

Accuracy of component-resolved diagnostics in peanut allergy: Systematic literature review and meta-analysis

Caroline Nilsson¹  | Malin Berthold² | Barbara Mascialino² | Michelle E Orme³ | Sigrid Sjölander² | Robert G Hamilton⁴

¹Dept. Clinical Science and Education, Karolinska Institutet, Sachs' Children and Youth Hospital, Sodersjukhuset, Stockholm, Sweden

²Thermo Fisher Scientific, Uppsala, Sweden

³ICERA Consulting Ltd, Swindon, UK

⁴Johns Hopkins University School of Medicine, Baltimore, MD, USA

Correspondence

Caroline Nilsson, Dept. Clinical Science and Education, Karolinska Institutet, Sachs' Children and Youth Hospital, Sodersjukhuset 118 83 Stockholm, Sweden.
Email: Caroline.A.Nilsson@sl.se

Funding information

This work was supported by Thermo Fisher Scientific.

Editor: Hugh Sampson

Abstract

Background: Peanut allergy diagnosis relies on clinical reactivity to peanut supported by detection of specific IgE (sIgE) antibodies. Extract-based sIgE tests have low specificity, so component-resolved diagnostics may complement whole-extract testing.

Methods: We systematically collected peanut allergen component data in seven databases and studied the diagnostic accuracy of peanut storage proteins (Arah1, 2, 3) and cross-reactive peanut proteins (Arah8 PR-10 and Arah9 lipid transfer protein) through meta-analyses. The systematic literature review included studies employing peanut components and oral food challenge (OFC) as reference standard in patients suspected of peanut allergy. Data for component sIgE at pre-defined detection thresholds were extracted and combined in random-effects bivariate meta-analyses. Risk of bias was assessed as recommended by Cochrane, with two additional quality items of importance for this review.

Results: Nineteen eligible studies presented data suitable for meta-analysis. In cross-sectional pediatric studies, the pooled sensitivity of Arah2-sIgE at 0.35 kU_A/L cutoff was 83.3% [95% CI 75.6, 88.9] and specificity in diagnosing objective peanut allergy was 83.6% [95% CI 77.4, 88.4]. Compared with 0.1 and 1.0 kU_A/L, this threshold provided the best diagnostic accuracy. At 0.35 kU_A/L, Arah1 and Arah3 had comparable specificity (86.0% and 88.0%, respectively) but significantly lower sensitivity compared with Arah2 (37.0% and 39.1%, respectively; $P < .05$).

Conclusion: sIgE to Arah2 can enhance the certainty of diagnosis and reduce the number of OFC necessary to rule out clinical peanut allergy in unclear cases.

KEYWORDS

allergen, Arah1, Arah2, Arah3, Arah8, component-resolved diagnostics, peanut, storage protein

1 | INTRODUCTION

Peanut allergy, particularly in children, is a significant medical concern worldwide, with a rising prevalence and increased healthcare

costs.^{1,2} Clinical symptoms range from oral itching or tingling, localized urticaria, nausea, abdominal pain, vomiting, wheezing, and breathlessness to systemic life-threatening anaphylaxis.³ Peanut extract specific immunoglobulin E (sIgE) is measured for diagnosis,⁴ but traditional extract-based sensitization tests are limited by a low

specificity (59%, 95% confidence interval [CI] 45%-72%),⁵ as sIgEs to proteins of little clinical relevance are also measured. In recent years, the development of peanut allergen component-resolved diagnostics (CRD) has provided additional diagnostic information and complementary clinical value.⁶ In CRD, sIgE to individual allergens is measured, and sensitization to primary and cross-reactive peanut allergens can be distinguished.⁷

Several peanut component proteins have been described.⁸ Arah1, 2, and 3 are heat- and proteolysis-resistant seed storage proteins that are considered major peanut allergens. Further, Arah5, 8, and 9 allergens belong, respectively, to the profilin, Betv1 homologue, and lipid transfer protein (LTP) families. Arah4 is an isoform of Arah3, while Arah6 is structurally similar to Arah2.⁹ Seed storage proteins have limited potential for cross-reactivity, which is relevant for diagnostic purposes, because IgE to highly cross-reactive allergenic molecules lack specificity.⁶ Studies have shown that sensitization to storage proteins in nuts and seeds is associated with more severe symptoms, while sensitization to pollen cross-reactive PR-10 proteins, homologous to the major birch pollen allergen Betv1, predominantly induces mild local symptoms (oral allergy syndrome).¹⁰ Sensitization to the heat and enzyme-stable non-specific LTP with cross-reacting epitopes to other nsLTP is common in the Mediterranean area.¹¹

There have been recent attempts to systematically search the literature to summarize the diagnostic accuracy of peanut components through meta-analyses^{12,13}; however, as too few studies met the inclusion criteria in those reviews, only narrative syntheses were presented. In light of the growing number of studies using CRD in the diagnosis of peanut allergy, we conducted a systematic literature review with the objective of assessing the quality and consistency of evidence that sensitization to components is helpful in reducing both the time to diagnosis and the need for oral food challenges (OFC). In our study, quantitative meta-analyses were conducted to summarize the findings and determine the diagnostic accuracy of peanut storage proteins (Arah1, 2, 3), the PR-10 protein Arah8, and the Arah9 LTP at pre-defined cutoffs in patients suspected of peanut allergy based on previous reactions or sensitization to peanut.

2 | METHODS

2.1 | Search strategy

Seven electronic databases were systematically searched (MEDLINE, MEDLINE In-Process, EMBASE, PubMed, Cochrane Central Register of Controlled Trials, NIH Clinicaltrials.gov, and WHO International Clinical Trials Registry Platform) for records published prior to October 3, 2018, using the search terms "peanut hypersensitivity" or "nut hypersensitivity" as index terms with peanut* or groundnut* or hazelnut* or cobnut* or filbert* and allerg* or sensitivit* or hypersensitiv* or reaction in the title or abstract, and with "immunoglobulin e" as an index term or "immunoglobulin e" or "sIgE" in

Key Message

We present the first meta-analysis on diagnostic accuracy of peanut components in patients suspected of peanut allergy. We demonstrate that sIgE to peanut storage proteins Arah1, 2 and 3 are highly specific for objective peanut allergy in children, while Arah8- and Arah9-sIgE are of low clinical relevance. We highlight Arah2 as a key marker of high accuracy in children. sIgE to Arah2 could increase the certainty of peanut allergy diagnosis. A correct final diagnosis could be reached more quickly and safely, and reduce the number of oral food challenges needed.

the abstract or title. A first literature search was conducted up to January 22, 2016, and an updated literature search was done from January 2016 to October 3, 2018. Complementary hand searching of reference lists of selected systematic reviews published between 2011 and October 3, 2018, in relevant allergy journal websites was also undertaken. The detailed search strategy is available on request.

2.2 | Inclusion criteria and data extraction

Included studies meeting pre-defined eligibility criteria were published in English between January 1, 2010, and October 3, 2018, enrolled at least 15 patients of any age suspected of peanut allergy, and where sIgE to at least one peanut allergen component (Arah1, 2, 3, 6, 8, 9) had been measured. Oral food challenges (blind or open) was the reference standard; exceptions included patients classified as peanut allergic based on a recent anaphylaxis event or other convincing evidence confirmed by an allergist. To be included in the review, a minimum of 50% of patients must have received an OFC.

Reviews, abstracts, case reports, and editorials were excluded. Full-text articles were reviewed by two external independent expert analysts, and disagreements were resolved through discussion. Extracted data were summarized into 2 × 2 tables describing the index test results at each reported cutoff (Table S1). Since data at pre-defined thresholds were extracted, studies using semi-quantitative methods for sIgE determinations were not included. A meta-analysis that includes studies with mixed thresholds will produce an estimate that relates to an unspecified average threshold that is not clinically meaningful.¹⁴ Therefore, to be included in the meta-analysis, peanut component data needed to be reported at a cutoff of either 0.10, 0.35, 1.0, or 5.0 kU_A/L. Peanut extract sIgE data at 0.35 kU_A/L were used as a reference for results interpretation.

The reviewers assessed risk of bias of the included studies using 11 quality items listed in the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy,¹⁵ plus an additional two quality items of importance for this review ("Were cutoff values established before the study was started?" and "Was the study free of commercial funding?"). As per the Cochrane recommendations, a

benchmarking exercise was conducted prior to the quality assessment to determine the minimum criteria for each quality item. A quality item was coded “yes” if it met the benchmark criteria, “no” if it did not meet the benchmark criteria, or “unclear” if there was insufficient information available to make a judgment.¹⁵

2.3 | Diagnostic accuracy determination—statistical analyses

From the constructed 2×2 tables, we calculated estimates of sensitivity and specificity with 95% CIs, and the data were visualized as paired forest plots. The Lieberman et al study¹⁶ covered four sites, one of which (Site 2) included a patient population that was not relevant (treated/immunotherapy). One cohort in the Lieberman et al study¹⁶ (Site 4) was identical to the cohort investigated by Glaumann et al¹⁷ and already included in the analysis dataset; therefore, data from this cohort were not included in the meta-analysis.

The primary diagnostic meta-analysis included all studies that met the inclusion criteria presenting data at the pre-defined threshold $0.35 \text{ kU}_A/\text{L}$. Secondary diagnostic meta-analyses focused on pediatric subjects and, depending on the availability of data, were performed at the commonly used $0.10 \text{ kU}_A/\text{L}$ (the analytical limit of detection) and $0.35 \text{ kU}_A/\text{L}$ thresholds applied in the retrieved studies and also at $1.0 \text{ kU}_A/\text{L}$ for sIgE to Arah2. For each analysis and threshold, a random-effects meta-analysis model using the Reitsma bivariate method¹⁸ was run to estimate the tests' pooled sensitivities, pooled specificities, and area under the curve (AUC). Outcomes were plotted as forest plots and as summary receiver operating characteristic (sROC) curves. From sROC analyses, the tests' diagnostic accuracies were considered significantly different if there was no overlap of the 95% CIs ellipses. Heterogeneity was assessed with the Higgins I^2 test,¹⁹ which is the total between study variance divided by the total variance expressed as a percentage; when I^2 is lower than 40%, the heterogeneity between studies is considered low.²⁰ Diagnostic odds ratios (DOR) and positive and negative likelihood ratios (LR+/LR-) were calculated; LRs 95% CIs were calculated using the Log method.²¹ The “Mada” package of the statistical software R (version 3.3.0)^{22,23} was used to fit all analyses.¹⁸ The statistical significance level was set at 0.05.

2.4 | Estimation of predicted clinical implications

The clinical implications of the key findings from the diagnostic meta-analyses were calculated and projected using the average disease prevalence from the included pediatric studies to estimate the percentage of patients who would be accurately diagnosed with peanut components at 0.10 and $0.35 \text{ kU}_A/\text{L}$ cutoffs. Results were grouped as “correctly classified” (the sum of true positives [TPs] and true negatives [TNs]) – or “incorrectly classified” (the sum of false positives [FPs] and false negatives [FNs]).

3 | RESULTS

3.1 | Study characteristics and methodological quality

The systematic literature search identified 2225 unique citations. After excluding 2025 citations, 200 publications were reviewed in full leading to the identification of 19 studies relevant for inclusion in the meta-analysis (Figure 1A, Table 1).^{16,17,24-39}

The included studies presented data from Europe, the United States, Canada, Asia, and Australia. Seventeen concerned only infants/children (<18 years), one included adults only, and one reported data on a mixed adult-child population (Table 1).²⁴ A cross-sectional design was used in 17 studies, while two studies had a case-control design. The diagnostic accuracy at the $0.35 \text{ kU}_A/\text{L}$ threshold was reported in 16 studies for Arah2-sIgE,^{16,17,24-26,28-32,34-37,39} in 8 studies for Arah1-and Arah3-sIgE,^{16,17,24,28,32,35,36} and in 9 studies for Arah8-sIgE (Table 1).^{16,17,24,28,32,35,36,39} Finally, six studies reported data for Arah9 at the $0.35 \text{ kU}_A/\text{L}$ cutoff.^{17,24,28,29,35,36} In all included studies, the same assay platform was used to quantify sIgE levels (ImmunoCAP™). Extracted data underlying the primary and secondary meta-analyses are listed in the online supplement (Table S1).

The assessment of methodological quality of included studies indicated that no concerns regarding the applicability of the studies were found. Eight studies were marked down because a positive OFC could have been determined by subjective clinical symptoms, or diagnosis of peanut allergy was based on subjective clinical evidence of allergy other than anaphylaxis.^{24,27,29-31,34,35,38} Eight studies were marked down because not all patients received the same reference standard. Some patients were classified based on OFC and others based on clinical history or previous anaphylaxis. This does not imply that the methodological quality of these studies was low; differential verification of disease status is standard practice since OFC would not be appropriate for all patients.^{24,25,27,30,31,34,35,37,39} Some studies were marked down for using both blind and open OFC, but the rationale for not using double-blind placebo controlled food challenge (DBPCFC) in younger patients was justified, as per clinical recommendations. Overall, the risk of bias in the studies included in the analyses did not compromise the quality of our diagnostic meta-analyses (Figure 1B). A detailed analysis is provided in the online supplement (Table S2).

3.2 | Diagnostic accuracy determination—meta-analyses

3.2.1 | Primary analysis: all included studies at $0.35 \text{ kU}_A/\text{L}$

Forest plots of diagnostic sensitivity and specificity of each component sIgE at $0.35 \text{ kU}_A/\text{L}$ cutoff per included study are shown in Figure 2. Across studies, the diagnostic sensitivity of Arah2-sIgE

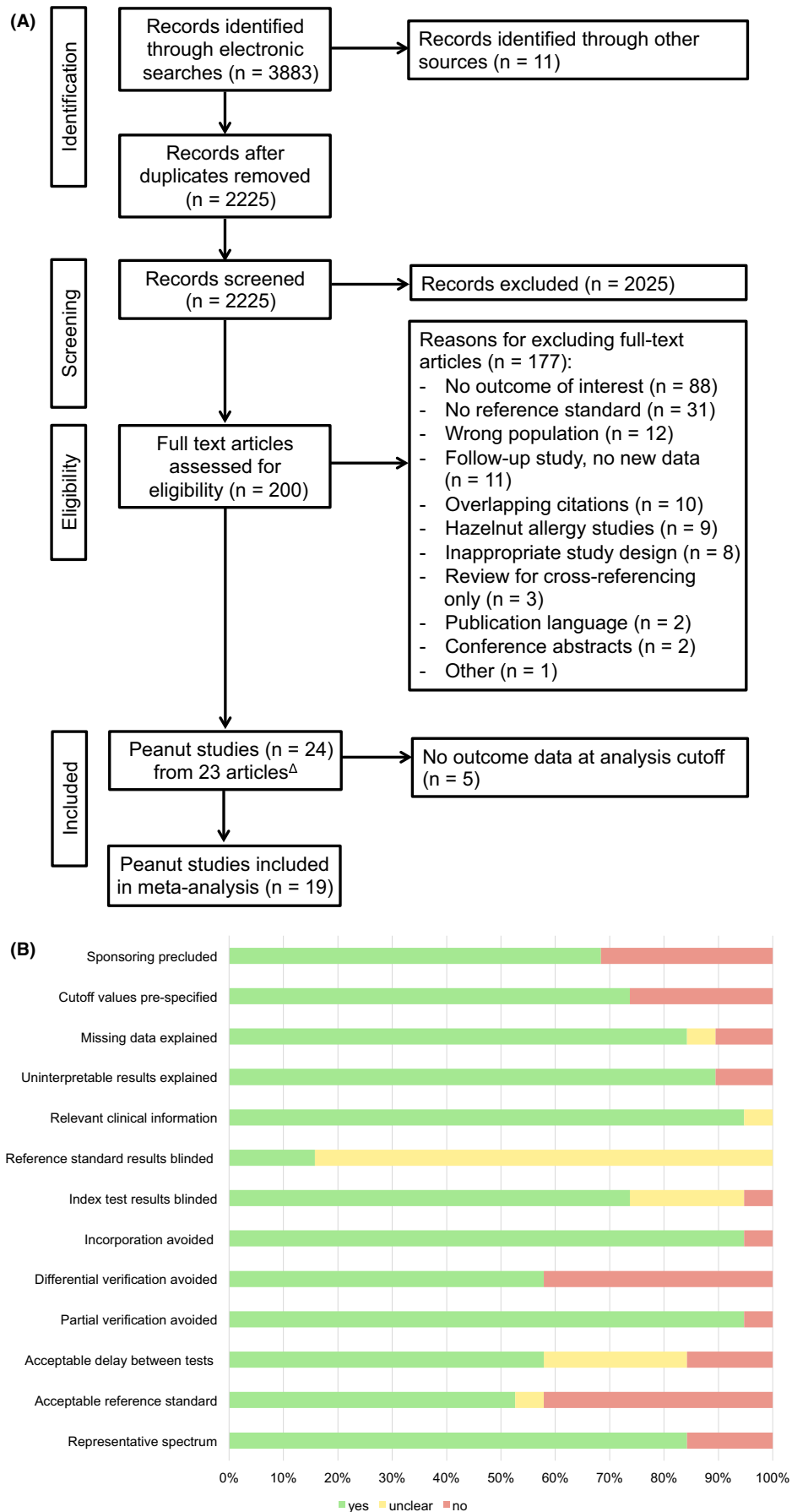


FIGURE 1 Study characteristics. A, PRISMA flow diagram of included studies ^ΔLiebermann et al report two studies of interest.¹⁶ B, Risk of bias and applicability concerns. Reviewer judgments on 13 quality items presented as percentages across included studies

TABLE 1 Study characteristics

Study	Population (N)	Age range, y	Country	Design	Reference standard	Technique used	Peanut component/ extract	IgE cutoff relevant for meta-analyses (kU _A /L)
Beyer et al (2015) ²⁵	Children (210)	2.1-7.7	Germany	CS	DBPCFC or open OFC	Quantitative	Arah2	0.1, 0.35, 1.0
							Peanut extract	0.1, 0.35, 1.0
Ebisawa et al (2012) ²⁸	Children (57)	2-13	Japan	CS	Open OFC	Quantitative	Arah1	0.1, 0.35
							Arah2	0.1, 0.35
							Arah3	0.1, 0.35
							Arah8	0.1, 0.35
							Arah9	0.1, 0.35
							Peanut extract	0.1, 0.35
Ebisawa et al (2015) ²⁷	Children (165)	1-16	Japan	CS	Open OFC or detailed anamnesis	Quantitative	Arah2	0.1
							Peanut extract	0.1
Glaumann et al (2012) ¹⁷	Children (38)	4-19	Sweden	CS	DBPCFC	Quantitative	Arah1	0.1, 0.35
							Arah2	0.1, 0.35
							Arah3	0.1, 0.35
							Arah8	0.1, 0.35
							Arah9	0.1, 0.35
							Peanut extract	0.1, 0.35
Keet et al (2013) ²⁹	Children (61)	2.2-18.2	USA	CS	Open OFC	Quantitative/ Semi- quantitative	Arah1	0.1
							Arah2	0.1, 0.35
							Arah3	0.1
							Arah8	0.1
							Arah9	0.1, 0.35
Klemans et al (2013a) ³⁰	Adults (94)	30 ± 12.5	The Netherlands	CS	DBPCFC	Quantitative	Arah2	0.1, 0.35, 1.0
Klemans et al (2013b) ³¹	Children (100)	4-8	The Netherlands	CS	DBPCFC or open OFC	Quantitative	Arah2	0.35, 1.0
Kukkonen et al (2015) ³²	Children (102)	6-18	Finland	CS	DBPCFC	Quantitative/ Semi- quantitative	Arah1	0.35
							Arah2	0.35
							Arah3	0.35
							Arah8	0.35
Leo et al (2015) ³³	Children (30)	3-18	Canada	CS	Open OFC	Quantitative	Arah2	1.0
Lieberman et al (2013) Site 1: Mount Sinai ^{b16}	Children (45)	IQR 5-10.5	USA	CS	DBPCFC	Quantitative	Arah1	0.35
							Arah2	0.35
							Arah3	0.35
							Arah8	0.35
							Peanut extract	0.35

(Continues)

TABLE 1 (Continued)

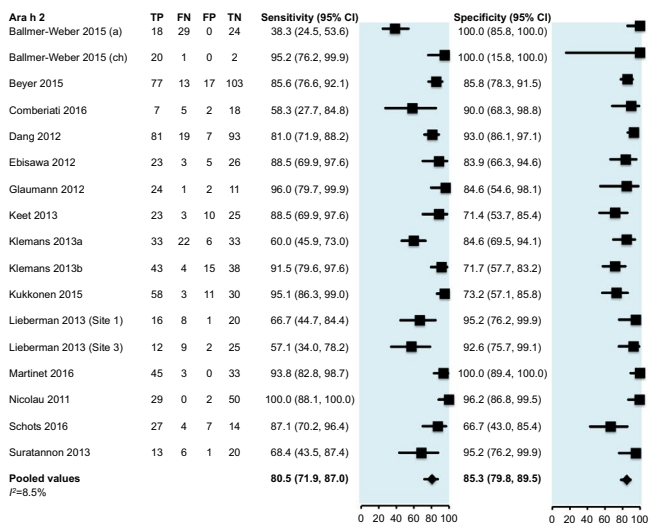
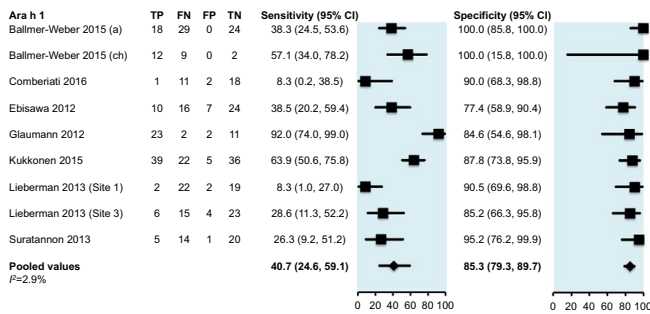
Study	Population (N)	Age range, y	Country	Design	Reference standard	Technique used	Peanut component/ extract	IgE cutoff relevant for meta-analyses (kU _A /L)
Lieberman et al (2013) Site 3: Sachs Open ^{b16}	Children (48)	IQR 6-13.5	Sweden	CS	Open OFC	Quantitative	Arah1	0.35
							Arah2	0.35
							Arah3	0.35
							Arah8	0.35
							Peanut extract	0.35
Nicolaou et al (2011) ³⁴	Children (81)	7-14	UK	CS	OFC or a convincing history	Quantitative	Arah2	0.35
Suratannon et al (2013) ³⁵	Children (40)	5-18	Thailand	CS	OFC	Quantitative	Peanut extract	0.35
							Arah1	0.35
							Arah2	0.35
							Arah3	0.35
							Arah8	0.35
Ballmer-Weber et al (2015) ²⁴	Children and adults (94)	NR	EUR ^a	CC	DBPCFC or a case history of anaphylaxis	Quantitative	Arah9	0.35
							Arah1	0.1, 0.35
							Arah2	0.1, 0.35
							Arah3	0.1, 0.35
							Arah8	0.1, 0.35
Dang et al (2012) ²⁶	Infants (200)	11-15 mo	Australia	CC	OFC	Quantitative	Arah9	0.1, 0.35
							Arah2	0.1, 0.35
							Peanut extract	0.35
							Arah1	0.35
							Arah2	0.35
Comberiati et al (2016) ³⁶	Children (32)	IQR 6-11	Italy	CS	Open OFC	Quantitative	Arah3	0.35
							Arah8	0.35
							Arah9	0.35
							Peanut extract	0.35
							Arah2	0.35
Martinet et al, 2016 ³⁹	Children (81)	7.7 (SD 4.4)	France	CS	Open OFC or recent severe anaphylaxis	Quantitative	Arah8	0.35
							Peanut extract	0.35
							Arah2	0.35
Schots et al (2016) ³⁷	Children (52)	5 (SD 4.2)	The Netherlands	CS	Open OFC or DBPCFC	Quantitative	Arah2	0.35
Van Erp et al (2017) ³⁸	Children (81)	IQR 5.5-10.9	The Netherlands	CS	DBPCFC	Quantitative	Arah2	0.1

Abbreviations: CC, case-control; CS, cross-sectional; DBPCFC, double-blind placebo controlled food challenge; IQR, interquartile range; NR, not reported; OFC, oral food challenge; SD, standard deviation.

^aBulgaria, Czech Republic, France, Greece, Iceland, Italy, the Netherlands, Poland, Lithuania, Spain, Switzerland, and UK.

^bLieberman et al 2013¹⁶ reported data from four study sites. Site 2 was not included because it involved the wrong study population (clinical trial of allergy treatment). Site 4 was the same population as Glaumann et al, 2012.¹⁷

(A1)



(B)

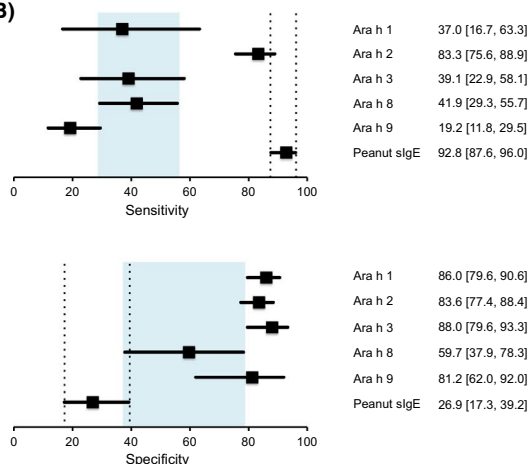
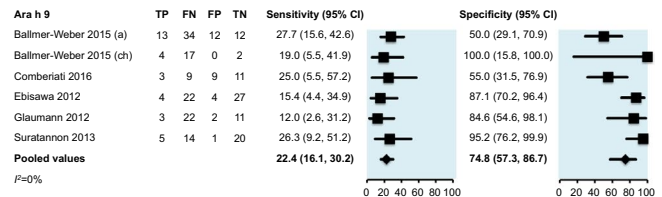
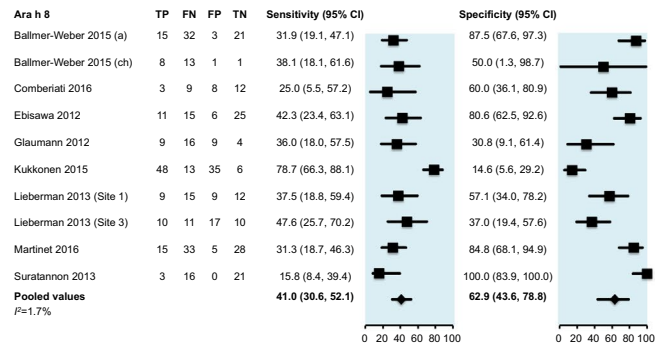
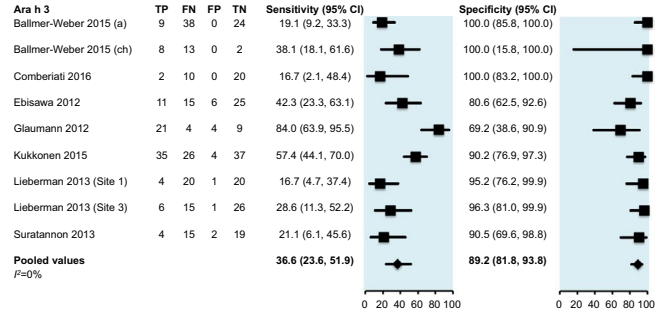


FIGURE 2 Diagnostic accuracy of slgE to peanut components. A, Sensitivity and specificity of slgE to peanut components per included study, with pooled estimates (primary analysis: 0.35 kU_A/L cutoff). (a), adults; (ch), children; CI, confidence interval; FN, false negatives; FP, false positives; TN, true negatives; TP, true positives. B, Pooled estimates of sensitivity and specificity for peanut component slgE and slgE to peanut extract at 0.35 kU_A/L threshold in cross-sectional pediatric studies (secondary analysis). Based on data from^{16,17,25,28,29,31-37,39}

varied from 38.3% to 100.0%, while the specificity ranged from 66.7% to 100.0%. Ara h1-slgE and Ara h3-slgE showed similar sensitivities and specificities within studies (Figure 2), with larger differences in sensitivities (8.3%-92.0% for Ara h1 and 16.7%-84.0% for Ara h3) than specificities (77.4%-100.0% for Ara h1 and 69.2%-100.0% for Ara h3). Ara h8-slgE showed broad variation in both sensitivity (15.8%-78.7%) and specificity (14.6%-100.0%) between

(A2)



studies. Ara h9 sensitivity values ranged between 12.0% and 27.7% and displayed some variation in specificity (50%-100%).

The average pooled sensitivity of Ara h2-slgE (80.5% [95% CI 71.9, 87.0]) differed significantly ($P < .05$) from that of other peanut components included in the analysis: Ara h1-slgE (40.7% [24.6, 59.1], Ara h3-slgE (36.6% [23.6, 51.9], Ara h8-slgE (41.0% [30.6, 52.1]), and Ara h9-slgE (22.4% [16.1, 30.2]). The average pooled specificity of

TABLE 2 Analysis of pediatric cross-sectional studies: pooled sensitivity and specificity (bivariate analyses) for all components and for peanut extract at common thresholds

Component or extract/threshold	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	AUC	DOR [95% CI]	LR+ [95% CI]	LR- [95% CI]
Arah1						
0.10 kU _A /L	64.5 [27.1, 89.9]	61.9 [42.2, 78.4]	0.66	3.3 [0.9, 12.6]	1.69 [1.22, 2.35]	0.57 [0.41, 0.81]
0.35 kU _A /L	37.0 [16.7, 63.3]	86.0 [79.6, 90.6]	0.85	4.3 [1.5, 12.2]	2.64 [1.75, 3.99]	0.73 [0.65, 0.83]
Arah2						
0.10 kU _A /L	92.1 [88.2, 94.8]	62.8 [55.3, 69.7]	0.89	27.4 [11.4, 65.8]	2.48 [2.16, 2.84]	0.13 [0.09, 0.18]
0.35 kU _A /L	83.3 [75.6, 88.9]	83.6 [77.4, 88.4]	0.90	29.1 [17.7, 47.9]	5.08 [4.14, 6.23]	0.2 [0.16, 0.25]
1.0 kU _A /L	71.2 [63.8, 77.6]	88.7 [80.2, 93.8]	0.82	23.9 [8.2, 69.8]	6.3 [4.29, 9.25]	0.32 [0.26, 0.41]
Arah3						
0.10 kU _A /L	61.9 [24.0, 89.3]	55.0 [36.4, 72.2]	0.58	2.3 [0.5, 11.0]	1.38 (1.02, 1.86)	0.69 [0.49, 0.98]
0.35 kU _A /L	39.1 [22.9, 58.1]	88.0 [79.6, 93.3]	0.80	5.6 [3.1, 9.9]	3.26 (2.11, 5.03)	0.69 [0.61, 0.79]
Arah8						
0.10 kU _A /L	44.7 [23.3, 68.4]	57.2 [35.1, 76.8]	0.51	1.0 [0.3, 3.6]	1.04 (0.78, 1.40)	0.97 [0.77, 1.21]
0.35 kU _A /L	41.9 [29.3, 55.7]	59.7 [37.9, 78.3]	0.47	1.0 [0.5, 1.8]	1.04 (0.83, 1.30)	0.97 [0.83, 1.14]
Arah9						
0.10 kU _A /L	32.4 [14.4, 57.7]	77.8 [66.9, 85.9]	0.77	1.5 [0.3, 6.3]	1.46 (0.86, 2.46)	0.87 [0.72, 1.06]
0.35 kU _A /L	19.2 [11.8, 29.5]	81.2 [62.0, 92.0]	0.21	1.1 [0.4, 3.1]	1.02 (0.55, 1.91)	1.00 [0.86, 1.15]
Peanut extract slgE						
0.35 kU _A /L	92.8 [87.6, 96.0]	26.9 [17.3, 39.2]	0.79	5.2 [1.8, 14.8]	1.27 (1.18, 1.37)	0.27 [0.17, 0.42]

Note: Arah1 and Arah3 data from^{16,17,28,29,32,35,36}; Arah2 data from^{16,17,25,27-29,31-39}; Arah8 data from^{16,17,28,29,32,35,36,39}; Arah9 data from^{17,28,29,35,36}; peanut extract data from^{16,17,25,28,33,34,36,39}

Abbreviations: AUC, area under the curve; CI, confidence interval; DOR, diagnostic odds ratio; LR, likelihood ratio.

Arah8 slgE (62.9% [43.6, 78.8]) differed significantly ($P < .05$) from that of the peanut storage proteins included in the analysis: Arah1-slgE (85.3% [79.3, 89.7]), Arah2-slgE (85.3% [79.8, 89.5]), and Arah3-slgE (89.2% [81.8, 93.8]).

3.2.2 | Secondary analysis—cross-sectional pediatric studies

To increase the stringency, all further analyses focused on data from cross-sectional pediatric studies only, excluding data from one adult study³⁰ and two case-control studies.^{24,26} The pooled sensitivity of slgE to Arah2 (83.3% [75.6, 88.9]) at 0.35 kU_A/L cutoff was significantly higher than that of any other peanut component slgE ($P < .05$, Figure 2B). No difference in pooled sensitivities was detected between slgE to Arah1, Arah3, or Arah8 (ranging from 39.1% for Arah2-slgE to 41.9% for Arah8-slgE (Figure 2B, Table 2). Arah9 sensitivity was lower than Arah1, 3, and 8, although not significantly (19.2% [11.8, 29.5]). The pooled sensitivities of Arah2-slgE and peanut extract slgE (92.8% [87.6, 96.0]) overlapped, while all other peanut component slgE was significantly less sensitive than peanut extract slgE ($P < .05$). Pooled specificities of slgE to Arah1 (86.0% [79.6, 90.6]), Arah2 (83.6% [77.4, 88.4]), Arah3 (88.0% [79.6, 93.3]), and Arah9 (81.2% [62.0, 92.0]) did not differ from each other and were all more specific

than Arah8 (59.7% [37.9, 78.3]), (Figure 2B). The Arah1, 2, and 3 storage proteins and Arah9 showed significantly higher specificity than slgE to peanut extract (26.9% [17.3, 39.2]).

Figure 3 displays the pooled sensitivities and specificities from cross-sectional pediatric studies of all peanut component slgE at 0.35 kU_A/L and the sROC curves, showing that slgE to Arah2 has the highest diagnostic accuracy and the best data consistency, as indicated by the narrow 95% CI ellipse ($I^2 = 15.5\%$). In contrast, Arah8-slgE and Arah9-slgE have low diagnostic performance, as reflected by the shape of the sROC curves and the wide CIs. Arah1 and Arah3-slgE are characterized by similar overall diagnostic accuracies.

The sensitivity, specificity, AUC, DOR, and positive and negative likelihood ratios (LR+/LR-) were calculated for slgE to all peanut components at the 0.10 and 0.35 kU_A/L cutoffs, as well as at 1.0 kU_A/L for Arah2-slgE (Table 2). Pooled sensitivities and specificities of Arah2-slgE at the three cutoffs are depicted in sROC plots in Figure 3B. There was no significant difference in sensitivity of any of the peanut component slgE between 0.10 kU_A/L and 0.35 kU_A/L cutoffs (Table 2). However, as expected, the specificity of Arah2-slgE was significantly higher at 0.35 kU_A/L (83.6% [77.4, 88.4]) and 1.0 kU_A/L (88.7% [80.2, 93.8]) than at the lower 0.10 kU_A/L threshold (62.8% [55.3, 69.7]). Further increasing the cutoff to 1.0 kU_A/L did not significantly increase the specificity (Table 2, Figure 3B). Unlike the seed storage proteins, no significant change in specificity

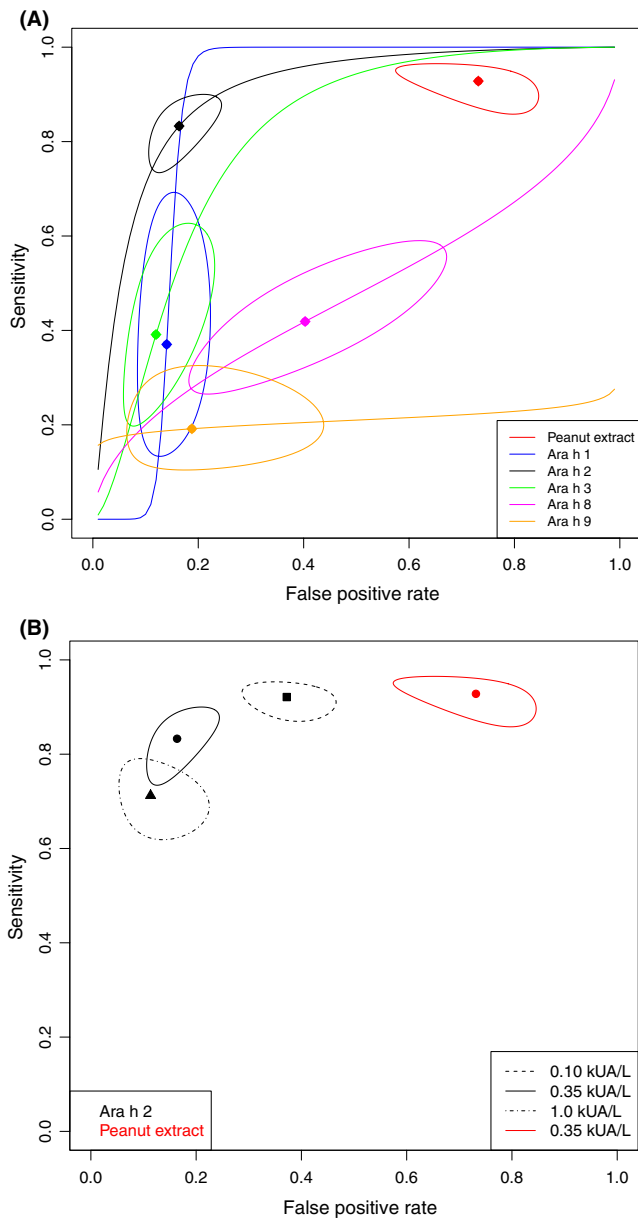


FIGURE 3 SROC curves in cross-sectional pediatric studies. A, sIgE to peanut components and peanut extract at 0.35 kUA/L threshold. Diamonds indicate pooled estimates, and ellipses indicate 95% CIs. Based on data from.^{16,17,25,28,29,31-37,39} B, SROC curves comparing Ara h 2-sIgE at different thresholds. Symbols indicate pooled estimates, and ellipses indicate 95% CIs. 0.1 kUA/L data from seven studies (black square symbol with dashed line), 0.35 kUA/L data from 13 studies (black round symbol with solid line), and 1.0 kUA/L data from four studies (black triangular symbol with dashed and dotted line) based on data from cross-sectional studies in children. Red symbol shows data for sIgE to peanut extract at 0.35 kUA/L for comparative purposes. Based on data from.^{16,17,25,28,29,31,32,34-37,39}

for sIgE to Ara h 8 or Ara h 9 was detected by raising the cutoff from 0.10 kUA/L to 0.35 kUA/L (Table 2).

Compared with other components analyzed, Ara h 2-sIgE at 0.35 kUA/L showed favorable values in the diagnostic parameters

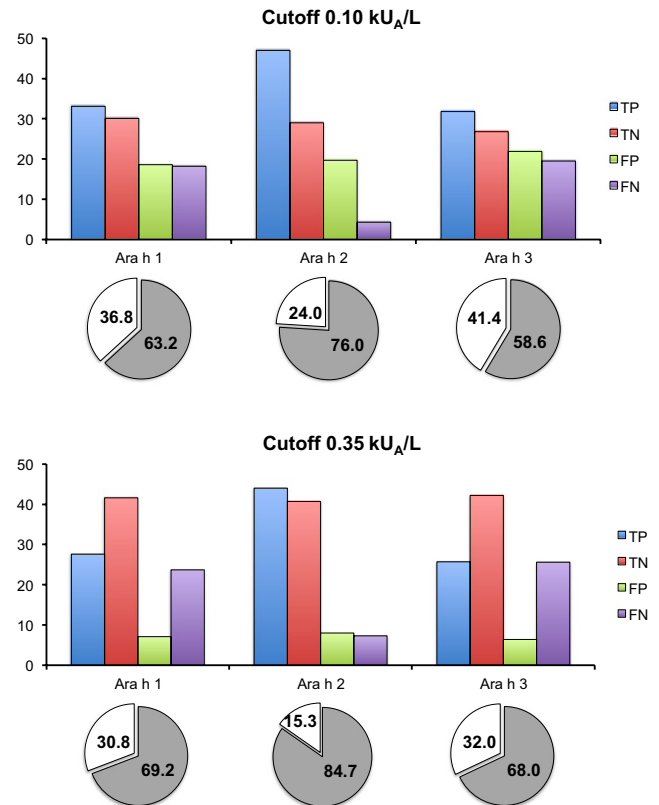


FIGURE 4 Diagnostic outcome of sIgE to peanut storage proteins in children at thresholds of 0.10 and 0.35 kUA/L using the disease prevalence of included studies (459/947, 48.5%). Histograms show percent false negative (FN), false positive (FP), true negative (TN), and true positive (TP), and pie charts depict percentage of correctly diagnosed patients (gray) vs misdiagnosed patients (white). Y-axes represent percentages; histograms show TPs (blue), TNs (red), FPs (green), and FNs (purple). In the pie charts, the gray slice represents the percentage of correctly diagnosed individuals (TPs + TNs), while the white slice the percentage of incorrectly classified individuals (FPs + FNs)

calculated, with a DOR of 29.1 [17.7, 47.9], LR+ of 5.1 [4.1, 6.2], and LR- of 0.2 [0.2, 0.3] (Table 2).

3.3 | Clinical implications of key findings

Based on the diagnostic performance and disease prevalence of the retrieved cross-sectional pediatric studies included in the secondary analyses (459/947 pediatric patients, 48.5%), the merits of using peanut component sIgE testing in a hypothetical population of children were calculated (Figure 4, Table S3). Ara h 2-sIgE would correctly classify 83.5% of the children and would give 8.1% FN results using the 0.35 kUA/L cutoff. Ara h 1-sIgE and Ara h 3-sIgE would correctly diagnose 62.2% and 64.3% of subjects, respectively. The diagnostic capacity of Ara h 8-sIgE is considerably lower, with 51.0% of children correctly diagnosed (20.8% FPs and 28.2% FNs). Similarly, Ara h 9-sIgE would correctly diagnose 51.1% of children (9.7% FPs and 39.2% FNs).

4 | DISCUSSION

In the scientific literature, there is an increasing body of evidence demonstrating the utility of CRD in the workup of peanut-allergic patients, showing that sIgE to peanut allergen components can help differentiate between clinical manifestations of peanut allergy.^{6,40} Through a systematic approach, we collected available published data on the use of CRD in diagnosing allergy in patients suspected of peanut allergy and employed tailored meta-analyses at commonly used cutoffs to quantify and compare the diagnostic accuracies of available sIgE peanut components.

Results show that sIgE to storage proteins Arah1, Arah2, and Arah3 confer high specificity in diagnosing objective peanut allergy in children, while overall sIgE to Arah8 and Arah9 has limited diagnostic accuracies. Arah2-sIgE displays the highest overall diagnostic accuracy, with both highest likelihood of correctly ruling in and lowest likelihood for incorrectly ruling out peanut allergy. In children, the sensitivity of Arah2-sIgE is not significantly different from that of sIgE to peanut extract (Figure 2B), supporting its role as a primary sensitizer in peanut allergy,^{24,41,42} also reflected by the consistent low variation in data for this component.

The observed limited diagnostic utility of Arah8 was expected in light of its extensive cross-reactivity with birch pollen-derived Betv1, heavily influencing peanut sensitization in birch-rich areas.⁴³ In Northern Europe, Arah8 sensitization at most elicits local oral symptoms, as demonstrated in a study where Swedish children were sensitized to Arah8 but not to peanut storage proteins.⁴⁴ Similarly, the limited diagnostic accuracy of Arah9 found in our meta-analysis is most likely ascribable to regional differences with cross-reactivity between LTPs that are prominent in southern Europe, where LTPs play an important role in food allergy.⁴⁵ Our Arah9 data were based on results from several countries, but only one from the Mediterranean area (Italy),³⁶ which limits the global validity of our results. Nevertheless, it should be noted that Arah2 is also a marker of primary peanut allergy in Mediterranean countries.^{36,46} The sensitivity and specificity data presented here are in agreement with a previous systematic review that did not carry out a meta-analysis.¹³ The lower pooled specificity of sIgE to peanut extract in our study compared to that of Soares-Wieser et al⁵ (peanut sIgE sensitivity 59%) may be explained by the fact that we did not systematically collect these data, by the different search criteria, by the pooling of data from different cutoffs, and by different methods used for meta-analyses.

The strengths of the present meta-analysis consist in the thorough methodology applied where data were pooled using a robust meta-analysis method.¹⁵ The pediatric dataset used in the sensitivity analysis included only studies with cross-sectional design, which closely resembles the clinical situation and minimizes the risk of overestimating diagnostic parameters.⁴⁷ In comparison with Klemans et al,¹³ our study included a greater number of studies and applied stricter inclusion criteria with regard to the number of patients and the use of reference standard. Indeed, based on I^2 measurements, the heterogeneity between studies included in the meta-analyses was considered low. Moreover, both DBPCFC and open challenges

were accepted for defining peanut allergy, as it is acknowledged that DBPCFC are seldom performed in clinical practice. A recent systematic literature review on food components only allowed for DBPCFC as reference standard,¹² resulting in the retrieval of only two studies, and hence, no meta-analyses could be performed. In this study, we allowed for the inclusion of studies in which some patients were diagnosed as peanut-allergic based on recent anaphylactic events, and this also ensured the inclusion of severely peanut-allergic subjects, thus better representing the spectrum of patients suspected of peanut allergy who would present to clinical practice. Our inclusion criteria ensured that study populations and designs were adequate for combining in a meta-analysis, as per Cochrane recommendations (Table S2).¹⁵ As described in the methods, some articles were not included in the meta-analysis because the data were not reported at any of the pre-specified cutoffs of 0.1, 0.35, 1.0, or 5.0 kU_A/L.

In clinical practice, the risk of under-diagnosing a potentially severe allergy has to be thoroughly considered, while overdiagnosis may impair patient and caregivers' quality of life.⁴⁸ We addressed diagnostic cutoff levels for optimal balance of over- and under-diagnosis. In a population with the same disease prevalence as in the included studies (48.5%), 83.5% of the children would be correctly diagnosed applying Arah2-sIgE at 0.35 kU_A/L cutoff. As low levels of sIgE to storage proteins may also be clinically relevant, especially in young children, it may be important to quantify the sIgE levels down to 0.10 kU_A/L and to carefully review the clinical history of each patient.^{6,49} Our data point to the importance of selecting the threshold for Arah2 carefully. By lowering the cutoff level of sIgE to Arah2 from 0.35 kU_A/L to 0.10 kU_A/L, fewer peanut-allergic patients would be classified as FNs (Figure 4). One might speculate that if the suspicion of peanut allergy remains after the Arah2 level is found to be <0.35 kU_A/L, in clinical practice, it might be worthwhile to use the lower cutoff to minimize the risk of missing patients, even though the number of FPs will increase.

Testing for sIgE to additional peanut storage proteins Arah1 and Arah3, and in the Mediterranean area potentially also Arah9, could be considered to limit the risk of misclassifying patients. In our study, we could not evaluate whether simultaneous testing for sIgE to storage proteins Arah1 and Arah3 in addition to Arah2 would increase the proportion of correctly classified children with peanut allergy, as these sIgEs cannot be considered independent from sIgE to Arah2.⁵⁰ It is known that multisensitization to peanut storage proteins appears to be associated with an increased overall risk for reactions (including systemic reactions) compared with mono-sensitization.^{32,51,52} Also, for patients who are negative to Arah2 and suspected of peanut allergy, it could be useful to test for Arah1 and Arah3, as recently suggested by Magnúsdóttir and colleagues.⁵³

The limitations of our study are related to the scarcity of studies on adult populations, which did not enable meta-analyses; therefore, the role of peanut CRD in adults remains to be investigated. However, based on our results, one could speculate that sIgE to Arah2 alone would be sufficient to correctly identify the vast majority of suspected peanut-allergic patients. Prospective studies designed to evaluate a stepwise testing approach in the diagnostic

workup of children suspected of peanut allergy will be needed for application in clinical practice.

The data retrieved from the systematic review enabled meta-analyses of sIgE to Ara h1, Ara h2, Ara h3, Ara h8, and Ara h9, each at several pre-defined cutoffs. Some components exhibit different diagnostic accuracies in different geographic areas; more data are needed to demonstrate the clinical utility of Ara h9 in Mediterranean patients. Finally, this systematic review did not retrieve studies presenting quantitative data on Ara h6-sIgE meeting the pre-defined cutoffs, so further analysis of this component is needed.

In conclusion, systematically collected data show that sIgE to peanut seed storage proteins confers high specificity in the diagnosis of childhood peanut allergy, and that sIgE to Ara h2 has consistently high diagnostic accuracy for objective peanut allergy in children across geographic locations.¹³ Using CRD, a correct final diagnosis could be reached more quickly and safely and reducing the number of OFCs needed.

ACKNOWLEDGMENTS

We thank PHMR Health Economics, Pricing & Reimbursement for performing the systematic literature review and Dr Vanessa Gray-Schopfer, OmniScience SA, for providing medical writing assistance funded by Thermo Fisher Scientific. We extend our thanks to Mark Orme, ICERA Ltd, who assisted with the updated data extraction and data verification. The authors were fully responsible for contents and editorial decisions for this manuscript.

CONFLICT OF INTEREST

Drs Berthold, Mascialino, and Sjölander are employees of Thermo Fisher Scientific. Dr Orme has received consultation fees from Thermo Fisher Scientific. The authors have no competing interests to declare.

AUTHOR CONTRIBUTIONS

CN, MB, BM, SS, and RH contributed to the conception and design of the study. MB, BM, MO, and SS contributed to acquisition of data. MO performed the systematic literature search and data extraction, and BM performed the meta-analyses. All authors contributed to analysis and interpretation of data and were involved in drafting and revising the manuscript. All authors approved the final version for publication.

ORCID

Caroline Nilsson  <https://orcid.org/0000-0003-2040-8428>

REFERENCES

- Boudreau-Romano S, Qamar N. Peanut allergy: changes in dogma and past, present, and future directions. *Pediatr Ann*. 2018;47:e300-e304.
- Scott LA, Berni TR, Berni ER, De Vries J, Currie CJ. Evaluation of the healthcare resource use and the related financial costs of managing peanut allergy in the United Kingdom. *Expert Rev Clin Immunol*. 2019;15:889-896.
- Anagnostou K, Clark A. The management of peanut allergy. *Arch Dis Child*. 2015;100:68-72.
- Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. *J Allergy Clin Immunol*. 2012;130:1260-1274.
- Soares-Weiser K, Takwoingi Y, Panesar SS, et al. The diagnosis of food allergy: a systematic review and meta-analysis. *Allergy*. 2014;69:76-86.
- Hamilton RG, Kleine-Tebbe J. Molecular allergy diagnostics: analytical features that support clinical decisions. *Curr Allergy Asthma Rep*. 2015;15:57.
- van Erp FC, Klemans RJ, Meijer Y, van der Ent CK, Knulst AC. Using component-resolved diagnostics in the management of peanut-allergic patients. *Curr Treat Options Allergy*. 2016;3:169-180.
- Canonica GW, Ansotegui IJ, Pawankar R, et al. A WAO - ARIA - GA(2)LEN consensus document on molecular-based allergy diagnostics. *World Allergy Organ J*. 2013;6:17.
- Tuano KS, Davis CM. Utility of component-resolved diagnostics in food allergy. *Curr Allergy Asthma Rep*. 2015;15:32.
- Matricardi PM, Kleine-Tebbe J, Hoffmann HJ, et al. EAACI molecular allergology user's guide. *Pediatr Allergy Immunol*. 2016;27(Suppl 23):1-250.
- Lauer I, Dueringer N, Pokoj S, et al. The non-specific lipid transfer protein, Ara h 9, is an important allergen in peanut. *Clin Exp Allergy*. 2009;39:1427-1437.
- Flores Kim J, McCleary N, Nwaru BI, Stoddart A, Sheikh A. Diagnostic accuracy, risk assessment, and cost-effectiveness of component-resolved diagnostics for food allergy: a systematic review. *Allergy*. 2018;73(8):1609-1621.
- Klemans RJ, van Os-Medendorp H, Blankestijn M, Bruijnzeel-Koomen CA, Knol EF, Knulst AC. Diagnostic accuracy of specific IgE to components in diagnosing peanut allergy: a systematic review. *Clin Exp Allergy*. 2015;45:720-730.
- Macaskill P, Gatsonis C, Deeks JJ, Harbord RM, Takwoingi Y. Chapter 10: Analysing and Presenting Results. In: Deeks JJ, Bossuyt PM, Gatsonis C, eds. *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Version 1.0* [online]. London, UK: The Cochrane Collaboration; 2010. <http://srdta.cochrane.org/>. Accessed November 22, 2016.
- Reitsma JB, Rutjes AWS, Whiting P, Vlassov VV, Leeflang MMG, Deeks JJ. Chapter 9: Assessing methodological quality. In: Deeks JJ, Bossuyt PM, Gatsonis C, eds. *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Version 1.0.0*. London, UK: The Cochrane Collaboration; 2009. <http://srdta.cochrane.org/>. Accessed January 22, 2019.
- 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;1:75-82.
- Glaumann S, Nopp A, Johansson SG, Rudengren M, Borres MP, Nilsson C. Basophil allergen threshold sensitivity, CD-sens, IgE-sensitization and DBPCFC in peanut-sensitized children. *Allergy*. 2012;67:242-247.
- Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *J Clin Epidemiol*. 2005;58:982-990.
- Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557-560.
- On behalf of the Cochrane Statistical Methods Group. Chapter 9: Analysing data and undertaking meta-analyses. In: Deeks JJ, Higgins JPT, Altman DG, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* [updated March 2011]. London, UK: The Cochrane Collaboration. <https://handbook-5-1.cochrane.org/>. Accessed January 22, 2019.

21. Altman D, Machin D, Bryant T, Gardner M. *Statistics with Confidence: Confidence Intervals and Statistical Guidelines*. 2nd ed. London, UK: BMJ Books; 2000.
22. Doebler P. Mada: Meta-Analysis of Diagnostic Accuracy. 2017. <https://cran.r-project.org/web/packages/mada/index.html>. Accessed January 22, 2019.
23. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna: R Foundation for Statistical Computing. 2016. <https://www.R-project.org/>. Accessed January 22, 2019.
24. Ballmer-Weber BK, Lidholm J, Fernández-Rivas M, et al. IgE recognition patterns in peanut allergy are age dependent: perspectives of the EuroPrevall study. *Allergy*. 2015;70:391-407.
25. 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;70:90-98.
26. 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;129:1056-1063.
27. Ebisawa M, Moverare R, Sato S, Borres MP, Ito K. The predictive relationship between peanut- and Ara h 2-specific serum IgE concentrations and peanut allergy. *J Allergy Clin Immunol Pract*. 2015;3(131-2):e1.
28. Ebisawa M, Moverare 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;23:573-581.
29. 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;1:101-103.
30. Klemans RJB, Broekman HCHP, Knol EF, et al. Ara h 2 is the best predictor for peanut allergy in adults. *J Allergy Clin Immunol Pract*. 2013;1(632-8):e1.
31. Klemans RJB, 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;131:157-163.
32. Kukkonen AK, Pelkonen AS, Makinen-Kiljunen S, Voutilainen H, Makela MJ. Ara h 2 and Ara 6 are the best predictors of severe peanut allergy: a double-blind placebo-controlled study. *Allergy*. 2015;70:1239-1245.
33. 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;3:968-969.
34. Nicolaou N, Murray C, Belgrave D, Poorafshar M, Simpson A, Custovic A. Quantification of specific IgE to whole peanut extract and peanut components in prediction of peanut allergy. *J Allergy Clin Immunol*. 2011;127:684-685.
35. Suratannon N, Ngamphaiboon J, Wongpiyabovorn J, Puripokai P, Chatchatee P. Component-resolved diagnostics for the evaluation of peanut allergy in a low-prevalence area. *Pediatr Allergy Immunol*. 2013;24:665-670.
36. Comberiati P, Colavita L, Minniti F, et al. Utility of specific IgE to Ara h 2 in Italian allergic and tolerant children sensitized to peanut. *Int J Mol Cell Med*. 2016;5:160-166.
37. 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? *Diagnosis (Berl)*. 2016;3:31-35.
38. 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(358-60):e8.
39. Martinet J, Couderc L, Renosi F, Bobee 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 food allergy. *Int Arch Allergy Immunol*. 2016;169:216-222.
40. Sicherer SH, Wood RA. Advances in diagnosing peanut allergy. *J Allergy Clin Immunol Pract*. 2013;1:1-13; quiz 4.
41. Valcour A, Jones JE, Lidholm J, Borres MP, Hamilton RG. Sensitization profiles to peanut allergens across the United States. *Ann Allergy Asthma Immunol*. 2017;119(262-6):e1.
42. Namork E, Stensby BA. Peanut sensitization pattern in Norwegian children and adults with specific IgE to peanut show age related differences. *Allergy Asthma Clin Immunol*. 2015;11:32.
43. Mittag D, Akkerdaas J, Ballmer-Weber BK, et al. Ara h 8, a Bet v 1-homologous allergen from peanut, is a major allergen in patients with combined birch pollen and peanut allergy. *J Allergy Clin Immunol*. 2004;114:1410-1417.
44. Asarnoj A, Nilsson C, Lidholm J, et al. Peanut component Ara h 8 sensitization and tolerance to peanut. *J Allergy Clin Immunol*. 2012;130:468-472.
45. Schocker F, Lüttkopf D, Scheurer S, et al. Recombinant lipid transfer protein Cor a 8 from hazelnut: a new tool for in vitro diagnosis of potentially severe hazelnut allergy. *J Allergy Clin Immunol*. 2004;113:141-147.
46. Pedrosa M, Boyano-Martinez T, Garcia-Ara MC, Caballero T, Quirce S. Peanut seed storage proteins are responsible for clinical reactivity in Spanish peanut-allergic children. *Pediatr Allergy Immunol*. 2012;23:654-659.
47. Rutjes AW, Reitsma JB, Vandenbroucke JP, Glas AS, Bossuyt PM. Case-control and two-gate designs in diagnostic accuracy studies. *Clin Chem*. 2005;51:1335-1341.
48. Cummings AJ, Knibb RC, Erlewyn-Lajeunesse M, King RM, Roberts G, Lucas JS. Management of nut allergy influences quality of life and anxiety in children and their mothers. *Pediatr Allergy Immunol*. 2010;21:586-594.
49. Hamilton RG. Clinical laboratories worldwide need to report IgE antibody results on clinical specimens as analytical results and not use differential positive thresholds. *J Allergy Clin Immunol*. 2015;136:811-812.
50. Bublin M, Kostadinova M, Radauer C, et al. IgE cross-reactivity between the major peanut allergen Ara h 2 and the nonhomologous allergens Ara h 1 and Ara h 3. *J Allergy Clin Immunol*. 2013;132:118-124.
51. Asarnoj A, Moverare R, Östblom E, et al. IgE to peanut allergen components: relation to peanut symptoms and pollen sensitization in 8-year-olds. *Allergy*. 2010;65:1189-1195.
52. Astier C, Morisset M, Roitel O, et al. Predictive value of skin prick tests using recombinant allergens for diagnosis of peanut allergy. *J Allergy Clin Immunol*. 2006;118:250-256.
53. Magnúsdóttir H, Vídarsdóttir A, Ludvíksson B, et al. Ara h 1 and Ara h 6 Sensitization Causes Clinical Peanut Allergy in Ara h 2-Negative Individuals. *Int Arch Allergy Immunol*. 2019;178:66-75.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Nilsson C, Berthold M, Mascialino B, Orme ME, Sjölander S, Hamilton RG. Accuracy of component-resolved diagnostics in peanut allergy: Systematic literature review and meta-analysis. *Pediatr Allergy Immunol*. 2020;00:1-12. <https://doi.org/10.1111/pai.13201>

Supplementary material

eTable 1. Extracted data and calculated sensitivity and specificity

From all eligible studies (0.35 kU_A/L cut-off); [†]cross-sectional studies on children (0.35 kU_A/L cut-off) [‡]case-control studies on children

Index test	Reference	True Positives	False Negatives	False Positives	True Negatives	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]
Ara h 1	Ballmer-Weber, 2015 (a) [‡]	18	29	0	24	38.3 [24.5, 53.6]	100.0 [85.8, 100.0]
	Ballmer-Weber, 2015 (ch) [‡]	12	9	0	2	57.1 [34.0, 78.2]	100.0 [15.8, 100.0]
	Comberiati, 2016 [†]	1	11	2	18	8.3 [0.2, 38.5]	90.0 [68.3, 98.8]
	Ebisawa, 2012 [†]	10	16	7	24	38.5 [20.2, 59.4]	77.4 [58.9, 90.4]
	Glaumann, 2012 [†]	23	2	2	11	92.0 [74.0, 99.0]	84.6 [54.6, 98.1]
	Kukkonen, 2015 [†]	39	22	5	36	63.9 [50.6, 75.8]	87.8 [73.8, 95.9]

Index test	Reference	True Positives	False Negatives	False Positives	True Negatives	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]
	Lieberman, 2013 (Site 1) [†]	2	22	2	19	8.3 [1.0, 27.0]	90.5 [69.6, 98.8]
	Lieberman, 2013 (Site 3) [†]	6	15	4	23	28.6 [11.3, 52.2]	85.2 [66.3, 95.8]
	Suratannon, 2013 [†]	5	14	1	20	26.3 [9.2, 51.2]	95.2 [76.2, 99.9]
Ara h 2	Ballmer-Weber, 2015 (a)	18	29	0	24	38.3 [24.5, 53.6]	100.0 [85.8, 100.0]
	Ballmer-Weber, 2015 (ch) [‡]	20	1	0	2	95.2 [76.2, 99.9]	100.0 [15.8, 100.0]
	Beyer, 2015 [†]	77	13	17	103	85.6 [76.6, 92.1]	85.8 [78.3, 91.5]
	Comberiati, 2016 [†]	7	5	2	18	58.3 [27.7, 84.8]	90.0 [68.3, 98.8]
	Dang, 2012 [‡]	81	19	7	93	81.0 [71.9, 88.2]	93.0 [86.1, 97.1]

Index test	Reference	True Positives	False Negatives	False Positives	True Negatives	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]
	Ebisawa, 2012 [†]	23	3	5	26	88.5 [69.9, 97.6]	83.9 [66.3, 94.6]
	Glaumann, 2012 [†]	24	1	2	11	96.0 [79.7, 99.9]	84.6 [54.6, 98.1]
	Keet, 2013 [†]	23	3	10	25	88.5 [69.9, 97.6]	71.4 [53.7, 85.4]
	Klemans, 2013a [†]	33	22	6	33	60.0 [45.9, 73.0]	84.6 [69.5, 94.1]
	Klemans, 2013b [†]	43	4	15	38	91.5 [79.6, 97.6]	71.7 [57.7, 83.2]
	Kukkonen, 2015 [†]	58	3	11	30	95.1 [86.3, 99.0]	73.2 [57.1, 85.8]
	Lieberman, 2013 (Site 1) [†]	16	8	1	20	66.7 [44.7, 84.4]	95.2 [76.2, 99.9]
	Lieberman, 2013 (Site 3) [†]	12	9	2	25	57.1 [34.0, 78.2]	92.6 [75.7, 99.1]

Index test	Reference	True Positives	False Negatives	False Positives	True Negatives	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]
	Martinet, 2016 [†]	45	3	0	33	93.8 [82.8, 98.7]	100.0 [89.4, 100.0]
	Nicolau, 2011 [†]	29	0	2	50	100.0 [88.1, 100.0]	96.2 [86.8, 99.5]
	Schots, 2016 [†]	27	4	7	14	87.1 [70.2, 96.4]	66.7 [43.0, 85.4]
	Suratannon, 2013 [†]	13	6	1	20	68.4 [43.5, 87.4]	95.2 [76.2, 99.9]
Ara h 3	Ballmer-Weber, 2015 (a)	9	38	0	24	19.1 [9.2, 33.3]	100.0 [85.8, 100.0]
	Ballmer-Weber, 2015 (ch) [‡]	8	13	0	2	38.1 [18.1, 61.6]	100.0 [15.8, 100.0]
	Comberiati, 2016 [†]	2	10	0	20	16.7 [2.1, 48.4]	100.0 [83.2, 100.0]
	Ebisawa, 2012 [†]	11	15	6	25	42.3 [23.3, 63.1]	80.6 [62.5, 92.6]

Index test	Reference	True Positives	False Negatives	False Positives	True Negatives	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]
	Glaumann, 2012 [†]	21	4	4	9	84.0 [63.9, 95.5]	69.2 [38.6, 90.9]
	Kukkonen, 2015 [†]	35	26	4	37	57.4 [44.1, 70.0]	90.2 [76.9, 97.3]
	Lieberman, 2013 (Site 1) [†]	4	20	1	20	16.7 [4.7, 37.4]	95.2 [76.2, 99.9]
	Lieberman, 2013 (Site 3) [†]	6	15	1	26	28.6 [11.3, 52.2]	96.3 [81.0, 99.9]
	Suratannon, 2013 [†]	4	15	2	19	21.1 [6.1, 45.6]	90.5 [69.6, 98.8]
Ara h 8	Ballmer-Weber, 2015 (a)	15	32	3	21	31.9 [19.1, 47.1]	87.5 [67.6, 97.3]
	Ballmer-Weber, 2015 (ch) [‡]	8	13	1	1	38.1 [18.1, 61.6]	50.0 [1.3, 98.7]
	Comberiati, 2016 [†]	3	9	8	12	25.0 [5.5, 57.2]	60.0 [36.1, 80.9]

Index test	Reference	True Positives	False Negatives	False Positives	True Negatives	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]
	Ebisawa, 2012 [†]	11	15	6	25	42.3 [23.4, 63.1]	80.6 [62.5, 92.6]
	Glaumann, 2012 [†]	9	16	9	4	36.0 [18.0, 57.5]	30.8 [9.1, 61.4]
	Kukkonen, 2015 [†]	48	13	35	6	78.7 [66.3, 88.1]	14.6 [5.6, 29.2]
	Lieberman, 2013 (Site 1) [†]	9	15	9	12	37.5 [18.8, 59.4]	57.1 [34.0, 78.2]
	Lieberman, 2013 (Site 3) [†]	10	11	17	10	47.6 [25.7, 70.2]	37.0 [19.4, 57.6]
	Martinet, 2016 [†]	15	33	5	28	31.3 [18.7, 46.3]	84.8 [68.1, 94.9]
	Suratannon, 2013 [†]	3	16	0	21	15.8 [8.4, 39.4]	100.0 [83.9, 100.0]
Analysis 9	Ballmer-Weber, 2015 (a)	13	34	12	12	27.7 [15.6, 42.6]	50.0 [29.1, 70.9]

Index test	Reference	True Positives	False Negatives	False Positives	True Negatives	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]
	Ballmer-Weber, 2015 (ch) [‡]	4	17	0	2	19.0 [5.5, 41.9]	100.0 [15.8, 100.0]
	Comberiati, 2016 [†]	3	9	9	11	25.0 [5.5, 57.2]	55.0 [31.5, 76.9]
	Ebisawa, 2012 [†]	4	22	4	27	15.4 [4.4, 34.9]	87.1 [70.2, 96.4]
	Glaumann, 2012 [†]	3	22	2	11	12.0 [2.6, 31.2]	84.6 [54.6, 98.1]
	Suratannon, 2013 [†]	5	14	1	20	26.3 [9.2, 51.2]	95.2 [76.2, 99.9]
Peanut sIgE	Ballmer-Weber, 2015 (a)	33	14	13	11	70.2 [55.1, 82.7]	45.8 [25.6, 67.2]
	Ballmer-Weber, 2015 (ch) [‡]	20	1	1	1	95.2 [76.2, 99.9]	50.0 [1.3, 98.7]
	Beyer, 2015 [†]	86	4	89	31	95.6 [89.0, 98.8]	25.8 [18.3, 34.6]

Index test	Reference	True Positives	False Negatives	False Positives	True Negatives	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]
	Comberiati, 2016 [†]	11	1	17	3	91.7 [61.5, 99.8]	15.0 [3.2, 37.9]
	Dang, 2012 [‡]	91	9	32	68	91.0 [83.6, 95.8]	68.0 [57.9, 77.0]
	Ebisawa, 2012 [†]	26	0	24	7	100.0 [86.8, 100.0]	22.6 [9.6, 41.1]
	Glaumann, 2012 [†]	25	0	9	4	100.0 [86.3, 100.0]	30.8 [9.1, 61.4]
	Leo, 2015 [†]	19	1	7	3	95.0 [73.1, 99.9]	30.0 [6.7, 65.3]
	Lieberman, 2013 (Site 1) [†]	20	4	19	2	83.3 [62.6, 95.3]	9.5 [1.2, 30.4]
	Lieberman, 2013 (Site 3) [†]	18	3	23	4	85.7 [63.7, 97.0]	14.8 [4.2, 33.7]
	Martinet, 2016 [†]	47	1	9	24	97.9 [88.9, 100.0]	72.7 [54.5, 86.7]

Index test	Reference	True Positives	False Negatives	False Positives	True Negatives	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]
	Nicolau, 2011 [†]	28	1	38	14	96.6 [84.2, 99.9]	26.9 [15.6, 41.0]

From all children cross-sectional studies (0.10 kU_A/L cut-off)

Index test	Reference	True Positives	False Negatives	False Positives	True Negatives	Sensitivity (%)	Specificity (%)
Ara h 1	Ebisawa, 2012	19	7	16	15	73.1 [52.2, 88.4]	48.4 [30.2, 66.9]
	Glaumann, 2012	23	2	5	8	92.0 [74.0, 99.0]	61.5 [31.6, 86.1]
	Keet, 2013	6	20	7	28	23.1 [9.0, 43.7]	80.0 [63.1, 91.6]
Ara h 2	Beyer, 2015	84	6	40	80	93.3 [86.1, 97.5]	66.7 [57.5, 75.0]
	Ebisawa, 2012	24	2	14	17	92.3 [74.9, 99.1]	54.8 [36.0, 72.7]
	Ebisawa, 2015	62	8	44	50	87.1 [77.0, 94.0]	53.2 [42.6, 63.6]
	Glaumann, 2012	24	1	4	9	96.0 [79.7, 99.9]	69.2 [38.6, 90.9]
	Keet, 2013	25	1	16	19	96.2 [80.4, 99.9]	54.3 [36.7, 71.2]

Index test	Reference	True Positives	False Negatives	False Positives	True Negatives	Sensitivity (%)	Specificity (%)
	Martinet, 2016	45	3	1	32	93.8 [82.8, 98.7]	97.0 [84.2, 99.9]
	Van Erp, 2017	47	0	10	24	100.0 [92.5, 100.0]	70.6 [52.5, 84.9]
Ara h 3	Ebisawa, 2012	17	9	18	13	65.4 [44.3, 82.8]	41.9 [24.6, 60.9]
	Glaumann, 2012	24	1	6	7	96.0 [79.7, 99.9]	53.8 [25.1, 80.8]
	Keet, 2013	6	20	9	26	23.1 [9.0, 43.7]	74.3 [56.7, 87.5]
Ara h 8	Ebisawa, 2012	17	9	14	17	65.4 [44.3, 82.8]	54.8 [36.0, 72.7]
	Glaumann, 2012	17	8	10	3	68.0 [46.5, 85.1]	23.1 [5.0, 53.8]
	Keet, 2013	3	23	15	20	11.5 [2.5, 30.2]	57.1 [39.4, 73.7]
	Martinet, 2016	17	31	5	28	35.4	84.8

Index test	Reference	True Positives	False Negatives	False Positives	True Negatives	Sensitivity (%)	Specificity (%)
						[22.2, 50.5]	[68.1, 94.9]
Ara h 9	Ebisawa, 2012	15	11	6	25	57.7 [36.9, 76.7]	80.6 [62.5, 92.6]
	Glaumann, 2012	8	17	5	8	32.0 [15.0, 53.5]	61.5 [31.6, 86.1]
	Keet, 2013	3	23	6	29	11.5 [2.5, 30.2]	82.9 [66.4, 93.4]

From all children cross-sectional studies (1.0 kU_A/L cut-off)

Index test	Reference	True Positives	False Negatives	False Positives	True Negatives	Sensitivity (%)	Specificity (%)
Ara h 2	Beyer, 2015	70	20	7	113	77.8 [67.8, 85.9]	94.2 [88.4, 97.6]
	Klemans, 2013b	35	12	8	45	74.5 [59.7, 86.1]	84.9 [72.4, 93.3]
	Leo, 2015	13	7	2	8	65.0 [40.8, 84.6]	80.0 [44.4, 97.5]
	Martinet, 2016	31	17	0	33	64.6 [49.5, 77.8]	100.0 [89.4, 100.0]

eTable 2. Quality assessment of included studies.

Coding for judgment	Representative spectrum	Acceptable reference standard	Acceptable delay between tests	Partial verification avoided	Differential verification avoided	Incorporation avoided	Index test results blinded	Reference standard results blinded	Relevant clinical information	Uninterpretable results explained	Missing data explained	Cut-off values pre-specified	Sponsoring precluded
Ballmer-Weber 2015	no	no	no	yes	no	yes	yes	yes	unclear	yes	yes	yes	yes
Beyer 2015	yes	yes	yes	yes	no	yes	yes	unclear	yes	yes	yes	yes	no
Comberiati 2016	yes	yes	yes	yes	yes	yes	yes	unclear	yes	yes	unclear	yes	yes
Dang 2012	yes	yes	yes	yes	yes	yes	yes	unclear	yes	yes	yes	yes	yes
Ebisawa 2012	yes	yes	yes	yes	yes	yes	yes	unclear	yes	yes	yes	yes	yes
Ebisawa 2015	yes	no	no	yes	no	yes	yes	unclear	yes	yes	no	no	no
Glaumann 2012	yes	yes	yes	yes	yes	yes	yes	unclear	yes	yes	yes	yes	no
Keet 2013	yes	no	no	no	yes	yes	unclear	unclear	yes	yes	yes	yes	yes
Klemans 2013 (adult study)	yes	no	yes	yes	yes	yes	yes	unclear	yes	yes	yes	no	no
Klemans 2013 (children study)	yes	no	unclear	yes	no	yes	unclear	unclear	yes	yes	yes	no	no

Coding for judgment	Representative spectrum	Acceptable reference standard	Acceptable delay between tests	Partial verification avoided	Differential verification avoided	Incorporation avoided	Index test results blinded	Reference standard results blinded	Relevant clinical information	Uninterpretable results explained	Missing data explained	Cut-off values pre-specified	Sponsoring precluded
Kukkonen 2015	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Leo 2015	no	unclear	unclear	yes	yes	no	no	yes	yes	yes	yes	no	yes
Lieberman 2013 (Site 1)	yes	yes	yes	yes	yes	yes	yes	unclear	yes	no	yes	yes	yes
Lieberman 2013 (Site 3)	yes	yes	yes	yes	yes	yes	yes	unclear	yes	no	yes	yes	yes
Martinet 2016	yes	yes	unclear	yes	no	yes	unclear	unclear	yes	yes	yes	yes	yes
Nicolaou 2011	no	no	unclear	yes	no	yes	yes	unclear	yes	yes	no	no	yes
Schots 2016	yes	yes	yes	yes	no	yes	yes	unclear	yes	yes	yes	yes	yes
Suratannon 2013	yes	no	unclear	yes	no	yes	unclear	unclear	yes	yes	yes	yes	yes
van Erp 2017	yes	no	yes	yes	yes	yes	yes	unclear	yes	yes	yes	yes	no

- Representative spectrum: Three studies excluded patients and may not be representative of patients who will receive the test in clinical practice (Ballmer-Weber, 2015; Leo, 2015; Nicolaou, 2011).
- Acceptable reference standard: Eight studies were marked down because a positive OFC challenge could have been determined by subjective clinical symptoms, or diagnosis of peanut allergy was based on subjective clinical evidence of allergy other than anaphylaxis (Ballmer-Weber, 2015; Ebisawa, 2015; Keet, 2013; Klemans, 2013a; Klemans, 2013b; Nicolaou, 2011; Suratannon, 2013; van Erp, 2017).
- Acceptable delay between tests: Three studies were marked down because peanut allergy was based on clinical history or previous anaphylaxis made more than six months prior to study enrolment (Ballmer-Weber, 2015; Ebisawa, 2015; Keet, 2013).
- Partial verification avoided: One study was marked down because one patient initially failed a peanut challenge and passed 2.4 years later and had sera available from both times (Keet, 2013).
- Differential verification avoided: Eight studies were marked down because not all patients received the same reference standard. Some patients were classified based on OFC and others based on clinical history or previous anaphylaxis. This does not imply that the methodological quality of these studies was low; differential verification of disease status is standard practice since OFC would not be appropriate for all patients (Ballmer-Weber, 2015; Beyer, 2015; Ebisawa, 2015; Klemans, 2013b; Martinet, 2016; Nicolaou, 2011; Schots, 2016; Suratannon, 2013).
- Incorporation avoided: One study was marked down because the index test (Ara h 2 level) was part of the diagnostic pathway (Leo, 2015).
- Index test results blinded: One study was marked down because patients with Ara h 2 sIgE ≤ 10 kU/L were invited for an oral challenge; therefore, index test results were known (Leo, 2015).
- Uninterpretable results explained: Two studies were marked down because the publication does not report number of tests that were uninterpretable (Lieberman, 2013 Site 1 and Site 3).
- Missing data explained: Two studies were marked down because no explanation was provided for missing sIgE data in individual patients (Ebisawa, 2015; Nicolaou, 2011). One study did not explain a discrepancy in data between a Table and a Figure within the publication (Comberiati, 2016).
- Cut-off values pre-specified: Four studies were marked down because cut-off values were not established before the study was started (Ebisawa, 2015; Klemans, 2013a; Klemans, 2013b; Leo, 2015; Nicolaou, 2011).

- Sponsoring precluded: Six studies were not free of commercial funding, or did not specify the source of funding (Beyer, 2015; Ebisawa, 2015; Glaumann, 2012; Klemans, 2013a; Klemans, 2013b; van Erp, 2017).

eTable 3. Diagnostic outcome of sIgE to peanut components in children at thresholds of 0.10, 0.35, and 1.0 kU_A/L using the disease prevalence of included cross-sectional studies (459/947, 48.5%).

	Peanut component (kU_A/L threshold)		
Test Result	Ara h 1 (0.10)	Ara h 1 (0.35)	Ara h 1 (1.0)
True Positive	31.3	17.9	NA
True Negative	31.9	44.3	NA
False Positive	19.6	7.2	NA
False Negative	17.2	30.6	NA
Correctly diagnosed	63.2	62.2	NA
Total misclassified	36.8	37.8	NA
Test Result	Ara h 2 (0.10)	Ara h 2 (0.35)	Ara h 2 (1.0)
True Positive	44.7	40.4	34.5
True Negative	32.3	43.1	45.7
False Positive	19.2	8.4	5.8
False Negative	3.8	8.1	14.0
Correctly diagnosed	77.0	83.5	80.2
Total misclassified	23.0	16.5	19.8
Test Result	Ara h 3 (0.10)	Ara h 3 (0.35)	Ara h 3 (1.0)
True Positive	30.0	19.0	NA
True Negative	28.3	45.3	NA
False Positive	23.2	6.2	NA
False Negative	18.5	29.5	NA
Correctly diagnosed	58.3	64.3	NA
Total misclassified	41.7	35.7	NA
Test Result	Ara h 8 (0.10)	Ara h 8 (0.35)	Ara h 8 (1.0)
True Positive	21.7	20.3	NA
True Negative	29.5	30.7	NA
False Positive	22.0	20.8	NA

False Negative	26.8	28.2	NA
Correctly diagnosed	51.2	51.0	NA
Total misclassified	48.8	49.0	NA
Test Result	Ara h 9 (0.10)	Ara h 9 (0.35)	Ara h 9 (1.0)
True Positive	15.7	9.3	NA
True Negative	40.1	41.8	NA
False Positive	11.4	9.7	NA
False Negative	32.8	39.2	NA
Correctly Diagnosed	55.8	51.1	NA
Total Misclassified	44.2	48.9	NA
True Positive benefit: shorter diagnosis delay, appropriate treatment; True Negative benefit: reassurance and avoidance of oral food challenge & cost savings; False Positive: detrimental to quality of life and avoidable costs; False Negative: may cause delayed diagnosis, with potential risks for patients.			