*Practice parameter*

# Peanut allergy diagnosis: A 2020 practice parameter update, systematic review, and GRADE analysis

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**Given the burden of disease and the consequences of a diagnosis of peanut allergy, it is important that peanut allergy be accurately diagnosed so that an appropriate treatment plan can be developed. However, a test that indicates there is peanut sensitization present (eg, a "positive" test) is not always associated with clinical reactivity. This practice parameter addresses the diagnosis of IgE-mediated peanut allergy, both in children and adults, as pertaining to 3 fundamental questions, and based on the systematic reviews and meta-analyses, makes recommendations for the clinician who is evaluating a patient for peanut allergy. These questions relate to when diagnostic tests should be completed, which diagnostic tests to utilize, and the utility (or lack thereof) of diagnostic testing to predict the severity of a future allergic reaction to peanut. (J Allergy Clin Immunol 2020;146:1302-34.)**

***Key words:*** *Peanut allergy, diagnosis, practice parameter update, systematic review, GRADE analysis, Ara h 2, peanut components, skin prick testing, serologic IgE testing, likelihood ratio, evidence to recommendation, meta-analysis, cost-effectiveness analysis*

*Abbreviations used*

| | |
|---|---|
| AAAAI: | American Academy of Allergy, Asthma, and Immunology |
| ACAAI: | American College of Asthma, Allergy, and Immunology |
| AMSTAR: | Assessing the Methodological Quality of Systematic Reviews |
| FPIES: | Food protein induced enterocolitis syndrome |
| GRADE: | Grading of Recommendations, Assessment, Development, and Evaluation |
| JTFPP: | Joint Task Force on Practice Parameters |
| $KU_A$: | Kilo allergen unit |
| NIAID: | National Institutes of Allergy and Infectious Disease |
| OFC: | Oral food challenge |
| PICO: | Population, intervention, comparator, and outcome |
| PPV: | Positive predictive value |
| PRISMA: | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| sIgE: | Serum-specific IgE |
| SPT: | Skin prick test |

## EXECUTIVE SUMMARY

IgE-mediated peanut allergy has an estimated prevalence of between 0.2% and 4.5%, depending on geographic area of the world and the methodology used for assessment. While the prevalence in the United States appears to have tripled in a recent 10-year period, in the United Kingdom, the prevalence seems to have plateaued over a similar period, denoting regional heterogeneity in such trends. Peanut allergy is associated with substantial economic and psychologic burden on families that is associated with poor quality of life and high anxiety related to the potential consequences of their child having a severe allergic reaction. Peanut allergy is often a severe and usually a lifelong allergy that is a leading cause of food-related anaphylaxis. One

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peanut allergy treatment has been approved by the US Food and Drug Administration, and several other emerging treatments are approaching consideration for US Food and Drug Administration approval. However, presently peanut allergy is managed through peanut avoidance and by carrying emergency medication such as autoinjectable epinephrine to treat symptoms that may arise from unintended ingestion.

Given this burden of disease and the consequences of diagnosis, it is important that peanut allergy be accurately diagnosed so that an appropriate treatment plan can be developed. However, a positive peanut test result is not always associated with clinical reactivity. This practice parameter addresses the diagnosis of IgE-mediated peanut allergy, both in children and adults, as pertaining to 3 fundamental questions (see Box 1). This parameter exclusively discusses IgE-mediated peanut allergy and all references herein pertain to IgE-mediated food allergy to peanut only and not to peanut as a potential trigger in eosinophilic esophagitis or non-IgE-mediated food allergy such as food protein induced enterocolitis syndrome (FPIES). Similarly, emerging technologies such as basophil activation testing were also not included in this analysis.

Diagnostic testing for peanut allergy is used to help make a diagnosis where there is suspicion of a peanut allergy based on the clinical history. Failure to make a correct diagnosis can result in either unnecessary avoidance in a nonallergic person, or erroneous guidance that the patient can safely ingest peanut *ad libitum* when there is in fact an allergy—both of which are problematic situations. A correct diagnosis facilitates peanut avoidance and counseling when the patient is at risk of potential life-threatening complications of peanut allergy and therefore is advised to carry epinephrine for use in case of symptomatic accidental ingestion. Alternatively, exclusion of peanut allergy allows peanut to be incorporated into the diet without concern, eliminating the burden of precautions and fear. Changes in peanut sensitization levels over time, compared with baseline, may be associated with whether the individual with allergy is likely to be outgrowing their peanut allergy. Although previous research in patients with established peanut allergy reported clinical diagnostic cutoff points for >95% chance of reaction and for <50% chance of reaction to oral food challenge (OFC), these are not necessarily predictive of clinical outcomes in all settings and patients, as they are highly dependent on the baseline prevalence of

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**Box 1.** GRADE questions evaluated in this practice parameter

PICO questions: GRADE analysis of diagnostic testing in the diagnosis of peanut allergy

1. Should diagnostic testing for peanut allergy be performed in adults and children with a history of suspected peanut allergy who are requesting evaluation for peanut allergy?
2, *A*. In the patient presenting for evaluation of suspected peanut allergy, which of the 3 tests—SPT, sIgE to whole peanut, or Ara h 2—would provide the highest diagnostic accuracy as determined by the more optimal positive/negative likelihood ratio?
2, *B*. In a patient presenting for evaluation of suspected peanut allergy, does testing for peanut components in addition to either SPT or sIgE to whole peanut increase the diagnostic accuracy?
3. In the patient presenting for evaluation of suspected peanut allergy, can the results of a diagnostic test be used to predict the severity of a future allergic reaction?

peanut allergy in the particular population studied, which may vary. This practice parameter uses likelihood ratios as the main statistic in this analysis, given this metric is not dependent on a population prevalence of disease, and is more adaptable to individual clinical settings.

The expert panel developed the key PICO (population, intervention, comparator, and outcome) questions to be addressed, and after a systematic review of the literature (>1300 references searched), a meta-analysis of the evidence, and a GRADE (Grading of Recommendations, Assessment, Development and Evaluation) analysis (a well-established methodology for developing evidence-based guidelines) of the results (see Table I) made its recommendations. All the recommendations were conditional in strength, with low or very low certainty of evidence. Thresholds for detection of sensitization were at 3 mm for skin prick test (SPT), and 0.35 $KU_A$/L ($KU_A$ = kilo allergen unit) for both whole peanut serum-specific IgE (sIgE) and component-specific peanut sIgE, based on the most widely reported levels evaluated in the literature. Additional cutoffs were considered, but their use would have posed a significant limitation to the analysis, given very limited study numbers reporting these values. Extensive sensitivity analysis was performed to confirm the results.

The expert panel suggested that diagnostic testing for peanut allergy be used in patients with a high pretest probability of peanut allergy, or prior to an OFC for patients with moderate pretest probability of peanut allergy, as a preference-sensitive choice, but discourages testing in patients with a low or very low pretest probability of peanut allergy. If a single diagnostic test were to be used, testing for the Ara h 2 component would provide the most diagnostic accuracy, as determined by the more optimal positive/negative likelihood ratio among the presently available testing options. However, this is contingent on Ara h 2 component testing becoming more commonly available as a stand-alone test, as opposed to being primarily offered by laboratories as a panel with other peanut components. The literature search did not provide patient-level data to determine the value of testing for peanut components in addition to SPT or sIgE to whole peanut to increase diagnostic accuracy, including isolated Ara h 2 in that context. The clinician should not use the results of a SPT, sIgE to whole peanut extract, or sIgE to peanut components to determine an allergy phenotype or to predict the severity of a future reaction (eg, will the patient have anaphylaxis to peanut). An additional supplemental cost-effectiveness analysis of the potential testing options presented in the Online Repository (available at www.jacionline.org) confirms use of Ara h 2 as the optimal choice when compared to peanut SPT and whole peanut sIgE. There remain important knowledge gaps and the need for well-designed studies to address these questions, as well as the need for patient-level data to be made available when reporting test sensitivity/specificity to enhance the ability to perform future meta-analyses that can explore different cutoff levels. These recommendations, which are detailed below, are summarized in Table II.[1]

## Question 1. Should diagnostic testing for peanut allergy be performed in adults and children with a history of suspected peanut allergy who are requesting evaluation for peanut allergy?

**Recommendation 1, *A*. We suggest in favor of diagnostic (SPT or sIgE) testing for peanut allergy (1) when patients have physician-judged high pretest probability of peanut allergy, or (2) prior to an OFC for patients with moderate pretest probability of peanut allergy. For both situations, shared decision making has been employed to arrive at the final decision. Conditional recommendation. Certainty of evidence: Very low.**

**Recommendation 1, *B*. We suggest against diagnostic testing in patients where there is low or very low pretest probability of peanut allergy. Conditional recommendation. Certainty of evidence: Very low.**

This question was not searched in a systematic manner as the content experts were unaware of any single research study that addressed this question. The work group performed a PubMed literature search that did not identify any articles that address this question, which by default limits the certainty of evidence. For this reason, the work group and Joint Task Force on Practice Parameters (JTFPP) felt that it would therefore not be an appropriate utilization of valuable resources to perform a librarian-conducted formal literature search. However, expert evidence was collected both from the content experts and the JTFPP. Expert evidence differs from expert opinion in that the former does not include a judgment on the evidence and offers a systematic and transparent appraisal of the evidence, which differentiates this as an acceptable alternative to making a recommendation under GRADE. The guideline working group related that when evaluating their collective patient experiences, diagnostic testing could be of value to confirm peanut allergy in high-risk individuals for which an oral challenge might not be advisable or agreed to by patients. However, the work group also acknowledged that in a patient presenting with a classical history, the diagnosis could be made on the basis of history

**TABLE I.** The GRADE system of recommendations and evidence certainty

| Strength of recommendation | | |
|---|---|---|
| | **For the patient** | **For the clinician** |
| Strong | Most individuals in this situation would prefer the recommended course of action and only a small proportion would not. | The attending provider should strongly consider the recommended course of action as a first-line management. Formal decision aids may have less of a role to help individuals make decisions consistent with their values and preferences. |
| Conditional | The majority of individuals in this situation would prefer the suggested course of action, but many would not. | Different choices may be appropriate for different patients. Decision aids may be useful in helping individuals in making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working toward a decision. |
| **Certainty in estimates of effect/quality rating both for outcome and for an entire evidence base as it pertains to a PICO question** | | |
| High | There is high confidence that the true effect lies close to that of the estimate of the effect. | |
| Moderate | There is moderate confidence in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. | |
| Low | There is limited confidence in the effect estimate. The true effect may be substantially different from the estimate of the effect. | |
| Very low | There is very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect | |

Additional information regarding GRADE methodology, including how recommendations are formulated and the evidence certainty is rated can be found in Shaker et al[1] and on the Joint Task Force on Allergy Practice Parameters website (https://www.allergyparameters.org/resources-for-understanding-grade/).

**TABLE II.** Summary recommendations in evaluating the patient with suspected peanut allergy

| Question | Recommendation | Evidence certainty | Risk of bias |
|---|---|---|---|
| 1. Should diagnostic testing for peanut allergy be performed in adults and children with a history of suspected peanut allergy who are requesting evaluation for peanut allergy? | 1, *A*. We suggest in favor of diagnostic (SPT or sIgE) testing for peanut allergy (1) when patients have physician-judged high pretest probability of peanut allergy, or (2) prior to an OFC for patients with moderate pretest probability of peanut allergy. For both situations, shared decision making has been employed to arrive at the final decision.<br>1, *B*. We suggest against diagnostic testing in patients where there is low or very low pretest probability of peanut allergy. | Very low | Not rated |
| 2, *A*. In the patient presenting for evaluation of suspected peanut allergy, which of the 3 tests —SPT, sIgE to whole peanut, or Ara h2—would provide the highest diagnostic accuracy as determined by the more optimal positive/negative likelihood ratio? | 2, *A*. We suggest in favor of Ara h 2 diagnostic testing in a patient presenting for evaluation of suspected peanut allergy for which a single diagnostic test is to be used, as Ara h 2 would provide the best diagnostic accuracy as determined by virtue of more optimal positive/negative likelihood ratios. However, while Ara h 2 has the greatest specificity, it has lower sensitivity than SPT and sIgE, and in a patient with a high prior probability, the clinician may use Ara h 2, SPT, or sIgE to confirm the diagnosis of peanut allergy. | Low | High |
| 2, *B*. In a patient presenting for evaluation of suspected peanut allergy, does testing for peanut components in addition to either SPT or sIgE to whole peanut increase the diagnostic accuracy? | 2, *B*. We suggest against routine use of component testing in addition to either to SPT or sIgE to whole peanut to increase diagnostic accuracy. | Very low | High |
| 3. In the patient presenting for evaluation of suspected peanut allergy, can the results of a diagnostic test be used to predict the severity of a future allergic reaction? | 3. We suggest against the clinician using the results of a SPT, sIgE to whole peanut extract, or sIgE to peanut components to determine the severity of an allergy phenotype or to predict the severity of a future reaction. | Very low | High |

alone without further testing in some circumstances. The expert panel related that they suggested an OFC when there was a moderate probability of peanut allergy but that a large proportion of their patients may prefer a diagnostic test prior to the OFC. Similarly, the collective personal experience of the expert panel was that diagnostic testing in patients with a low probability of peanut allergy (eg, sibling has peanut allergy and patient has never ingested peanut) often identified patients

who were sensitized but not truly allergic. Unfortunately, many of these patients refused an OFC and likely avoided peanut unnecessarily.

These recommendations are in alignment with previous expert guidelines and practice parameters on food allergy diagnosis and management, which provide similar consensus regarding the indications for testing for the presence of food sensitization, including peanut, in evaluating a possible diagnosis of food allergy. While screening of foods in infants prior to initial food introduction is discouraged, testing to peanut in infants who are at high risk for peanut allergy (under the very prescribed context of those infants with either severe eczema and/or egg allergy) is the one notable exception, which was recommended prior to initial peanut introduction per the 2017 National Institutes of Allergy and Infectious Disease (NIAID) addendum guidelines.

### Question 2, *A*. In the patient presenting for evaluation of suspected peanut allergy, which of the 3 tests—SPT, sIgE to whole peanut, or Ara h 2—would provide the highest diagnostic accuracy as determined by the more optimal positive/negative likelihood ratio?

**Question 2, *B*. In a patient presenting for evaluation of suspected peanut allergy, does testing for peanut components in addition to either SPT or sIgE to whole peanut increase the diagnostic accuracy?**

**Recommendation 2, *A*. We suggest in favor of Ara h 2 diagnostic testing in a patient presenting for evaluation of suspected peanut allergy for which a single diagnostic test is to be used, as Ara h 2 would provide the best diagnostic accuracy as determined by virtue of more optimal positive/negative likelihood ratios. However, while Ara h 2 has the greatest specificity, it has lower sensitivity than SPT and sIgE, and in a patient with a high prior probability, the clinician may use Ara h 2, SPT, or sIgE to confirm the diagnosis of peanut allergy. Conditional recommendation. Certainty of evidence: Low.**

**Recommendation 2, *B*. We suggest against routine use of component testing in addition to either SPT or sIgE to whole peanut to increase diagnostic accuracy. Conditional recommendation. Certainty of evidence: Very low.**

For GRADE analysis, Ara h 2 was compared with SPT and sIgE to whole peanut for the diagnosis of peanut allergy. The literature search did not provide patient-level data to determine the value of testing for peanut components in addition to or reflexively with SPT or sIgE to whole peanut to increase diagnostic accuracy. In addition, expert evidence was not available to assist in answering this question. Thus, the use and value of components, including reflexive use of Ara h 2, remains a knowledge gap. There is an unclear utility for measuring sIgE to any other commercially available peanut components given the limited available data on performance of components beyond Ara h 2. Further research is needed to clarify the value of tandem testing, particularly with regard to Ara h 2, Ara h 6, and Ara h 8. While Ara h 2 had the greatest specificity in confirming the diagnosis, it had lower sensitivity when compared with SPT or sIgE. In evaluating diagnostic accuracy, the summary receiver operating characteristic curves demonstrated greatest area under the curve for Ara h 2 (0.92) when compared with those for SPT (0.89) and sIgE (0.81). We caution the clinician that despite undetectable sensitization on SPT, sIgE, or Ara h 2 testing, that there is a small possibility the individual could still be allergic to peanut and similarly that detection of sensitization does not always infer clinical allergy. If clinical suspicion remains elevated, further evaluation through an OFC is potentially indicated.

### Question 3. In the patient presenting for evaluation of suspected peanut allergy, can the results of a diagnostic test be used to predict the severity of a future allergic reaction?

**Recommendation 3. We suggest against the clinician using the results of a SPT, sIgE to whole peanut extract, or sIgE to peanut components to determine the severity of an allergy phenotype or to predict the severity of a future reaction. Conditional recommendation. Certainty of evidence: Very low.**

There were inadequate patient-level data to formulate a GRADE recommendation on the use of a peanut diagnostic test for predicting the severity of a future allergic reaction across a continuous range of test result values; however, dichotomous cutoff values of 10 mm (SPT), 50 $KU_A$/L (peanut sIgE), and 2 $KU_A$/L (Ara h 2 [sIgE]) demonstrated low sensitivity and specificity for a future severe reaction.

## INTRODUCTION

This article is a GRADE-based practice parameter for the use of diagnostic testing in evaluating patients with peanut allergy.[1] This practice parameter is divided into several components: (1) a narrative review primer to provide background and context on peanut allergy and the principles of how to apply diagnostic testing for peanut allergy; (2) a meta-analysis and systematic review of peanut allergy diagnostic testing with GRADE recommendations (including supporting tables and figures); and an Online Repository comprising (3) the literature search terms and features of the included articles, (4) a cost-effectiveness analysis of the use of the diagnostic tests, and (5) the GRADE evidence to recommendation framework, which details the considerations that went into formulating the GRADE recommendation.

## A PRIMER ON THE DIAGNOSIS OF PEANUT ALLERGY

### Prevalence of peanut allergy

In the general population, the prevalence of peanut allergy is approximately 1.5% when the diagnosis is based on OFC or highly convincing history, and 0.2% to 0.4% when it is based on OFC alone.[2] These values differ based on age, race, ethnicity, and geography, but the evidence is not available to precisely determine what those differences are. Recent Australian data representative of the greater Victoria province in 1-year-olds suggests the rate of peanut allergy could be as high as 3%, with as many as 23% of these cases resolving by age 4 years, and 31% by age 6 years.[2-5] US estimates range between 1.4%and 4.5%, based on various indirect methods, including phone surveys, Internet surveys, and

analysis of clinical history and epinephrine prescribing patterns.[6-10] Also, the prevalence of peanut allergy may change with age. Prevalence estimates also vary depending on how peanut allergy is defined. Many studies use peanut sensitization (at a particular level of detection) to define peanut allergy, while others accept a convincing history of a clinical reaction.[6,9-11] However, the criterion standard is an OFC in which a clear outcome based on peanut ingestion is determined.[2] Unsurprisingly, reported prevalence rates are higher in studies that include patients diagnosed based on either peanut sensitization and/or a reported convincing clinical history compared with estimates derived from patients diagnosed objectively through OFC.[3,6] However, there may be some ethical and practical concern in performing OFC for the purpose of confirming prevalence rates using this criterion standard in such aforementioned individuals who already have a clinical diagnosis.[2,12] Understanding the prevalence rate of a specific allergy helps to determine the relative likelihood that any patient being evaluated could have the allergy and sets the basis for interpreting any diagnostic test that may be able to infer likelihood of diagnosis through simple tools such as Fagan nomograms.[13,14] For review, the positive likelihood ratio (in food allergy) represents the percentage of individuals with food allergy who have detectable sensitization, divided by the percentage of people without food allergy who also have detectable sensitization (and the negative likelihood ratio is the converse). These are dependent on test sensitivity and specificity, and not on disease prevalence, making them ideal for clinical decision making across different settings. Use of likelihood ratios can be reviewed in more detail elsewhere.[13] In this practice guideline, we emphasize the use of the likelihood ratio as the main tool for clinical decision making given uncertainties in the prevalence of food allergy in any given clinical population. Therefore, it is essential for a clinician to understand how and when performing specific diagnostic tests would provide the highest (or lowest) utility to help gauge when such tests would be of value in clinical decision making.

## Making the diagnosis

**Available diagnostic tests for assessing peanut sensitization.** Peanut-specific IgE can be assessed with either an SPT or a serologic *in vitro* (blood) test. SPT assesses the presence of sIgE through formation of a wheal and erythema following percutaneous introduction of the target allergen. SPTs are based on extracts of whole peanut and therefore do not provide information about sensitization to individual peanut proteins (peanut components), though extracts of recombinant components have been studied in research situations. Prick-to-prick testing with ingestible peanut products (eg, peanut butter, powder, or kernels) as an alternative to testing with peanut extracts has been advocated by some, but the reproducibility, validity and reliability of this procedure is not established as a marker of sensitization, and this additional test in combination with the clinical history has uncertain value for clinical decision making.[15-17]

Various *in vitro* tests for specific IgE are available using a variety of technologies. Modern-day serologic IgE tests rely on allergens that are attached to a solid phase substrate and detect IgE bound to those allergens using anti-human IgE antibodies conjugated to enzymes that create a colored (enzyme-linked immunosorbent assay) or fluorescent (fluorescent enzyme immunoassay) product. There also are technologies that measure the capture of specific IgE bound to allergen in liquid phase with subsequent detection using an appropriate enzyme-substrate. The amount of sIgE is determined by comparing the dilution curves of the unknown samples with a calibration curve based on samples with known sIgE.[15] Nonspecific IgE binding resulting in false positive results (eg, falsely indicating sensitization) is a potential risk when samples are assessed from patients that are known to have high total IgE levels, but these results are accounted for by the manufacturer in how the instruments are calibrated. Generally, these tests are considered to be quantitative and to have a relatively low coefficient of variance (eg, approximately 5%). Most commercially available tests for peanut-specific IgE measure sIgE directed at an extract of whole peanut, similar to what is used in skin testing. However, most allergens contain multiple epitopes, each of which may be associated with the ability to specifically bind IgE and the potential for resulting distinct symptom patterns.[15,17] Patients may be sensitized to ≥1 components, which represent major allergens within peanut that IgE can bind to (such as the major allergens Ara h 1, Ara h 2, or Ara h 3).[17] There are now commercially available tests to measure select peanut components. Components are not available for skin testing outside of the research setting.[16]

**Evaluation of suspected peanut allergy.** To properly use any allergy diagnostic test to evaluate for possible peanut allergy, the pretest probability must be determined, which is accomplished through taking a comprehensive history.[2,12,16] Typically, patients present to a clinician for an evaluation of a suspected history of peanut allergy, usually having experienced symptoms (in some form) believed to be attributable to peanut ingestion, which represents a situation in which there is high pretest probability. However, sometimes tests are performed to evaluate individuals without such a history (possibly as part of a diagnostic testing panel), such as someone who has never eaten peanut before, or even in individuals who eat peanut and do not develop symptoms. As a general rule, persons who can eat peanut without developing symptoms are by definition not allergic and should not be tested for peanut allergy.[2] Furthermore, food allergy testing should be conducted as narrowly as possible, and allergy clinicians should avoid searching for sensitization to other "common" allergens that may be offered as a several item panel if such allergens were not suspected in the history. Serologic testing can always be ordered as single items, and the allergy clinician should consider taking the time to educate non-specialist-referring clinicians as to why use of panel tests is potentially problematic or why use of testing should be avoided when the history is not clearly indicative of a suspected food allergy.[2,16] The situation is a bit more nuanced when considering an individual for testing who has never before ingested peanut, or in someone where oropharyngeal symptoms most consistent with pollen food allergy syndrome present distinctly, in the absence of other typical IgE-mediated symptoms. In general, when the pretest probability for allergy is very low, so that even if the test were detecting sensitization, the posttest probability of allergy would still remain low. However, there may be certain situations where a patient who has never before ingested peanut has other risk factors, such as moderate or severe eczema poorly responsive to therapy or a history of other food allergy, which may elevate the pretest probability above that of the general population (but still lower than someone presenting with a history of a suspected reaction).[16,17] In these scenarios, the clinician may desire to test these patients given the pretest probability is potentially elevated or for more practical reasons such as if the test result will help the patient to make a

decision whether they will introduce peanut. This is an example of preference-sensitive care and requires delicate handling of the risks and benefits of all available options of how to manage detectable sensitization on testing with lower yet still elevated pretest probability. With a detectable sensitization obtained in this context, performing an OFC (presuming both clinician and patient are willing) can be very helpful but needs to be balanced by how strongly the clinician and patient believe the positive test result indicates a high probability of clinical allergy and the understanding of the risk and downstream consequences of a conflating sensitization and allergy.[2,16,18]

However, most cases do not present asymptomatically. In assessing the clinical history, close attention should be paid to the nature of the presenting symptoms (to make sure these are consistent with mast-cell mediator release characteristic of an IgE-mediated reaction) and the timing of when these symptoms developed in association with known or suspected peanut ingestion. Symptoms typically develop within minutes to up to about 2 hours if they are related to the peanut ingestion and rarely develop outside this time window. Nonclassical symptoms or time courses that fall outside this interval should decrease the suspicion of peanut allergy, though the clinician may have to consider the significance of an eruption/exacerbation of atopic dermatitis in a child potentially associated with peanut ingestion several hours after ingestion.[12,16] Diagnostic testing in the patient with a reasonable pretest probability, established by eliciting a concerning or likely history of symptom development attributable to peanut ingestion, can then be used to help determine the likelihood of a clinical allergy.[15,16] This describes a high-utility setting of how such tests can be used. One exception of note is FPIES to peanut. This is a non-IgE- but immune-mediated reaction, which has a delayed onset presentation (typically 1-4 hours after ingestion), resulting in protracted vomiting to the point that lethargy and color change (eg, cyanosis, pallor) ensue, and in rare instances, bloody diarrhea may result at 6 to 12 hours. These symptoms represent this very distinct entity, which is hallmarked by isolated gastrointestinal involvement. FPIES is a clinical diagnosis, and testing for the presence of IgE for peanut FPIES is not recommended. FPIES diagnosis and management is discussed elsewhere, and this practice parameter does not refer to peanut FPIES management.[19]

**Potential exceptions for testing.** A major possible exception are high-risk infants being considered for early peanut introduction. As specified in the 2017 NIAID addendum guidelines for the prevention of peanut allergy, a special case may be made for screening infants who present with egg allergy and/or severe atopic dermatitis in the first 4 to 6 months of life that is poorly controlled despite escalating skin care.[20] In formulating the Addendum Guidelines for the Prevention of Peanut Allergy, an expert panel appointed by the NIAID recommended that this presentation in these infants represents an elevated pretest probability of some likelihood of "preexisting" peanut allergy (based on data from the Learning Early About Peanut Allergy Study, which used these particular risk factors).[21,22] Therefore, in this highly specific subgroup, the prior NIAID guideline did recommend strong consideration that either peanut SPT or sIgE testing be obtained and interpreted before early peanut introduction in these infants. However, outside of this very circumscribed group, there are otherwise no formal recommendations that any individual should have peanut SPT or sIgE testing before peanut introduction specifically as a screening measure for risk assessment.[20]

Historically, another potential exception involved testing children with moderate to severe atopic dermatitis to the 8 common food allergens (including peanut), even if these foods were never previously consumed.[12] This practice reflected a concern that eczema is a precursor symptom of and a significant risk factor for developing food allergy and represents a situation where the pretest probability is potentially raised over that of the baseline general population to some degree. In these children, a diagnosis of allergy was typically made based on research that extrapolated positive predictive values (PPVs) taken from groups of children at referral centers with severe eczema who underwent OFC.[23] In recent years, this practice has largely fallen out of favor as there has been better understanding of (1) the limitations of sensitization as a determinant of clinical allergy, (2) the pathogenesis of atopic dermatitis occurring independently and not as a marker pathognomonic for undiagnosed food allergy, (3) the risks of prolonged allergen avoidance as a factor that may paradoxically increase the risk of food allergy development, and (4) the observation that indiscriminant "screening creep" was occurring in children without risk factors or overt symptoms and the predictive values were being used to establish "diagnosis" out of their very tightly established context.[2] The underlying properties of the diagnostic tests themselves make their use as diagnostic screening measures perilous, given they are poorly specific and of optimal utility in the setting of high pretest probability.[2] Asymptomatic, clinically irrelevant peanut sensitization is not uncommon.[24]

**Interpreting peanut allergy sensitization.** Allergy testing only confirms or refutes the presence of sensitization, requires "clinical correlation" not unlike a radiographic image, and does not independently diagnose allergic disease.[15] Pretest probability can be translated to posttest odds, using the positive or negative likelihood ratios associated with the sensitivity and specificity of these tests, which can then be used to provide a recommendation regarding diagnosis.[13,14] Thus the presence/absence of sensitization increases or decreases the estimated likelihood that a patient may experience a reaction following peanut ingestion. The final probability of reaction is dependent both on the pretest probability and the characteristics of the diagnostic test. While this can be translated using a Fagan nomogram,[14] the process is rather intuitive in clinical practice in many situations. Individuals with a strong history (eg, high pretest probability) who are sensitized above a critical threshold can be more confidently diagnosed with peanut allergy, and a person with a nonspecific/weak history (eg, low pretest probability) and a negative or equivocally positive test indicating the presence of sensitization can be more confidently assessed as not having peanut allergy. In individuals with more questionable histories with a less clear pretest probability, the test positive or negative likelihood ratio then becomes more crucial in influencing the direction of the decision making, and ultimately diagnostic confidence may be low enough that an OFC still may be necessary to definitively establish diagnosis.[2,16,18] Please see Box 2 and Box 3 for further details about defining allergen sensitization and interpreting pretest probability.

**Clinical conundrums related to testing.** As alluded to earlier, there are situations where the clinician may encounter a patient in whom testing was potentially inappropriately obtained, such as in a person with no risk factors and no history of peanut ingestion leading to symptoms. These individuals may be peanut sensitized, but the sensitization is difficult to interpret given the

**Box 2.** Defining allergic sensitization and a positive test

Allergic sensitization is denoted by the presence of detectable allergen-specific IgE, either through a serologic assay or through SPT. All tests for sensitization have a threshold where the test is considered to be positive, as well as either a detection limit or a reporting limit. For SPT, the most commonly reported convention for where a test is considered "positive" for the presence of allergen-specific IgE is when the allergen-specific test is 3 mm of wheal diameter greater than that of a simultaneously placed glycerinated saline control. As discussed in the 2008 diagnostic testing practice parameter,[15] different testing devices produce some degree of variation in the size range of negative controls, as does variation related to the tester. Wheal size is recommended to be measured as the average length of the 2 longest bisecting planes, though many clinics may elect to measure the longest single plane.

For sIgE tests using fluorescent enzymatic immunoassay detection, the instruments have both detection limits and reporting limits that have influenced test results. However, each instrument has particular reporting and detection ranges, and these differ between commercial tests. The technical detection limit for these machines is typically 0.1 $KU_A$/L, and antibody levels above this threshold are reported as they are detected to an upper reporting limit of 100 $KU_A$/L. Quantification of levels >100 $KU_A$/L is possible through sample dilution. For many years, the reporting limit was conventionally set at <0.35 $KU_A$/L, though in recent years, this has been replaced by the detection limit of 0.1 $KU_A$/L. Using the older convention of the 0.35 $KU_A$/L reporting limit, positive sensitization was considered to be 0.36 $KU_A$/L or higher. With the newer convention of using the 0.1 $KU_A$/L detection limit as the reporting limit, positive sensitization would therefore be 0.11 $KU_A$/L. This creates a conundrum of how to interpret sensitization between 0.11 $KU_A$/L and 0.35 $KU_A$/L, which prior to the change in reporting convention would have fallen into the "negative" range. It is debatable that such sensitization is clinically relevant or that many clinicians would only consider sensitization >0.7 $KU_A$/L as clinically relevant. Nonetheless, studies may report positive sensitization at 0.11 $KU_A$/L in a binary fashion. One additional classification that is seen are classes representing sextiles of IgE quantity detected between the upper and lower reporting limits. These are arbitrary conventions that date back to the quartiles originally described for RAST, adjusted for the fluorescent enzymatic immunoassay method. Levels below the reporting unit are class 0, and then classes 1 to 6 range from the lower limit (class 1) to the highest levels (class 6) detectable that are reported. These class designations have no clinical relevance in and of themselves, and no reference to class designations is made in this document.

In this practice parameter, if the term positive is used, in relation to either form of test, it is in this sense that this refers to positive detection of sensitization (eg, a positive test). Unequivocally, positive detection of sensitization is not synonymous with a positive clinical diagnosis of allergy. A positive diagnosis is predicated on both a demonstrated clinical history of allergy and the presence of detectable sensitization or, in very circumscribed instances, very high levels of sensitization in infants with very particular preexisting risk factors who have never ingested peanut previously.

**Box 3.** Examples of pretest probability in determining whether diagnostic testing is indicated

High pretest probability should be considered as a situation where there was ingestion of peanut and typical IgE-mediated symptoms of an allergic reaction resulted, either directly observed or reported, or for an infant meeting NIAID early peanut introduction high-risk criteria prior to peanut introduction. Testing is of the highest utility in these scenarios, and peanut sensitization above a certain threshold is of high likelihood to be associated with the highest posttest odds of a diagnosis of peanut allergy.

Moderate pretest probability should be considered as a situation where there is less clarity that peanut was ingested and resulted in IgE-mediated symptoms, but there is some consideration for this in explaining an allergic reaction under evaluation. In some instances it may represent situations where the patient has not previously consumed peanut but could be considered at a risk greater than that of the general population for peanut allergy based on the presence of certain types of other food allergies, certain atopic comorbidities (eg, severe eczema), or certain children outside the first year of life with delayed peanut introduction. Testing is of unclear utility in these situations and not necessarily associated with posttest odds that clarify clinical decision making. An OFC may be required to definitively establish a diagnosis when there is peanut sensitization above a certain threshold.

Low pretest probability should be considered in any of the following situations where (1) there is very little uncertainty that the person is peanut tolerant (eg, eats peanut without becoming symptomatic); (2) peanut was unrelated to the allergic reaction being evaluated (eg, it is clear that a single allergen other than peanut likely caused the aforementioned reaction and the product was peanut-free, or peanut is being tested solely because it is part of a multiallergen panel and there is no specific independent concern for peanut allergy itself); (3) family history of peanut allergy or allergic disease; (4) general curiosity about what someone could speculatively be allergic to; or (5) for an infant meeting addendum 2 or 3 criteria for NIAID early peanut introduction guidelines prior to peanut introduction. In some instances it may represent any of the following situations where the patient has not previously consumed peanut but the clinician may have concerns (1) that the patient is at a risk greater than the general population for peanut allergy based on the presence of certain types of other food allergies; (2) there is a possibility for cross-reactivity or certain atopic comorbidities (eg, mild or moderate eczema); or (3) for certain children outside the first year of life with delayed peanut introduction but who have no baseline risk factors. Testing in these situations is of exceptionally limited to no utility whatsoever, is not associated with any shift of posttest odds over baseline, and is not indicated. An OFC is likely required to establish that the peanut sensitization detected is clinically irrelevant.

lack of clinical data to determine context of the test value. Here we see 2 possible management choices. In clinical practice, many may follow prior data establishing PPVs (most representative of small populations of eczematous children undergoing OFC at a referral center) for large skin tests or elevated peanut sIgE that may result in a potential misdiagnosis of peanut allergy leading to unnecessary avoidance.[12,25,26] Alternatively, this could be viewed as a situation where a test was obtained with low pretest probability, requiring OFC to provide diagnostic clarity. In some scenarios, where it is very likely that sensitization may not be associated with clinical reactivity, there may be benefit to performing a supervised OFC. A less challenging conundrum is the use of so-called alternative tests for peanut allergy that are becoming popular and are frequently utilized by non-board-certified allergists or marketed directly to patients to order for use at home without provider involvement. Testing for peanut-specific $IgG_4$ in either the symptomatic or nonsymptomatic patient is not indicated, and no role for $IgG_4$ levels in the current diagnostic paradigm exists.[27,28] The role of $IgG_4$ is not well understood, but in studies of food oral immunotherapy and pollen/venom immunotherapy, $IgG_4$ levels to the allergen in question have been noted to increase as the patient becomes desensitized. As such, no defined association between allergic reactivity and $IgG_4$ levels exists. In addition, a multitude of other nonvalidated alternative tests are utilized by alternative medicine practitioners but have no role in the diagnosis of peanut allergy. This includes mediator release testing, antigen leukocyte antibody testing, Nambudripad's Allergy Elimination Technique, muscle-provocation testing, electrodermal analysis, and hair/urine analysis.[27,28] Clinicians should be aware of these tests, as well as the lack of evidence supporting use, as patients may either request such testing, or have already been subjected to them. Both the American Academy of Allergy, Asthma, and Immunology (AAAAI) and the American College of Asthma, Allergy, and Immunology (ACAAI) have discouraged use of these alternative tests.

**Utility of the OFC in diagnosing peanut allergy.** The OFC remains the criterion reference standard test to define peanut or any food allergy.[2,18] The modern practice of this procedure was developed by Dr. Charles May in 1976, who described oral food provocation challenge in 38 patients with asthma and suspected immediate hypersensitivity to food.[29] The OFC generally provides a definitive diagnosis as the outcome is apparent—under medical supervision to observe the outcome, either the person will tolerate ingestion or react. OFCs are rarely indeterminate, so long as the patient can cooperate and ingest the full challenge dose or subjective symptoms can be avoided. While the double-blind, placebo-controlled food challenge is considered the most objective form of OFC (and decreases the likelihood of subjective symptoms complicating the interpretation of the outcome), open OFCs are usually sufficient for clinical diagnosis and are more practical to conduct, though this has not been directly studied for comparison and represents expert opinion.[2,18] Inherent in the label "challenge," this implies the outcome is not known beforehand, and thus any challenge carries a risk of a potential allergic reaction, including anaphylaxis, which the clinician must be prepared to potentially treat, and the patient be made aware of such risks. Detailed guidance on conducting OFCs in patients is provided elsewhere.[18] OFCs are considered both time- and resource-intensive by some and require dedicated office space and provider expertise, which may make them less appealing to some providers to conduct.[30] However, this is a routine office-based procedure with a superb safety record in the hands of experienced clinicians.[18]

A decision to offer an OFC is complex and individualized, and providers approach this with a variable degree of expertise, comfort, and desire to offer the procedure.[18] OFC can be used to rule in as well as rule out a diagnosis. However with very high or very low pretest probability, the necessity to offer diagnostic OFC may be low (eg, when either the outcome is very likely to result in a reaction or very likely to be tolerated).[2,31,32] This procedure becomes of greater importance when the probability of having had a reaction to peanut is poorly determinable based on pretest probability, and testing does not provide much assistance in formulating posttest odds. In this context, the OFC can provide an objective outcome to inform decision making. However, while in such situations there may be obvious utility to perform an OFC, the decision to ultimately do so may depend on patient-specific and provider-specific factors such as anxiety, vulnerability, and desire to eat peanut, as well as the clinical judgment and willingness of the clinician to perform the procedure.[18,31] Patients and families that are particularly anxious about eating peanut might prefer to avoid peanut, even with a lower probability of reaction, rather than undergo OFC.

## SYSTEMATIC REVIEW, META-ANALYSIS, AND GRADE RECOMMENDATIONS ON THE USE OF PEANUT ALLERGY DIAGNOSTIC TESTING

### Overview of guideline development process

This practice parameter was developed using the GRADE approach. GRADE is a well-established methodology for developing evidence-based guidelines and is detailed elsewhere.[33-35] In formulating the replies to our key questions, we took into account the quality of evidence for assessing test sensitivity/specificity, combining this with how the recommendations would be implemented and the knowledge translated, including cost-effectiveness of the recommendations. Table II details the GRADE recommendations and evidence ratings. For more details of the GRADE process, please refer to the JTFPP website primer (www.allergyparameters.org).

In 2017, the JTFPP submitted a concept for a peanut allergy clinical practice guideline to the AAAAI/ACAAI parent organizations. The JTFPP identified 4 liaisons to help identify content experts to form a working group. The work group conducted periodic calls to develop central questions to be answered through systematic reviews using the GRADE process and developed a search strategy to identify and review the relevant literature. The working group was divided into individual subgroups to evaluate the identified literature and draft the recommendations based on the GRADE analysis and following AMSTAR (Assessing the Methodological Quality of Systematic Reviews) 2 criteria for systematic reviews.[36] A working draft was prepared by the work group, which was then reviewed and modified by the JTFPP. Both groups were provided the opportunity to comment, propose changes, and approve or disapprove each statement. Consensus was sought and reached for each recommendation's direction and strength. Actual or potential conflicts of interest were disclosed annually and transparency of discussion was maintained. A final draft was then approved by the JTFPP and sent to AAAAI- and ACAAI-appointed reviewers who were asked to comment on the statements and the rationale within free text fields. All these comments and suggestions were discussed during a JTFPP

teleconference. For each comment or suggestion, the JTFPP evaluated whether the statement needed to be adapted, again taking into account the balance between desirable and undesirable consequences of the alternative management strategies, the quality of the evidence, and the variability in values and preferences.

Concurrent with the AAAAI and ACAAI review, a working draft of the guideline was then posted on the AAAAI, ACAAI, and JTFPP websites for all members and the public at large to review. For each comment or suggestion, the JTFPP evaluated whether the statement needed to be adapted, again taking into account the balance between desirable and undesirable consequences of the alternative management strategies, the quality of the evidence, and the variability in values and preferences. The finalized draft was then sent to this journal for additional peer review before publication.

## GRADE methodology

**Development of searchable questions.** Prior to conducting a literature search, 3 prespecified PICO format questions were formulated by the work group and the JTFPP as per standard GRADE approach.[35] The population for study included published data for patients with known or highly suspected peanut allergy, who underwent OFC (open or blinded) to establish/confirm a clinical outcome of peanut allergy in ≥50% of participants, where both serologic assessment of peanut allergen components (Ara h 1, 2, 3, 6, 8) and/or SPT to whole peanut extract or sIgE testing to whole peanut were obtained as markers of peanut sensitization.

The questions developed were the following:

1. Should diagnostic testing for peanut allergy be performed in adults and children with a history of suspected peanut allergy who are requesting evaluation for peanut allergy?
   *Population*: Adults and children presenting for the evaluation of suspected peanut allergy.
   *Intervention*: Perform a diagnostic test for peanut allergy based on history provided.
   *Comparator*: Do not perform a diagnostic test for peanut allergy based on history provided.
   *Outcomes*: Accuracy of history in determining need for diagnostic testing for peanut allergy.

2, *A*. In the patient presenting for evaluation of suspected peanut allergy, which of the 3 tests—SPT, sIgE to whole peanut, or Ara h 2 would provide the highest diagnostic accuracy as determined by the more optimal positive/negative likelihood ratio?
   *Population*: Adults and children presenting for the evaluation of peanut allergy.
   *Intervention*: Use SPT or sIgE whole peanut or both to determine peanut sensitization to assist in the diagnosis of peanut allergy.
   *Comparator*: Use OFC.
   *Outcomes*: Diagnostic accuracy of peanut allergy testing (true/false positive, true/false negative tests).

2, *B*. In a patient presenting for evaluation of suspected peanut allergy, does testing for peanut components in addition to either SPT or sIgE to whole peanut increase the diagnostic accuracy?
   *Population*: Adults and children presenting for the evaluation of peanut allergy.
   *Intervention*: Use peanut component testing, such as Ara h 2, in addition to SPT or sIgE whole peanut to determine peanut sensitization to assist in the diagnosis of peanut allergy.
   *Comparator*: Use OFC.
   *Outcomes*: Diagnostic accuracy of peanut allergy testing (true/false positive, true/false negative tests).

3. In the patient presenting for evaluation of suspected peanut allergy, can the results of a diagnostic test be used to predict the severity of a future allergic reaction?
   *Population*: Adults and children presenting for the evaluation of suspected peanut allergy.
   *Intervention*: Perform a diagnostic test(s) for peanut allergy to help predict the severity of a future allergic reaction to peanuts.
   *Comparator*: Predict the severity of a future allergic reaction to peanuts based solely on the history and without the use of a diagnostic test for peanut allergy.
   *Outcomes*: Accurate prediction of the severity of a future allergic reaction to peanuts.

**Literature search and study eligibility.** In conjunction with a medical librarian (K.S.), a detailed prespecified search strategy was developed with input from the working group, as well as based on recently published systematic reviews on peanut allergy diagnostic testing. Study selection was limited to human subjects of any age who were seeking evaluation for the diagnosis of peanut allergy and English language studies published or in press starting from 1946 to 2018. The finalized search parameters were then independently run on Medline (PubMed 1946-2018) and Embase (Elsevier 1947-2018) databases, with the results combined and filtered for duplicates. A total of 1314 potential references were identified and transferred into Covidence (https://www.covidence.org) for review by 4 work group members (M.G., M.S., J.W., J.O.), where 127 studies were identified for full text review by the same 4 members, resulting in a final selection of 89 studies for data extraction pertaining to searchable questions under GRADE format. (See Fig 1, *A-D* for the overall PRISMA [Preferred Reporting Items for Systematic Reviews and Meta-Analyses] diagram[37] and diagrams by individual searchable question and the Literature Search Terms and Included Studies section in the Online Repository at www.jacionline.org). The search results were combined and culled for duplicate entries, then uploaded into Covidence, where a minimum of 2 study team members independently reviewed each study for eligibility for full-text review, to determine inclusion, with this process repeated to determine the final studies for data extraction. Conflicts regarding inclusion were resolved by a third study team member. Studies where OFC was not performed as part of the assessment accompanying the diagnostic testing were excluded (including cohort and observational studies based on patient-reported or chart-reported history of peanut allergy involving the use of the aforementioned diagnostic tests without OFC confirmation) but the protocol was inclusive of either prospective, retrospective, cross-sectional, or case-control methodologies from both pediatric and adult populations. The full-text versions of the final studies meeting inclusion were reviewed for data extraction of the measures of diagnostic accuracy including sensitivity, specificity, positive/negative predictive value, and the number of true positives,

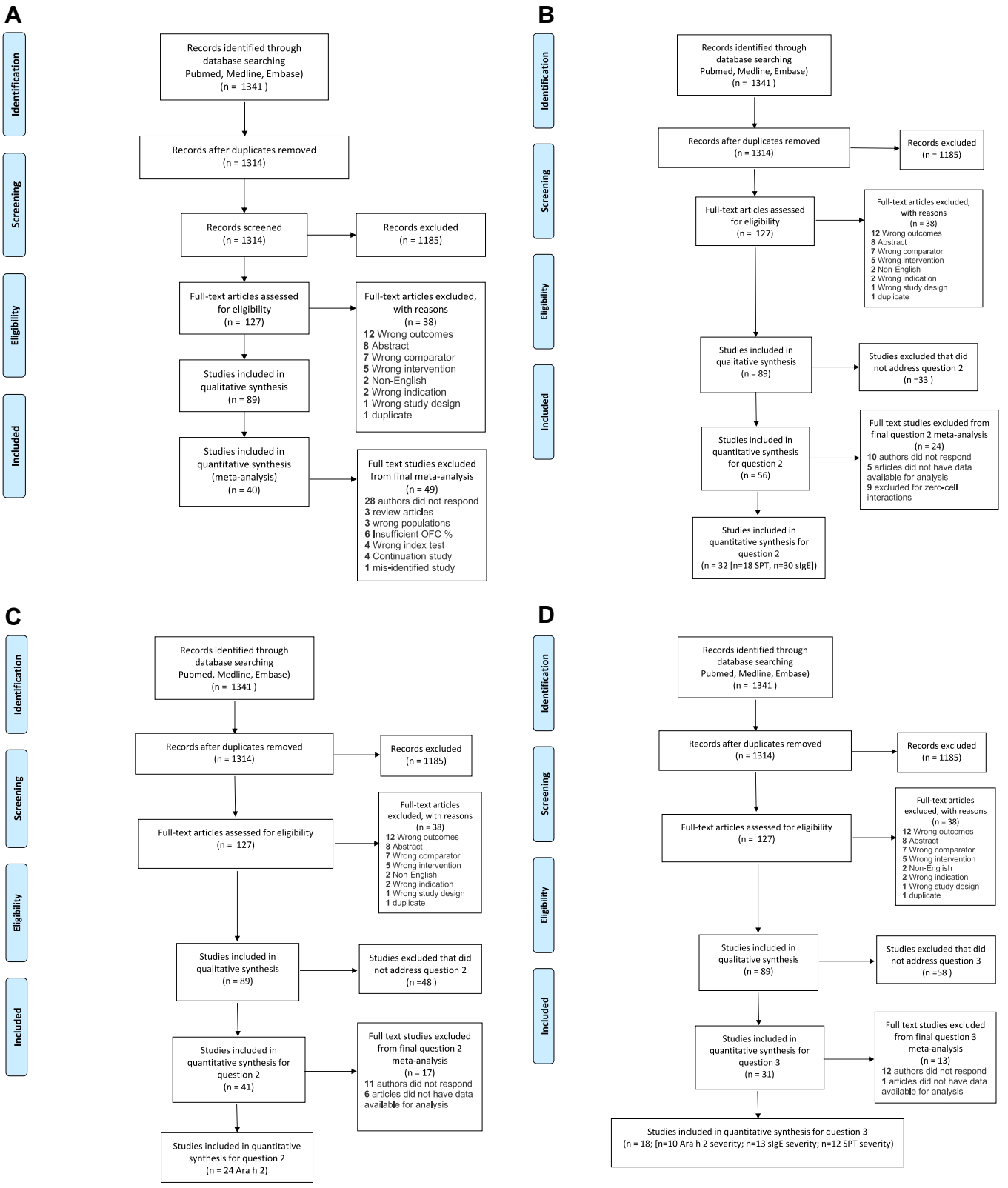


**FIG 1.** PRISMA diagram. **A,** This flow diagram is the search strategy for the overall parameter. **B, C, D,** These flow diagrams represent the strategies for questions 2*A*, 2*B*, and 3, respectively.

false positives, true negatives, and false negatives. Individual study authors were contacted to provide additional data for the following reasons:

1. To clarify information pertaining to number of successful and nonsuccessful challenges relative to a reported cutoff level of the test in question, where such data were not available or calculable, so that sensitivity and specificity could be calculated (eg, obtain the cells to inform true/false positive and true/false negative according to our prespecified thresholds).
2. To request data not presented/analyzed in the selected paper according to the cutoff levels chosen as part of this review, to enable retallying of the true/false positive and true/false negative cases.
3. To see whether additional data that had not been published regarding other searchable questions were potentially available.

Studies selected for data extraction were excluded if the aforementioned measures of diagnostic testing accuracy were not directly reported in the manuscript; on final review the population, use/application of the index test or use/application of the reference standard was deemed to not fit the prespecified inclusion criteria; or the study team could not/did not provide the additional details for more tailored data that we requested to be reported per our extraction parameters.

**Outcomes and data synthesis.** Based on the diagnostic test used, the extracted number of true positives, false positives, true negatives, and false negatives with respect to OFC outcome were recorded into an Excel spreadsheet (Microsoft, Redmond, Wash), as classified by a conservative cutoff level of these tests (for diagnosis: >0.35 $KU_A$/L for sIgE and Ara h 2 sIgE, ≥3 mm for SPT; for severity: >50 $KU_A$/L for sIgE, >2 $KU_A$/L Ara h 2 sIgE, ≥10 mm for SPT) relative to the OFC performed in the study. To assess potential influence of Ara h 6 and Ara h 8 on diagnostic accuracy, prespecified subgroup analyses were planned based on data availability. Meta-analysis of the pooled sensitivity, specificity, positive, and negative likelihood ratios (with visual display of these ratios) on a Fagan nomogram set to a range of potential lower (30%) and higher (70%) situational pretest probabilities (representing a clinical suspicion of a diagnosis based on history before a test is performed) of a patient having peanut allergy. Data analysis was performed in Stata (version 15; StataCorp, College Station, Tex) using the MIDAS command (Peto method, random effects model).[38] Study heterogeneity was reported by the $I^2$ statistic. Risk of bias was assessed using the QUADAS-2 tool (Bristol Medical School: Population Health Sciences, University of Bristol, Bristol, UK). Publication bias was assessed using funnel plots when possible.[39] GRADEpro software (McMaster University and Evidence Prime Inc, Hamilton, Ontario, Canada) was used to construct the evidence profiles and calculate the absolute effects.[40] Prespecified sensitivity analyses were planned to explore inclusion only of trials with double-blinded challenges as opposed to other challenge types to assess the effects of geographical region of study and pediatric versus nonpediatric studies if permissible. Additional *post hoc* sensitivity analyses were performed to verify impact of inclusion of any study on the estimates where there was elevated risk of bias based on patient selection and flow/timing, comparison of individual pooled test precision where SPT/sIgE, sIgE/Ara h 2, or all 3 tests were simultaneously performed (which per the JTFPP was prioritized as the top sensitivity analysis to report despite this being *post hoc*, given it most directly answers the searched questions). Data were additionally synthesized narratively. The systematic review process followed AMSTAR 2 criteria.[36] Lastly, cost-effectiveness analysis using simulated cohorts with Markov modeling over a 20-year horizon, from a societal perspective, was performed to assess simulated health and economic benefits of the use of the individual diagnostic tests (see the Methods, Results, and Discussion for the Analysis of Health and Economic Benefits of Peanut Diagnostic Strategies section in the Online Repository at www.jacionline.org).

**Reaching work group consensus on statements and conclusions.** Where GRADE was not appropriate to answer a particular question, the work group employed a modified Delphi process for the determination of the strength of the recommendation and the statement profile for each question. The Delphi method is a structured, interactive, decision making process used by a panel of experts to arrive at a consensus when there are differing views and perspectives.[41-43] For any statement or conclusion in which there was a difference of opinion, a modified Delphi method was used. Work group members provided anonymous answers via e-mail to the JTFPP administrative director to the questions being considered. The administrative director provided via teleconference an anonymous summary of the experts' answers and reasons they provided for their responses. The work group members discussed all the answers and then were encouraged to modify their answers on the next round(s) of e-mail voting and teleconferences until a consensus was reached.

## RESULTS

### Question 1. Should diagnostic testing for peanut allergy be performed in adults and children with a history of suspected peanut allergy who are requesting evaluation for peanut allergy?

**Recommendation 1, *A*. We suggest in favor of diagnostic (SPT or sIgE) testing for peanut allergy (1) when patients have physician-judged high pretest probability of peanut allergy, or (2) prior to an OFC for patients with moderate pretest probability of peanut allergy. For both situations, shared decision making has been employed to arrive at the final decision. Conditional recommendation. Certainty of evidence: Very low.**

**Recommendation 1, *B*. We suggest against diagnostic testing in patients where there is low or very low pretest probability of peanut allergy. Conditional recommendation. Certainty of evidence: Very low.**

*Agreement by the work group:* By Delphi: Recommendation 1, *A*: 9 of 9 agree; Recommendation 1, *B*: 9 of 9 agree.

*Quality of evidence:* This question was determined to not be searchable under GRADE format.

*Evidence summary:* This question was not searched in a systematic manner as the content experts were unaware of any single research study that addressed this question. However, expert evidence was collected both from the content experts, the JTFPP, and the known prior literature most relevant to this topic. Expert evidence differs from expert opinion, in that the former does not include a judgment on the evidence and offers a systematic and transparent appraisal of the evidence.[44]

**TABLE III.** Situations of low to moderate pretest probability for peanut allergy where testing may be a preference-sensitive care option to offer in the evaluation of a patient*

| Situations where a clinician might be considering testing for peanut allergy† | Pros for testing | Cons for testing |
|---|---|---|
| A young child >1 y but <3 y with multiple asthma hospitalizations, on chronic inhaled steroids, with known milk allergy who has not yet tried peanut. | Possible elevated risk for an additional food allergy in someone who already has 1 food allergy.<br>Parents may not introduce peanut without a positive test, leading to additional risk from delayed introduction. | While the risk could be elevated over baseline, it is unclear whether the absolute risk is elevated more than the low probability scenario of a 30% pretest probability where a positive test was not shown to appreciably shift the posttest odds. |
| A young child >1 y but <3 y without eczema with prior anaphylaxis to 1 or more foods, but who has not yet tried peanut. | Possible elevated risk for an additional food allergy in someone who already has 1 food allergy.<br>Parents may not introduce peanut without a positive test, leading to additional risk from delayed introduction. | While the risk could be elevated over baseline, it is unclear whether the absolute risk is elevated more than the low probability scenario of a 30% pretest probability where a positive test was not shown to appreciably shift the posttest odds. |
| A child in the <1 y with eczema suspected to be flared by 1 legume, and anaphylaxis to hummus who has not yet tried peanut. | Possible elevated risk for an additional food allergy in someone who already has 1 food allergy.<br>Parents may not introduce peanut without a positive test, leading to additional risk from delayed introduction. | While the risk could be elevated over baseline, it is unclear whether the absolute risk is elevated more than the low probability scenario of a 30% pretest probability where a positive test was not shown to appreciably shift the posttest odds.<br>By NIAID addendum criteria, the eczema does not place this child at high risk. |
| A 6-month-old child with mild eczema tolerating a milk-based formula, who has not tried egg or peanut. Their older sibling has milk, egg, and peanut allergy. | Parents may be reluctant to introduce peanut without a negative test, based on the experience with the older child, leading to additional risk from delayed introduction.<br>Some clinicians ascribe to older literature that has suggested the younger sibling may be at some degree of increased risk of developing peanut allergy, though such literature did not account for the highly important factor of delayed introduction. | While the risk could be elevated over baseline, it is unclear whether the absolute risk is elevated more than the low probability scenario of a 30% pretest probability where a positive test was not shown to appreciably shift the posttest odds.<br>By NIAID addendum criteria, the eczema does not place this child at high risk.<br>Recent data has shown that testing the younger sibling is not cost-effective until the prevalence of peanut allergy in siblings is shown to be >11% and all such screened children also undergo an OFC to provide a definitive outcome. |

*See Box 3 for explanation of what high, moderate, and low pretest probability represent in the context of evaluating peanut allergy.
†These are hypothetical examples of situations that the work group members felt could represent potential scenarios that a clinician may evaluate under the context of a preference-sensitive care option. The choice of specific allergens, ages, and comorbidities are for illustration purposes only. Other allergens, ages, and comorbidities may represent possible presentations for consideration.

Testing for peanut allergy is of the highest utility when there is a history of a known or suspected ingestion of peanut leading to symptoms of an IgE-mediated reaction. The identification of individuals for whom testing is indicated requires careful consideration of the clinical history and of epidemiologic risk factors that may increase or decrease the odds of having peanut allergy (eg, severe atopic dermatitis or another food allergy). Persons with no history of peanut ingestion or an unknown history of ingestion (without other potential risk factors for developing food allergy) or who asymptomatically ingest peanut with impunity should generally not be tested for peanut allergy.[2,16] The estimated pretest probability of peanut allergy in these situations is very low. In most circumstances, detection of sensitization will not shift the posttest odds of diagnosis appreciably and will require peanut challenge to resolve the diagnosis. Peanut allergy testing itself is not definitively diagnostic of peanut allergy, as asymptomatic sensitization is not uncommon.[24] Therefore, identifying individuals with a strong pretest probability for peanut allergy is imperative in the optimal use of diagnostic testing and making an accurate diagnosis of peanut allergy.

Apart from the high-risk infant meeting the NIAID peanut allergy prevention guidelines addendum 1 criteria,[20] there are potential situations where some providers may ascribe a higher pretest probability of peanut allergy to a child who has never eaten peanut, and the providers feel that testing may be desired. These generally apply to individuals who are peanut-naïve with other potential risk factors for developing food allergy (eg, moderate to severe eczema and/or other food allergy),[12,23] where the pretest probability may be variably elevated but generally perceived as greater than that of the general population, though still lower than someone with a suspected reaction history. For example, consider the cases of the younger sibling of a peanut allergic child whose family is reluctant to introduce peanut; a child with milk, egg, tree nut, or other food allergy; or the child with delayed peanut introduction for other reasons.[12,45] The decision to test in these circumstances represents a preference-sensitive care option, and in

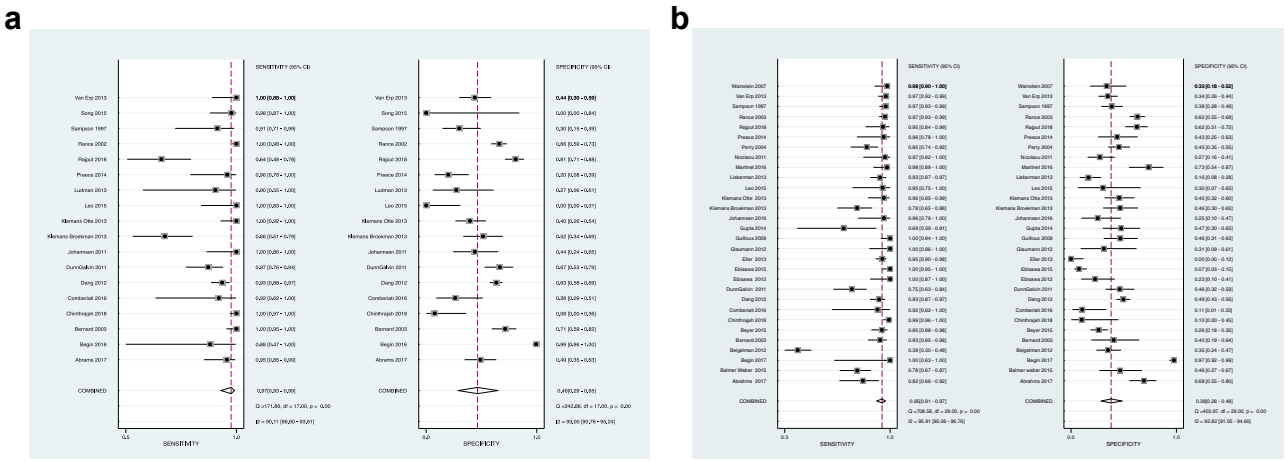


**FIG 2.** Summary forest plots for sensitivity and specificity of SPT at 3 mm and sIgE testing at 0.35 $KU_A$/L. The plots detail the summary test measures **(A)** for SPT at 3 mm and **(B)** for sIgE at 0.35 $KU_A$/L.

**TABLE IV.** Summary statistics with 95% CIs for SPT, sIgE, and Ara h 2 peanut diagnostic testing and assessment of reaction severity

| | Outcome | Sensitivity | Specificity | Positive likelihood ratio | Negative likelihood ratio |
|---|---|---|---|---|---|
| Diagnostic test | | | | | |
| SPT 3 mm | Diagnosis | 0.97 (0.93-0.99) | 0.46 (0.29-0.65) | 1.82 (1.29-2.57) | 0.05 (0.02-0.18) |
| sIgE 0.35 $KU_A$/L | Diagnosis | 0.95 (0.91-0.97) | 0.38 (0.28-0.48) | 1.52 (1.3-1.77) | 0.14 (0.08-0.24) |
| Ara h 2 sIgE 0.35 $KU_A$/L | Diagnosis | 0.86 (0.81-0.89) | 0.84 (0.79-0.89) | 5.5 (3.99-7.56) | 0.17 (0.13-0.23) |
| Ara h 2 sIgE 2 $KU_A$/L | Severe reaction | 0.78 (0.69-0.85) | 0.45 (0.28-0.63) | 1.4 (1.08-1.83) | 0.5 (0.37-0.66) |
| sIgE 50 $KU_A$/L | Severe reaction | 0.39 (0.26-0.53) | 0.89 (0.75-0.95) | 3.4 (1.57-2.03) | 0.69 (0.56-0.84) |
| SPT 10 mm | Severe reaction | 0.37 (0.22-0.55) | 0.62 (0.44-0.77) | 0.98 (0.71-1.35) | 1 (0.84-1.22) |
| Sensitivity analyses | | | | | |
| SPT 3 mm* | SPT and sIgE assessed in same study | 0.98 (0.92-0.99) | 0.5 (0.31-0.69) | 1.94 (1.32-2.86) | 0.04 (0.01-0.15) |
| sIgE 0.35 $KU_A$/L* | SPT and sIgE assessed in same study | 0.94 (0.9-0.97) | 0.46 (0.32-0.6) | 1.75 (1.35-2.26) | 0.13 (0.07-0.21) |
| sIgE 0.35 $KU_A$/L* | sIgE and Ara h 2 assessed in same study | 0.95 (0.93-0.97) | 0.3 (0.21-0.41) | 1.36 (1.19-1.56) | 0.47 (0.26-0.87) |
| Ara h 2 sIgE 0.35 $KU_A$/L* | sIgE and Ara h 2 assessed in same study | 0.85 (0.79-0.9) | 0.86 (0.79-0.9) | 5.87 (4.02-8.58) | 0.18 (0.12-0.25) |
| SPT 3 mm* | SPT/sIgE/Ara h 2 assessed in same study | 0.98 (0.89-1) | 0.39 (0.22-0.6) | 1.63 (1.19-2.23) | 0.04 (0.01-0.25) |
| sIgE 0.35 $KU_A$/L* | SPT/sIgE/Ara h 2 assessed in same study | 0.95 (0.91-0.97) | 0.4 (0.3-0.5) | 1.58 (1.35-1.84) | 0.12 (0.07-0.22) |
| Ara h 2 sIgE 0.35 $KU_A$/L* | SPT/sIgE/Ara h 2 assessed in same study | 0.83 (0.74-0.9) | 0.79 (0.73-0.85) | 4.03 (3.11-5.21) | 0.21 (0.14-0.32) |

*Test sensitivity and specificity are being reported for pooled studies for the particular individual test evaluated in the setting where multiple tests were run simultaneously in patients undergoing OFC. Please refer to Tables VIII to X for reporting of additional sensitivity analyses.

the context of shared decision making and a thorough explanation of the risks and benefits associated with the preference-sensitive care choices, testing for peanut sensitization may be a reasonable choice. This choice is subject to shared decision making with the patient. Consideration of the risks and benefits of the potential use of oral challenge to help confirm the test results, the magnitude of the degree to which the risk is appreciably different than that of the general population, as well as the potential for the likelihood and consequences of overdiagnosis resulting from detection of asymptomatic peanut sensitization if a challenge is not performed. No decision aid for this has been developed, however, though this would be potentially useful.

To some degree, clinicians should be advised that they should be prepared to offer OFC to patients where the pretest probability is no higher than moderate, uncertainty remains, and the patient still desires testing. The risks and consequences of a diagnosis of varying potential accuracy or probability related to a potentially false positive detection of sensitization may or may not outweigh the potential benefit gained through an at-home introduction or an in-office OFC for some families. Table III details some considerations for these situations. Testing the younger sibling of an individual with peanut allergy (who does not otherwise meet the peanut allergy prevention guidelines addendum 1 high-risk criteria) before peanut introduction has not been shown to be

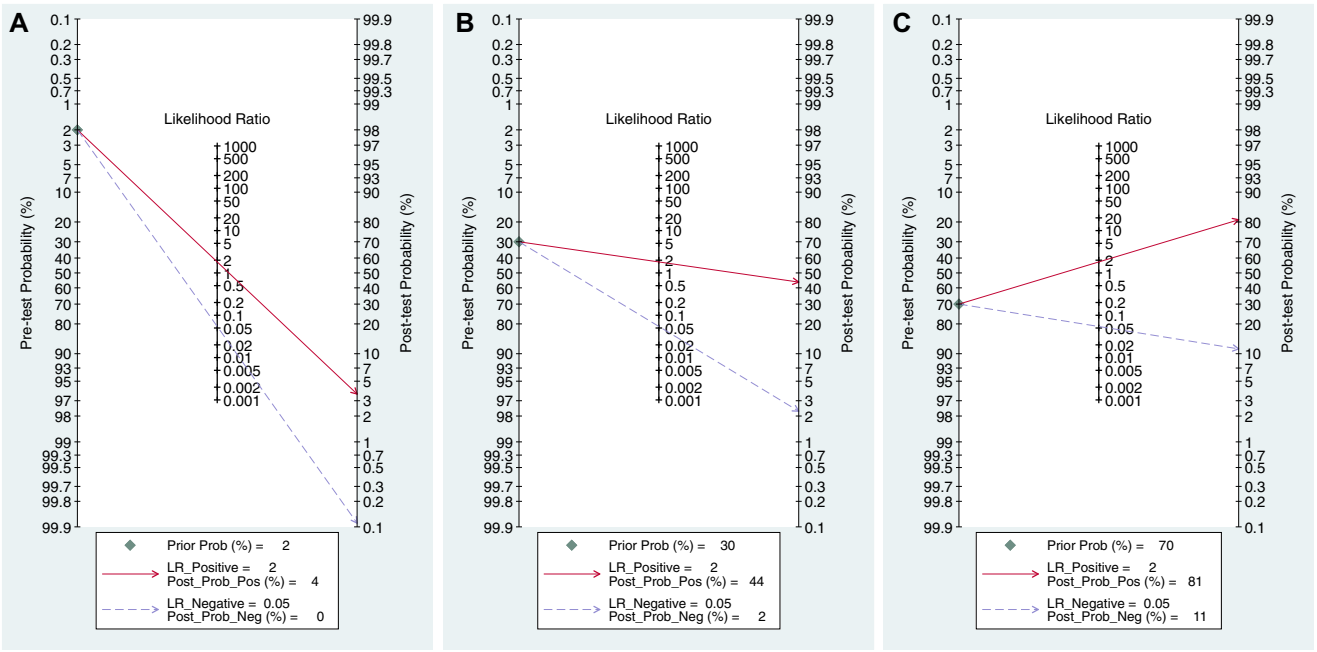


**FIG 3.** Fagan nomograms for SPT 3 mm performance at low, moderate, and high pretest probability (*Prob*). These nomograms show that the positive (*Pos*) likelihood ratio (*LR*) for sensitization at 3 mm (1.57) at **(A)** 2% or **(B)** 30% pretest probability do not translate to posttest odds >50%, but at **(C)** the 70% pretest probability, this is raised to 80%. The negative (*Neg*) likelihood ratio (0.13) does largely decrease posttest odds in all 3 scenarios.

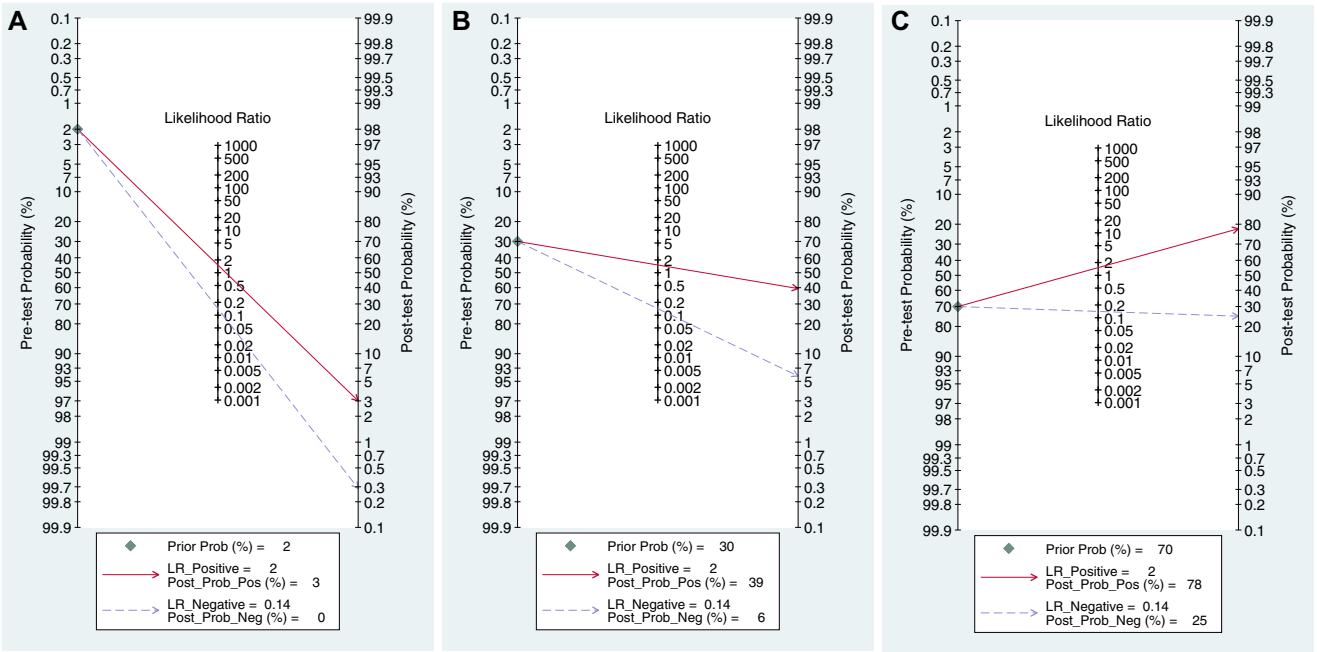


**FIG 4.** Fagan nomograms for sIgE 0.35 $KU_A/L$ performance at low, moderate, and high pretest probability. These nomograms show that the positive likelihood ratio for sensitization at 3 mm (1.45) at **(A)** 2% or **(B)** 30% pretest probability do not translate to posttest odds >50%, but at **(C)** the 70% pretest probability, this is raised to 80%. The negative likelihood ratio (0.17) does largely decrease posttest odds in all 3 scenarios.

cost-effective unless (1) the baseline prevalence of peanut allergy in younger siblings is >11%; (2) every peanut sensitized child undergoes an OFC to determine actual outcome; and (3) the health utility detriment from the initial reaction to peanut was only experienced with at-home introduction and not with an OFC in the office. Without OFC being performed, pretesting was only cost-effective if the baseline prevalence of peanut allergy in younger siblings was >63%.[46]

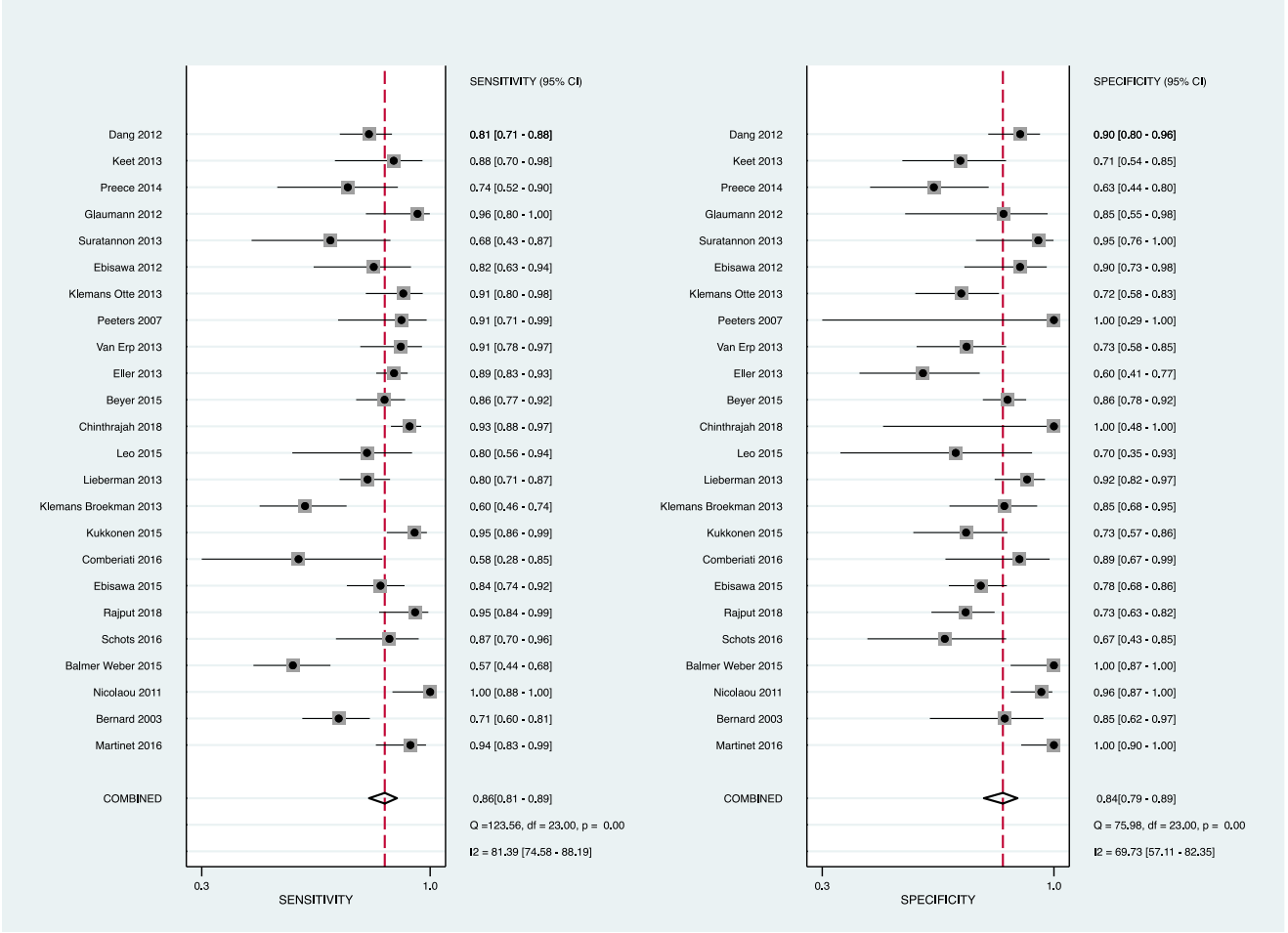


**FIG 5.** Summary forest plots for sensitivity and specificity of Ara h 2 sIgE testing at 0.35 $KU_A/L$.

More importantly, it is also crucial to consider the patient who presents to the allergist's office with a test indicating detection of peanut sensitization, but who has never eaten peanut before. Here, the context (eg, the presumed pretest probability) under which the test denoting sensitization was obtained (and its potential interpretation) also requires careful consideration. This as well may represent a situation of a preference-sensitive choice where a role for shared decision making arises, and consideration for the benefit of performing an OFC to better determine the outcome should be very carefully weighed against the risk of potential misdiagnosis (and recommended avoidance) from a falsely positive test. The presence of the detectable peanut sensitization itself cannot, however, be used as a condition of "elevated" pretest probability (which is determined solely by the clinical history).

## Question 2, *A*. In the patient presenting for evaluation of suspected peanut allergy, which of the three tests—SPT, sIgE to whole peanut, or Ara h 2—would provide the highest diagnostic accuracy as determined by the more optimal positive/negative likelihood ratio?

**Question 2, *B*. In a patient presenting for evaluation of suspected peanut allergy, does testing for peanut components in addition to either SPT or sIgE to whole peanut increase the diagnostic accuracy?**

**Recommendation 2, *A*. We suggest in favor of Ara h 2 diagnostic testing in a patient presenting for evaluation of suspected peanut allergy for which a single diagnostic test is to be used, as Ara h 2 would provide the best diagnostic accuracy as determined by virtue of more optimal positive/negative likelihood ratios. However, while Ara h 2 has the greatest specificity, it has lower sensitivity than SPT and sIgE, and in a patient with a high prior probability, the clinician may use Ara h 2, SPT, or sIgE to confirm the diagnosis of peanut allergy. Conditional recommendation. Certainty of evidence: Low.**

**Recommendation 2, *B*. We suggest against routine use of component testing in addition to either SPT or sIgE to whole peanut to increase diagnostic accuracy. Conditional recommendation. Certainty of evidence: Very low.**

*Clinical statement:* For GRADE analysis, Ara h 2 peanut sIgE was compared with SPT and sIgE to whole peanut for the diagnosis of peanut allergy. Providers can interchangeably use either SPT or serologic testing for whole peanut extract IgE, taking into account availability of the test, patient preference, safety, cost, and whether there are patient factors that preclude use of one or both tests. Both tests have high sensitivity but poor specificity in identifying OFC-reactive patients at cutoff levels of 3 mm

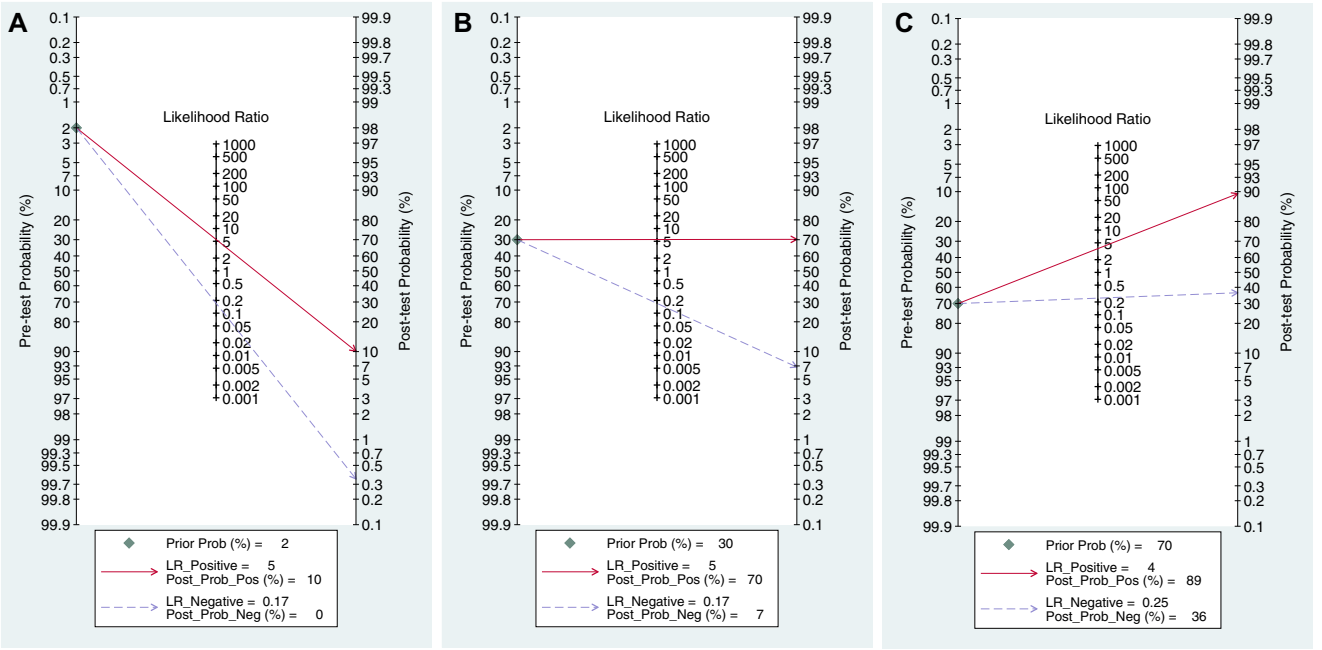


**FIG 6.** Fagan nomograms for Ara h 2 sIgE 0.35 $KU_A$/L performance at low, moderate, and high pretest probability. These nomograms show that the likelihood ratio for Ara h 2 sensitization at 0.35 $KU_A$/L (3.65) at **(A)** 2% or **(B)** 30% pretest probability translate to post-test odds of 7% and 61%, but at **(C)** the 70% pretest probability translates to 89% posttest odds. The negative likelihood ratio (0.25) does largely decrease posttest odds in all 3 scenarios.

wheal size SPT or 0.35 $KU_A$/L peanut-specific IgE. No data were available regarding use of the tests in tandem or reflexively. In sensitivity analyses where both tests were available, there was minimal difference in the overall sensitivity/specificity between these modalities, and these were similar to the precision in the base analyses of each test individually. However, as a single stand-alone test, compared with either SPT or sIgE testing to whole peanut extract, Ara h 2 has the most optimal combination of positive and negative likelihood ratio and has much higher specificity, likely decreasing the number of false positive cases where sensitization is detected. While Ara h 2 had the greatest specificity in confirming the diagnosis, it had lower sensitivity when compared with SPT or sIgE. In evaluating diagnostic accuracy, the summary receiver operating characteristic curves demonstrated greatest area under the curve for Ara h 2 (0.92) when compared with SPT (0.89) and sIgE (0.81). Despite the test characteristics, future research is needed to better clarify the role of Ara h 2 as a stand-alone measure of peanut sensitization in the patient seeking evaluation for possible peanut allergy. In studies where Ara h 2 was evaluated with whole peanut sIgE or where all 3 tests were evaluated, the precision advantage for Ara h 2 did not change. A potential risk associated with using Ara h 2 as a stand-alone test is that an individual with allergy may be sensitized to other components but not to Ara h 2, though this may be balanced by superior test precision of this approach and was accommodated for in design of the meta-analysis, which used OFC as the gold standard for diagnosis. We caution the clinician that despite undetectable sensitization on SPT, sIgE, or Ara h 2 testing, there is a small possibility the individual could still be peanut allergic. If clinical suspicion remains elevated, further evaluation through an OFC is potentially indicated.

The literature search did not provide patient-level data to determine the value of testing for peanut components in addition to SPT or sIgE to whole peanut to increase diagnostic accuracy. Thus, the use and value of components, including reflexive use of Ara h 2, remains a knowledge gap. There is an unclear utility for measuring sIgE to any other commercially available peanut components (Ara h 1, 3, 6, 8, 9) if peanut sIgE is elevated or SPT >3 mm (both indicating sensitization), given the limited available data on performance of components beyond Ara h 2.

*Evidence summary (Questions 2,* A *and 2,* B*):* For SPT and sIgE to whole peanut, from the 89 articles selected for final evidence synthesis, 56 directly pertained to this question. Of these, 32 had data available for extraction (5 studies had no data available, 10 authors did not respond to requests for data, and 9 studies had available data but could not be analyzed due to zero-cell interactions in the 2 × 2 table). A total of 18 studies (n = 2124 patients) were pooled for evidence synthesis for SPT[23,47-63] and 30 studies (n = 3989 patients) for sIgE.[23,47-57,59-61,63-77] No literature was identified that detailed the simultaneous, tandem, or reflexive use of both SPT and sIgE to whole peanut. Fig 2 details the summary forest plot for the pooled sensitivity, specificity, and both positive and negative likelihood ratios for an SPT to whole peanut extract of 3 mm or greater (Fig 2, *A*) and for peanut serum-specific IgE of 0.35 $KU_A$/L or higher (Fig 2, *B*). The summary measures for each test are presented in Table IV. Heterogeneity across these studies was high, and this is reflected in a downgrading under inconsistency. Figs 3 and 4 detail Fagan nomograms for a practical general example of how to roughly interpret the utility of these tests, set at a prespecified pretest probability of 2% (general population prevalence), 30% (low suspicion), and 70% (high suspicion). These nomograms show that the likelihood ratio for

**TABLE V.** GRADE table of evidence certainty, SPT

| Outcome | No. of studies and patients | Study design | Factors that may decrease CoE | | | | | Effect per 1000 patients tested (95% CI) | | | Test accuracy CoE |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Risk of bias | Indirectness | Inconsistency | Imprecision | Publication bias | Pretest probability of 2% | Pretest probability of 30% | Pretest probability of 70% | |
| True positives (patients with peanut allergy) | 18 studies 961 patients | Cross-sectional (cohort type accuracy study) | Serious* | Not serious | Serious† | Not serious | None | 19 (18-19) | 291 (270-279) | 679 (630-651) | ⊕⊕◯◯ Low |
| False negatives (patients incorrectly classified as not having peanut allergy) | | | | | | | | 1 (1–2) | 9 (21–30) | 21 (49–70) | |
| True negatives (patients without peanut allergy) | 18 studies 1163 patients | Cross-sectional (cohort type accuracy study) | Serious* | Not serious | Serious† | Not serious | None | 451 (284-637) | 322 (203-455) | 138 (87-195) | ⊕⊕◯◯ Low |
| False positives (patients incorrectly classified as having peanut allergy) | | | | | | | | 529 (343-696) | 378 (245-497) | 162 (105-213) | |

*CoE*, Certainty of evidence.

Question: In the patient presenting for evaluation of suspected peanut allergy, which of the 3 tests—SPT, sIgE to whole peanut, or Ara h 2 would provide the highest diagnostic accuracy as determined by the more optimal positive/negative likelihood ratio? In evaluating the performance of SPT, the total number of studies and patients entered into the analysis were as follows: 18 studies, 2124 patients; sensitivity: 0.97 (95% CI: 0.93-0.90); specificity: 0.46 (95% CI: 0.29-0.65); prevalences: 2%, 30%, and 70%. This table was compiled with data taken from:[23,47-63].

*Multiple studies had potential for selection bias due to nonconsecutive, nonrandomized, or otherwise unexplained selective enrollment of the study population within the potentially eligible cohort. There were multiple studies with issues relative to the flow/timing of when index diagnostic test was performed relative to the reference OFC.

†$I^2$ for sensitivity was 90.1% and for specificity was 93%.

sensitization at 3 mm or 0.35 $KU_A$/L at 2% or 30% pretest probability do not translate to posttest odds >50%, but at the 70% pretest probability this is raised to ~80%. Negative likelihood ratios do largely decrease posttest odds in all 3 scenarios. Based on these data, both SPT and sIgE to whole peanut can be used interchangeably, and this is a preference-sensitive choice given no discernable advantage in terms of test precision. There were no data noted that indicate using both tests together was disadvantageous. Both SPT and sIgE to whole peanut have similarly high sensitivity but poor specificity, with serologic testing having slightly higher specificity in identifying patients who are OFC-reactive at the assessed cutoff levels. Table IV additionally includes sensitivity analysis for the individual sensitivity/specificity of SPT and sIgE assessed when both tests were assessed in the same study. The clinician should be advised of the inherent weaknesses of either of these tests having relatively poor specificity, in that this may predispose to a higher rate of falsely positive detection of peanut sensitization.

For Ara h 2 component-specific IgE, from the 89 articles selected for final evidence synthesis, 41 directly pertained to this question. Of these, 24 had data available for extraction (11 authors did not respond to a request for additional data, 6 articles did not have data available). This resulted in a total of 24 studies (n = 2289 patients) pooled for evidence synthesis.[49-52,56,57,59,60,63,64,66-70,73-75,78-82] The summary measures for Ara h 2 are presented in Table IV. Fig 5 details the summary forest plot for the pooled sensitivity and specificity, for Ara h 2 peanut sIgE of 0.35 $KU_A$/L or higher. Heterogeneity across these studies was high. Fig 6 details Fagan nomograms for the use of these tests, set at a prespecified pretest probability of 2% (population prevalence), 30% (low suspicion), and 70% (high suspicion). These nomograms show that the likelihood ratio for Ara h 2 sensitization at 0.35 $KU_A$/L at 2% or 30% pretest probability translate to posttest odds of 10% and 70%, but at the 70% pretest probability translates to 89% posttest odds. Negative likelihood ratios do largely decrease posttest odds in all 3 scenarios.

We were unable to find sufficient number of studies to analyze any other individual peanut components or pool the use of

**TABLE VI.** GRADE table of evidence certainty, sIgE testing

| Outcome | No. of studies and patients | Study design | Factors that may decrease CoE | | | | | Effect per 1000 patients tested (95% CI) | | | Test accuracy CoE |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Risk of bias | Indirectness | Inconsistency | Imprecision | Publication bias | Pretest probability of 2% | Pretest probability of 30% | Pretest probability of 70% | |
| True positives (patients with peanut allergy) | 30 studies 2046 patients | Cross-sectional (cohort type accuracy study) | Serious* | Not serious | Serious† | Not serious | None | 19 (18-19) | 285 (273-291) | 665 (637-679) | ⊕⊕◯◯ Low |
| False negatives (patients incorrectly classified as not having peanut allergy) | | | | | | | | 1 (1-2) | 15 (9-27) | 35 (21-63) | |
| True negatives (patients without peanut allergy) | 30 studies 1937 patients | Cross-sectional (cohort type accuracy study) | Serious* | Not serious | Serious† | Not serious | None | 372 (274-470) | 266 (196-336) | 114 (84-144) | ⊕⊕◯◯ Low |
| False positives (patients incorrectly classified as having peanut allergy) | | | | | | | | 608 (510-706) | 434 (364-504) | 186 (156-216) | |

Question: In the patient presenting for evaluation of suspected peanut allergy, which of the 3 tests—SPT, sIgE to whole peanut, or Ara h 2 would provide the highest diagnostic accuracy as determined by the more optimal positive/negative likelihood ratio? In evaluating the performance of whole peanut sIgE, the total number of studies and patients entered into the analysis were as follows: 30 studies, 3983 patients; sensitivity: 0.95 (95% CI: 0.91-0.97); specificity: 0.38 (95% CI: 0.28-0.48); prevalences: 2%, 30%, and 70%. This table was compiled with data taken from:[23,47-57,59-61,63-77].

*Multiple studies had potential for selection bias due to nonconsecutive, nonrandomized, or otherwise unexplained selective enrollment of the study population within the potentially eligible cohort. There were multiple studies with issues relative to the flow/timing of when index diagnostic test was performed relative to the reference OFC.

†$I^2$ for sensitivity was 95.9% and for specificity was 92.8%.

component panels. Therefore, we can offer no comment regarding the role or significance of evaluating these other components individually or in aggregate, or what the clinical implications of their use may be. Similarly, there were no studies identified comparing reflexive use of Ara h 2 or any components after SPT or sIgE. There were no studies identified that evaluated the comparative efficacy of Ara h 2 as a stand-alone test compared with any other component or whole peanut SPT or sIgE in their use for clinical decision making. A potential advantage of Ara h 2 relative to SPT and sIgE to whole peanut is higher specificity, which may reduce the number of falsely positive cases of sensitization identified, though a disadvantage is this could risk a falsely negative case if someone is sensitized to other components but not Ara h 2. However, the high sensitivity and specificity of the test may limit this risk. In studies where Ara h 2 was evaluated with whole peanut sIgE or where all 3 tests were evaluated, Ara h 2 consistently had slightly lower sensitivity but much higher specificity, and a more optimal positive/negative likelihood ratio, comparatively. This is similar to the difference noted in the base case where the tests were evaluated individually (Table IV).

*Quality of Evidence:* Tables V[23,47-63] and VI[23,47-57,59-61,63-77] detail the summary of GRADE evidence for both SPT and sIgE. There is moderate certainty of evidence for use of either test, and the estimate was downgraded 1 point for risk of bias. Table VII[49-52,56,57,59,60,63,64,66-70,73-75,78-82] details the certainty of evidence for the use of Ara h 2. There is low certainty of evidence, and this estimate was downgraded 1 point for risk of bias and 1 point for inconsistency.

In practice, SPT and sIgE are often used interchangeably and at the preference of the ordering clinician or the family. Many clinicians may use these tests in tandem with one another as well, though no evidence exists to specifically evaluate this practice. However, this meta-analysis highlights that Ara h 2 is the single best choice based on the most optimal combination of positive and negative likelihood ratios, leveraged by a very high specificity

**TABLE VII.** GRADE table of evidence certainty, Ara h 2 sIgE testing

| Outcome | No. of studies and patients | Study design | Factors that may decrease CoE | | | | | Effect per 1000 patients tested (95% CI) | | | Test accuracy CoE |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Risk of bias | Indirectness | Inconsistency | Imprecision | Publication bias | Pretest probability of 2% | Pretest probability of 30% | Pretest probability of 70% | |
| True positives (patients with peanut allergy) | 24 studies 1336 patients | Cross-sectional (cohort type accuracy study) | Serious* | Not serious | Serious† | Not serious | None | 17 (16-18) | 258 (243-267) | 602 (567-623) | ⊕⊕◯◯ Low |
| False negatives (patients incorrectly classified as not having peanut allergy) | | | | | | | | 3 (2-4) | 42 (33-57) | 98 (77-133) | |
| True negatives (patients without peanut allergy) | 24 studies 953 patients | Cross-sectional (cohort type accuracy study) | Serious* | Not serious | Serious† | Not serious | None | 823 (774 to 872) | 588 (553 to 623) | 252 (237 to 267) | ⊕⊕◯◯ Low |
| False positives (patients incorrectly classified as having peanut allergy) | | | | | | | | 157 (108-206) | 112 (77-147) | 48 (33-63) | |

Question: In the patient presenting for evaluation of suspected peanut allergy, which of the 3 tests—SPT, sIgE to whole peanut, or Ara h 2 would provide the highest diagnostic accuracy as determined by the more optimal positive/negative likelihood ratio? In evaluating the performance of Ara h 2 specific sIgE, the total number of studies and patients entered into the analysis were as follows: 24 studies, 2289 patients; sensitivity: 0.86 (95% CI: 0.81-0.89); specificity: 0.84 (95% CI: 0.79-0.89); prevalences: 2%, 30%, and 70%. This table was compiled with data taken from:[49-52,56,57,59,60,63,64,66-70,73-75,78-82].

*Multiple studies had potential for selection bias due to nonconsecutive, nonrandomized, or otherwise unexplained selective enrollment of the study population within the potentially eligible cohort. There were multiple studies with issues relative to the flow/timing of when index diagnostic test was performed relative to the reference OFC.

†$I^2$ for sensitivity was 81.4% and specificity was 69.7%.

that clinically can translate to a much lower change of a falsely positive diagnosis of peanut allergy. The reduction in the false positive case provides tremendous clinical value. A 2009 systematic review by Chafen et al[83] noted no statistically significant differences between the diagnostic utility of food-specific SPT and sIgE when comparing their summary receiver operating characteristic curves. A 2015 systematic review by Klemans et al[84] noted the sensitivity of peanut SPT was 0.66 to 1, the specificity 0 to 0.95, and the positive and negative likelihood ratios between 1 to 3.91 and 0 to 0.65, respectively. For peanut sIgE, this had sensitivity between 0.8 and 1, specificity between 0 and 0.63, and positive and negative likelihood ratios between 0.95 to 2.15 and 0 to 0.56, respectively.[84] Overall both SPT and sIgE to whole peanut have very similar test precision, with a very slight relative advantage in sensitivity (0.02) and specificity (0.08) for skin testing over sIgE testing. In the setting of the high-risk infant being evaluated for early peanut introduction, the NIAID addendum guidelines on peanut allergy prevention specifically recommended SPT as the preferred modality when available, though nonallergists can elect to send peanut sIgE and refer patients for further evaluation or recommend at-home introduction in this population.[20] This recommendation was based on data from the LEAP (Learning Early About Peanut) study, suggesting that SPT provided better classification of infants who are peanut allergic after peanut challenge than serologic testing.[22]

There is widespread availability of component testing and several publications have concluded that Ara h 2 may have unique diagnostic value, which has led to debate about whether the clinician should routinely test for IgE to peanut components and base diagnostic decisions solely on these results.[84] In practice, the clinician has the option to request tests for peanut components in combination with whole peanut SPT and/or peanut-specific IgE or to request tests for component testing as a stand-alone test (the Ara h 2 reference code is f423 under Current Procedural Terminology code 86003). While peanut components are run as single individual tests, these are most commonly offered as a panel by

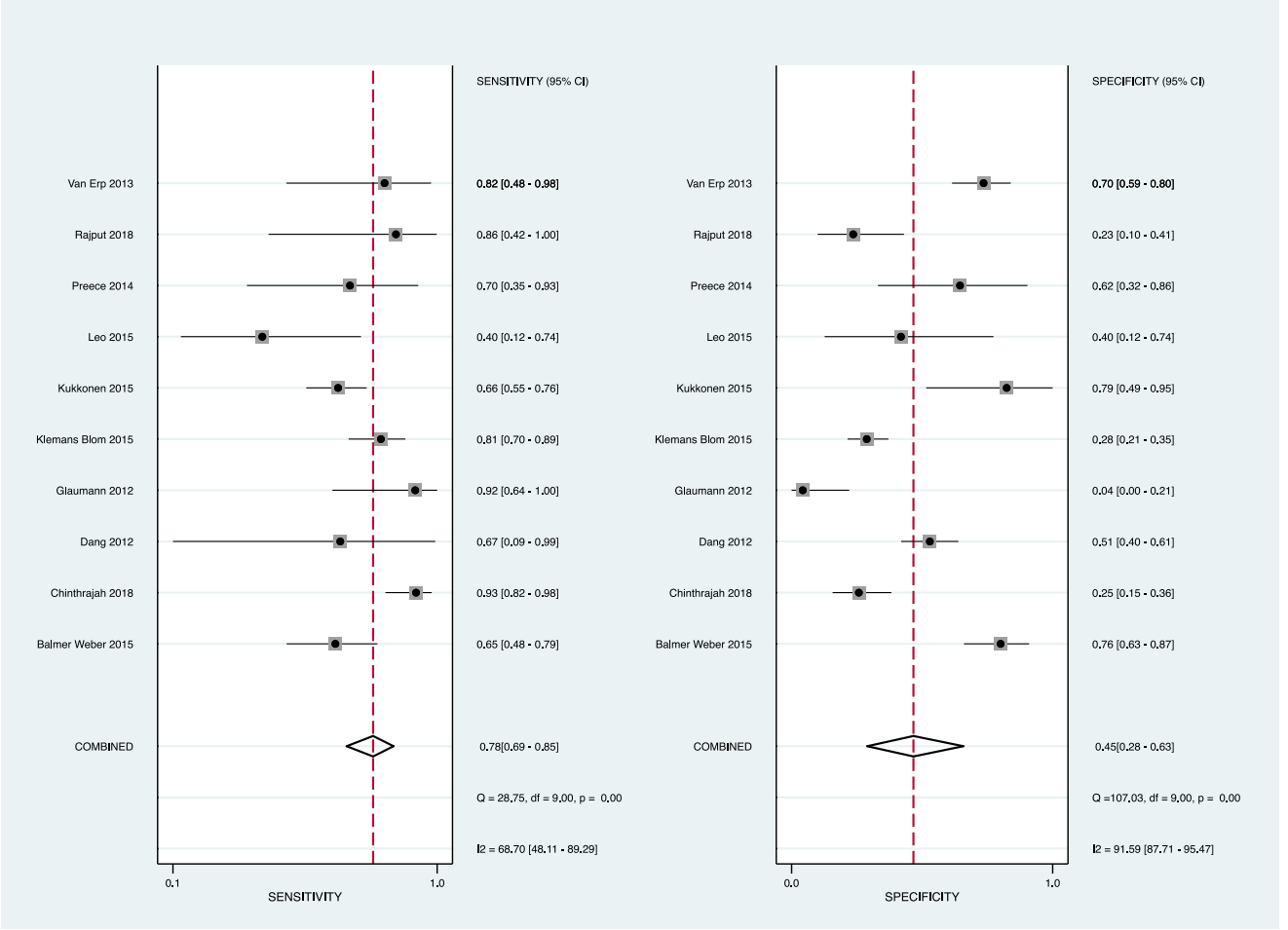


**FIG 7.** Summary forest plots for sensitivity and specificity of Ara h 2 sIgE testing at 2 $KU_A/L$, indicating a severe reaction.

commercial labs at present. To date, no practice parameter or clinical practice guideline has advocated selective use of a single component or a panel of components over whole peanut SPT or sIgE; indicated how components, including just assessment of Ara h 2, could be used in tandem or reflexively with these tests; or specifically recommended how use of components definitively provides a diagnostic advantage.[2,16] There is limited study of other component testing that was found in this literature search. Ara h 6 sensitization is an emerging area of investigation,[85] and studies of Ara h 8 monosensitization suggested a potential role in discriminating asymptomatic peanut sensitization from allergy, more likely to have clinical relevance in geographic areas where birch pollen is endemic.[86,87] However, we found few studies that reported challenge-proven outcomes meeting our selection criteria for components apart from Ara h 2 and very limited number of studies that evaluated use of single versus panels of peanut components. Thus, we are precluded from commenting any further on specific use of components such as Ara h 6 or Ara h 8, and their potential value in assisting the clinician in making a diagnosis of peanut allergy.

No studies were identified evaluating tandem use of SPT and sIgE to whole peanut. Many studies had both SPT and sIgE measured together, and the individual results are incorporated in the respective analyses. However, we offer no recommendation to this tandem approach, perceived to be commonly done in practice. In studies where both SPT and sIgE were reported, the pooled sensitivity/specificity results were very similar to the base analyses and reflective of those same small differences. Similarly, no studies were identified evaluating reflexive or tandem use of Ara h 2 or any component with SPT and sIgE to whole peanut, and it is unclear how component testing would be optimally positioned in a clinician's arsenal. Future studies are required to further evaluate Ara h 2 as a stand-alone marker, if components should be tested reflexively after sensitization to whole peanut is denoted or even tested at all. Importantly, in the context of either very strong or very weak pretest probability, it is debatable whether components (including Ara h 2) offer any additional diagnostic leverage over whole peanut testing or supersede the OFC if there was any doubt. In such circumstances, even the good positive likelihood ratio associated with Ara h 2 would not likely change the clinical decision making or provide more value than the OFC.

Ara h 2 may have more value than other testing options in the context of a questionable history and whole peanut sensitization given its higher specificity, in particular in areas with high birch (or birch cross-reactive) pollen. However, additional research is needed to more robustly evaluate such use, and we noted insufficient numbers of studies specifically for this application.

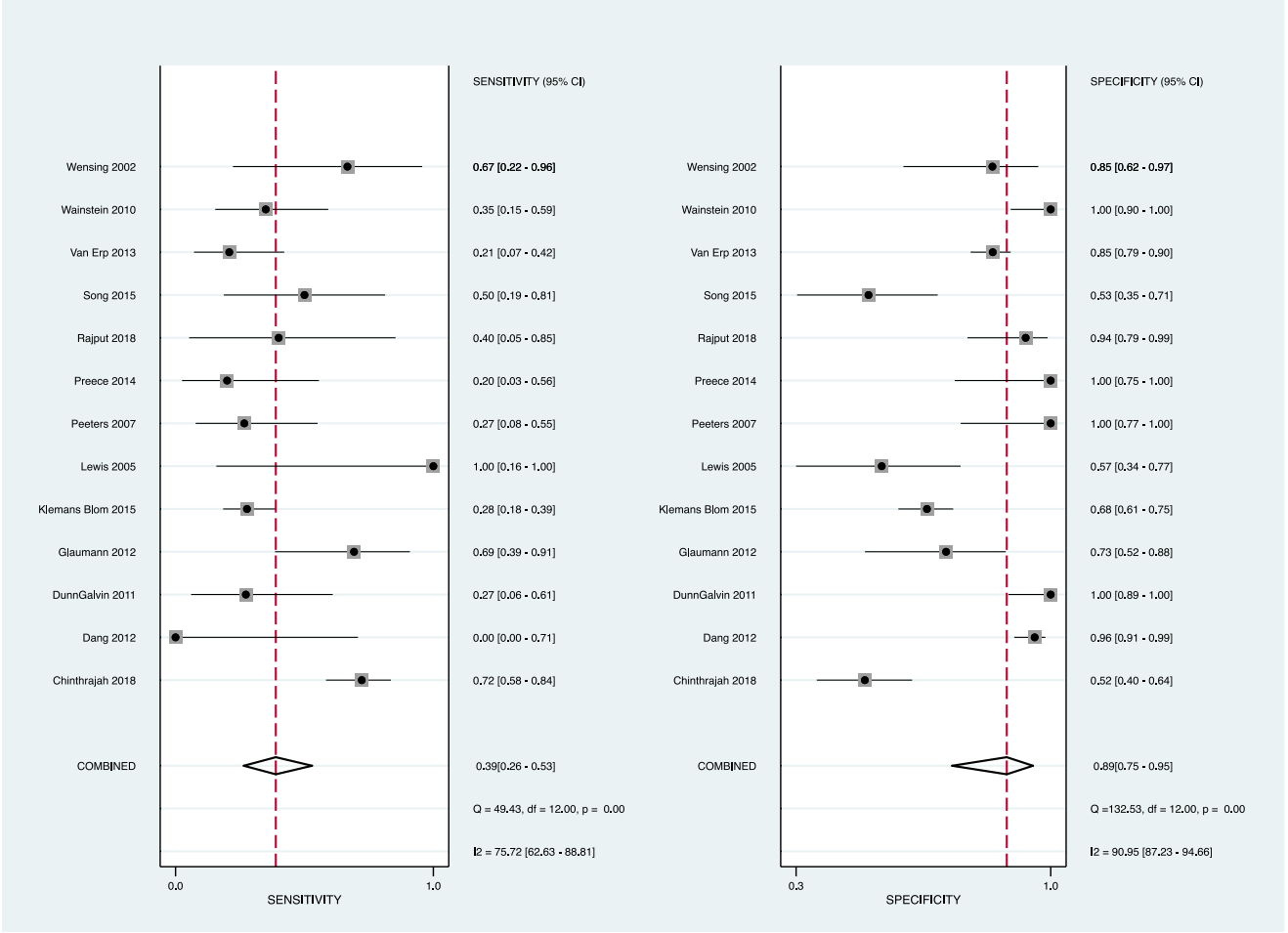


**FIG 8.** Summary forest plots for sensitivity and specificity of sIgE testing at 50 $KU_A/L$, indicating a severe reaction.

There is no universal cutoff value for any component (including Ara h 2) that can used to reliably predict peanut allergy—such levels vary considerably by geographic region, population tested, and possibly by age.[84] As was noted in Question 1, there may be situations where a clinician may ascribe a higher pretest probability to a child who has never eaten peanut before (apart from those falling under NIAID guidelines for peanut allergy prevention addendum 1 recommendations) and desire to obtain Ara h 2 component testing. Overall, use of Ara h 2 at present is limited in the capacity of a corroborating test, indicated when there is sufficient pretest probability for peanut allergy, and not in the capacity of a screening test where there is no pretest probability. This is demonstrated in the Fagan nomograms in Fig 6, which may help illustrate practical general examples of how the test may be reasonably interpreted under different hypothetical pretest probabilities.

There are several other considerations regarding test preference, including safety, cost, and patient features that may drive the choice, availability, and practice patterns. SPT is associated with an exceptionally rare risk of systemic reactions (0.077%, with 75% of cases attributable to food), though those doing skin testing should be prepared to potentially treat anaphylaxis.[15,88] There also are data demonstrating that there are more side effects from sIgE testing than from SPT based on assessment in the NHANES (National Health and Nutrition Examination Survey) study. The costs of SPT and sIgE tests vary among offices and laboratories, but they have been reported to be from 2 to 7 times less expensive per test for SPT (typically ~$8 per SPT and $10 to $20 per allergen for sIgE test, including components, though components are presently available only as a full panel). Certain patient-related factors may make SPT difficult to perform, such as inability to stop medications with antihistamine activity, severe dermatographism, unstable asthma, patients who may be averse to or afraid of the procedure (such as young children), and hard to control eczema with extensive skin involvement.[15] However, because SPT can be done on the back or arm or may be possible on other unaffected areas of skin, it is often possible to do the test even with extensive eczema or delay this until the eczema flare has calmed down. The advantage of SPT is that it is a point of care test that can be rapidly performed in clinic, but a trained specialist generally performs this. There are few limitations to sIgE testing, and often multiple allergens can be assessed from 2 to 5 mL of blood obtained from routine venipuncture. The test is not point of care, however.[15] As was noted in Question 1, there may be situations in which a clinician may ascribe a higher pretest probability to a child who has never eaten peanut before (apart from those falling under NIAID addendum 1 recommendations),[20] and the clinician desires to obtain information regarding

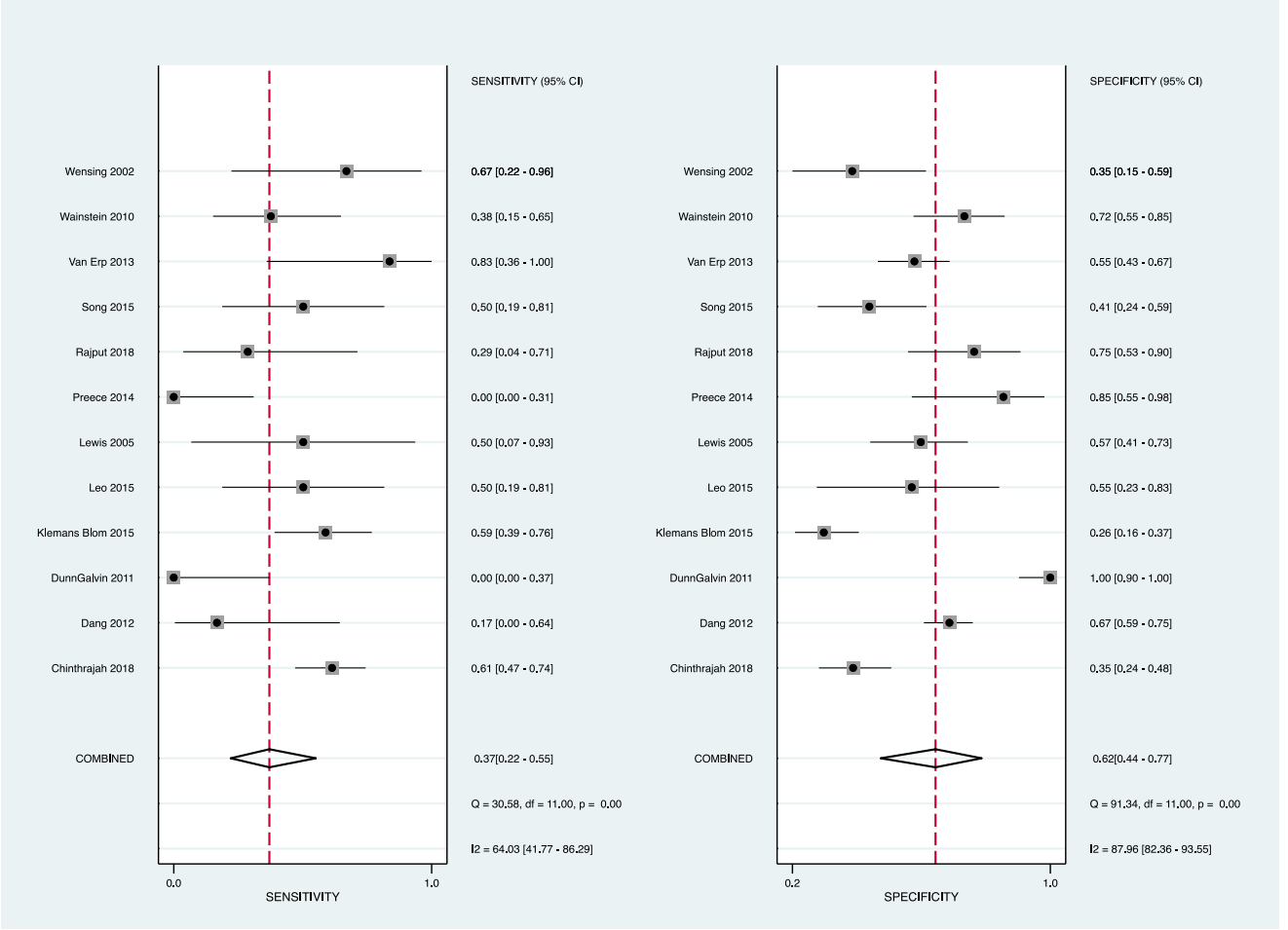


**FIG 9.** Summary forest plots for sensitivity and specificity of SPT at 10 mm, indicting a severe reaction.

peanut allergy using SPT or sIgE. The Fagan nomograms in Figs 3, 4, and 6 may help provide guidance for how the test may be reasonably interpreted in such a scenario.

Test thresholds of 3 mm for SPT and 0.35 $KU_A/L$ for sIgE and Ara h 2 sIgE were chosen for analysis of this question. These represent sensitization levels at which a patient traditionally would be considered to have a test indicating allergic sensitization. These are the most widely published cutoff levels in the literature, though higher levels, including levels indicative of reported PPVs have also been reported, and more recently, lower levels of 0.1 $KU_A/L$ are being commonly reported.[84,89] We considered different levels (both higher and lower) but disfavored such an approach as this would have reduced the number of citations that would have been available and made the analysis even more dependent on the goodwill of authors sending us data reconfigured to our needs. A problem unique to the newer conventions of reporting to the technical lower limit of detection at 0.1 $KU_A/L$ is that many studies otherwise eligible for inclusion in our search were performed before reporting to this lower standard was available and would have limited our total numbers. More importantly, we are unaware of any literature indicating that sensitization between 0.1 and 0.34 $KU_A/L$ is of clinical significance, as opposed to ample literature that clearly has defined sensitization >0.35 $KU_A/L$ as significant.[2] Lastly, we did not attempt to provide a PPV for these cutoff levels. The PPV is dependent on a population prevalence of disease, which we do not know and did not assess. Instead, we report likelihood ratios and provide example Fagan nomograms for how the test results could be interpreted at a clinic level, which is a more accurate and appropriate analysis.[90]

## Question 3. In the patient presenting for evaluation of suspected peanut allergy, can the results of a diagnostic test be used to predict the severity of an allergic reaction?

**Recommendation 3. We suggest against the clinician using the results of an SPT, sIgE to whole peanut extract, or sIgE to peanut components to determine an allergy phenotype or to predict the severity of a future reaction. Conditional recommendation. Certainty of evidence: Very low.**

*Clinical statement:* There was inadequate patient-level data to formulate a GRADE recommendation on the use of a peanut diagnostic test for predicting the severity of a future allergic reaction across a continuous range of test result values; however, dichotomous cutoff values of 10 mm (SPT), 50 $KU_A/L$, and 2 $KU_A/L$ (Ara h 2) demonstrated low sensitivity and specificity for a future severe reaction.

*Evidence summary:* From the 89 articles selected for final evidence synthesis, 31 directly pertained to this question. Of these,

**TABLE VIII.** GRADE table of evidence certainty, Ara h 2 sIgE to assess reaction severity

| Outcome | No. of studies and patients | Study design | Factors that may decrease CoE | | | | | Effect per 1000 patients tested (95% CI) | | | Test accuracy CoE |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Risk of bias | Indirectness | Inconsistency | Imprecision | Publication bias | Pretest probability of 2% | Pretest probability of 30% | Pretest probability of 70% | |
| True positives (patients with severe peanut allergy) | 10 studies 308 patients | Cross-sectional (cohort type accuracy study) | Serious* | Not serious | Very serious†‡§ | Not serious | None | 16 (14-17) | 234 (207-255) | 546 (483-595) | ⊕⊕◯◯ Very low |
| False negatives (patients incorrectly classified as not having severe peanut allergy) | | | | | | | | 4 (3-6) | 66 (45-93) | 154 (105-217) | |
| True negatives (patients without severe peanut allergy) | 10 studies 380 patients | Cross-sectional (cohort type accuracy study) | Serious* | Not serious† | Very serious†‡§ | Not serious | None | 441 (274-617) | 315 (196-441) | 135 (84-189) | ⊕⊕◯◯ Very low |
| False positives (patients incorrectly classified as having severe peanut allergy) | | | | | | | | 539 (363-706) | 385 (259-504) | 165 (111-216) | |

Question: In the patient presenting for evaluation of suspected peanut allergy, can the results of a diagnostic test be used to predict the severity of a future allergic reaction? In evaluating the performance of Ara h 2 specific sIgE >2 $KU_A$/L, the total number of studies and patients entered into the analysis were as follows: 10 studies, 845 patients; sensitivity: 0.78 (95% CI: 0.69-0.85); specificity: 0.45 (95% CI: 0.28-0.63); prevalences: 2%, 30%, and 70%. This table was compiled with data taken from:[50,52,55,57,59,60,63,64,70,79].

*Multiple studies had potential for selection bias due to nonconsecutive, nonrandomized, or otherwise unexplained selective enrollment of the study population within the potentially eligible cohort. Multiple studies with issues relative to the flow/timing of when index diagnostic test was performed relative to the reference OFC.

†$I^2$ for sensitivity was 68.7% and for specificity was 91.6%.

‡The heterogeneity for the estimate was very high.

§The criteria to assess severity were not uniform among all studies included.

16 had data available for extraction (12 authors did not respond to a request for additional data, 1 study did not have data available). A total of 18 studies were pooled for evidence synthesis (10 for Ara h 2 at 2 $KU_A$/L, n = 845 patients;[50,52,55,57,59,60,63,64,70,79] 13 for whole peanut sIgE at 50 $KU_A$/L, n = 1051 patients;[50,52,53,59,60,62,63,70,80,91-94] 12 for SPT 10 mm, n = 737 patients[50,52,53,57,59,60,62,63,91-94]). The summary measures for each test are presented in Table IV. Figs 7 to 9 detail the summary forest plot for the pooled sensitivity and specificity for cutoff levels for severe reactions for Ara h 2 peanut sIgE of 2 $KU_A$/L or higher, whole peanut sIgE at 50 $KU_A$/L, and for SPT 10 mm. Due to both low sensitivity and specificity, with no individual measure >0.68 for any of these analyses, likelihood ratios and Fagan nomograms were not reported. Heterogeneity across these studies was high. Based on these data, this analysis notes exceptionally poor sensitivity and specificity for these cutoff values, which differs from a similar analysis by Klemans et al[84] in a 2015 systematic review where Ara h 2 as a marker of severity was concluded to have more potential. Klemans et al[84] explored several different cutoff levels than we did in this analysis, though did so with far fewer studies included per cutoff level investigated. Therefore, the results of this analysis should be interpreted as a significant caution to clinicians against using the dichotomous sensitization cutoffs studied to whole peanut (skin/blood) or peanut component (blood) as a surrogate to determine whether someone will have a future severe reaction or has a "severe" reaction

**TABLE IX.** GRADE table of evidence certainty, peanut sIgE to assess reaction severity

| Outcome | No. studies and patients | Study design | Factors that may decrease CoE | | | | | Effect per 1000 patients tested (95% CI) | | | Test accuracy CoE |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Risk of bias | Indirectness | Inconsistency | Imprecision | Publication bias | Pretest probability of 2% | Pretest probability of 30% | Pretest probability of 70% | |
| True positives (patients with severe peanut allergy) | 13 studies 256 patients | Cross-sectional (cohort type accuracy study) | Serious* | Not serious | Very serious†‡§ | Not serious | None | 8 (5-11) | 117 (78-159) | 273 (182-371) | ⊕◯◯◯ Very low |
| False negatives (patients incorrectly classified as not having severe peanut allergy) | | | | | | | | 12 (9-15) | 183 (141-222) | 427 (329-518) | |
| True negatives (patients without severe peanut allergy) | 13 studies 795 patients | Cross-sectional (cohort type accuracy study) | Serious* | Not serious | Very serious†‡§ | Not serious | None | 872 (735-931) | 623 (525-665) | 267 (225-285) | ⊕◯◯◯ Very low |
| False positives (patients incorrectly classified as having severe peanut allergy) | | | | | | | | 108 (49-245) | 77 (35-175) | 33 (15-75) | |

Question: In the patient presenting for evaluation of suspected peanut allergy, can the results of a diagnostic test be used to predict the severity of a future allergic reaction? In evaluating the performance of whole peanut sIgE >50 $KU_A$/L, the total number of studies and patients entered into the analysis were as follows: 13 studies, 1051 patients; sensitivity: 0.39 (95% CI: 0.26-0.53); specificity: 0.89 (95% CI: 0.75-0.95); prevalences: 2%, 30%, and 70%. This table was compiled with data taken from:[50,52,53,59,60,62,63,70,80,91-94].

*Multiple studies had potential for selection bias due to nonconsecutive, nonrandomized, or otherwise unexplained selective enrollment of the study population within the potentially eligible cohort. There were multiple studies with issues relative to the flow/timing of when index diagnostic test was performed relative to the reference OFC.

†$I^2$ for sensitivity was 75.7% and for specificity was 90.9%.

‡The criteria to assess severity were not uniform among all studies.

§The heterogeneity for the estimate was very high.

phenotype. This caution is pending further future studies of much higher quality, more consistently defining severity, with less selection bias, and with more patient level data for analysis. There were insufficient numbers of other studies to comment regarding the role or significance of evaluating these other components individually or in aggregate to determine whether there is any test that may infer reaction severity.

*Evidence strength:* Tables VIII,[50,52,55,57,59,60,63,64,70,79] IX,[50,52,53,59,60,62,63,70,80,91-94] and X[50,52,53,57,59,60,62,63,91-94] detail the certainty of evidence for the use of Ara h 2, sIgE, and SPT at these stated cutoff levels for the assessment of the severity of a reaction. There is very low certainty of evidence for all 3 of these measures, and this estimate was downgraded 1 point for risk of bias and 2 points for inconsistency (based on the high heterogeneity of the sensitivity and specificity of pooled studies and a different definition of severity among the studies).

There is no relationship indicating that the degree of sensitization is predictive of the underlying severity of the reaction to peanut, using either skin or serologic markers, whole allergen or component. This includes any single test, component, or panel of tests. Importantly, the clinician is advised against making the interpretation that sensitization (at the thresholds evaluated) will predict whether someone will have a severe reaction or not. Per our meta-analysis, at the cutoff levels reported, there is no clearly predictive relationship with reaction severity from available data

**TABLE X.** GRADE table of evidence certainty, peanut sIgE to assess reaction severity

| Outcome | No. of studies and patients | Study design | Factors that may decrease CoE | | | | | Effect per 1000 patients tested (95% CI) | | | Test accuracy CoE |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Risk of bias | Indirectness | Inconsistency | Imprecision | Publication bias | Pretest probability of 2% | Pretest probability of 30% | Pretest probability of 70% | |
| True positives (patients with severe peanut allergy) | 12 studies 166 patients | Cross-sectional (cohort type accuracy study) | Serious* | Not serious | Very serious†‡§ | Not serious | None | 7 (4-11) | 111 (66-165) | 259 (154-385) | ⊕◯◯◯ Very low |
| False negatives (patients incorrectly classified as not having severe peanut allergy) | | | | | | | | 13 (9-16) | 189 (135-234) | 441 (315-546) | |
| True negatives (patients without severe peanut allergy) | 12 studies 571 patients | Cross-sectional (cohort type accuracy study) | Serious* | Not serious | Very serious†‡§ | Not serious | None | 608 (431-755) | 434 (308-539) | 186 (132-231) | ⊕◯◯◯ Very low |
| False positives (patients incorrectly classified as having severe peanut allergy) | | | | | | | | 372 (225-549) | 266 (161-392) | 114 (69-168) | |

Question: In the patient presenting for evaluation of suspected peanut allergy, can the results of a diagnostic test be used to predict the severity of a future allergic reaction? In evaluating the performance of peanut SPT wheal size >10 mm, the total number of studies and patients entered into the analysis were as follows: 12 studies, 737 patients; sensitivity: 0.37 (95% CI: 0.22 to 0.55); specificity: 0.62 (95% CI: 0.44 to 0.77); prevalences: 2%, 30%, and 70%. This table was compiled with data taken from:[50,52,53,57,59,60,62,63,91-94].

*Multiple studies had potential for selection bias due to nonconsecutive, nonrandomized, or otherwise unexplained selective enrollment of the study population within the potentially eligible cohort. There were multiple studies with issues relative to the flow/timing of when index diagnostic test was performed relative to the reference OFC.

†$I^2$ for sensitivity was 64% and for specificity was 87.9%.

‡The criteria to assess severity were not uniform among all studies included.

§The heterogeneity for the estimate was very high.

(regardless of the criteria used to define severity) at the levels of sensitization evaluated. Severe reactions can still occur with low/lower sensitization levels. Multiple practice parameters, guidelines, and systematic reviews have repeatedly emphasized these points.[12,16] A few individual peanut component-based studies have suggested some degree of association between the recognition of discrete levels of Ara h 2 and history of a severe allergic reaction, though a greater number of studies have noted no such association, and many of these have multiple biases.[84] At our chosen cutoff levels (Ara h 2: 2 $KU_A$/L; SPT: 10 mm, sIgE: 50 $KU_A$/L), we were unable to identify a relationship to severity, though if patient-level data were available for pooling and evaluation of sensitization as continuous variables, it is possible a relationship could exist. We caution that there is very serious risk of bias among even the few numbers of studies we included. In particular, many studies did not assess severity using Ara h 2, and small inclusion numbers may present a misleading estimate due to omission of data.

There is some evidence that singular recognition of Ara h 8 sensitization (in the absence of other component recognition) may be suggestive as a potential discriminator of pollen cross-sensitization in individuals residing in particular geographic areas (eg, birch-pollen endemic areas such as the northeast United States or northern Europe) who are likely to only experience oropharyngeal, transient itching from peanut ingestion (eg, pollen food allergy syndrome).[17] However, we could not analyze this question due to low study numbers evaluating this relationship that met inclusion criteria (specifically that 50% of

**TABLE XI.** Additional sensitivity analyses

| Test | Outcome | Analyses | Sensitivity | Specificity | Positive LR | Negative LR |
|---|---|---|---|---|---|---|
| SPT 3 mm | Diagnosis | Exclusion of studies with high risk of bias | 0.96 | 0.48 | 1.85 | 0.08 |
| | | Pediatric studies only | 0.97 | 0.52 | 2.02 | 0.06 |
| | | Open OFC studies only | 0.96 | 0.53 | 2.04 | 0.08 |
| | | DBPCFC studies only | 0.99 | 0.38 | 1.60 | 0.03 |
| | | European studies only | 0.98 | 0.56 | 2.23 | 0.04 |
| | | Non-European studies only | 0.97 | 0.32 | 1.43 | 0.09 |
| sIgE >0.35 $KU_A$/L | Diagnosis | Exclusion of studies with high risk of bias | 0.96 | 0.44 | 1.71 | 0.09 |
| | | Pediatric studies only | 0.94 | 0.41 | 1.59 | 0.15 |
| | | Open OFC studies only | 0.94 | 0.4 | 1.57 | 0.15 |
| | | DBPCFC studies only | 0.97 | 0.42 | 1.67 | 0.07 |
| | | European studies only | 0.95 | 0.38 | 1.53 | 0.13 |
| | | Non-European studies only | 0.95 | 0.37 | 1.51 | 0.14 |
| Ara h 2 sIgE >0.35 $KU_A$/L | Diagnosis | Exclusion of studies with high risk of bias | 0.86 | 0.81 | 4.53 | 0.17 |
| | | Pediatric studies only | 0.85 | 0.85 | 5.67 | 0.18 |
| | | Open OFC studies only | 0.85 | 0.85 | 5.67 | 0.18 |
| | | DBPCFC studies only | 0.87 | 0.83 | 5.12 | 0.16 |
| | | European studies only | 0.88 | 0.85 | 5.87 | 0.14 |
| | | Non-European studies only | 0.83 | 0.84 | 5.19 | 0.20 |
| Ara h 2 sIgE >2 $KU_A$/L | Severity | Exclusion of studies with high risk of bias | 0.75 | 0.42 | 1.29 | 0.60 |
| | | Pediatric studies only | 0.72 | 0.49 | 1.41 | 0.57 |
| | | Open OFC only | 0.64 | 0.43 | 1.12 | 0.84 |
| | | DBPCFC only | 0.8 | 0.44 | 1.43 | 0.45 |
| | | European studies only | 0.77 | 0.43 | 1.35 | 0.53 |
| | | Non-European studies only | 0.71 | 0.44 | 1.27 | 0.66 |
| sIgE >50 $KU_A$/L | Severity | Exclusion of studies with high risk of bias | 0.36 | 0.88 | 3.00 | 0.73 |
| | | Pediatric studies only | 0.38 | 0.92 | 4.75 | 0.67 |
| | | Open OFC only | 0.29 | 0.97 | 9.67 | 0.73 |
| | | DBPCFC studies only | 0.47 | 0.71 | 1.62 | 0.75 |
| | | European studies only | 0.38 | 0.86 | 2.71 | 0.72 |
| | | Non-European studies only | 0.44 | 0.92 | 5.50 | 0.61 |
| SPT 10 mm | Severity | Exclusion of studies with high risk of bias | 0.41 | 0.57 | 0.95 | 1.04 |
| | | Pediatric studies only | 0.29 | 0.71 | 1.00 | 1.00 |
| | | Open OFC studies only | 0.26 | 0.69 | 0.84 | 1.07 |
| | | DBPCFC studies only | 0.62 | 0.41 | 1.05 | 0.93 |
| | | European studies only | 0.39 | 0.67 | 1.18 | 0.91 |
| | | Non-European studies only | 0.36 | 0.59 | 0.88 | 1.08 |

*DBPCFC*, Double-blind, placebo-controlled food challenge.

the population underwent OFC). Furthermore, while some expert opinions may support that Ara h 8 monosensitization is a potential indicator of pollen-food allergy syndrome and surrogate for low risk of a severe reaction, these findings lack definitive confirmation in this and a prior meta-analysis.[84] Importantly, we found insufficient numbers of studies for components apart from Ara h 2 meeting our criteria to pool for analysis and cannot comment on the clinical utility of these tests without further rigorous study to validate this concept.

Regional geography may influence component sensitization patterns, in particular with the pollen cross-sensitized individuals, which complicate assessing the relationship between sensitization and severity. A study has shown differences in component recognition patterns in patients in northern Europe (Sweden), southern Europe (Spain), and the United States (New York City), as well as differing patterns among different regions in the United States (as noted for birch endemic areas such as the northeast, which may complicate the use of any particular component as a phenotypic discriminator).[87] For instance, in birch endemic areas, Ara h 8 may behave as a cross-sensitizing marker and has been proposed to help identify such individuals from those recognizing other proteins in peanut. Ara h 9 could have relevance as a component associated with lipid transfer protein syndrome in certain areas of the world (such as the Mediterranean coast), with high potential to cause systemic reaction in sensitized individuals, whereas elsewhere it behaves similarly to Ara h 8 as a marker of tree pollen sensitization.[17] Therefore, it is unclear the degree to which severity of a reaction may be affected by such geographical differences influencing component recognition, and this area of component research remains promising, but at present represents a knowledge gap.

Importantly, there are issues of bias that must strongly be considered regarding the studies noting an association between sensitization levels and severity. Most of these studies suffer from multiple biases, the most concerning of which is patient selection from serum banks within retrospective cohorts, and lack of generalizability of the sample used for analysis. Many of these studies also lack clear comparison to a reference (gold) standard, tended to be conducted only in certain aged samples, and lacked prospective use of an OFC complicating an objective determination of reaction severity. Study of severe reactions is further hampered given a predilection to not challenge strongly sensitized individuals with a supporting clinical history, as well as ethical considerations to promptly treat reactions when individuals are challenged, which preclude determining how severe a reaction could be.

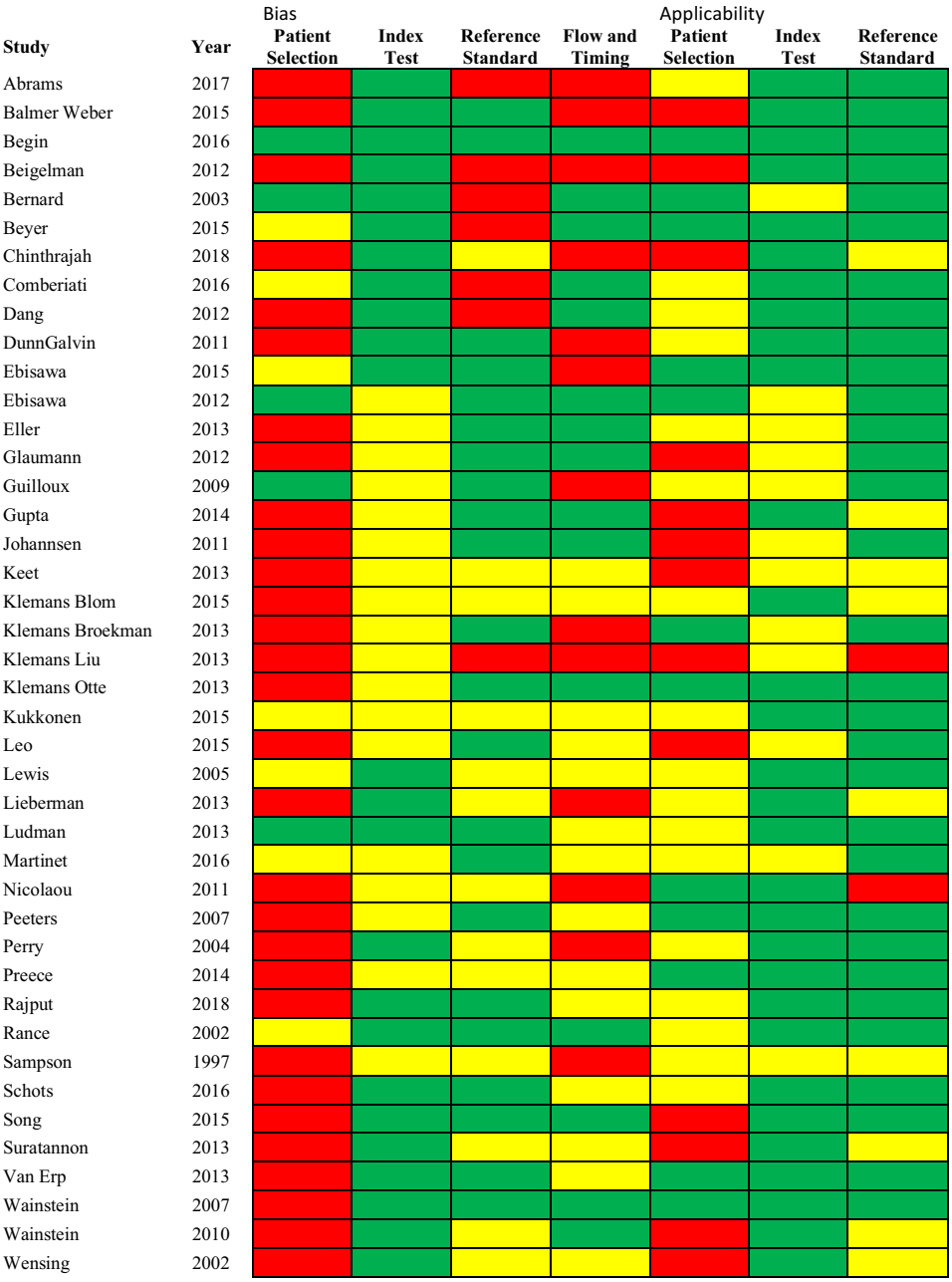


**FIG 10.** Risk of bias assessment.

The cutoff levels chosen for this analysis were based on review of the literature, where we could include the maximal number of studies and represent realistically large sensitization levels. For reasons discussed previously, we do not report to the lower limit of detection or other levels of sensitization, nor have we attempted to derive a PPV for severe reactivity.

## ANALYSIS OF HEALTH AND ECONOMIC BENEFITS OF PEANUT DIAGNOSTIC STRATEGIES

Cost-effectiveness of peanut allergy diagnostic options was evaluated with decision analysis informed by results of the meta-analysis of diagnostic operating characteristics of single Ara h 2 sIgE, whole peanut sIgE, and SPT. The results of this, showing Ara h 2 to be the superior choice in terms of overall cost-savings and accumulation in terms of QALY, are detailed in the Methods, Results, and Discussion section; Tables E1 and E2; and Figs E1 to E4 (all in the Online Repository available at www.jacionline.org).

### Sensitivity analyses

In our protocol, we prespecified sensitivity analyses based on OFC type, geographical region of where the study was conducted, and patient age. We performed additional *post hoc* sensitivity analyses for studies that had high risk of bias where both patient selection and flow/timing were noted to be issues. These results are shown in Tables IV and XI and Figs E5 to E11 (in the Online

Repository at www.jacionline.org). Additional supplemental figures display summary receiver operating characteristic curves, as an alternative to the sensitivity forest plots for the skin test, sIgE, and Ara h 2 cutoffs (Fig E10) and for potential reaction severity (Fig E11).

Finally we performed an additional, more detailed sensitivity analysis of a very limited number of studies to further assess Question 3 and explore size of SPTs and levels of sIgE to peanut or its components as predictors of severe allergic reactions. Of the available data from the diagnostic dataset, we then meta-analyzed across studies any adjusted measures of association for SPTs, sIgE to either whole peanut or Ara h 2. In some cases, we generated these data using each study's reported primary data by logistic regression adjusting for, at minimum, age and sex. For SPTs of ≥8 mm, random effects meta-analysis of Preece et al, van Erp et al, and Lewis et al showed the adjusted odds ratio to be 1.05 (95% CI: 0.95-1.15) for systemic reactions.[59,63,92] Pooling van Erp et al, Ballmer-Weber et al, and Glaumann et al, yielded an adjusted odds ratio of 1.02 (95% CI: 1.00-1.05) for Ara h 2 >2 and systemic reactions.[63,64,70] While this may be statistically significant, a 2%, even a 5% (the upper limit of the 95% CI), increase in odds is not clinically significant. Lastly, we pooled Ballmer-Weber et al, Glaumann et al, Lewis et al, and Wensing et al and found a pooled adjusted odds ratio of 1.78 (95% CI: 0.64-4.96) for peanut IgE > 50 $KU_A$/L and systemic reactions. [64,70,92,94] These data lend support to the current recommendation and highlight sparsity of data on prognostic performance of these commonly employed biomarkers, leading to imprecision and therefore, less certainty regarding which factors to test for and counsel patients around. They also highlight the need for uniform data collection and reporting in food allergy studies involving tests.

## Risk of bias assessment

Risk of bias was assessed using the QUADAS-2 assessment tool.[39] This noted some instances where high risk was noted pertaining to the studies for either risk of bias or applicability. The results of this analysis are detailed in Fig 10. Sensitivity analyses for all 3 searchable questions were completed after removing studies judged to have high risk for bias based on patient selection and flow/timing of the testing and challenge, but this did not alter the pooled sensitivity and specificity estimates to an appreciable or significant degree.

## General limitations of this practice parameter and GRADE recommendations

There are multiple limitations to this analysis. Foremost, we were only able to address 3 prespecified questions, including 1 that was not searchable, in the scope of this analysis. This does not imply that there are other factors or issues within peanut allergy diagnostic testing that are less important. The JTFPP did limit the questions investigated for pragmatic reasons to ensure that we could produce a GRADE-based parameter in the time frame allotted. All parameters going forward give priority to offering focused updates to formerly published documents using GRADE format. Therefore, this practice parameter updates the diagnostic testing parameter from 2008,[15] with a focus on the use of diagnostic testing for peanut allergy. GRADE is not the only system for evidence-based reviews, but is the chosen system for the JTFPP. GRADE has multiple noted limitations, including forced downgrading of certainty and strength of recommendation based on particular study attributes, and a general trend that the overall strength of recommendations are rarely strong.[33-35] Peanut components were not commercially available before the latter part of the 2000s and thus this may have introduced not-at-random factors about the types of patients studied in those compared with earlier studies when components were not available. Fairly low cutoff levels were chosen in the analysis for reasons detailed in the subsections, but this remains a limitation in that the relative precision of the test may perform differently at different levels.

We found a scarcity of available studies in our literature search that met the OFC criteria and explored use of these tests at a general population level. Therefore, most included studies either involved a referral center cohort, or in many cases, a referral center cohort enriched for patients with known sensitization (skin and/or serologic IgE testing) as selection criteria before being offered OFC. In choosing the selection criteria and evaluating studies for final inclusion, it was felt that this was an acceptable approach given that the specialist clinician would generally be dealing with issues surrounding test interpretation in this population and be less concerned with false negative rates from the general population (which the pooled sensitivity and specificity may inaccurately estimate in this analysis). We have accounted for this by downgrading the risk of bias (on account of risk of bias from patient selection) category in the GRADE certainty of evidence table, which factors into the overall certainty of the recommendations. Additionally, the analyses involve pooling of studies for assessment of severity that did not all use the same severity criteria (they were similar enough to pool but the rankings reflected different criteria that have evolved over time) and most had wide CIs, requiring us to downgrade 2 points for inconsistency.

The limitations of lack of studies evaluating a tandem or reflexive approach, or the robustness of studies pertaining to other components beyond Ara h 2 (necessary to allow for meta-analysis) have already been mentioned, as has the lack of a consistent objective grading criteria, the small number of studies evaluating reaction severity, as well as differences noted in the timing/flow and selection processes of each of these studies. This is accounted for in grading the certainty of evidence and risk of bias. As well, the aforementioned sensitivity analyses were done to further confirm whether inclusion of those studies felt to be most at risk would alter the estimates, which they did not. We could not stratify by allergic comorbidity (in particular, presence of atopic dermatitis) or age with accuracy due to limited available data in the reporting, which would allow for such stratifications to be made, though we did perform sensitivity analysis on challenge type, adult versus pediatric studies, as well as by region of the world (Europe, North America) in which the data were observed. Statistically, the pooling of data is limited by high heterogeneity, with some included studies having high risk of bias.

## Knowledge gaps

Within in the scope of these questions, multiple gaps in the current knowledge base were identified that could not be resolved through our literature search and meta-analysis. These include, but are not limited to:

- A lack of identified studies that systematically evaluate when someone should be tested for peanut allergy.

**Box 4.** Key questions in peanut allergy diagnostic testing

**Are there any clinical indications to obtain peanut allergy testing for a patient who is eating peanut without immediate onset or reproducible symptoms?**

In general, no. However, rare exceptions to this include part of the evaluation of patients with eosinophilic esophagitis where dietary elimination is considered as a treatment option, which is a highly specific context with very particular (non-IgE-mediated) symptoms, which is beyond the scope of this practice parameter.

**Which test should be ordered in the evaluation of patients who have never ingested peanut (ie, prior to early introduction for at risk infants)?**

Peanut SPT and sIgE testing is poorly specific and in general should not be used as a screening tool for someone who has never eaten peanut before and developed symptoms. When used as part of the early introduction guidelines for infants younger than 6 months of age who have severe eczema and/or egg allergy, both SPT and peanut sIgE tests can be utilized. There is no current role for component testing in this context. Even in patients with very high peanut-specific IgE levels, without a history denoting that they have eaten peanut and become symptomatic, these are very difficult to interpret, and OFC should be considered to definitively diagnose such patients. A shared decision-making approach can be employed here, given that some parents and clinicians may strongly feel that such test values represent a high likelihood of clinical allergy, despite the absent history.

**Are there cutoff levels for peanut SPT or sIgE testing that diagnoses peanut allergy?**

A universal cutoff level does not exist. These are technically difficult to generate, given that these are based on accurately knowing the population prevalence of peanut allergy. Cutoff levels are only relative probabilities that are imperfect and have an error rate that will potentially misclassify individuals. When prevalence of disease is not known, the likelihood ratio is a more applicable test. This tells the likelihood of a positive test in someone with the disease compared with the likelihood of a positive test in someone without disease and can help convert the pretest probability that someone has the disease to a posttest odds using a Fagan nomogram. Thus, as stand-alone measures, neither SPT nor sIgE test results can be interpreted as diagnostic for peanut allergy.

**Should peanut allergy testing be considered in children with moderate to severe atopic dermatitis?**

Atopic dermatitis is caused by changes in the epidermal skin barrier and is generally not due to food allergy, though children with persistent and refractory moderate to severe atopic dermatitis may be at higher risk of developing food allergy. Peanut allergy testing should not be a standard part of the evaluation for any patient with atopic dermatitis. However, in a very small subset of infants and young children with severe, treatment-refractory atopic dermatitis may benefit from select food testing, including peanut allergy testing if the clinical history suggests peanut has not yet been introduced or if there is suspicion that peanut ingestion is temporally associated with flares.

**Should children with a family history of peanut allergy in another sibling be evaluated for peanut allergy prior to this being introduced?**

Screening of younger siblings for peanut allergy should not be routinely performed, and there is no evidence that such individuals are at higher risk for developing peanut allergy based on the sibling history alone. To facilitate timely introduction and prevent delay, there could be consideration for a role for testing when parents are overly anxious about introducing peanut and will not introduce peanut to their child through any other means. However, such testing must be interpreted properly and a positive result not be considered diagnostic for peanut allergy. In these situations, either SPT or sIgE testing may be utilized. Data exist to show that this practice is not cost-effective until there is a much higher baseline prevalence of peanut allergy in the population, and then it is only cost-effective if sensitized children undergo challenge rather than avoid peanut based on strong sensitization. There is no indication to utilize component testing in this context.

**Are all patients with detectable Ara h 2 clinically allergic to peanuts?**

No. Detectable isolated sensitization to Ara h 2 is not diagnostic for peanut allergy, and a diagnosis can only be made where the individual is sensitized in the context of a known or suspected reaction after eating peanut. There are no well-established cutoff levels for Ara h 2 at this time that indicate the presence of allergy versus sensitization. However, when compared with whole peanut SPT and sIgE tests, Ara h 2 testing has vastly increased specificity, though this is still largely dependent on the context in which any testing is indicated. Patients may have detectable Ara h 2 but exhibit no clinical reactivity on ingestion of peanut.

**Does component testing predict the severity of future reactions?**

No test, including components, has good sensitivity or specificity to indicate the severity of symptoms of a future reaction. Component testing may have a potential role to help identify sensitization patterns that indicate recognition of cross sensitization with pollen allergens as opposed to more primary allergens unique to peanut, though the clinical significance of this is still to be defined.

**When should component testing be ordered as the initial diagnostic test?**

The role of component testing is evolving, and it is unclear how and when these tests should be used. Comparatively, testing for Ara h 2 compared with whole peanut SPT and sIgE testing does have significantly higher specificity, which may translate to a lower likelihood of a false positive diagnosis if testing is run in the right context. Moreover, in this context, use of Ara h 2 as a stand-alone test is highly cost-effective. However, there is a present knowledge gap whether Ara h 2 should be the initial test ordered.

- A lack of identified studies that evaluate the tandem or reflexive use of whole peanut extract SPT and whole peanut sIgE in combination.
- A lack of identified studies that evaluate the tandem or reflexive use of whole peanut extract SPT and whole peanut sIgE in combination with peanut components.
- A lack of identified studies that evaluate the tandem or reflexive use of ≥1 peanut components.
- A lack of identified studies that evaluate Ara h 1, 3, 6, 8, and 9 performance or whether severity or reaction phenotypes are associated with recognition of these components.

- A lack of identified studies that consistently or systematically study reaction severity using unified criteria or cutoff markers or evaluate this question at different cutoff levels.
- A lack of identified studies that study any of the searchable questions at a population level that are less enriched for already sensitized individuals as opposed to within more clustered clinical referral centers.
- A lack of identified studies that trace longitudinal outcomes and natural history of disease to better understand the full scope of the ramifications of diagnostic testing choices to inform best practices.
- A lack of clear understanding and inconsistent use of diagnostic cutoff points for the use of these tests.
- A lack of consistent reporting at an individual level of allergic cofactors that may influence the performance of these diagnostic tests in relation to the food challenge outcome to assess the influence of such covariates.

Box 4 addresses a number of the key take-home messages and knowledge gaps.

## BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

### Potential benefits

The potential benefit of this analysis is the appropriate management of patients with peanut allergy. See the discussion for each question in the guideline document for benefits of tests. Cost-effectiveness analysis was undertaken to further explore such health benefits. Please refer to eSupplement 3 in the Online Repository (available at www.jacionline.org), which comprehensively details the evidence to recommendation process.

### Potential harms

The potential harms include adverse effects associated with incorrect diagnosis of peanut allergy. See the discussion for each question in the guideline document for adverse events of specific interventions. Cost-effectiveness analysis was undertaken to further explore such health detriments. Please refer to eSupplement 3 in the Online Repository, which comprehensively details the evidence to recommendation process.

## QUALIFYING STATEMENTS

This clinical practice guideline was designed to facilitate informed decision making on the diagnosis of children and adults with suspected peanut allergy. It was not intended to define a standard of care and should not be construed as such. It should not be interpreted as a prescription for an exclusive course of management.

## SUMMARY AND CONCLUSIONS

In making a diagnosis of peanut allergy, it is important to clearly understand the indications for running a diagnostic test. Patients with a history of peanut ingestion leading to symptom development benefit most from peanut allergy diagnostic testing.[2] With the exception of patients who are not newborn infants under the age of 4 to 6 months of life who have either egg allergy or severe eczema,[20] there is no clear indication for any form of peanut allergy testing in someone who has not yet eaten peanut and subsequently developed symptoms of an allergic reaction. Testing only determines the presence or absence of peanut sensitization and alone does not allow a definite diagnosis without a history to provide context as to what happens on peanut ingestion.[15] Use of the tests in these contexts helps translate the pretest probability of allergy (eg, based on the history) into posttest probability of a peanut allergy diagnosis.[13] In some cases, an OFC may be necessary to definitively rule in or rule out a diagnosis, but this may be a patient preference–sensitive decision. In terms of choice of tests, when assessing for whole peanut sensitization, there is little practical difference between use of SPT or sIgE—both are highly sensitive but relatively poorly specific, and may be prone to false positive detection of sensitization in certain contexts. Use of testing to the peanut component Ara h 2 has the best profile of high sensitivity, high specificity, and optimal positive/negative likelihood ratio, and is probably the most accurate single test that is available in terms of a test that could be sent with the lowest potential risk of false positive sensitization being detected. However, how this test should be used in the work up of the patient with suspected peanut allergy remains unresolved and not prospectively validated in terms of clinical pathways as to how such properties could be leveraged. We do present evidence herein that shows that using Ara h 2 as a sole diagnostic test in the evaluation of peanut allergy could be cost-effective, given the cost-savings at a societal level (with downstream costs considered) associated with a significant simulated reduction in the number of false positive cases, as a possible application of how the test could be used. At the dichotomous cutoffs evaluated, no whole peanut allergen or component test dictates severity of a future reaction or a reaction phenotype.

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