

Journal Pre-proof

Accurate prediction of peanut allergy in one-third of adults using a validated Ara h 2 cutoff

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PII: S2213-2198(20)31245-9

DOI: <https://doi.org/10.1016/j.jaip.2020.11.024>

Reference: JAIP 3268

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 2 June 2020

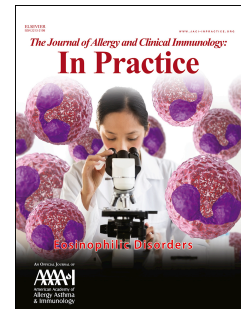
Revised Date: 2 November 2020

Accepted Date: 9 November 2020

Please cite this article as: Kansen HM, van Erp FC, Knulst AC, Ehlers AM, Lyons SA, Knol EF, Meijer Y, Otten HG, van der Ent CK, Le TM, Accurate prediction of peanut allergy in one-third of adults using a validated Ara h 2 cutoff, *The Journal of Allergy and Clinical Immunology: In Practice* (2020), doi: <https://doi.org/10.1016/j.jaip.2020.11.024>.

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1 Title

2 Accurate prediction of peanut allergy in one-third of adults using a validated Ara h 2 cutoff

3 Short title

4 sIgE to peanut components in adults

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24 Competing interests

25 The authors have declared that they have no competing interests in relation to this study.
26 Outside submitted work, dr. Knol reports personal fees from Thermo Fisher Diagnostics; Ms.
27 Ehlers reports that her research position at the UMC Utrecht is partially funded by
28 EUROIMMUN AG, Lübeck, Germany; Dr. van der Ent reports grants from GSK, grants from
29 Nutricia, grants from TEVA, grants from Gilead, grants from Vertex, grants from ProQR, grants
30 from Proteostasis, grants from Galapagos NV, grants from Eloxx. In addition, Dr. van der Ent
31 has a patent 10006904 with royalties paid.

32 Funding

33 ImmunoCAP material was provided by Thermo Fisher Scientific (Uppsala, Sweden).

34 **Word count abstract:** 240

35 **Word count text:** 3269

36 **Figures/tables:** 3/2

37 **Online repository tables/figures:** 3/1

ABSTRACT

Background: The diagnostic value of peanut components is extensively studied in children, but to a lesser extent in adults with suspected peanut allergy. The use of peanut components in daily practice may reduce the need for double-blind placebo-controlled food challenges (DBPCFCs), however validation studies are currently lacking.

Objective: To 1) evaluate the diagnostic value of (combined) peanut components and 2) validate a previous found Ara h 2 cutoff level with 100% positive predictive value (PPV) in adults with suspected peanut allergy.

Methods: Adults who underwent a peanut DBPCFC were included: 84 patients from a previous study (2002 to 2012) and 70 new patients (2012 to 2019). Specific IgE to peanut extract, Ara h 1, 2, 3, 6 and 8 was measured using ImmunoCAP. Diagnostic value was assessed with an area under the curve (AUC) analysis.

Results: In total, 95 (62%) patients were peanut allergic. sIgE to Ara h 2 and Ara h 6 were the best predictors with an AUC (95% CI) of 0.85 (0.79-0.91) and 0.85 (0.79-0.92), respectively. The Ara h 2 cutoff level with 100% PPV (≥ 1.75 kU_A/L) was validated in the 70 new patients. Thirty percent of all included patients could be classified correctly as peanut allergic using this validated cutoff level.

Conclusion: sIgE to Ara h 2 and Ara h 6 have equally high discriminative ability. Peanut allergy can be predicted accurately in one-third of adults using a validated cutoff level of sIgE to Ara h 2.

HIGHLIGHTS**What is already known about this topic?**

- The diagnostic value of peanut components is extensively studied in children, but less in adults.
- An Ara h 2 cutoff level (≥ 1.75 kU_A/L) with 100% positive predictive value (PPV) has been reported in adults.

What does this article add to our knowledge?

- sIgE to Ara h 2 and 6 have equally high discriminative ability in adults.
- The validated Ara h 2 cutoff predicts peanut allergy in one-third of adults.

How does this study impact current management guidelines?

- sIgE to Ara h 2 should be used to reduce the need for double-blind placebo-controlled food challenges using the validated 100% positive predictive cutoff level of ≥ 1.75 kU_A/L in adults.

71 **KEYWORDS**

72 Adults

73 Ara h 2

74 Ara h 6

75 Component-resolved diagnostics

76 Food challenge

77 Peanut allergy

78 Peanut components

79 Specific IgE

80 **ABBREVIATIONS**

81	AUC	area under the curve
82	CI	confidence interval
83	DBPCFC	double-blind placebo-controlled food challenge
84	IQR	interquartile range
85	NPV	negative predictive value
86	PPV	positive predictive value
87	ROC	receiver-operating characteristic
88	slgE	specific immunoglobulin E

89 INTRODUCTION

90 Peanut allergy affects up to 0.60% of adults in Europe.(1–3) The reference standard to
91 diagnose or exclude peanut allergy is a double-blind placebo-controlled food challenge
92 (DBPCFC).(4) However, a DBPCFC is time-consuming, labor-intensive, costly and not without
93 risks because of the potential for severe allergic reactions including anaphylaxis.(5) Given these
94 limitations, new diagnostic strategies have been evaluated that could reduce the number of
95 DBPCFCs.(6)

96
97 Serology tests may be used to reduce the number of DBPCFCs when validated cutoff levels are
98 used.(7–9) Sensitization to peanut component allergens (e.g. component-resolved diagnostics)
99 has emerged as a useful tool to diagnose peanut allergy with increased diagnostic accuracy
100 compared to sensitization to crude peanut extract or skin prick testing.(8,10–16) Currently, 17
101 peanut allergens have been described by the World Health Organization and International
102 Union of Immunological Societies (WHO/IUIS) Allergen Nomenclature Sub-committee.(17) Ara
103 h 2 and Ara h 6 are seed storage proteins and 2S albumins with highly similar protein
104 structure(18), and have been recognized as the most important allergens associated with
105 peanut allergy.(8,10,15) Ara h 7 is a third 2S albumin and is gaining attention as predictor for
106 peanut allergy.(11) Ara h 1 and Ara h 3 are also seed storage proteins and, together with Ara h
107 2, have been designated as the major peanut allergens.(19,20) Ara h 8 is a Bet v 1 homologous
108 pathogenesis-related (PR)-10 protein which cross-sensitizes with major-birch pollen allergen
109 Bet v 1 in adults.(21) Isolated sensitization to Ara h 8 is associated with mild or no symptoms,
110 although the role of Ara h 8 in multiple sensitized patients remains unclear.(22) Finally, Ara h 9
111 is a lipid transfer protein, and a major allergen in the Mediterranean area.(23)

112

Current evidence on cutoff levels for peanut components in adults is limited, as the majority of research has been conducted in children. Furthermore, validation studies of the diagnostic value of peanut components are currently lacking. Validation studies are warranted to implement research findings into daily practice. A previous study performed in our center included 84 adults, and showed that peanut allergy can be predicted with 100% positive predictive value (PPV) using a sIgE to Ara h 2 cutoff level of ≥ 1.75 kU_A/L.(16) Other recent studies have shown that the discriminative ability of sIgE to Ara h 6 is comparable to sIgE to Ara h 2.(8,15,24) Peanut component Ara h 6 has mainly been studied using a multiplex assay as opposed to a singleplex assay.(14,15,24,25) The results of a multiplex assay are semi-quantitative and therefore, these results cannot be used to determine cutoff levels.(26)

In the current study, we aimed to evaluate the diagnostic value of sIgE to peanut extract, Ara h 1, 2, 3, 6 and 8, and combinations, using a singleplex assay in adults with suspected peanut allergy. Furthermore, we aimed to validate the previously published cutoff level of sIgE to Ara h 2 with 100% positive predictive value (i.e. ≥ 1.75 kU_A/L).

METHODS

Study population

All 84 adult patients who participated in the previous diagnostic study and underwent a double-blind placebo-controlled food challenge (DBPCFC) for peanut at the University Medical Centre Utrecht between 2002 and June 2012 were eligible for inclusion.(16) Furthermore, we expanded the cohort with patients who underwent a DBPCFC for peanut between June 2012 and May 2019 (n=120). The DBPCFC was performed because of a suspected peanut allergy based on clinical history or sensitization. Patients with an inconclusive DBPCFC result (n=18) or without leftover serum (n=32) were excluded from the analysis. Included and excluded patients were comparable in age, gender, presence of allergic rhinitis, severity of peanut allergy and levels of sIgE to peanut extract and components (see Online Repository Table E1). The previous and current study were approved by the ethical committee of the University Medical Center Utrecht (no. 18-428).

Oral food challenges

DBPCFCs were performed in a clinical setting equipped for resuscitation in accordance with the international consensus protocol as previously described.(27–29) The DBPCFC result was considered positive when objective symptoms occurred (“positive objective”), or when subjective symptoms lasted for at least 45 minutes, or occurred to at least 3 subsequent doses (“positive subjective”). The severity of the DBPCFC was based on the adapted Mueller score: 0. oral symptoms, 1. cutaneous symptoms, 2. gastrointestinal symptoms, 3. respiratory symptoms and 4. cardiovascular symptoms.(16,30) Both the results and the severity of the DBPCFC was discussed among two food allergy experts (HK, TL). Any discrepancies between the two experts were resolved by discussion and consensus, or by consulting a third expert (FE), if necessary.

Sensitization (sIgE) measurements

Specific IgE (sIgE) values to peanut extract and peanut components Ara h 1, 2, 3, 6 and 8 were determined using the ImmunoCAP platform (Thermo Fisher Scientific Uppsala, Sweden). In the previous diagnostic study, sIgE to peanut extract, Ara h 1, 2, 3 and 8 was already measured in all patients (n=84). In these patients Ara h 6 was determined as part of the current study in those with available leftover serum (n=48). In all newly included (n = 70) patients, we determined Ara h 1, 2, 3, 6 and 8.

In peanut allergic patients without sensitization to peanut components or peanut extract as measured using the ImmunoCAP platform, sensitization to Ara h 1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 14 and 15 was assessed using a line blot (EUROLINE, EUROIMMUN, Lübeck, Germany) as described elsewhere.(11)

Statistical analyses

The differences between patients with a positive and a negative DBPCFC result were analyzed using the chi-square test and Mann-Whitney U test, when appropriate. The diagnostic value of sIgE to peanut extract and peanut components was assessed by the area under the curve (AUC) of the receiver-operating characteristic (ROC). The AUC values were compared using DeLong's test for correlated ROC curves.(31) To evaluate the diagnostic value of all serology tests combined (i.e. sIgE to peanut extract, Ara h 1, 2, 3, 6 and 8), logistic least absolute shrinkage and selection operator (LASSO) regression analysis was performed. The LASSO regression method is based on the regular least-squares method, but includes an additional parameter λ to prevent overfitting and automatically deletes unnecessary covariates.(32) We used cross-validation to select λ .

The previously published cutoff level of sIgE to Ara h 2 with 100% positive predictive value (PPV) was validated by calculating the PPV of this cutoff level (≥ 1.75 kU_A/L) in the newly included patients (43 peanut allergic and 27 peanut tolerant patients). The sample size needed

179 to have 95% confidence and 80% power to detect a difference of 5% from a presumed PPV of
180 98% was 31 cases.(33) In addition, the cutoff levels with optimal positive and negative
181 predictive values with corresponding sensitivities and specificities were calculated for peanut
182 extract and all peanut components. Statistical analyses were performed in SPSS for Windows
183 (version 25.0. Armonk, NY: IBM Corp) and R (pROC package v 1.15.3, randomForest package
184 v 4.6-14, OptimalCutpoints package v 1.1-4).

RESULTS

In total, 154 adults were included after a positive (n=95) or a negative (n=59) DBPCFC result. A positive DBPCFC result was based on objective symptoms in 69 (73%) patients and on only subjective symptoms in 26 (27%) patients. Patients with a positive DBPCFC result were significantly younger compared to patients with a negative DBPCFC result (median age 25 and 34 years, respectively) and had higher levels of sIgE to peanut extract, Ara h 1, 2, 3 and 6 (Table 1). The level of sIgE to Ara h 8 was comparable between patients with a positive and a negative DBPCFC result.

Specific IgE to Ara h 2 and Ara h 6 are the best predictors of peanut allergy

The levels of sIgE to peanut extract, Ara h 1, 2, 3 and 8 were available in all 154 patients and the level of sIgE to Ara h 6 in 118 patients. The diagnostic value of sIgE to peanut extract, Ara h 1, 2, 3 and 8 were comparable in the cohort of 118 and 154 patients (see Online Repository Table E2). The discriminative abilities of sIgE to Ara h 2 and sIgE to Ara h 6 for predicting peanut allergy were high and comparable, with an AUC (95% CI) value of 0.85 (0.79-0.91) and 0.85 (0.79-0.92), respectively (Figure 1A). The discriminative ability of the combination of sIgE to Ara h 2 and 6 was comparable to the individual components, with an AUC (95% CI) of 0.85 (0.78-0.92). The AUC values of sIgE to Ara h 2 and Ara h 6 were significantly higher than the AUC values of sIgE to peanut extract, Ara h 1, Ara h 3 and Ara h 8 (see Online Repository Table E3). When serology tests were used to predict peanut allergy with objective symptoms, the AUC values of sIgE to Ara h 2 and Ara h 6 increased slightly to respectively 0.90 (0.85-0.95) and 0.90 (0.84-0.96) (Figure 1B). The concentrations of sIgE to Ara h 2 and Ara h 6 were strongly correlated (Spearman's rho correlation coefficient 0.93; $p < 0.01$). The concentration of sIgE to Ara h 2 was weakly correlated with the eliciting dose of objective symptoms (Spearman's rho correlation coefficient 0.30; $p = 0.04$), while the concentration of sIgE to Ara h 6 was not correlated with the eliciting dose.

The final covariates included in the LASSO model for predicting peanut allergy were sIgE to Ara h 1 and Ara h 6, with Ara h 6 as the most influential predictor. The AUC-value of the LASSO model was 0.85 (0.78-0.92).

The Ara h 2 cutoff level with 100% positive predictive value is validated

A previous study performed in our center, including 84 adults, showed that peanut allergy can be diagnosed in 28% of patients by using a sIgE to Ara h 2 cutoff level with 100% positive predictive value (PPV) of ≥ 1.75 kU_A/L.(16) In the expanded cohort, including 84 adults from the previous study and 70 adults who were challenged after the first study, this cutoff level has again 100% positive predictive value (Table 2). Thus, we were able to confirm the previously published cutoff level of Ara h 2 in a larger group of adult patients. Thirty-two percent of patients had an Ara h 2 value above the validated cutoff level and could be predicted correctly as peanut allergic. Eighty-eight percent of patients above the Ara h 2 cutoff level had a positive DBPCFC result with objective symptoms. The optimal Ara h 2 cutoff level with 100% PPV in patients who were not part of the previous diagnostic study (n=70) was ≥ 0.43 kU_A/L. Six patients had an Ara h 2 level between 0.43 kU_A/L and 1.74 kU_A/L and were all peanut allergic (4 with objective symptoms and 2 with subjective symptoms).

Cutoff levels for Ara h 6 and other peanut components

The Ara h 6 cutoff level with 100% PPV was ≥ 1.80 kU_A/L, comparable to the Ara h 2 cutoff level (Table 2). Twenty-eight percent of patients had an Ara h 6 value above this cutoff level and could be predicted correctly as peanut allergic. The highest NPVs were observed for Ara h 6 and Ara h 8 at a cutoff of 0.1 kU_A/L and were 81% and 88%, respectively. The NPVs for sIgE to peanut extract, Ara h 1, Ara h 2 and Ara h 3 (at a cut off of 0.1 kU_A/L) were 78%, 58%, 79% and 62%, respectively.

Higher titers in patients with objective symptoms

Figure 2 shows the percentage of patients with and without sensitization (cutoff 0.10 kU_A/L) to peanut components and peanut extract per DBPCFC result (i.e. positive with objective symptoms, positive with subjective symptoms and negative) and the titers of sensitization. Patients with a positive DBPCFC result with objective symptoms recognized Ara h 1, 2, 3 and 6 more often and had a higher titer compared to patients with subjective symptoms or a negative DBPCFC result. A large proportion of patients recognized Ara h 8 (75%) and peanut extract (89%), irrespective of the DBPCFC result.

Peanut allergic patients without sensitization to Ara h 1, 2, 3 and 6

In 16 (17%) patients with a positive DBPCFC result we did not detect sensitization to Ara h 1, 2, 3 and 6 (Figure 3). Five of 16 patients had objective symptoms Mueller grade 3 during the DBPCFC. Peanut allergic patients with undetectable sensitization to Ara h 1, 2, 3 and 6 were sensitized to Ara h 8 and peanut extract (n=8), to Ara h 8 only (n=2), to peanut extract only (n=2) or were not sensitized to peanut extract or any of the peanut components (n=4).

Additional diagnostic testing on a line blot (EUROLINE) was performed, measuring Ara h 1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 14 and 15, in 14 of 16 patients with leftover serum available after the ImmunoCAP measurements. Again, no sensitization to Ara h 1, 2, 3 or 6 was measured on the line blot. Furthermore, all patients were tested negative to Ara h 5, 7, 10, 11, 14 and 15. Two patients were sensitized to Ara h 9 (patient ID 3 and ID 14 in Figure 3) on the line blot.

DISCUSSION

In the current study, we showed that Ara h 2 and Ara h 6 are the best predictors of peanut allergy in adults with suspected peanut allergy. Our validated Ara h 2 cutoff level with 100% positive predictive value (PPV) (cutoff ≥ 1.75 kU_A/L) can be used to accurately predict peanut allergy in one-third of patients. Furthermore, we were the first to investigate the diagnostic value of sIgE to Ara h 6 using a singleplex assay in adults and were able to identify a cutoff level of Ara h 6 with 100% PPV (cutoff ≥ 1.80 kU_A/L), again applicable to almost one-third of patients.

Our results are in line with previous research that identified Ara h 2 and Ara h 6 as the best predictors of peanut allergy.(8,14,15) The AUC value of sIgE to Ara h 2 was lower in our study in adults (AUC 0.85) compared to the AUC values reported in studies in children (AUC 0.90-0.96).(14,34) In addition, we observed a lower cutoff level of Ara h 2 with 100% PPV (cutoff ≥ 1.75 kU_A/L) compared to children (cutoff 4.0-5.0 kU_A/L).(8,35) The Ara h 2 cutoff with 100% PPV was even lower in the subset of patients who were not part of the previous diagnostic study and underwent a DBPCFC between 2012 and 2019 (cutoff ≥ 0.43 kU_A/L). This disparity could not be explained by differences in age, sex, sensitization levels or DBPCFC outcome (i.e. allergy versus tolerance) between both cohorts or by differences in the ratio of specific to total IgE (data not shown). The AUC value of sIgE to Ara h 6 using a singleplex assay in our study (AUC 0.85) was comparable to the AUC value of sIgE to Ara h 6 using a multiplex assay in adults (AUC 0.82), but lower than observed in children using a multiplex assay (AUC 0.98).(14,15) The lower diagnostic value of peanut components in adults compared to children could be explained by the higher proportion of birch pollen-related peanut allergy in adults. In patients with birch pollen allergy, cross-sensitization of Ara h 8 with major birch pollen allergen Bet v 1 occurs and these patients have mainly mild or subjective symptoms after peanut ingestion, making it more difficult to discriminate between presence and absence of allergy.(12,14,16) As shown in the current

study, adult peanut allergic patients with subjective symptoms were less often sensitized to Ara h 2 and Ara h 6 and had lower titers, resulting in a lower diagnostic value. Further insight into the levels of IgE sensitization over time, from childhood to adulthood, could contribute to a better understanding of the differences between children and adults.

The concentrations of sIgE to Ara h 2 and Ara h 6 were highly correlated in our and previous studies.(36,37, 38) In addition, the combination of Ara h 2 and 6 did not improve the diagnostic accuracy in the current study. The extensive overlap in sIgE reactivity and comparable diagnostic accuracy, indicate that ImmunoCAP results for either Ara h 2 or Ara h 6 are sufficient in the diagnostic work-up of a suspected peanut allergy in adults. Multivariable analyses revealed that a combination of Ara h 1 and Ara h 6 had the highest diagnostic accuracy, with an AUC comparable to those of Ara h 2 and Ara h 6 alone, despite regularization (i.e. shrinkage of the coefficients) (AUC 0.85). At present, however, we recommend using sIgE reactivity to peanut component Ara h 2 in daily practice, as the cutoff level is validated in the current study, implementation in daily practice is straightforward, and interpretation of sIgE-levels to one peanut component is more intuitive than of a clinical prediction rule based on the Lasso model. Moreover, a recent study in children showed that Ara h 2 is likely the dominant allergen despite similarities with Ara h 6(38).

Thirty-two percent of patients could be classified correctly as peanut allergic when using the validated cutoff level of sIgE to Ara h 2 with 100% positive predictive value (PPV) (cutoff ≥ 1.75 kU_A/L). This cutoff level of Ara h 2 could be used in daily clinical practice to select patients for oral food challenges. In patients with an Ara h 2 level above the cutoff level, peanut allergy is diagnosed with (almost) 100% accuracy without an oral food challenge. In these patients, a 1-day oral food challenge may still be performed, in accordance with the patient and physician preference, to assess the severity of the allergic reaction and the eliciting dose. In patients with

an Ara h 2 level below the cutoff level, peanut allergic status cannot be predicted. In these patients, a 2-day double-blind placebo-controlled food challenge is needed to confirm or exclude peanut allergy (see Online Repository Figure E1).

It must be noted that sIgE to Ara h 2 and Ara h 6 cannot be used to rule out peanut allergy in adults. In 16 peanut allergic patients (17%) in our cohort we did not detect sensitization to Ara h 2 and Ara h 6, nor for Ara h 1 or Ara h 3. In these patients, sensitization to peanut allergens might not have been detected by the ImmunoCAP platform or peanut allergy might have been caused by sensitization to other peanut components. Therefore, a different diagnostic testing modality was used to test a large number of peanut components (Ara h 1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 14 and 15), resulting in 2 of 16 patients recognizing Ara h 9. Ten of 16 (63%) patients were sensitized to the birch pollen related allergen Ara h 8, and 3 of these 10 patients that only recognized Ara h 8 experienced objective respiratory symptoms during the double-blind placebo-controlled food challenge (DBPCFC). However, the sensitization rate to Ara h 8 in peanut-tolerant patients was comparable (64%), thus sIgE to Ara h 8 was not predictive of clinical reactivity to peanut. A comparable frequency (18%) of allergic patients with negative serology tests, including Ara h 1, 2, 3 and 6, was reported in peanut allergic patients in the EuroPrevall study.⁽³⁶⁾ The authors hypothesized that peanut oleosins may have caused allergic reactions in these patients. Interestingly, all peanut allergic patients with negative Ara h 1, 2, 3 and 6 results in our study were tested negative to peanut oleosins (i.e. Ara h 10, 11, 14 and 15). Thus, peanut allergy in non-sensitized patients as detected in this and previous studies might be caused by sensitization to thus far unidentified peanut components.

A limitation of our study was that we only included patients with a conclusive DBPCFC result, and with leftover serum available from a tertiary center. However, we believe our sample was a representative sample as we did not observe significant differences between included and

excluded patients. Furthermore, the percentage of positive DBPCFCs in our study (62%) was comparable to other studies (43-66%).(16, 39,40) Strengths of our study were that we included a large cohort of adult patients who all underwent a standardized DBPCFC for peanut allergy, we measured a large number of peanut components, we performed a validation of our previous results and were able to confirm these findings.(16)

In conclusion, we showed that specific IgE to Ara h 2 and Ara h 6 are the best predictors of peanut allergy in adults. Furthermore, we validated our previously published Ara h 2 cutoff level with 100% positive predictive value. The validated Ara h 2 cutoff level should be implemented in daily practice to reduce the need for double-blind placebo-controlled food challenges, as all adults with an Ara h 2 ≥ 1.75 kU_A/L were peanut allergic.

ACKNOWLEDGMENTS

We thank L. Bok^a and A. Kooij^a for performing ImmunoCAP measurements. We thank M. Smits^{a,b,c} for performing EUROLINE measurements and P.M.J. Welsing^a for giving statistical advice. We acknowledge R. Klemans^d for providing data from the previous diagnostic study. ImmunoCAP material was provided by Thermo Fisher Scientific (Uppsala, Sweden). The EUROLINE material was provided by EUROIMMUN (Lübeck, Germany).

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REFERENCES

1. Nwaru BI, Hickstein L, Panesar SS, Roberts G, Muraro A, Sheikh A. Prevalence of common food allergies in Europe: A systematic review and meta-analysis. *Allergy*. 2014;69(8):992–1007.
2. Lyons SA, Burney PGJ, Ballmer-Weber BK, Fernandez-Rivas M, Barreales L, Clausen M, et al. Food Allergy in Adults: Substantial Variation in Prevalence and Causative Foods Across Europe. *J Allergy Clin Immunol Pract*. 2019;7(6):1920–8.
3. Soller L, Ben-Shoshan M, Harrington DW, Knoll M, Fragapane J, Joseph L, et al. Adjusting for nonresponse bias corrects overestimates of food allergy prevalence. *J Allergy Clin Immunol Pract*. 2015;3(2):291-293.e2.
4. Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Beyer K, Bindslev-Jensen C, et al. EAACI Food Allergy and Anaphylaxis Guidelines: Diagnosis and management of food allergy. *Allergy*. 2014;69(8):1008–25.
5. Niggeman B, Yürek S, Beyer K. Severe anaphylaxis requiring intensive care during oral food challenge—It is not always peanuts. *Pediatr Allergy Immunol*. 2017;28(2):201–3.
6. Koplin JJ, Perrett KP, Sampson HA. Diagnosing Peanut Allergy with Fewer Oral Food Challenges. *J Allergy Clin Immunol Pract*. 2019;7(2):375–80.
7. Dang TD, Tang M, Choo S, Licciardi P V., Koplin JJ, Martin PE, et al. Increasing the accuracy of peanut allergy diagnosis by using Ara h 2. *J Allergy Clin Immunol*. 2012;129(4):1056–63.
8. 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.
9. van Erp FC, Klemans RJB, Meijer Y, van der Ent CK, Knulst AC, Erp FC Van, et al. Using Component-Resolved Diagnostics in the Management of Peanut-Allergic Patients. *Curr Treat Options Allergy*. 2016;169–80.

- 384 10. Hazebrouck S, Guillon B, Paty E, Dreskin SC, Adel-Patient K, Bernard H. Variable IgE
385 cross-reactivity between peanut 2S-albumins: The case for measuring IgE to both Ara h 2
386 and Ara h 6. *Clin Exp Allergy*. 2019;49(8):1107–15.
- 387 11. Blankestijn MA, Otten HG, Suer W, Weimann A, Knol EF, Knulst AC. Specific IgE to
388 peanut 2S albumin Ara h 7 has a discriminative ability comparable to Ara h 2 and 6. *Clin*
389 *Exp Allergy*. 2017;48(1):60-65.
- 390 12. Beyer K, Grabenhenrich L, Härtl M, Beder A, Kalb B, Ziegert M, et al. Predictive values of
391 component-specific IgE for the outcome of peanut and hazelnut food challenges in
392 children. *Allergy Eur J Allergy Clin Immunol*. 2015 Jan;70(1):90–8.
- 393 13. Ebisawa M, Moverare R, Sato S, Borres MP, Ito K. The predictive relationship between
394 peanut- and Ara h 2-specific serum IgE concentrations and peanut allergy. *J Allergy Clin*
395 *Immunol Pr*. 2015;3(1):131-2.e1.
- 396 14. Kukkonen AK, Pelkonen AS, Makinen-Kiljunen S, Voutilainen H, Makela MJ. Ara h 2 and
397 Ara 6 are the best predictors of severe peanut allergy: a double-blind placebo-controlled
398 study. *Allergy*. 2015 Oct;70(10):1239–45.
- 399 15. Klemans RJB, Knol EF, Bruijnzeel-Koomen CAFM, Knulst AC. The diagnostic accuracy
400 of specific IgE to Ara h 6 in adults is as good as Ara h 2. *Allergy*. 2014 Aug;69(8):1112–4.
- 401 16. Klemans RJB, Broekman HCHP, Knol EF, Bruijnzeel-Koomen CAFM, Otten HG,
402 Pasmans SGMA, et al. Ara h 2 is the best predictor for peanut allergy in adults. *J Allergy*
403 *Clin Immunol Pract*. 2013;1(6):632-638.e1.
- 404 17. Chapmah M, Pomés A, Breiteneder H, Ferreira F. Nomenclature and structural biology of
405 allergens. *J Allergy Clin Immunol*. 2007;119:414–20.
- 406 18. Koppelman SJ, de Jong GAH, Laaper-Ertmann M, Peeters KABM, Knulst AC, Hefle SL,
407 et al. Purification and immunoglobulin E-binding properties of peanut allergen Ara h 6:
408 evidence for cross-reactivity with Ara h 2. *Clin Exp Allergy*. 2005 Apr;35(4):490–7.
- 409 19. Burks AW, Cockrell G, Stanley JS, Helm RM, Bannon GA. Recombinant peanut allergen

- 410 Ara h I expression and IgE binding in patients with peanut hypersensitivity. *J Clin Invest.*
411 1995 Oct;96(4):1715–21.
- 412 20. Rabjohn P, Helm EM, Stanley JS, West CM, Sampson HA, Burks AW, et al. Molecular
413 cloning and epitope analysis of the peanut allergen Ara h 3. *J Clin Invest.* 1999
414 Feb;103(4):535–42.
- 415 21. Mittag D, Akkerdaas J, Ballmer-Weber BK, Vogel L, Wensing M, Becker W-M, et al. Ara h
416 8, a Bet v 1-homologous allergen from peanut, is a major allergen in patients with
417 combined birch pollen and peanut allergy. *J Allergy Clin Immunol.* 2004
418 Dec;114(6):1410–7.
- 419 22. Asarnoj A, Nilsson C, Lidholm J, Glaumann S, Ostblom E, Hedlin G, et al. Peanut
420 component Ara h 8 sensitization and tolerance to peanut. *J Allergy Clin Immunol.* 2012
421 Aug;130(2):468–72.
- 422 23. Lauer I, Dueringer N, Pokoj S, Rehm S, Zoccatelli G, Reese G, et al. The non-specific
423 lipid transfer protein, Ara h 9, is an important allergen in peanut. *Clin Exp Allergy.* 2009
424 Sep;39(9):1427–37.
- 425 24. Agabriel C, Ghazouani O, Birnbaum J, Liabeuf V, Porri F, Gouitaa M, et al. Ara h 2 and
426 Ara h 6 sensitization predicts peanut allergy in Mediterranean pediatric patients. *Pediatr*
427 *Allergy Immunol.* 2014 Nov;25(7):662–7.
- 428 25. Asarnoj A, Glaumann S, Elfstrom L, Lilja G, Lidholm J, Nilsson C, et al. Anaphylaxis to
429 peanut in a patient predominantly sensitized to Ara h 6. *Int Arch Allergy Immunol.*
430 2012;159(2):209–12.
- 431 26. Canonica GW, Ansotegui IJ, Pawankar R, Schmid-Grendelmeier P, Van Hage M, Baena-
432 Cagnani CE, et al. A WAO-ARIA-GA2LEN consensus document on molecular-based
433 allergy diagnostics. *World Allergy Organ J.* 2013;6(1):1.
- 434 27. Peeters KABM, Koppelman SJ, Van Hoffen E, Van Der Tas CWH, Den Hartog Jager CF,
435 Penninks AH, et al. Does skin prick test reactivity to purified allergens correlate with

- clinical severity of peanut allergy? Clin Exp Allergy. 2007;37(1):108–15.
28. Taylor SL, Hefle SL, Bindslev-Jensen C, Atkins FM, Andre C, Bruijnzeel-Koomen C, et al. A consensus protocol for the determination of the threshold doses for allergenic foods: how much is too much? Clin Exp Allergy. 2004 May;34(5):689–95.
29. Vlieg-Boerstra BJ, Herpertz I, Pasker L, Van Der Heide S, Kukler J, Jansink C, et al. Validation of novel recipes for double-blind, placebo-controlled food challenges in children and adults. Allergy Eur J Allergy Clin Immunol. 2011;66(7):948–54.
30. Mueller HL. Diagnosis and Treatment of Insect Sensitivity. J Asthma Res. 1966;3(4):331–3.
31. DeLong ER., DeLong DM., Clarke-Pearson DL. Comparing the Areas under Two or More Correlated Receiver Operating Characteristic Curves: A Nonparametric Approach. Biometrics. 1988;44(3):837–45.
32. Tibshirani R. Regression Shrinkage and Selection via the Lasso. J Roy Stat Soc B. 1996;58(1):267–88.
33. Dhand NK, Khatkar MS. Statulator: An online statistical calculator. Sample Size Calculator for Estimating a Single Proportion [Internet]. 2014. [cited 2020 Mar 5]. Available from: <http://statulator.com/SampleSize/ss1P.html>
34. Klemans RJB, Otte D, Knol M, Knol EF, Meijer Y, Gmelig-Meyling FHJ, 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):157–63.
35. Kim HY, Han Y, Kim K, Lee JY, Kim MJ, Ahn 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):156–60.
36. Ballmer-Weber BK, Lidholm J, Fernandez-Rivas M, Seneviratne S, Hanschmann KM, Vogel L, et al. IgE recognition patterns in peanut allergy are age dependent: perspectives

- 462 of the EuroPrevall study. *Allergy*. 2015;70(4):391–407.
- 463 37. Koid AE, Chapman MD, Hamilton RG, van Ree R, Versteeg SA, Dreskin SC, et al. Ara h
464 6 complements Ara h 2 as an important marker for IgE reactivity to peanut. *J Agric Food*
465 *Chem*. 2014 Jan;62(1):206–13.
- 466 38. Hemmings H, Du Toit G, Radulovic S, Lack G, Santos AF. Ara h 2 is the dominant peanut
467 allergen despite similaritis with Ara h 6. *J Allergy Clin Immunol*. 2020; S0091-
468 6749(20)30433-4.
- 469 39. Zambrano Ibarra G, Fuentes Aparicio V, Infante Herrero S, Blanca M, Zapatero Remon L.
470 Peanut Allergy in Spanish Children: Comparative Profile of Peanut Allergy versus
471 Tolerance. *Int Arch Allergy Immunol*. 2019;178(4):370–6.
- 472 40. Grabenhenrich L, Lange L, Härtl M, Kalb B, Ziegert M, Finger A, et al. The component-
473 specific to total IgE ratios do not improve peanut and hazelnut allergy diagnoses. *J*
474 *Allergy Clin Immunol*. 2016;137(6):1751-1760.e8.

FIGURE LEGENDS

Figure 1. ROC-curves of serology tests to predict a positive DBPCFC result (A) or a positive DBPCFC result with objective symptoms (B)

The Lasso model included sIgE to Ara h 1 and Ara h 6 to predict peanut allergy (A) and sIgE to peanut extract, Ara h 1, Ara h 6 and Ara h 8 to predict peanut allergy with objective symptoms (B).

Abbreviations: AUC, area under the curve; CI, confidence interval; DBPCFC, double-blind placebo-controlled food challenge; n, number; ROC, receiver-operating characteristic.

Figure 2. Percentage of patients with sensitization to peanut extract or peanut components and titers of sensitization, per DBPCFC result

The percentage of patients is shown in blue bars and the median (interquartile range) titers of sIgE are displayed in the center of the bars in black color. Sensitization is defined as a value of ≥ 0.10 kU_A/L. Specific IgE titers are displayed on logarithmic scales (base 10).

Abbreviations: DBPCFC, double-blind placebo-controlled food challenge; sIgE, specific IgE.

Figure 3. Sensitization pattern in 16 peanut allergic patients without sensitization to Ara h 2 and Ara h 6

[†]Symptoms during the oral food challenge: S, subjective; O, objective.

[‡]Severity of symptoms during the oral food challenge based on the Mueller score with 0. Oral symptoms, 2. Gastro-intestinal symptoms and 3. Respiratory symptoms.(16,30)

Abbreviations: ID, patient number; O, objective; S, subjective; Sev, severity; Sym, symptoms.

TABLES

Table 1. Characteristics of participating patients and details of double-blind placebo-controlled food challenges

	Total	Positive DBPCFC result	Negative DBPCFC result	P value
	154	95 (62)	59 (38)	
Age, median (IQR)	27 (22-38)	25 (21-31)	34 (24-43)	<0.0005
Male gender	52 (34)	35 (37)	17 (29)	0.306
Allergic rhinitis [†]	69 (45)	30 (32)	22 (37)	0.236
Sensitization, median (IQR)				
slgE peanut extract	1.65 (0.35-11.05)	6.20 (0.72-23.70)	0.44 (0.16-1.65)	<0.0005
slgE Ara h 1	0.02 (0.00-0.61)	0.10 (0.01-7.58)	0.00 (0.00-0.03)	<0.0005
slgE Ara h 2	0.16 (0.03-3.50)	2.20 (1.14-10.00)	0.03 (0.00-0.08)	<0.0005
slgE Ara h 3	0.03 (0.01-0.18)	0.07 (0.01-0.92)	0.01 (0.00-0.03)	<0.0005
slgE Ara h 6 [‡]	0.07 (0.00-3.14)	1.37 (0.08-9.50)	0.00 (0.00-0.03)	<0.0005
slgE Ara h 8	2.02 (0.11-8.57)	2.05 (0.24-8.70)	1.50 (0.03-8.53)	0.198
DBPCFC period				0.952
2003-2012	84 (55)	52 (55)	32 (54)	
2012-2019	70 (45)	43 (45)	27 (46)	
DBPCFC result				NA
Positive objective	69 (45)	69 (73)	NA	
Positive subjective	26 (17)	26 (27)	NA	
Negative	59 (38)	NA	59 (100)	
Severity positive DBPCFC result [§]				NA
Mueller 0	15 (16)	15 (16)	NA	
Mueller 1	16 (17)	16 (17)	NA	
Mueller 2	32 (34)	32 (34)	NA	
Mueller 3	28 (29)	28 (29)	NA	
Mueller 4	2 (2)	2 (2)	NA	

Value are n (%) unless otherwise indicated.

[†]Missing data n=85[‡]Missing data n=36

[§]Missing data n=1. Severity of symptoms during the oral food challenge based on the Mueller score with 0. oral symptoms, 1. cutaneous symptoms, 2. gastrointestinal symptoms, 3. respiratory symptoms and 4. cardiovascular symptoms.(16,30)

Abbreviations: DBPCFC, double-blind placebo-controlled food challenge; NA, not applicable;

slgE, specific IgE.

Table 2. Validation of sIgE to Ara h 2 cutoff level and cutoff levels with optimal positive and negative predictive values

	n	Cutoff kUA/L	PPV % (N/D) [†]	NPV % (N/D) [‡]	Sens % (N/D) [§]	Spec % (N/D) [*]
Validation						
sIgE to Ara h 2	70	1.75	100 (25/25)	60 (27/45)	58 (25/43)	100 (27/27)
Optimal PPV cutoff levels						
sIgE to Ara h 2	154	1.75	100 (49/49)	56 (59/105)	52 (49/95)	100 (59/59)
sIgE to Ara h 6	118	1.80	100 (33/33)	55 (47/85)	46 (33/71)	100 (47/47)
sIgE to Ara h 1	154	2.47	100 (34/34)	49 (59/120)	36 (34/95)	100 (59/59)
sIgE to Ara h 3	154	0.88	100 (25/25)	46 (59/129)	2625 (95)	100 (59/59)
sIgE to Ara h 8	154	100	100 (1/1)	39 (59/153)	1 (1/95)	100 (59/59)
sIgE to peanut extract	154	15.10	100 (32/32)	48 (59/122)	34 (32/95)	100 (59/59)
Optimal NPV cutoff levels						
sIgE to Ara h 2	154	0.02	71 (89/126)	79 (22/28)	94 (89/95)	37 (22/59)
sIgE to Ara h 6	118	0.04	86 (56/65)	72 (38/53)	79 (56/71)	81 (38/47)
sIgE to Ara h 1	154	0.05	89 (57/64)	58 (52/90)	60 (57/95)	88 (52/59)
sIgE to Ara h 3	154	0.01	67 (84/125)	62 (18/29)	88 (84/95)	31 (18/59)
sIgE to Ara h 8	154	0.01	64 (94/146)	88 (7/8)	99 (94/95)	12 (7/59)
sIgE to peanut extract	154	0.11	68 (94/139)	78 (14/18)	96 (94/98)	24 (14/59)

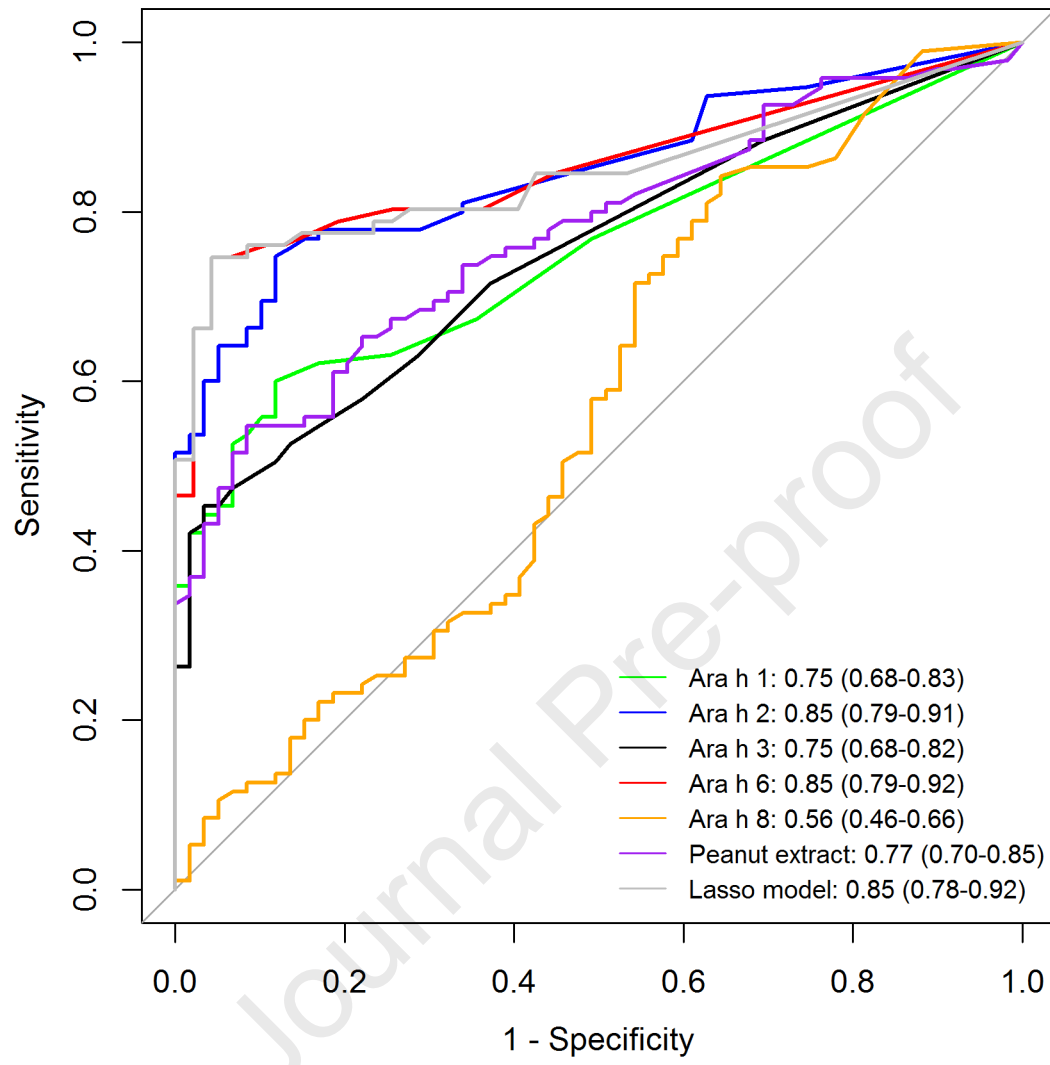
[†] Numerator: TP, denominator: TP + FP. [‡] Numerator: TN, denominator: TN + FN. [§] Numerator: TP, denominator: TP + FN.

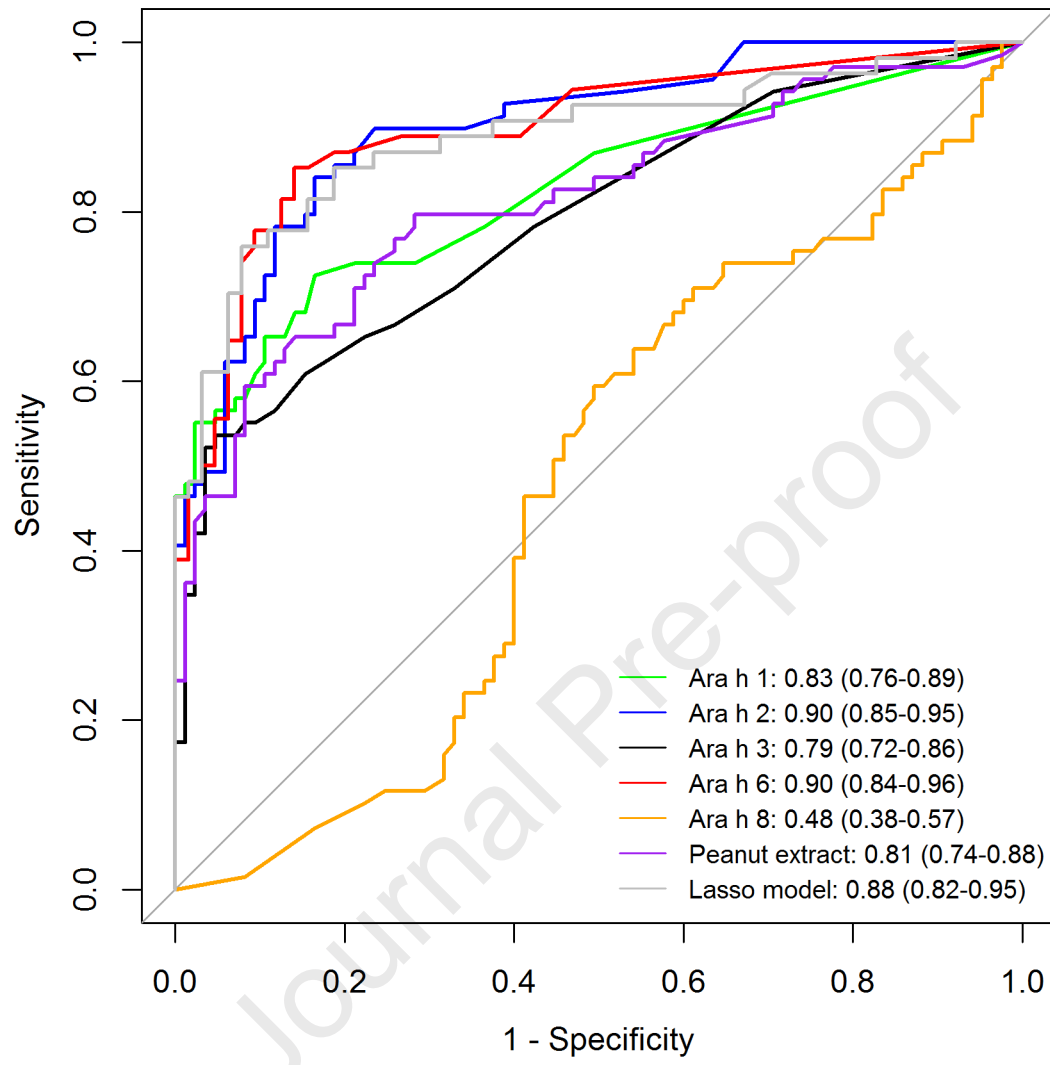
^{*} Numerator: TN, denominator: TN + FP.

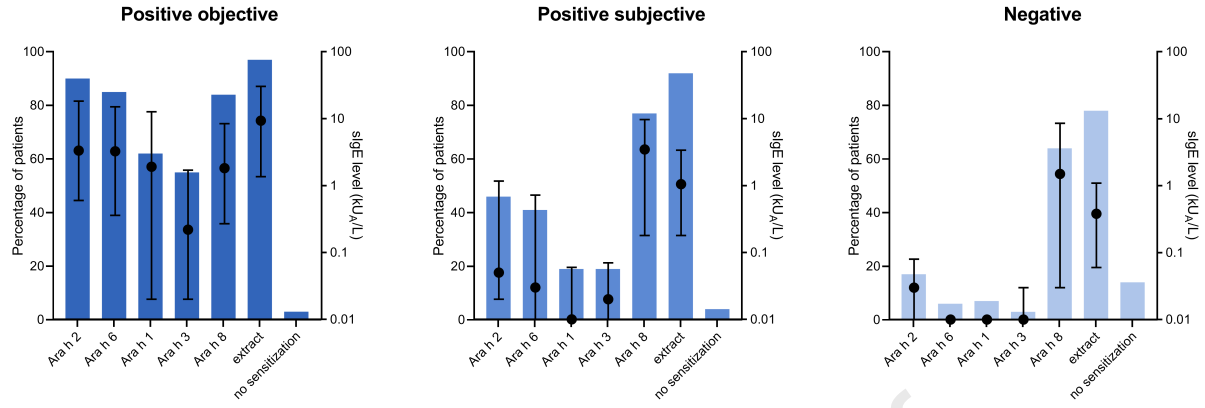
Abbreviations: D, denominator; FN, false negative results; FP, false positive results; n, number of patients included; N, numerator;

NPV, negative predictive value; PPV, positive predictive value; Sens, sensitivity; sIgE, specific IgE; Spec, specificity; TN, true

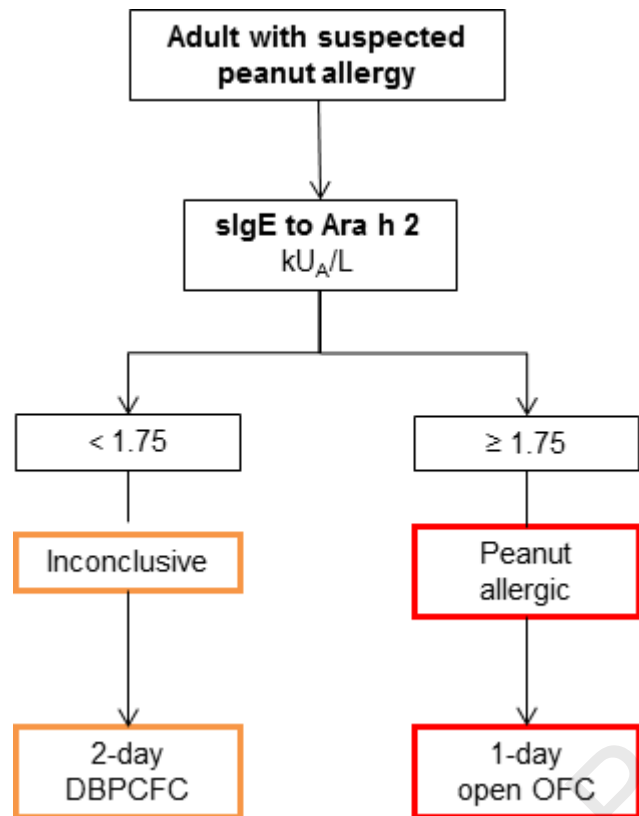
negative results; TP, true positive results.







ID	Ara h 2	Ara h 6	Ara h 1	Ara h 3	Ara h 8	extract	Sym [†]	Sev [†]	slgE level (kU _A /L)
1	0.02	0	0	0	0	0	O	3	50.00 - 100.00
2	0	0	0	0.01	0.01	0	S	0	
3	0	0	0	0.01	0.01	1.05	S	0	17.50 - 49.90
4	0.01	0	0	0	0.01	0.19	S	0	
5	0.02	0	0	0	0.01	0	O	2	3.50 - 17.49
6	0.02	0	0	0	0.01	0.01	O	2	
7	0.03	0.01	0.01	0.01	0.50	0.01	O	3	0.70 - 3.49
8	0	0	0	0	1.39	0.03	S	2	
9	0.04	0.04	0.04	0.08	3.70	0.11	S	0	0.35 - 0.69
10	0.06	0.08	0.05	0.07	3.80	2.30	O	3	
11	0	0	0	0.01	7.20	0.16	S	0	0.10 - 0.34
12	0.04	0.01	0.01	0.01	8.11	0.15	O	3	
13	0.02	0	0	0	10.60	2.17	S	2	0 - 0.09
14	0.05	0.01	0.01	0.01	14.50	0.66	O	3	
15	0.06	0	0	0	16.80	1.08	S	0	
16	0	0	0	0.01	20.60	0.54	S	0	



ONLINE REPOSITORY - Tables

Accurate prediction of peanut allergy in one third of adults using a validated Ara h 2 cutoff

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Table E1. Baseline characteristics of included and excluded patients.

	Included	Excluded	n available	P value
	154 (75)	50 (25)		
Age, mean (SD)	27 (22-38)	24.5 (20.3-31)	32	0.055
Male gender	52 (34)	19 (38)	50	0.585
Allergic rhinitis [†]	52 (75)	11 (73)	15	0.869
Sensitization, median (IQR)				
slgE peanut	1.65 (0.35-11.05)	2.35 (0.71-22.40)	23	0.377
slgE Ara h 1	0.02 (0.00-0.61)	0.00 (0.00-0.01)	4	-
slgE Ara h 2	0.16 (0.03-3.50)	0.38 (0.00-1.37)	19	0.424
slgE Ara h 3	0.03 (0.01-0.18)	0.00 (0.00-0.01)	4	-
slgE Ara h 6	0.07 (0.00-3.14)	0.02 (0.00-0.53)	6	-
slgE Ara h 8	2.02 (0.11-8.57)	1.23 (0.01-8.75)	18	0.428
DBPCFC result [‡]			50	<0.0005
Positive	95 (62)	20 (40)		
Inconclusive	0	18 (36)		
Negative	59 (38)	12 (24)		0.213
Severity positive DBPCFC result			11	
Mueller 0	15 (16)	2 (18)		
Mueller 1	16 (17)	2 (18)		
Mueller 2	32 (34)	7 (64)		
Mueller 3	28 (30)	0		
Mueller 4	2 (2)	0		

Values are n (%) unless otherwise indicated.

[†]Missing data included patients n=85

[‡]One of the reasons for exclusion was an inconclusive DBCPFC result. The proportion of positive and negative DBPCFC results were comparable between groups (p=0.931).

[§]Missing data included patients n=2. Severity of symptoms during the oral food challenge based on the Mueller score with 0. oral symptoms, 1. cutaneous symptoms, 2. gastrointestinal symptoms, 3. respiratory symptoms and 4. cardiovascular symptoms.(16,30)

Abbreviations: DBPCFC, double-blind placebo-controlled food challenge; IQR, interquartile range; SD, standard deviation; slgE, specific IgE.

Table E2. Diagnostic value of peanut components in subset of cohort with available sIgE to Ara h 6 (n=118)

	AUC (95% CI)
sIgE extract	0.76 (0.68-0.85)
sIgE Ara h 1	0.76 (0.68-0.84)
sIgE Ara h 2	0.85 (0.78-0.92)
sIgE Ara h 3	0.75 (0.67-0.84)
sIgE Ara h 8	0.57 (0.46-0.68)

Abbreviations: AUC, area under the curve; CI, confidence interval; sIgE, specific IgE.

Table E3. DeLong's test for comparing two ROC curves

	slgE Ara h 6	slgE extract	slgE Ara h 1	slgE Ara h 3	slgE Ara h 8
slgE Ara h 2	0.87	0.02	<0.01	<0.01	<0.01
slgE Ara h 6		0.02	<0.01	<0.01	<0.01
slgE extract			0.61	0.56	<0.01
slgE Ara h 1				0.93	<0.01
slgE Ara h 3					<0.01
slgE Ara h 8					

Data are p-values corrected for multiple testing using the Benjamini-Hochberg procedure.

Significant p-values are in **boldface**.

ONLINE REPOSITORY – Text file

Accurate prediction of peanut allergy in one third of adults using a validated Ara h 2 cutoff

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Figure legends

Figure E1. Diagnostic flowchart for adults with suspected peanut allergy

Abbreviations: DBPCFC, double-blind placebo-controlled food challenge; OFC, oral food challenge.

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