hen's egg allergy (16, 18). Highlighted are the diagnostic tests which have evidence of having high sensitivity or specificity (over 90%) for each specific cut-off value. We also used cut-offs of 3 mm for SPT and 0.35 kU_A/L for sIgE. Analysis undertaken for tests and foods where three or more studies reported these thresholds.

[a]Bivariate binomial model failed to converge due to over dispersed parameter along with limited number of studies.

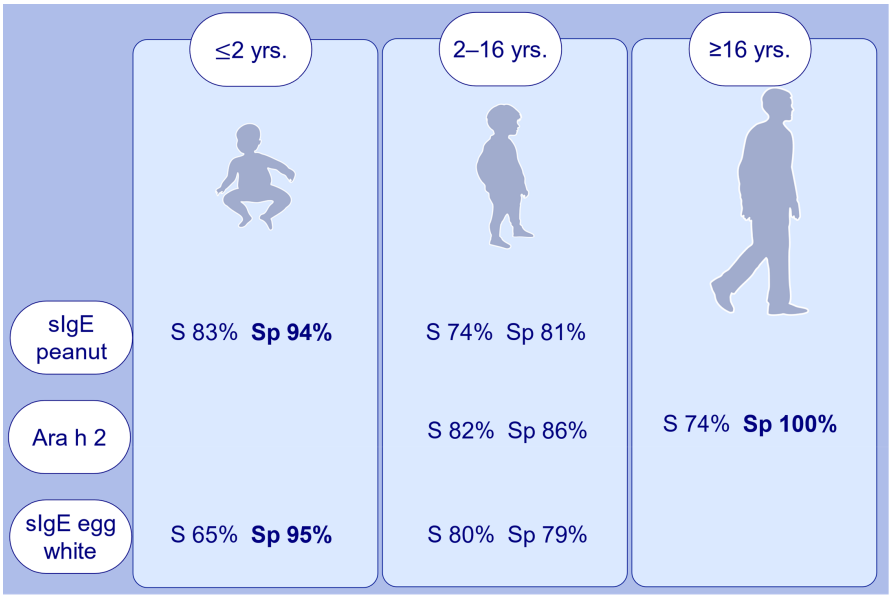

FIGURE 4 Accuracy of diagnostic tests for IgE-mediated FA according to age groups.Abbreviations: Ara h 2, Arah 2-specific IgE; yrs, years; sIgE, specific IgE; S, sensitivity; Sp, specificity.

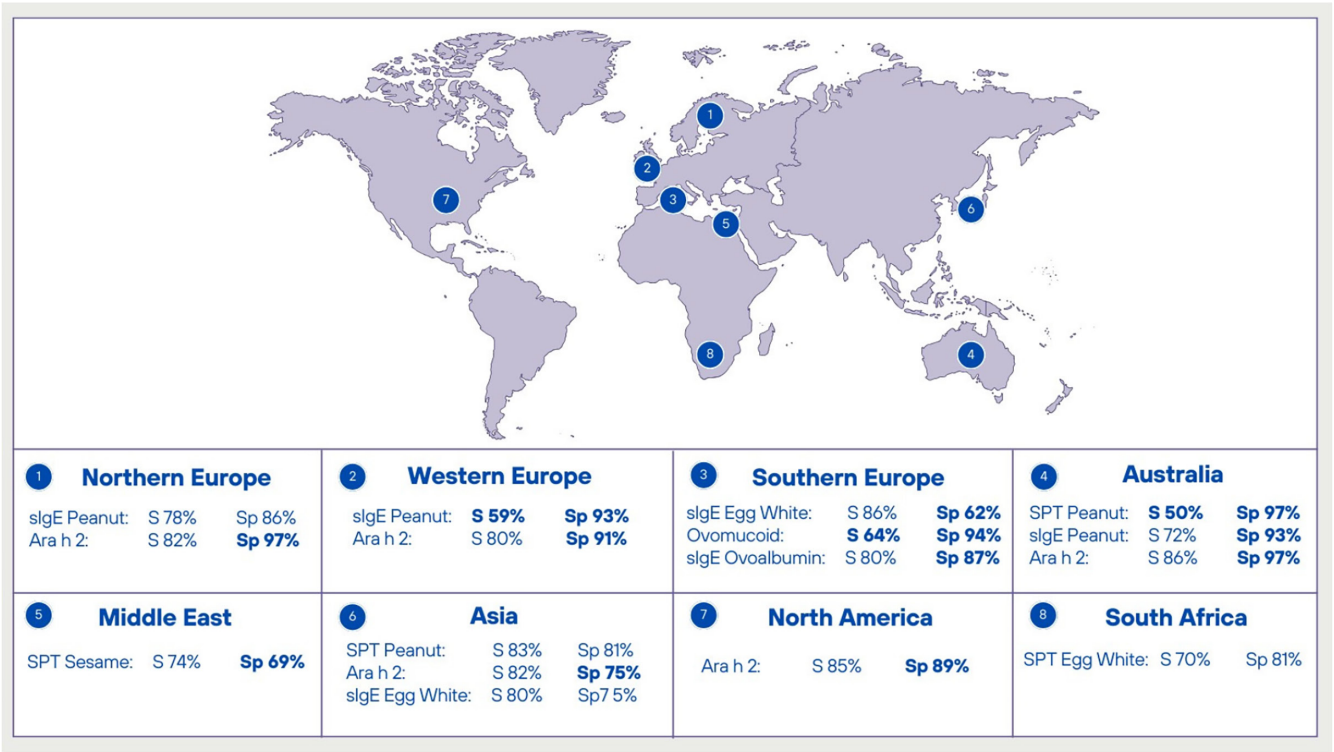

FIGURE 5 Accuracy of diagnostic tests for IgE-mediated FA according to geographical region. Abbreviations: sIgE, specific IgE; Ara h 2, Ara h 2-specific IgE; SPT, skin prick test.

variability in the definition of the target condition, in the interpretation of test results and in the characteristics of the study populations. The different diagnostic cut-offs implemented across the studies as well as the composition of the food extracts and commercial brands could affect the sensitivity and specificity of the tests determined in the meta-analyses. Most studies on FA diagnosis have been conducted in children. Of the studies included, 60.4% were undertaken in a population ≤12 years of age. While these studies have provided important insights, they may not be fully generalizable to adults. Our data highlight the important of having age validated cut-offs for FA diagnostic tests. Previous research has examined diagnostic test accuracy in specific age groups or ethnicities as one single population and pooled analysis of this data have thus far not been performed. While the individual raw data were not available, we were able to draw inferences of interest. For example, we found that peanut-sIgE had greater diagnostic accuracy in children under 2 years of age while Ara h 2-sIgE exhibited higher specificity among adults.

TABLE 8 Summary of accuracy of diagnostic tests for IgE-mediated FA.

Intervention	Population	Sensitivity (95% CI)	Specificity (95% CI)	Diagnostic accuracy	References
Peanut allergy					
SPT to peanut	Adults and children with suspected peanut allergy visiting a specialized allergy clinic	0.84 (0.69; 0.92)	0.86 (0.79; 0.91)	Moderate (Potential false negative and false positive results)	38,54,57,78,79,90,92,101,109,134,135,137,139,146,148,153,154,157,178
sIgE to peanut		0.81 (0.71; 0.88)	0.83 (0.71; 0.90)	Moderate (Potential false negative and false positive results)	38,44,54,60,61,65,68,73,79,88,89,90,94,110,117,134,135,139,146,148,154,157,169,178
Ara h 2-sIgE (ImmunoCAP)		0.82 (0.77; 0.86)	0.92 (0.87; 0.95)	High for ruling in peanut allergy	31,38,44,57,60,61,64,65,68,73,79,88,89,90,91,94,99,100,110,117,137,139,146,148,152,157
Ara h 2-sIgE (ISAC)		0.77 (0.64; 0.86)	0.93 (0.66; 0.99)	High for ruling in peanut allergy	78,79,91,97
BAT to peanut		0.84 (0.76; 0.90)	0.90 (0.83; 0.94)	High for ruling in peanut allergy	38,139,146,148
Raw egg allergy					
SPT to egg white	Adults and children with suspected raw egg allergy visiting a specialized allergy clinic	0.78 (0.49; 0.93)	0.80 (0.55; 0.93)	Moderate (Potential false negative and false positive results)	33,34,135,170
SPT to egg yolk		0.41 (0.21; 0.64)	0.96 (0.75; 0.99)	High for ruling in raw egg allergy	33,34,49
SPT to ovalbumin		0.57 (0.10; 0.94)	0.91 (0.59; 0.99)	High for ruling in raw egg allergy	33,34,49
sIgE to egg white		0.73 (0.60; 0.83)	0.88 (0.75; 0.95)	Moderate (Potential false negative and some false positive results)	33,34,43,59,72,76,135,140,170
sIgE to egg yolk		0.57 (0.35; 0.77)	0.88 (0.74; 0.95)	Moderate (Many false negative results and some false positive ones)	33,34,76,140
Ovomucoid-sIgE		0.55 (0.40; 0.70)	0.92 (0.83; 0.97)	High for ruling in raw egg allergy	34,43,59,72,76,170
Ovalbumin- sIgE		0.78 (0.58; 0.90)	0.79 (0.62; 0.90)	Moderate (Potential false negative and false positive results)	34,43,59,76,140,170
Cooked egg allergy					
SPT to egg white	Adults and children with suspected cooked egg allergy visiting a specialized allergy clinic	0.68 (0.37; 0.88)	0.77 (0.64; 0.86)	Moderate (Potential false negative and false positive results)	33,80,82,116,155,166
SPP to raw egg white		0.94 (0.76; 0.99)	0.66 (0.51; 0.78)	High for ruling out cooked egg allergy (Many false positive results)	33,80,124,166
sIgE to egg white		0.85 (0.77; 0.90)	0.73 (0.63; 0.80)	Moderate (Potential false negative and false positive results)	33,43,72,80,86,95,116,126,129,150,155,166,170
Ovomucoid-sIgE		0.74 (0.54; 0.87)	0.91 (0.87; 0.93)	High for ruling in cooked egg allergy	33,34,43,72,116,140,170
Ovalbumin-sIgE		0.65 (0.43; 0.82)	0.92 (0.83; 0.97)	High for ruling in cooked egg allergy	33,43,170

TABLE 8 (Continued)

Intervention	Population	Sensitivity (95% CI)	Specificity (95% CI)	Diagnostic accuracy	References
Baked egg allergy					
SPT to egg white	Adults and children with suspected baked egg allergy visiting a specialized allergy clinic	0.23 (0.01; 0.92)	0.85 (0.49; 0.97)	Moderate (Many potential false negative and some false positive results)	41,135,144,164
sIgE to egg white		0.40 (0.12; 0.77)	0.94 (0.45; 1.00)	High for ruling in baked egg allergy	41,135,144
Cow's milk allergy					
SPP to fresh cow's milk	Adults and children with suspected cow's milk allergy visiting a specialized allergy clinic	0.80 (0.53; 0.94)	0.90 (0.25; 1.00)	High for ruling in cow's milk allergy (Potential false negative results)	37,49,155,165,178
SPT to cow's milk		0.52 (0.24; 0.79)	0.80 (0.65; 0.90)	Moderate (Potential many false negative and some false positive results)	37,49,52,71,82,92,93,104,132,154,155,156,165,178
sIgE to cow's milk		0.82 (0.59; 0.94)	0.92 (0.80; 0.97)	High for ruling in cow's milk allergy (Potential false negative results)	37,51,52,71,92,93,95,104,132,141,150,154,155,165,176,178
Casein-sIgE		0.67 (0.53; 0.78)	0.93 (0.85; 0.97)	High for ruling in cow's milk allergy	32,37,51,52,71,125,132,165
Hazelnut allergy					
SPT to hazelnut	Adults and children with suspected hazelnut allergy visiting a specialized allergy clinic	0.82 (0.68; 0.91)	0.78 (0.44; 0.94)	Moderate (Potential false negative and false positive results)	48,50,62,112,121,146,154
sIgE to hazelnut		0.79 (0.71; 0.85)	0.62 (0.38; 0.81)	Moderate (Potential false negative and false positive results)	44,48,50,62,85,120,121,146,154
Cor a 14-sIgE		0.73 (0.53; 0.87)	0.95 (0.90; 0.98)	High for ruling in hazelnut allergy	44,47,48,50,62,64,68,120,121,146
Cashew nut allergy					
SPT to cashew	Adults and children with suspected cashew allergy visiting a specialized allergy clinic	0.93 (0.89; 0.96)	0.92 (0.82; 0.96)	High for ruling out and ruling in cashew nut allergy	53,122,146,154
sIgE to cashew		0.94 (0.89; 0.97)	0.64 (0.54; 0.74)	High for ruling out cashew nut allergy (Potential false positive results)	53,84,146,151,154
Ana o 3-sIgE		0.96 (0.91; 0.98)	0.94 (0.88; 0.97)	High for ruling out and ruling in cashew nut allergy	106,146,151
Walnut allergy					
sIgE to walnut	Adults and children with suspected walnut allergy visiting a specialized allergy clinic	0.87 (0.60; 0.97)	0.82 (0.60; 0.93)	Moderate (Potential false negative and false positive results)	39,45,67,154,172
Jug r 1-sIgE		0.77 (0.58; 0.89)	0.90 (0.78; 0.96)	High for ruling in walnut allergy	45,65,68
Almond allergy					
sIgE to almond	Adults and children with suspected almond allergy visiting a specialized allergy clinic	0.72 (0.62; 0.80)	0.95 (0.43; 1.00)	High for ruling in almond allergy (Potential false negative and false positive results)	87,146,154,172

(Continues)

TABLE 8 (Continued)

Intervention	Population	Sensitivity (95% CI)	Specificity (95% CI)	Diagnostic accuracy	References
Sesame seed allergy					
SPT sesame	Adults and children with suspected sesame allergy visiting a specialized allergy clinic	0.70 (0.55; 0.82)	0.89 (0.76; 0.95)	Moderate (Potential false negative and false positive results)	35,74,135,143,145,146,154
sIgE sesame		0.70 (0.23; 0.95)	0.83 (0.26; 0.99)	Moderate (Potential false negative and false positive results)	74,118,135,143,145,146,154
Ses i 1-sIgE		0.77 (0.64; 0.86)	0.87 (0.77; 0.92)	Moderate (Positive results rules in FA but some false positive results)	74,118,143
BAT sesame		0.89 (0.80; 0.94)	0.93 (0.76; 0.98)	High for ruling in sesame seed allergy. (Some potential false negative results)	35,74,146
Soy allergy					
SPT to soy	Adults and children with suspected soy allergy visiting a specialized allergy clinic	0.47 (0.11; 0.87)	0.79 (0.63; 0.89)	Moderate (Many potential false negative and false positive results)	63,97,155,177
sIgE to Soy		0.73 (0.62; 0.82)	0.75 (0.44; 0.92)	Low (Potential false negative and false positive results)	97,118,148,177
Gly m 4-sIgE		0.61 (0.36; 0.81)	0.69 (0.30; 0.92)	Low (Potential false negative and false positive results)	62,97,118
Wheat allergy					
SPT to wheat	Adults and children with suspected wheat allergy visiting a specialized allergy clinic	0.53 (0.23; 0.81)	0.72 (0.57; 0.84)	Low (Potential many false negative and some false positive results)	36,82,104,114,136,154,156,178
sIgE to wheat		0.72 (0.54; 0.84)	0.79 (0.68; 0.86)	Moderate (Potential false negative and false positive results)	32,36,55,56,77,104,114,128,130,136,150,154,158,178
w-5 gliadin-sIgE		0.79 (0.68; 0.88)	0.78 (0.66; 0.86)	Moderate (Potential false negative and false positive results)	32,56,77,128,130,136
Shrimp allergy					
SPT to shrimp	Adults and children with suspected shrimp allergy visiting a specialized allergy clinic	0.62 (0.44; 0.77)	0.90 (0.31; 0.99)	High for ruling in shrimp allergy (Potentially many false negative results)	156,160,163,173
sIgE to shrimp		0.96 (0.42; 1.00)	0.63 (0.46; 0.78)	High for ruling out shrimp allergy (Potentially many false positive results)	160,163,171,173
Pen a 1-sIgE		0.62 (0.45; 0.76)	0.89 (0.75; 0.95)	Moderate (When positive rules in shrimp allergy but some false positive results)	163,171,173

Note: The population included was adults and children with a suspected FA according to the different culprit foods. Interventions were the various diagnostic tests used for the diagnosis of IgE-mediated FA with their respective sensitivities and specificities. Highlighted results are shown for those with a sensitivity or specificity ≥90% at the optimal cut-off defined by Youden index or by the authors of the individual studies. Diagnostic accuracy was defined according to the sensitivity or specificity of the test, if ≥90% they accuracy was high, 89%–75% accuracy was moderate and ≤75% accuracy was low. For tests of high sensitivity or specificity, it is stated if they are useful for ruling in or out FA. SPT and sIgE are considered first line tests for all FA although their diagnostic accuracies between different food allergies vary. CRD can be used to support the diagnosis of FA as well as BAT in equivocal cases.

Abbreviations: BAT, basophil activation test; sIgE, specific IgE; SPP, skin prick by prick test; SPT, skin prick test.

Data included in the SR came mainly from Europe. Multiple geographical locations had only limited number or no studies, such as Southeast Asia, Middle East, Africa and Central and South America. Only 13.4% of eligible data were derived from multicentre studies, highlighting a need for future collaboration to understand differences across populations. The lack of representation from certain regions or populations can limit the generalizability of the findings and may not accurately reflect the diversity of FA and diagnostic accuracy of tests in the global population. While studies from Europe may provide valuable insights into the diagnosis in that region, it is important to recognize that test accuracy may vary in other parts of the world. We analysed the data for different geographical regions and saw that Ara h 2-sIgE presented higher specificity in Northern Europe and Australia than in North America or Asia.[182] Furthermore, various ethnicities within a geographical region could have different diagnostic test accuracies. Most studies included in this SR made no reference to ethnicity variations within the populations studied. Only 12 studies mentioned the ethnicity of the subjects enrolled and three studies[78-80] analysed the accuracy of diagnostic test between different ethnicities within the same population. Better descriptions of the study populations in future diagnostic test accuracy studies may help to establish more personalized approaches.

Another limitation of diagnostic studies is that the results are often dichotomous, meaning that a specific cut-off value is used to classify participants as allergic or tolerant, and this affects the reported diagnostic performance. For example, if a high cut-off value of 8 mm is used, sensitivity (proportion of participants with true FA with SPT ≥8 mm) would be relatively low while the specificity (proportion of true tolerant participants with SPT <8 mm) would be relatively high. This gives a misleading impression that the test has a low sensitivity when it may be good at ruling out FA when the SPT result is much lower (e.g. <3 mm). Ideally, a continuous model would be used linking actual results to probability of FA to accurately evaluate the results of allergy tests, but this approach requires additional raw data that were not available at this stage. Furthermore, we assessed the cut-offs employed in various studies; this approach using pooled estimates obtained may not accurately represent any specific cut-off point studied. Consequently, there is a need to exercise caution and rate the certainty of the findings lower due to the indirect nature of the evidence. The sensitivity and specificity of the tests rely on the chosen threshold. Tables S5 and S6 demonstrate that when the threshold is set sufficiently high, almost every test for every food exhibit high specificity. Similarly, by setting the threshold low enough, most tests can achieve high sensitivity. Instead of solely concentrating on pooled results to determine optimal thresholds, it is important to consider that different studies may have been designed to optimize different factors. Consequently, pooling them together may not yield meaningful results. Utilizing the Youden's index to maximize sensitivity and specificity can lead to a threshold that does not perform well for either metric. We performed meta-analyses for maximum sensitivity and specificity, whose aim was to provide insights into the specific cut-offs which could help rule in or out specific food allergies. A highly sensitive test when negative rules out FA while a highly specific test when positive rules in FA. The values obtained for the maximum specificity and sensitivity analysis were those provided by the authors as their maximum cut-offs; thus, the meta-analyses is dependent on the way the data are reported in the different studies.

4.4 | Implications for practice, policy and future research

In clinical practice, validated allergy tests can guide diagnosis and reduce the need for prolonged restrictive diets and high-risk OFC. To assist clinicians in decision-making, further research is necessary to determine the clinical impact and cost-effectiveness of allergy tests, including SPT, sIgE, MA and BAT, and their use in various combinations to provide optimal diagnostic pathway for individual foods that is guided by patient outcomes and health economics.

The utility of diagnostic tests differs between geographical regions. Stakeholders should promote studies that can correctly identify cut-offs for their specific populations considering ethnicity and age to improve the accurate diagnosis of IgE-mediated FA on a global scale. Ultimately, the goal of evaluating diagnostic strategies is to improve patient outcomes and inform clinical decision-making. The most appropriate study design should be chosen to achieve this goal, considering logistics and health economics in each geographical area.

Studies validating age-appropriate cut-offs are needed. There is lack of evidence in adult FA regarding of allergen exposure due to dietary habits and comorbidities, including cross-sensitization to aeroallergens. More evidence is needed to assess food allergies in toddlers specifically for CM, HE and peanut. Future research should consider specific cut-offs which guide diagnosis of tolerance to baked goods (specifically, to foods containing baked egg or baked milk) and safety of food introduction in IgE sensitized patients with no history of prior food ingestion. Establishing these parameters for clinical practice can prevent prolonged unnecessary restrictive diets and improve quality of life for patients.

There is limited evidence on diagnostic tests for less common allergens such as fish, a wide variety of shellfish, fruits, vegetables and legumes. Properly designed studies addressing allergy to these foods are needed.

To minimize bias and confounding, RCTs with DBPCFCs are required to evaluate accuracy of novel diagnostic strategies and their impact in patient outcomes and health economics. Such studies could provide high-quality evidence on the sensitivity, specificity and cost-effectiveness of these tools compared to current tests.

5 | CONCLUSIONS

There is strong evidence supporting the accuracy of SPT, sIgE and MA to support the diagnosis of peanut, CM, HE and tree nut allergies and of BAT to support the diagnosis of peanut and sesame allergies,

in patients with suggestive clinical history of IgE-mediated reactions. However, for other foods such as soy, sesame, wheat and shrimp, the evidence is not as robust. Cut-offs for optimal sensitivity (ruling out FA) may be useful for screening and to capture allergic sensitization. Cut-offs for optimal specificity (ruling in FA) may be useful to confirm the diagnosis of FA in sensitized patients. Further research is needed to evaluate the usefulness of combining existing diagnostic tests and to assess novel diagnostic techniques to minimize the need for OFCs. The upcoming FA diagnostic guidelines from EAACI will incorporate the findings of this SR and meta-analyses, along with expert opinions and other evidence, to provide practical recommendations for best practice to diagnose IgE-mediated FA.

AUTHOR CONTRIBUTIONS

All authors conceptualized the work, commented on the work and approved it for submission. MA, IB, AB, BB, MG, EvG, SJ, HJ, DL, AM-M, AP-Z, ES, Elk and DW searched for studies, extracted data and performed risk of biased analysis. BM and CaR did dual review, cleaning and formatting data extracted and risk of biased assessment. CaR, AFS, IS and GdT solved conflicts relating to studies inclusion, data summaries and risk of biased assessment. GR, DC and RP provided methodological guidance. CrR performed the data analysis. CaR and AFS and drafted the manuscript.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Cummings AJ, Knibb RC, Erlewyn-Lajeunesse M, King RM, Roberts G, Lucas JSA. Management of nut allergy influences quality of life and anxiety in children and their mothers. *Pediatr Allergy Immunol*. 2010;21(4 Pt 1):586-594.
2. Birdi G, Cooke R, Knibb R. Quality of life, stress, and mental health in parents of children with parentally diagnosed FA compared to medically diagnosed and healthy controls. *J Allergy*. 2016;2016:1497375.
3. Warren CM, Jiang J, Gupta RS. Epidemiology and burden of FA. *Curr Allergy Asthma Rep*. 2020;20(2):6.
4. Bilaver LA, Chadha AS, Doshi P, O'Dwyer L, Gupta RS. Economic burden of FA: a systematic review. *Ann Allergy Asthma Immunol*. 2019;122(4):373-380.e1.
5. Spolidoro GCI, Amera YT, Ali MM, et al. Frequency of FA in Europe: an updated systematic review and meta-analysis. *Allergy*. 2023;78(2):351-368.
6. Sicherer SH, Sampson HA. FA: a review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. *J Allergy Clin Immunol*. 2018;141(1):41-58.
7. Foong RX, Santos AF. Biomarkers of diagnosis and resolution of FA. *Pediatr Allergy Immunol*. 2021;32(2):223-233.
8. Soares-Weiser K, Takwoingi Y, Panesar SS, et al. The diagnosis of FA: a systematic review and meta-analysis. *Allergy*. 2014;69(1):76-86.
9. Muraro A, Werfel T, Hoffmann-Sommergruber K, et al. EAACI FA and anaphylaxis guidelines: diagnosis and management of FA. *Allergy*. 2014;69(8):1008-1025.
10. Campbell JM, Klugar M, Ding S, et al. Diagnostic test accuracy: methods for systematic review and meta-analysis. *Int J Evid Based Healthc*. 2015;13(3):154-162.
11. Chu DK, Golden DBK, Guyatt GH. Translating evidence to optimize patient care using GRADE. *J Allergy Clin Immunol Pract*. 2021;9(12):4221-4230.
12. Genuneit J, Jayasinghe S, Riggioni C, et al. Protocol for a systematic review of the diagnostic test accuracy of tests for IgE-mediated FA. *Pediatr Allergy Immunol*. 2022;33(1):e13684.
13. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
14. Hamza TH, van Houwelingen HC, Stijnen T. The binomial distribution of meta-analysis was preferred to model within-study variability. *J Clin Epidemiol*. 2008;61(1):41-51.
15. Zhou Y, Dendukuri N. Statistics for quantifying heterogeneity in univariate and bivariate meta-analyses of binary data: the case of meta-analyses of diagnostic accuracy. *Stat Med*. 2014;33(16):2701-2717.
16. Du Toit G, Santos A, Roberts G, Fox AT, Smith P, Lack G. The diagnosis of IgE-mediated FA in childhood. *Pediatr Allergy Immunol*. 2009;20(4):309-319.
17. Roberts G, Lack G. Diagnosing peanut allergy with skin prick and specific IgE testing. *J Allergy Clin Immunol*. 2005;115(6):1291-1296.
18. Sporik R, Hill DJ, Hosking CS. Specificity of allergen skin testing in predicting positive open food challenges to milk, egg and peanut in children. *Clin Exp Allergy*. 2000;30(11):1540-1546.
19. Sicherer SH, Sampson HA. Food hypersensitivity and atopic dermatitis: pathophysiology, epidemiology, diagnosis, and management. *J Allergy Clin Immunol*. 1999;104(3):S114-S122.
20. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic FA. *J Allergy Clin Immunol*. 2001;107(5):891-896.
21. Komata T, Söderström L, Borres MP, Tachimoto H, Ebisawa M. 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(5):1272-1274.
22. Boyano Martínez T, García-Ara C, DÍaz-Pena JM, Muñoz FM, García Sánchez G, Esteban MM. Validity of specific IgE antibodies in children with egg allergy. *Clin Exp Allergy*. 2001;31(9):1464-1469.
23. García-Ara C, Boyano-Martínez T, Díaz-Pena JM, Martín-Muñoz F, Reche-Frutos M, Martín-Esteban M. Specific IgE levels in the diagnosis of immediate hypersensitivity to cows' milk protein in the infant. *J Allergy Clin Immunol*. 2001;107(1):185-190.
24. Nyaga VN, Arbyn M. Metadta: a Stata command for meta-analysis and meta-regression of diagnostic test accuracy data—a tutorial. *Arch Public Health*. 2022;80(1):95.
25. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med*. 2011;155(8):529-536.
26. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926.
27. Schünemann HJ, Oxman AD, Brozek J, et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. *BMJ*. 2008;336(7653):1106-1110.
28. Brozek JL, Akl EA, Alonso-Coello P, et al. Grading quality of evidence and strength of recommendations in clinical practice guidelines. Part 1 of 3. An overview of the GRADE approach and grading quality of evidence about interventions. *Allergy*. 2009;64(5):669-677.
29. Brożek JL, Akl EA, Compalati E, et al. Grading quality of evidence and strength of recommendations in clinical practice guidelines. Part 3 of 3. The GRADE approach to developing recommendations. *Allergy*. 2011;66(5):588-595.
30. Brozek JL, Akl EA, Jaeschke R, et al. Grading quality of evidence and strength of recommendations in clinical practice guidelines. Part 2 of 3. The GRADE approach to grading quality of evidence about diagnostic tests and strategies. *Allergy*. 2009;64(8):1109-1116.
31. Agabriel C, Ghazouani O, Birnbaum J, et al. Ara h 2 and Ara h 6 sensitization predicts peanut allergy in Mediterranean pediatric patients. *Pediatr Allergy Immunol*. 2014;25(7):662-667.
32. Al Hawi Y, Nagao M, Furuya K, et al. Agreement between predictive, allergen-specific IgE values assessed by immunoCAP and IMMULITE 2000 3gAllergyTM assay systems for milk and wheat allergies. *Allergy Asthma Immunol Res*. 2021;13(1):141-153.
33. Alessandri C, Zennaro D, Scala E, et al. Ovomucoid (Gal d 1) specific IgE detected by microarray system predict tolerability to boiled hen's egg and an increased risk to progress to multiple environmental allergen sensitisation. *Clin Exp Allergy*. 2012;42(3):441-450.
34. Alvaro M, García-Paba MB, Giner MT, et al. Tolerance to egg proteins in egg-sensitized infants without previous consumption. *Allergy*. 2014;69(10):1350-1356.
35. Appel MY, Nachshon L, Elizur A, Levy MB, Katz Y, Goldberg MR. Evaluation of the basophil activation test and skin prick testing for the diagnosis of sesame FA. *Clin Exp Allergy*. 2018;48(8):1025-1034.
36. Asaumi T, Yanagida N, Sato S, Shukuya A, Nishino M, Ebisawa M. Provocation tests for the diagnosis of food-dependent exercise-induced anaphylaxis. *Pediatr Allergy Immunol*. 2016;27(1):44-49.

37. Ayats-Vidal R, Valdesoiro-Navarrete L, García-González M, Asensio-de la Cruz O, Larramona-Carrera H, Bosque-García M. Predictors of a positive oral food challenge to cow's milk in children sensitized to cow's milk. *Allergol Immunopathol*. 2020;48(6):568-575.
38. Bahri R, Custovic A, Korosec P, et al. Mast cell activation test in the diagnosis of allergic disease and anaphylaxis. *J Allergy Clin Immunol*. 2018;142(2):485-496.e16.
39. Ballmer-Weber BK, Lidholm J, Lange L, et al. Allergen recognition patterns in walnut allergy are age dependent and correlate with the severity of allergic reactions. *J Allergy Clin Immunol Pract*. 2019;7(5):1560-1567.e6.
40. Bartnikas LM, Sheehan WJ, Hoffman EB, et al. Predicting food challenge outcomes for baked milk: role of specific IgE and skin prick testing. *Ann Allergy Asthma Immunol*. 2012;109(5):309-313.e1.
41. Bartnikas LM, Sheehan WJ, Larabee KS, Petty C, Schneider LC, Phipatanakul W. Ovomucoid is not superior to egg white testing in predicting tolerance to baked egg. *J Allergy Clin Immunol Pract*. 2013;1(4):354-360.e2.
42. Bellini F, Ricci G, Remondini D, Pession A. Cow's milk allergy (CMA) in children: identification of allergologic tests predictive of FA. *Eur Ann Allergy Clin Immunol*. 2014;46(3):100-105.
43. 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(1):12-17.
44. Beyer K, Grabenhenrich L, Härtl M, et al. Predictive values of component-specific IgE for the outcome of peanut and hazelnut food challenges in children. *Allergy*. 2015;70(1):90-98.
45. 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(2):688-690.e4.
46. Blankestijn MA, den Hartog Jager CF, Blom WM, et al. A subset of walnut allergic adults is sensitized to walnut 11S globulin Jug r 4. *Clin Exp Allergy*. 2018;48(9):1206-1213.
47. 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(9):1412-1418.
48. Buyuktiryaki B, Cavkaytar O, Sahiner UM, et al. Cor a 14, hazelnut-specific IgE, and SPT as a reliable tool in hazelnut allergy diagnosis in eastern Mediterranean children. *J Allergy Clin Immunol Pract*. 2016;4(2):265-272.e3.
49. Calvani M, Berti I, Fiocchi A, et al. Oral food challenge: safety, adherence to guidelines and predictive value of skin prick testing. *Pediatr Allergy Immunol*. 2012;23(8):754-760.
50. Carraro S, Berardi M, Bozzetto S, Baraldi E, Zanconato S. COR a 14-specific IgE predicts symptomatic hazelnut allergy in children. *Pediatr Allergy Immunol*. 2016;27(3):322-324.
51. Castro AP, Pastorino AC, Gushken AKF, Kokron CM, Filho UD, Jacob CMA. Establishing a cut-off for the serum levels of specific IgE to milk and its components for cow's milk allergy: results from a specific population. *Allergol Immunopathol*. 2015;43(1):67-72.
52. Castro Neves A, Romeira AM, Marques JG, Matos V, Leiria Pinto P. Blood or skin: what is best in predicting cow's milk allergy diagnosis? *Eur Ann Allergy Clin Immunol*. 2020;52(4):160-164.
53. Cetinkaya PG, Karaguzel D, Esenboğa S, et al. Pistachio and cashew nut allergy in childhood: predictive factors towards development of a decision tree. *Asian Pac J Allergy Immunol*. 2021;39(1):53-61.
54. Chong KW, Saffari SE, Chan N, et al. Predictive value of peanut skin prick test, specific IgE in peanut-sensitized children in Singapore. *Asia Pac Allergy*. 2019;9(3):e21.
55. Christensen MJ, Eller E, Mortz CG, Bindslev-Jensen C. Patterns of suspected wheat-related allergy: a retrospective single-centre case note review in 156 patients. *Clin Transl Allergy*. 2014;4(1):39.
56. Christensen MJ, Eller E, Mortz CG, Brockow K, Bindslev-Jensen C. Exercise lowers threshold and increases severity, but wheat-dependent, exercise-induced anaphylaxis can Be elicited at rest. *J Allergy Clin Immunol Pract*. 2018;6(2):514-520.
57. Chua GT, Chong PC, Au EY, et al. Skin prick testing a better predictor than blood testing for the diagnosis of peanut allergy in Chinese children. *Asian Pac J Allergy Immunol*. 2021;39(4):241-248. doi:10.12932/AP-110319-0519
58. Cortot CF, Sheehan WJ, Permaul P, et al. Role of specific IgE and skin-prick testing in predicting food challenge results to baked egg. *Allergy Asthma Proc*. 2012;33(3):275-281.
59. Dang TD, Peters RL, Koplin JJ, et al. Egg allergen specific IgE diversity predicts resolution of egg allergy in the population cohort HealthNuts. *Allergy*. 2019;74(2):318-326.
60. Dang TD, Tang M, Choo S, et al. Increasing the accuracy of peanut allergy diagnosis by using Ara h 2. *J Allergy Clin Immunol*. 2012;129(4):1056-1063.
61. Datema MR, Eller E, Zwinderman AH, et al. Ratios of specific IgG_4 over IgE antibodies do not improve prediction of peanut allergy nor of its severity compared to specific IgE alone. *Clin Exp Allergy*. 2019;49(2):216-226.
62. Datema MR, van Ree R, Asero R, et al. Component-resolved diagnosis and beyond: multivariable regression models to predict severity of hazelnut allergy. *Allergy*. 2018;73(3):549-559.
63. De Swert LF, Gadisseur R, Sjölander S, Raes M, Leus J, van Hoeyveld E. Secondary soy allergy in children with birch pollen allergy may cause both chronic and acute symptoms. *Pediatr Allergy Immunol*. 2012;23(2):117-123.
64. Duan L, Celik A, Hoang JA, et al. Basophil activation test shows high accuracy in the diagnosis of peanut and tree nut allergy: The Markers of Nut Allergy Study. *Allergy*. 2021;76(6):1800-1812. doi:10.1111/all.14695 Epub 2020 Dec 29.
65. Ebisawa M, Movérare R, Sato S, Maruyama N, Borres MP, Komata T. Measurement of Ara h 1-, 2-, and 3-specific IgE antibodies is useful in diagnosis of peanut allergy in Japanese children. *Pediatr Allergy Immunol*. 2012;23(6):573-581.
66. Echeverria L, Martin-Muñoz MF, Martorell C, et al. Clinical and immunological profile of children aged 5-9 years with persistent egg allergy before oral immunotherapy with egg. A multicenter, randomized controlled trial of the Spanish Society of Pediatric Allergy, Asthma and Clinical Immunology (SEICAP). *Allergol Immunopathol*. 2018;46(5):415-420.
67. Elizur A, Appel MY, Nachshon L, et al. Clinical and molecular characterization of walnut and pecan allergy (NUT CRACKER Study). *J Allergy Clin Immunol Pract*. 2020;8(1):157-165.e2.
68. Eller E, Bindslev-Jensen C. Clinical value of component-resolved diagnostics in peanut-allergic patients. *Allergy*. 2013;68(2):190-194.
69. 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(4):556-562.
70. Esty B, Maciag MC, Bartnikas LM, et al. Predicting outcomes of baked egg and baked milk oral food challenges by using a ratio of food-specific IgE to total IgE. *J Allergy Clin Immunol Pract*. 2021;9(4):1750-1752.e1.
71. Franco JM, Pinheiro APSG, Vieira SCF, et al. Accuracy of serum IgE concentrations and papule diameter in the diagnosis of cow's milk allergy. *J Pediatr*. 2018;94(3):279-285.
72. Furuya K, Nagao M, Sato Y, Ito S, Fujisawa T, IPAD3g Investigators. 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(10):1435-1443.
73. Glaumann S, Nopp A, Johansson SGO, Rudengren M, Borres MP, Nilsson C. Basophil allergen threshold sensitivity, CD-sens, IgE-sensitization and DBPCFC in peanut-sensitized children. *Allergy*. 2012;67(2):242-247.

74. Goldberg MR, Appel MY, Nachshon L, et al. Combinatorial advantage of Ses i 1-specific IgE and basophil activation for diagnosis of sesame FA. *Pediatr Allergy Immunol*. 2021;32:1482-1489.
75. Grabenhenrich L, Lange L, Härtl M, et al. The component-specific to total IgE ratios do not improve peanut and hazelnut allergy diagnoses. *J Allergy Clin Immunol*. 2016;137(6):1751-1760.
76. Gradman J, Mortz CG, Eller E, Bindslev-Jensen C. Relationship between specific IgE to egg components and natural history of egg allergy in Danish children. *Pediatr Allergy Immunol*. 2016;27(8):825-830.
77. Graham F, Caubet JC, Ramadan S, Spoerl D, Eigenmann PA. Specific IgE decision point cutoffs in children with IgE-mediated wheat allergy and a review of the literature. *Int Arch Allergy Immunol*. 2020;181(4):296-300.
78. Gray CL, Levin ME, du Toit G. Ethnic differences in peanut allergy patterns in south African children with atopic dermatitis. *Pediatr Allergy Immunol*. 2015;26(8):721-730.
79. Gray CL, Levin ME, du Toit G. Which test is best for diagnosing peanut allergy in south African children with atopic dermatitis? *S Afr Med J*. 2016;106(2):214-220.
80. Gray CL, Levin ME, du Toit G. Egg sensitization, allergy and component patterns in African children with atopic dermatitis. *Pediatr Allergy Immunol*. 2016;27(7):709-715.
81. Gupta RS, Lau CH, Hamilton RG, Donnell A, Newhall KK. Predicting outcomes of oral food challenges by using the allergen-specific IgE-Total IgE ratio. *J Allergy Clin Immunol Pract*. 2014;2(3):300-305.
82. Imai T, Yanagida N, Ogata M, Komata T, Tomikawa M, Ebisawa M. The skin prick test is not useful in the diagnosis of the immediate type FA tolerance acquisition. *Allergol Int*. 2014;63(2):205-210.
83. Imakiire R, Fujisawa T, Nagao M, et al. Basophil activation test based on CD203C expression in the diagnosis of fish allergy. *Allergy Asthma Immunol Res*. 2020;12(4):641-652.
84. Inoue T, Ogura K, Takahashi K, et al. Risk factors and clinical features in cashew nut oral food challenges. *Int Arch Allergy Immunol*. 2018;175(1–2):99-106.
85. Inoue Y, Sato S, Takahashi K, et al. Component-resolved diagnostics can be useful for identifying hazelnut allergy in Japanese children. *Allergol Int*. 2020;69(2):239-245.
86. Nakamura R, Ishiwatari A, Higuchi M, et al. Evaluation of the luciferase assay-based in vitro elicitation test for serum IgE. *Allergol Int*. 2012;61(3):431-437.
87. Kabasser S, Hafner C, Chinthrajah S, et al. Identification of Pru du 6 as a potential marker allergen for almond allergy. *Allergy*. 2021;76(5):1463-1472.
88. Kansen HM, van Erp FC, Knulst AC, et al. Accurate prediction of Peanut allergy in one-third of adults using a validated Ara h 2 cut-off. *J Allergy Clin Immunol Pract*. 2021;9(4):1667-1674.e3.
89. Kaur N, Mehr S, Katelaris C, et al. Added diagnostic value of peanut component testing: a cross-sectional study in Australian children. *J Allergy Clin Immunol Pract*. 2021;9(1):245-253.e4.
90. Keet C, Plesa M, Szelag D, et al. Ara h 2-specific IgE is superior to whole peanut extract-based serology or skin prick test for diagnosis of peanut allergy in infancy. *J Allergy Clin Immunol*. 2021;147(3):977-983.e2.
91. Keet CA, Johnson K, Savage JH, Hamilton RG, Wood RA. Evaluation of Ara h2 IgE thresholds in the diagnosis of peanut allergy in a clinical population. *J Allergy Clin Immunol Pract*. 2013;1(1):101-103.
92. Kianifar HR, Pourreza A, Jabbari Azad F, Yousefzadeh H, Masomi F. Sensitivity comparison of the skin prick test and serum and fecal radio Allergosorbent test (RAST) in diagnosis of FA in children. *Rep Biochem Mol Biol*. 2016;4(2):98-103.
93. Kido J, Hirata M, Ueno H, et al. Evaluation of the skin-prick test for predicting the outgrowth of cow's milk allergy. *Allergy Rhinol*. 2016;7(3):139-143.
94. Kim HY, Han Y, Kim K, et al. Diagnostic value of specific IgE to peanut and ara h 2 in Korean children with peanut allergy. *Allergy Asthma Immunol Res*. 2016;8(2):156-160.
95. Kim J, Kim HY, Park MR, et al. Diagnostic decision points of specific IgE concentrations in korean children with egg and cow's milk allergies. *Allergy Asthma Immunol Res*. 2015;7(4):332-338.
96. Kiykim A, Karakoc-Aydiner E, Gunes E, et al. Evaluation of a Standardized Bakery Product (SUTMEK) as a potential tool for baked-Milk tolerance and immunotherapy research studies. *Int Arch Allergy Immunol*. 2019;178(1):1-9.
97. Klemans RJ, Knol EF, Bruijnzeel-Koomen CA, Knulst AC. The diagnostic accuracy of specific IgE to Ara h 6 in adults is as good as Ara h 2. *Allergy*. 2014;69(8):1112-1114.
98. 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(11):1396-1402.
99. Klemans RJ, Liu X, Knulst AC, et al. IgE binding to peanut components by four different techniques: Ara h 2 is the most relevant in peanut allergic children and adults. *Clin Exp Allergy*. 2013;43(8):967-974.
100. Klemans RJ, Otte D, Knol M, et al. The diagnostic value of specific IgE to Ara h 2 to predict peanut allergy in children is comparable to a validated and updated diagnostic prediction model. *J Allergy Clin Immunol*. 2013;131(1):157-163.
101. Klemans RJB. Diagnosis of peanut allergy. *[Dutch]. Ned Tijdschr voor Dermatologie en Venereol*. 2014;24(5):239-241.
102. Kocacik Uygun DF, Filiz S, Bingol A. An evaluation of banana allergy in children living in the Mediterranean region. *Turk J Med Sci*. 2018;48(3):469-475.
103. Kos S, Sanders RJ, Neele M, O'Sullivan N, Ruikes-Mertens S, Phaff RAS. Preliminary study in specific activity of molecular components in allergy: implications for diagnostics and relationship with disease severity. *Clin Chem Lab Med*. 2017;55(6):e113-e117.
104. Kotaniemi-Syrjanen A, Csonka P, Pelkonen AS, Mäkelä MJ. Likelihood of immediate food challenge reactions varies by age, history, allergens, and levels of sensitization. *Pediatr Allergy Immunol Pulmonol*. 2017;30(1):45-52.
105. Kwan A, Asper M, Lavi S, Lavine E, Hummel D, Upton JE. Prospective evaluation of testing with baked milk to predict safe ingestion of baked milk in unheated milk-allergic children. *Allergy Asthma Clin Immunol*. 2016;12(1):54.
106. Lange L, Finger A, Buderus S, Ott H. The ratio between Cor a 1- and hazelnut-specific IgE predicts negative challenge outcome in children. *Pediatr Allergy Immunol Pulmonol*. 2015;28(1):7-12.
107. 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(4):598-603.
108. Leo SH, Dean JM, Jung B, Kuzeljevic B, Chan ES. Utility of Ara h 2 sIgE levels to predict peanut allergy in Canadian children. *J Allergy Clin Immunol Pract*. 2015;3(6):968-969.
109. Li PH, Rutkowski K, Kennard L, et al. Challenge-confirmed peanut allergy in older patients: performance of skin tests, specific immunoglobulin E, and ara h 2. *Ann Allergy Asthma Immunol*. 2018;120(3):334-335.
110. Lieberman JA, Glaumann S, Batelson S, Borres MP, Sampson HA, Nilsson C. The utility of Peanut components in the diagnosis of IgE-mediated peanut allergy among distinct populations. *J Allergy Clin Immunol Pract*. 2013;1(1):75-82.
111. Lindvik H, Lødrup Carlsen KC, Mowinckel P, Navaratnam J, Borres MP, Carlsen KH. Conjunctival provocation test in diagnosis of peanut allergy in children. *Clin Exp Allergy*. 2017;47(6):785-794.
112. Ludman S, Ballabeni P, Eigenmann PA, Wassenberg J. Predicting positive food challenges in children sensitised to peanuts/tree nuts. *Pediatr Allergy Immunol*. 2013;24(3):276-281.
113. Mabelane T, Basera W, Botha M, Thomas HF, Ramjith J, Levin ME. Predictive values of alpha-gal IgE levels and alpha-gal IgE: Total IgE

ratio and oral food challenge-proven meat allergy in a population with a high prevalence of reported red meat allergy. *Pediatr Allergy Immunol*. 2018;29(8):841-849.
114. Makela MJ, Eriksson C, Kotaniemi-Syrjänen A, et al. Wheat allergy in children – new tools for diagnostics. *Clin Exp Allergy*. 2014;44(11):1420-1430.
115. Makita E, Yanagida N, Sato S, Asaumi T, Ebisawa M. Increased ratio of pollock roe-specific IgE to salmon roe-specific IgE levels is associated with a positive reaction to cooked pollock roe oral food challenge. *Allergol Int*. 2018;67(3):364-370.
116. Marriage DE, Erlewyn-Lajeunesse M, Unsworth DJ, Henderson AJ. Unscrambling egg allergy: the diagnostic value of specific IgE concentrations and skin prick tests for ovomucoid and egg white in the management of children with hen's egg allergy. *ISRN Allergy*. 2012;2012:627545.
117. Martinet J, Couderc L, Renosi F, Bobée V, Marguet C, Boyer O. Diagnostic value of antigen-specific immunoglobulin e immunoassays against ara h 2 and ara h 8 peanut components in child FA. *Int Arch Allergy Immunol*. 2016;169(4):216-222.
118. 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(1):163-171.
119. Maruyama N, Sato S, Cabanos C, Tanaka A, Ito K, Ebisawa M. Gly m 5/Gly m 8 fusion component as a potential novel candidate molecule for diagnosing soya bean allergy in Japanese children. *Clin Exp Allergy*. 2018;48(12):1726-1734.
120. 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(2):393-399.
121. Masthoff LJ, Pasmans SG, Hoffen E, et al. Diagnostic value of hazelnut allergy tests including rCor a 1 spiking in double-blind challenged children. *Allergy*. 2012;67(4):521-527.
122. McWilliam V, Peters RL, Allen KJ, et al. Skin prick test predictive values for the outcome of cashew challenges in children. *J Allergy Clin Immunol Pract*. 2020;8(1):141-148.e2.
123. Mehlich J, Fischer J, Hilger C, et al. The basophil activation test differentiates between patients with alpha-gal syndrome and asymptomatic alpha-gal sensitization. *J Allergy Clin Immunol*. 2019;143(1):182-189.
124. Miceli Sopo S, Greco M, Cuomo B, et al. Matrix effect on baked egg tolerance in children with IgE-mediated hen's egg allergy. *Pediatr Allergy Immunol*. 2016;27(5):465-470.
125. Michaud B, Aroulandom J, Baiz N, et al. Casein-specific IL-4- and IL-13-secreting T cells: a tool to implement diagnosis of cow's milk allergy. *Allergy*. 2014;69(11):1473-1480.
126. Min TK, Jeon YH, Yang HJ, Pyun BY. The clinical usefulness of IgE antibodies against egg white and its components in Korean children. *Allergy Asthma Immunol Res*. 2013;5(3):138-142.
127. Nacaroglu HT, Erdem SB, Karaman S, et al. Diagnostic values for egg white specific IgE levels with the skin prick test in Turkish children with egg white allergy. *Allergol Immunopathol*. 2017;45(5):445-451.
128. Nilsson N, Sjölander S, Baar A, et al. Wheat allergy in children evaluated with challenge and IgE antibodies to wheat components. *Pediatr Allergy Immunol*. 2015;26(2):119-125.
129. Okamoto S, Taniuchi S, Sudo K, et al. Predictive value of IgE/IgG4 antibody ratio in children with egg allergy. *Allergy Asthma Clin Immunol*. 2012;8(1):9.
130. Pacharn P, Siripipattanamongkol N, Pannakapitak N, et al. Accuracy of in-house alcohol-dissolved wheat extract for diagnosing IgE-mediated wheat allergy. *Asian Pac J Allergy Immunol*. 2020;38(2):102-107.
131. Palosuo K, Kukkonen AK, Pelkonen AS, Mäkelä MJ. Gal d 1-specific IgE predicts allergy to heated egg in Finnish children. *Pediatr Allergy Immunol*. 2018;29(6):637-643.
132. Payot F, Berthiller J, Kassai B, Brunet AS, Villard-Truc F, Lachaux A. Practical interest of both skin prick test and specific IgE in the evaluation of tolerance acquisition in IgE mediated cow's milk allergy (CMA). A clinical retrospective study in a cohort of 184 children. *Allergol Immunopathol*. 2014;42(5):395-401.
133. Percival E, Bhatia R, Preece K, et al. Reproducibility of serum IgE, Ara h2 skin prick testing and fraction of exhaled nitric oxide for predicting clinical peanut allergy in children. *Allergy Asthma Clin Immunol*. 2016;12(1):35.
134. Peters RL, Allen KJ, Dharmage SC, et al. Natural history of peanut allergy and predictors of resolution in the first 4 years of life: A population-based assessment. *J Allergy Clin Immunol*. 2015;135:1257-1266.e1–2.
135. Peters RL, Allen KJ, Dharmage SC, et al. Skin prick test responses and allergen-specific IgE levels as predictors of peanut, egg, and sesame allergy in infants. *J Allergy Clin Immunol*. 2013;132(4):874-880.
136. Phisitbuntoon T, Jirapongsananuruk O, Pacharn P, et al. A potential role of gliadin extract skin prick test in IgE-mediated wheat allergy. *Asian Pac J Allergy Immunol*. 2023;41:37-44.
137. Preece K, Bhatia R, Belcher J, et al. The fraction of exhaled nitric oxide improves prediction of clinical allergic reaction to peanut challenge in children. *Clin Exp Allergy*. 2014;44(3):371-380.
138. Rayes H, Raza A A, Williams A, Matthews S, Arshad SH. Specific IgE to recombinant protein (Ber e 1) for the diagnosis of Brazil nut allergy. *Clin Exp Allergy*. 2016;46(4):654-656.
139. Rentzos G, Lundberg V, Lundqvist C, et al. Use of a basophil activation test as a complementary diagnostic tool in the diagnosis of severe peanut allergy in adults. *Clin Transl Allergy*. 2015;5(1):22.
140. Rodriguez-Catalan J, González-Arias AM, Casas AV, Camacho GDR. Specific IgE levels as an outcome predictor in egg-allergic children. *Allergol Immunopathol*. 2021;49(1):79-86.
141. Ruinemans-Koerts J, Schmidt-Hieltjes Y, Jansen A, Savelkoul HFJ, Plaisier A, van Setten P. The basophil activation test reduces the need for a food challenge test in children suspected of IgE-mediated cow's milk allergy. *Clin Exp Allergy*. 2019;49(3):350-356.
142. Sackesen C, Suárez-Fariñas M, Silva R, et al. A new Luminex-based peptide assay to identify reactivity to baked, fermented, and whole milk. *Allergy*. 2019;74(2):327-336.
143. Saf S, Sifers TM, Baker MG, et al. Diagnosis of sesame allergy: analysis of current practice and exploration of sesame component Ses i 1. *J Allergy Clin Immunol Pract*. 2020;8(5):1681-1688.e3.
144. Saifi M, Swamy N, Crain M, Brown LS, Bird JA. Tolerance of a high-protein baked-egg product in egg-allergic children. *Ann Allergy Asthma Immunol*. 2016;116(5):415-419.
145. Salari F, Bemanian MH, Fallahpour M, et al. Comparison of diagnostic tests with oral food challenge in a clinical trial for adult patients with sesame anaphylaxis. *Iran J Allergy Asthma Immunol*. 2020;19(1):27-34.
146. Santos AF, Bergmann M, Brough HA, et al. Basophil activation test reduces Oral food challenges to nuts and sesame. *J Allergy Clin Immunol Pract*. 2021;9(5):2016-2027.e6.
147. Santos AF, Couto-Francisco N, Bécares N, Kwok M, Bahnson HT, Lack G. A novel human mast cell activation test for peanut allergy. *J Allergy Clin Immunol*. 2018;142(2):689-691.e9.
148. Santos AF, Douiri A, Bécares N, et al. Basophil activation test discriminates between allergy and tolerance in peanut-sensitized children. *J Allergy Clin Immunol*. 2014;134(3):645-652. doi:10.1016/j.jaci.2014.04.039 Epub 2014 Jul 25.
149. Sato M, Shukuya A, Sato S, et al. Oral challenge tests for soybean allergies in Japan: a summary of 142 cases. *Allergol Int*. 2016;65(1):68-73.
150. Sato S, Ogura K, Takahashi K, Sato Y, Yanagida N, Ebisawa M. 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(2):296-301.

151. Savvatianos S, Konstantinopoulos AP, Borgå Å, 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(1):192-194.
152. Schots M, de Mol AC, Vermeer HJ, Roosen YM, Vriesman AW. Is Ara h 2 indeed the best predictor for peanut allergy in Dutch children? *Diagnosi*. 2016;3(1):31-35.
153. Simms E, Foster G, Arias K, et al. Prediction of clinical peanut allergy status among children in Hamilton, Ontario using chart review data collected during 2012–2015. *Allergy Asthma Clin Immunol*. 2017;13(1):10.
154. Sindher S, Long AJ, Purington N, et al. Analysis of a large standardized food challenge data set to determine predictors of positive outcome across multiple allergens. *Front Immunol*. 2018;9:2689.
155. Sirin Kose S, Asilsoy S, Uzuner N, Karaman O, Anal O. Outcomes of baked Milk and egg challenge in cow's milk and hen's egg allergy: can tolerance Be predicted with allergen-specific IgE and prick-to-prick test? *Int Arch Allergy Immunol*. 2019;180(4):264-273.
156. Sripramong C, Visitsunthorn K, Srisuwatchari W, Pacharn P, Jirapongsananuruk O, Visitsunthorn N. Food sensitization and FA in allergic Thai patients from a tertiary care center in Thailand. *Asian Pac J Allergy Immunol*. 2022;40:147-154.
157. Suarez-Farinas M, Suprun M, Kearney P, et al. Accurate and reproducible diagnosis of peanut allergy using epitope mapping. *Allergy*. 2021;76:3789-3797.
158. Takahashi H, Matsuo H, Chinuki Y, et al. Recombinant high molecular weight-glutenin subunit-specific IgE detection is useful in identifying wheat-dependent exercise-induced anaphylaxis complementary to recombinant omega-5 gliadin-specific IgE test. *Clin Exp Allergy*. 2012;42(8):1293-1298.
159. Tan JW, Campbell DE, Turner PJ, et al. Baked egg food challenges – clinical utility of skin test to baked egg and ovomucoid in children with egg allergy. *Clin Exp Allergy*. 2013;43(10):1189-1195.
160. Thalayasingam M, Gerez IFA, Yap GC, et al. Clinical and immunochemical profiles of food challenge proven or anaphylactic shrimp allergy in tropical Singapore. *Clin Exp Allergy*. 2015;45(3):687-697.
161. Topcu ZIK, Kaklıkkaya N, Baki A, Orhan F. Characteristics of beef allergy in schoolchildren in Turkey. *Allergy Asthma Proc*. 2018;39(1):59-65.
162. Tosca MA, Pistorio A, Accogli A, Silvestri M, Rossi GA, Ciprandi G. Kiwifruit anaphylaxis: the usefulness of molecular-based allergy diagnostics. *J Investig Allergol Clin Immunol*. 2015;25(3):227-229.
163. Tuano KTS, Anvari S, Hanson IC, et al. Improved diagnostic clarity in shrimp allergic non-dustmite sensitized patients. *Allergy Asthma Proc*. 2018;39(5):377-383.
164. Turner PJ, Kumar K, Fox AT. Skin testing with raw egg does not predict tolerance to baked egg in egg-allergic children. *Pediatr Allergy Immunol*. 2014;25(7):657-661.
165. Uncuoglu A, Cogurlu MT, Eser Simsek I, Ergul N, Baydemir C, Aydogan M. Predicting outgrowth of IgE-mediated cow's milk allergy: diagnostic tests in children under two years of age. *Allergol Immunopathol*. 2019;47(5):449-456.
166. Uncuoglu A, Eser Simsek I, Cogurlu MT, Baydemir C, Aydogan M. Utility of fresh egg skin prick test and egg yolk specific immunoglobulin E for outgrowth. *Ann Allergy Asthma Immunol*. 2020;125(4):418-424.
167. van der Valk JPM, van Gerth Wijk R, Hoorn E, Groenendijk L, Groenendijk IM, de Jong NW. Measurement and interpretation of skin prick test results. *Clin Transl Allergy*. 2016;6(1):8.
168. van Erp FC, Knol EF, Pontoppidan B, Meijer Y, van der Ent CK, Knulst AC. The IgE and basophil responses to Ara h 2 and Ara h 6 are good predictors of peanut allergy in children. *J Allergy Clin Immunol*. 2017;139(1):358-360.e8.
169. van Veen WJ, Dikkeschei LD, Roberts G, Brand PL. Predictive value of specific IgE for clinical peanut allergy in children: relationship with eczema, asthma, and setting (primary or secondary care). *Clin Transl Allergy*. 2013;3(1):1-7.
170. Vazquez-Ortiz M, Pascal M, Jiménez-Feijoo R, et al. Ovalbumin-specific IgE/IgG4 ratio might improve the prediction of cooked and uncooked egg tolerance development in egg-allergic children. *Clin Exp Allergy*. 2014;44(4):579-588.
171. Vidal C, Bartolomé B, Rodríguez V, Armisén M, Linneberg A, González-Quintela A. Sensitization pattern of crustacean-allergic individuals can indicate allergy to molluscs. *Allergy*. 2015;70(11):1493-1496.
172. Virkud YV, Chen YC, Stieb ES, et al. Analysis of oral food challenge outcomes in IgE-mediated food allergies to almond in a large cohort. *J Allergy Clin Immunol Pract*. 2019;7(7):2359-2368.e3.
173. Wai CYY, Leung NYH, Leung ASY, et al. Cell-based functional IgE assays are superior to conventional allergy tests for shrimp allergy diagnosis. *J Allergy Clin Immunol Pract*. 2021;9(1):236-244.e9.
174. Yanagida N, Sato S, Maruyama N, et al. Specific IgE for fag e 3 predicts oral buckwheat food challenge test results and anaphylaxis: a pilot study. *Int Arch Allergy Immunol*. 2018;176(1):8-14.
175. Yanagida N, Sato S, Takahashi K, et al. Skin prick test is more useful than specific IgE for diagnosis of buckwheat allergy: a retrospective cross-sectional study. *Allergol Int*. 2018;67(1):67-71.
176. Yavuz ST, Buyuktiryaki B, Sahiner UM, et al. Factors that predict the clinical reactivity and tolerance in children with cow's milk allergy. *Ann Allergy Asthma Immunol*. 2013;110(4):284-289.
177. Yavuz ST, Sahiner UM, Buyuktiryaki B, et al. Role of specific IgE in predicting the clinical course of lentil allergy in children. *Pediatr Allergy Immunol*. 2013;24(4):382-388.
178. Zivanovic M, Atanasković-Marković M, Medjo B, et al. Evaluation of FA in children by skin prick tests with commercial extracts and fresh foods, specific IgE and, open oral food challenge-our five years experience in FA work-up. *Iran J Allergy Asthma Immunol*. 2017;16(2):127-132.
179. Luo Y, Bonagura VR, Rosenthal D. Variability of major allergens in commercially available peanut extracts for skin prick testing. *J Allergy Clin Immunol*. 2014;133(2):AB109.
180. Ruethers T, Taki AC, Nugraha R, et al. Variability of allergens in commercial fish extracts for skin prick testing. *Allergy*. 2019;74(7):1352-1363.
181. Asero R, Scala E, Villalta D, et al. Shrimp allergy: analysis of commercially available extracts for in vivo diagnosis. *J Investig Allergol Clin Immunol*. 2017;27(3):175-182.
182. Wang J, Liu W, Zhou C, et al. Multi-perspective observation on the prevalence of FA in the general Chinese population: a meta-analysis. *Nutrients*. 2022;14(23):5181.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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