

Advances in Diagnosing Peanut Allergy

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Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

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List of Design Committee Members: Scott H. Sicherer, MD, and Robert A. Wood, MD

Activity Objectives:

1. Review testing modalities for diagnosing peanut allergy.
2. Discuss sensitivity and specificity of skin prick testing and peanut-specific serum IgE concentrations.
3. Discuss various features of peanut proteins.
4. Review factors that may make component testing informative.

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Peanut allergy is often severe, potentially fatal, usually persistent, and appears to have increased in prevalence. An accurate diagnosis is essential because there is a significant burden on quality of life. The tools available for diagnosis include the medical history, skin prick test (SPT), determination of serum peanut-specific IgE antibodies (PN-IgE), and medically supervised oral food challenges. Numerous studies, almost exclusively in children, have correlated clinical outcomes against SPTs and PN-IgE with informative results. The diagnostic utility of SPT and PN-IgE is maximized by considering the degree of positive result and consideration of the medical history (*a priori*

estimation of risk). Emerging tests that evaluate IgE binding to specific proteins in peanut (component testing) add important additional diagnostic information in specific settings. Studies are increasingly focused on how the results of tests considered in combination (or performed serially) may increase diagnostic accuracy. Here, we review the utility of currently available tests and provide suggestions on how to best use them to accurately predict peanut allergy. Still, the physician-supervised oral food challenge remains the most definitive test available. © 2013 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol: In Practice 2013;1:1-13)

Key words: Peanut allergy; Specific IgE testing; Skin prick test; Diagnosis; Likelihood ratio; Predictive value; Component-resolved diagnosis

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Peanut allergy (PNA) is often severe, potentially fatal, and usually lifelong.^{1,2} In many countries, PNA has become alarmingly common, with greater than 1% of children and about 0.6% of adults affected, with evidence of increasing prevalence.¹⁻⁴ A diagnosis of PNA carries significant burdens on quality of life.^{5,6} Avoidance is difficult, and accidental exposure that results in allergic reactions is frequent.⁷⁻⁹ These factors underscore the importance of providing patients with an accurate diagnosis. Here, we review approaches to diagnosing PNA, provide advice to improve clinical diagnosis with the use of available tools, underscore important pitfalls, and present data on emerging diagnostic tests. A major caveat is that most of the studies involve only children. We discuss PNA, but the diagnostic approaches

Abbreviations used

LR- Likelihood ratio
 NPV- Negative predictive value
 OFC- Oral food challenge
 PNA- Peanut allergy
 PN-IgE- Peanut-specific serum IgE concentration
 PPV- Positive predictive value
 SPT- Skin prick test

are generally applicable to the diagnosis of allergy to any food. However, it must be recognized that the diagnosis of food allergy is far from a perfect science.

THE PROCESS OF DIAGNOSIS

The initiation of a process to diagnose PNA typically results from suspicion of an allergy. The suspicion may arise from a history of a clinical reaction such as anaphylaxis, from a notion of a patient being “high risk” on the basis of other atopic diseases (and lack of ingesting peanut), or because a skin prick test (SPT) or peanut-specific serum IgE concentration (PN-IgE) showed sensitization (a positive test for specific IgE). To apply the best tools available to secure a diagnosis, the clinician should have a thorough understanding of the diagnostic value of each test and when the test should be used.

The “diagnostic toolbox”

A recent Expert Panel Report sponsored by the National Institute of Allergy and Infectious Diseases¹⁰ outlined tests that are “recommended,” including a detailed medical history and physical examination, SPTs, allergen-specific serum IgE, elimination diets, and oral food challenges (OFCs). The Expert Panel recommended *against* the use of intradermal tests, total serum IgE, the Atopy Patch Test (for routine diagnosis or in combination with SPT and serum food-specific IgE), and a number of tests that are considered “nonstandardized and unproven procedures,” including basophil activation, lymphocyte stimulation, provocation-neutralization, applied kinesiology, and allergen-specific IgG₄. The physician-supervised OFC, a double-blind, placebo-controlled approach being the “gold standard,” is the most definitive test available. The specific approach to performing OFCs was reviewed and will not otherwise be detailed here.¹¹ OFCs are time consuming and have the potential to cause uncomfortable or even dangerous allergic reactions, making alternative means of diagnosis more appealing for clinicians and patients. Often, the resulting approach is to determine whether the diagnosis of a PNA is likely enough to warrant avoidance or unlikely enough to warrant an OFC (or, if sufficiently low risk, the patient may be permitted to ingest the food without medical supervision) to confirm tolerance.

Ideally, the clinician might be able to offer the patient an estimated risk of current PNA, and the patient and physician would together decide on a course of action, for example, to continue avoidance or to perform a supervised OFC. In addition to the recognized limitations in allergy testing, the decision-making process can be complex because of numerous factors that may be involved: social, emotional, practical, age, and others.^{11,12} There must be a discussion of the risks (What is the approximate chance that peanut be tolerated? Will the reaction be severe?) and benefits, which may vary by individual preference

(Will the patient eat peanut? What social or nutritional implications are involved?). For example, with a 20% chance of a negative (ie, peanut is tolerated) challenge, the parents of a 4-year-old child might opt against an OFC, waiting for better odds, whereas these may be very acceptable odds for a 17-year-old readying for college, or for a younger child with an isolated PNA when confirmation of tolerance would mean relief from all concerns about food allergy. Therefore, determining the probability of true PNA is the paramount goal in decision making.

Sensitized or clinically allergic?

Having a positive SPT or detectable PN-IgE (ie, evidence of sensitization), does not, in isolation, indicate a diagnosis of PNA.¹⁰ Clearly, there are peanut-sensitized persons (even some with markedly positive SPT or PN-IgE results) who can tolerate peanut. In fact, most persons in the general population who are peanut-sensitized are not allergic. In a population-based US study that performed SPTs (excluding persons with a self-reported PNA), 8.6% were sensitized.¹³ In a US population-based study (in 2005 to 2006; n = 8203) that included PN-IgE (ImmunoCAP; ThermoFisher Scientific, Waltham, Mass), 7.6% were sensitized (≥ 0.35 kU_A/L), with the highest rates, 10.7%, among those aged 6 to 19 years.¹⁴ In a UK birth cohort of 1029 children followed to age 8 years, 933 were tested by SPT or PN-IgE and 11.8% were sensitized.⁴ In a population-based sample of 12-month-old children in Australia, peanut sensitization by SPT was 8.9%.¹⁵ With the use of a liberal estimate of 1% to 2% of the pediatric population having PNA, it is clear that most persons in the general population who are peanut sensitized are not allergic.

The incidence of peanut sensitization and allergy increases dramatically when populations with atopy are evaluated. For example, in a study of 512 infants with a known milk or egg allergy or moderate-to-severe atopic dermatitis and a positive skin test to milk or egg, 69% were sensitized to peanut (an especially high rate given that infants with known peanut sensitization were excluded).¹⁶ Extrapolating from studies of children with strong personal atopic histories such as these, approximately 25% to 30% might be expected to have PNA.¹⁷⁻²¹ Another risk factor is a sibling history of PNA, which carries about a 7% risk of PNA.^{22,23} Given these striking data, it is clear that clinicians will encounter large numbers of sensitized persons who do not have true PNA and that an initial *estimate of risk should be made considering the epidemiologic factors described*.

A primer on test statistics

Test characteristics are generally determined against a “gold standard,” in this case ideally a double-blind, placebo-controlled OFC. Unfortunately, most studies do not universally apply this test for practical or ethical reasons. The studies that are reviewed here all lack what would be needed for ideal determination of test characteristics, specifically, an independent blind comparison with a “gold standard,” test evaluation in an appropriate spectrum of patients to reflect what the clinician would see in practice, use of the “gold standard” test for all patients regardless of test results, and validation in an independent sample.

The sensitivity and specificity of a test provides information about its ability to identify a condition. *Sensitivity* refers to the proportion of patients with an illness who test positive, and for PNA (as with food allergy in general) sensitivity of serologic or

skin tests are modestly high (>80%). *Specificity* refers to the proportion of persons without the disorder who test negative, and for PNA the specificity of the SPT and PN-IgE is lower than the sensitivity, typically 30% to 50%. A highly sensitive test is good at ruling out a diagnosis when the test is negative, and an extremely specific test is good at ruling in a diagnosis when the test is positive. The definition of a positive test will alter the sensitivity/specificity, and it is therefore sometimes helpful to consider the extremes (eg, large versus negative PST or highest versus undetectable PN-IgE) that carry better sensitivity or specificity. Unfortunately, most referral patients will not have these extreme test results, and so most estimations of risk will be in a range that requires an OFC.

The physician is most interested in the probability that a patient has PNA if the test is positive (*positive predictive value*, PPV, the proportion of those with a positive test who have a PNA) or does not have food allergy if the test is negative (*negative predictive value*, NPV, the proportion of those with a negative test who do not have a PNA). Because these indices of predictive value are population dependent, the predictive value drops (illness is overestimated) when results obtained in a referral center (high prevalence) are applied to unselected persons.

An additional means to evaluate a test result is to consider the chance that a person with PNA would have a positive test compared with the chance that one without PNA would have a negative test. This ratio is termed a *likelihood ratio*, LR [sensitivity/(1–specificity)]. If one knows the LR of a skin test and the pretest probability of food allergy, it is possible to calculate a post-test probability by multiplying the LR by the pretest probability odds.^{24,25} For example, if PNA is estimated to be 50% likely (1:1) and the test has a LR of 10, the post-test probability is 1×10 , or 10:1 odds of PNA. To convert that to a percentage, the equation is: post-test odds/(post-test odds + 1) or in this example $[10/11 = 91\%]$. Thus, knowing the test result raised the estimated chance of allergy from 50% to 91%. It should be evident that a test result with a LR of 1 will not be useful.

A nonogram can simplify this calculation to percentages rather than odds.²⁴ Figure 1 uses this nonogram and summarizes 4 examples. Once the post-test odds are known, consideration is given to perform another test (SPT, OFC, etc) to hone in further, or accept the post-test probabilities to make a decision. Although various studies have calculated different LR results for reasons described herein, *the concept of applying pretest probability is vital to improve diagnosis and also underscores the importance of a careful history.*

HISTORY, THE KEY DIAGNOSTIC TEST

Aside from patients who have never ingested peanut, the medical history alone provides important information to estimate a prior probability of PNA, and, in fact, may often be convincing enough to be virtually diagnostic. The history should include a careful assessment of the symptoms, timing in relation to peanut ingestion, consistency of symptoms, amount ingested, and eliciting cofactors such as exercise, alcohol use, or medications, and comorbid conditions.¹⁰ Consider two extreme examples of patients with PN-IgE levels of 20 kU_A/L, a level often considered diagnostic of PNA.^{26,27} The first is a patient who was tested to peanut on a “panel” of tests performed as part of an

evaluation for respiratory allergies. This patient routinely eats peanuts and peanut butter in full serving sizes and has never had a complaint. The correct diagnosis, based on the history, is that this patient does not have a PNA (prior probability is zero). The patient may be particularly sensitized to proteins in peanut that are labile, pollen-related ones, but this is a moot point (in this situation, although it may be crucially relevant in other circumstances) that needs no further evaluation for this patient. Testing to a tolerated food is poor practice because it is not only a waste of money, but it can also cause unnecessary avoidance and anxiety.²⁸

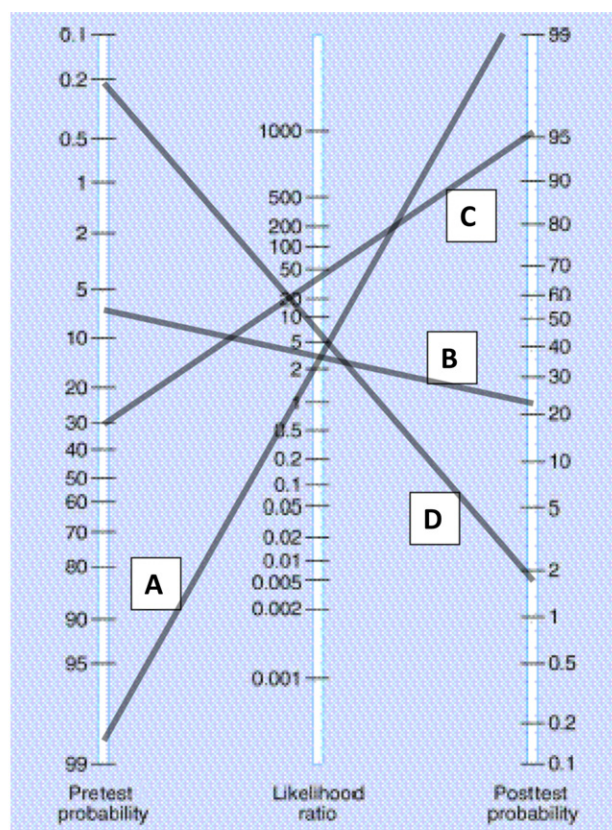
On the other extreme is a patient who has experienced 3 isolated ingestions of peanut and on each occasion experienced immediate symptoms of urticaria, angioedema, and wheezing. The most recent episode was 5 days before testing. One could argue that testing is unnecessary in this case, but a PN-IgE concentration of 20 kU_A/L, or for that matter any evidence of sensitization, would simply be confirmatory given the history, as the prior probability of PNA was 100%.

It is helpful for the clinician to consider the history and epidemiologic aspects of PNA (reviewed in the section entitled “Sensitized or clinically allergic?”) to determine an estimated prior probability. An excellent example of the relation of history and test result comes from Perry et al²⁹ whereby children with (n = 110) or without (n = 59) a history of possible reaction to peanut underwent OFCs (if they had not experienced a recent reaction). Considering those with a PN-IgE >5 kU_A/L, none with a past reaction history tolerated peanut, whereas 77% without a reaction history “passed” the OFC. Thus, the test results had different predictive values, depending on the history.

SKIN PRICK TESTS

SPT results are influenced by variables such as test reagents (the proteins extracted, commercial extracts are prepared from raw peanut, or present in home-made reagents for prick-prick testing), test device, pressure applied, timing when read, location of placement (upper back results in larger responses than volar aspect of the arm), patient factors, and methods of measuring results.^{30–32} Although these variables limit conclusions about outcomes related to specific test results, a number of studies suggest 2 important features of SPTs: (1) increasingly larger wheal sizes are correlated with increasing risk of clinical allergy and (2) reactions sometimes occur in patients with a “negative” skin test.

Table I summarizes SPT diagnostic characteristics from representative international studies (many are from Australia).^{4,26,33–40} When considering the application of these results to your practice, it is important to realize that some studies focused on younger age groups, some were population based, others were referral based, and various extracts and testing procedures were used. One study showed different results by age,³⁴ whereas another did not.²⁶ One study found raw extracts to perform better than commercial,³⁸ whereas another did not.³⁹ Commercial extracts derived from raw peanut may behave differently compared with, for example, a skin test performed with roasted peanut,³² but the diagnostic characteristics of this difference have not been extensively studied. Skin test sizes reflecting 100% specificity, or diagnostic value, varied by the study. This is understandable because different selection, ages, challenge criteria, tests, and so forth were used.^{26,34}



Scenario	History	Pretest probability	Test result	Conclusion
A	Child recently had 2 episodes of anaphylaxis to isolated ingestion of peanut	Almost obvious peanut allergy, 98% by history	PST 4 mm, LR ~2	Posttest probability > 99%, confirms allergy
B	Child has no medical illnesses, but never ate peanut and sibling has peanut allergy	Epidemiologic risk is 7%	PN-IgE 2 kU _A /L, LR~3	Posttest probability 25%, consider another test, such as OFC
C	Child with milk allergy and atopic dermatitis has not eaten peanut	Epidemiologic risk ~30%	PN-IgE 35 kU _A /L, LR ~ 30	Likely allergy (95%)
D	Child with allergic rhinitis ate peanut but stopped 2 months ago after a blood test was performed	Chance of becoming allergic since test was performed, < 1%	PN-IgE 15 kU _A /L, LR~8	Unlikely to be allergic (~2%), could perform OFC.

FIGURE 1. Hypothetical examples of applying pretest probability and likelihood ratios.

SERUM PN-IgE CONCENTRATION

A number of studies have related the outcomes of peanut OFCs (or convincing history) to PN-IgE (representative studies are shown in Table II).^{4,26,27,29,33,37,38,40} Similar to studies using SPTs, there are variations in results on the basis of population characteristics, but increasing IgE concentrations are associated with higher risks of clinical allergy. Here, we are not presenting 95% confidence intervals from all of the studies, but, when this is accounted for, more results overlap because small studies have wide confidence intervals.^{26,33,38} Thus, levels of ≥ 15 kU_A/L are usually, >95%, associated with clinical reactions. When evaluating studies, it is important to consider the specific test performed. Different manufacturers may report similar units of concentration of specific IgE, but the tests are not interchangeable (although they may correlate well).⁴¹⁻⁴³ Importantly,

reaction rates of approximately 20% have been noted among children with “undetectable” (<0.35 kU_A/L) PN-IgE (Table II).

COMPONENT TESTING

Peanut, like any food, is composed of many proteins (Table III). An immune response directed toward one or another protein (component of peanut) may have different implications, depending on characteristics of the protein.⁴⁴⁻⁴⁸ Ara h 1, 2, and 3 are seed storage proteins, are stable to heating, and are considered the major peanut allergens associated with primary sensitization to peanut. Ara H 4 is an isoform of Ara h 3 and Ara h 6 is homologous to Ara h 2. Ara h 5 is a profilin, a plant pan-allergen, and Ara h 8 is a Bet v 1 (birch pollen) homologue, both of which are labile proteins, which are not usually associated with severe

TABLE I. Examples of outcomes of peanut food challenge (or convincing clinical reactions) against SPT results

Age (y)	No. in study or tested	Skin test wheal (mm)	Probability of reaction/reaction rates	Comments	Reference
Mean, 5	41	3	PPV, 0.55 NPV, 0.75	US study, ~age 5 y, retrospective, all AD, not all OFC	Sampson 1997 ³³
8	899	3	PPV, 0.47 NPV, 1.0 LR, 40.3	UK birth cohort, mean wheal diameter, assumed allergic for 6 children with SPT >8 mm; allergy rate 2.1%	Nicolaou 2010 ⁴
		5	PPV, 0.82 NPV, 0.99 LR, 216		
		8	PPV, 0.86 NPV, 0.99 LR, 278		
Median, 3	95	8	~100%	Australia, referred for suspected allergy or retesting, lancet technique, commercial extracts, wheal diameter, open OFC, allergy rate 73%	Sporik 2000 ³⁴
<2		4	~100%		
Mean, 7	135	0	PPV, 0.13 LR, 0.15	UK study, mixed suspected allergy, ages 1-16 y, lancet technique, extract, longest diameter, open or double-blind OFC, allergy rate 50%	Roberts 2005 ²⁶
		3	PPV, 0.5 LR, 1		
		≥8	PPV, 0.94 NPV, 0.25 LR, 17.3		
Median, 5	140	<3	0/76 (0%)	Canada referral practice, commercial extract, wheal diameter, open or single-blind challenge, excluded children with histories and PST >5 mm, allergy rate 13%	Pucar 2001 ³⁵
		3-8	9/46 (20%)		
		9 to >12	9/18 (50%)		
>2	551	0	PPV, NC NPV, 0.9	Australia, allergy center, lancet, mean diameter, commercial extract, open or blinded OFC	Ho 2006 ³⁶
		≥3	PPV, 0.64 NPV, 0.92		
		≥6	PPV, 0.87 NPV, 0.76		
		≥8	PPV, 0.96 NPV, 0.63		
≤2	48	0	PPV, NC NPV, 0.92		
		≥3	PPV, 0.67 NPV, 0.90		
		≥4	PPV, 1.0 NPV, 0.85		
Mean, 4.5	84	≥8	PPV, 0.78 NPV, 0.63	Australia, referral center, children with positive skin test to peanut, commercial extract, mean wheal, open OFC or recent reaction, allergy rate 61%	Wainstein 2007 ³⁷
		≥15	PPV, 1.0 NPV, 0.40		
Median, 4	363	≥3	PPV, 0.74 NPV, 1.0	France, referral center, double-blind OFC, raw peanut, lancet, largest wheal diameter, allergy rate 49%	Rancé 2002 ³⁸
		≥16	PPV, -1.0 NPV, 0.55		
Median, 6	50	≥7	PPV, 0.93	Australia, referral, focused to additional prediction from SPT if sIgE-PN <10 kU _A /L, commercial extract, largest diameter, 3 challenges not done for large SPT, 5 challenges indeterminate, allergy rate 36%	Nolan 2007 ³⁹
Median, 3.3	49	≥7	PPV, 0.83	Australia, referral, younger than age 5 y, sensitized without ingestion, lancet, commercial extract, mean wheal diameter, allergy rate 49%	Johannsen 2011 ⁴⁰

AD, Atopic dermatitis.

TABLE II. Examples of outcomes of peanut food challenge (or convincing clinical reactions) against PN-IgE results

Age (y)	No. in study	Serum-specific IgE (kU _A /L)	Probability of reaction/reaction rates	Comments	Reference
Mean, 5	196	0.35	PPV, 0.78 NPV, 0.85	US study, ~age 5 y, retrospective, all AD, not all OFC, allergy rate 69%	Sampson 1997 ³³
		15	95%		
Median, 4	68	<0.35	~20%	US study, ~age 5 y, prospective, ~50% AD, 2% challenged (remainder by history), allergy rate 81%	Sampson 2001 ²⁷
		15	PPV, 1.0 NPV, 0.36		
Median, 5	173	2 (history of past reaction)	~50%	US study, included 8 adults, OFC if suspected tolerance (no recent reaction, IgE ~25% of 95% predictive values), allergy rate 41%	Perry 2004 ²⁹
		5 (no significant history)	~50%		
Median, 3.3	48	>2	PPV, 0.82 NPV, 0.2	Australia, referral, younger than age 5 y, sensitized without ingestion, allergy rate 49%	Johannsen 2011 ⁴⁰
8	582	0.35	PPV, 0.93 LR, 13.3	UK birth cohort, assumed allergic for reactions with IgE >15 kU _A /L, cohort allergy rate 2.1%	Nicolaou 2010 ⁴
		2	PPV, 0.47 LR, 26		
		5	PPV, 0.70 LR, 69		
		15	PPV, 0.92 LR, 325		
Mean, 7	136	<0.35	28% react LR, 0.32	UK study, mixed suspected allergy, ages 1-16 y, open or double-blind OFC, allergy rate 54%	Roberts 2005 ²⁶
		0.35-0.69	42% react LR, 0.6		
		0.7-3.4	73% react LR, 2.3		
		3.5-17.4	70% react LR, 1.92		
		17.5-49.9	90% react LR, 8.4		
Mean, 4.5	84	0.37	PPV, 0.70 NPV, 0.92	Australia, referral center, children with positive skin test to peanut, open OFC, allergy rate 61%	Wainstein 2007 ³⁷
		10	PPV, 1.0 NPV, 0.58		
Median, 4	363	≥0.35	PPV, 0.71 NPV, 0.95 LR, 2.6	France, referral center, double-blind OFC, allergy rate 49%	Rancé 2002 ³⁸
		≥57	PPV, 1.0 NPV, 0.55 LR, ∞		

AD, Atopic dermatitis.

PNA. Ara h 9 is a lipid transfer protein that is stable and has been associated with more severe symptoms as well as oral ones, among patients in Mediterranean regions, and may be related to primary sensitization to the major peach allergen Pru p 3 or possibly other fruits.^{44,45,49,50}

Evaluation of IgE binding to the various components and relating these patterns (and degree of binding) to outcomes has become an emerging diagnostic approach. Children with clinical PNA were noted to primarily bind Ara h 2 and Ara h 6.⁵¹ Various studies have suggested that IgE binding to Ara h 2 is particularly useful for diagnostics; Table IV shows predictive values of Ara h 2 from several studies.⁵²⁻⁵⁶ All of the studies have peculiarities that should be

recognized (eg, population based versus enriched with children with PNA versus referral populations versus inclusion of controls without sensitization). In general, the higher the concentration of Ara h 2-specific IgE, the more likely there is clinical allergy. The implications on diagnostic accuracy of testing peanut components by different commercially available means [eg, by microarray such as the ImmunoSorbent Allergen biochip assay, which is semi-quantitative versus ImmunoCAP-250 (both Thermofisher Scientific)] has not been fully evaluated, but likely differs because of performance characteristics of different test systems.⁵⁵

The pattern of binding to peanut proteins varies regionally, presumably on the basis of differences in environmental exposures,

TABLE III. Allergenic proteins in peanut

Allergenic protein	Plant family	Clinical implication
Ara h 1	Vicilin [7S globulin]	Correlated with reactivity
Ara h 2	Conglutin [2S albumin]	Best correlation with reactivity/severity
Ara h 3/4	Glycinin [11S globulin]	Correlated with reactivity
Ara h 5	Profilin [Bet v 2-like]	Not correlated with reactivity
Ara h 6	Conglutin [Ara h 2 homologue]	Correlated with reactivity
Ara h 7	Conglutin	
Ara h 8	Bet v 1-like	Not correlated with significant reactivity
Ara h 9	Nonspecific lipid transfer protein	Correlated with reactivity in some studies (see text)
Ara H 10, 11	Oleosin	

and provides insights important to evaluations anywhere. Vereda et al⁴⁴ evaluated component testing in children with peanut allergy from 3 regions, showing that Spanish patients ($n = 50$) were primarily sensitized to lipid transfer protein (Ara h 9), Swedish patients ($n = 35$) to birch-related protein (Ara h 8), and US patients ($n = 30$) to seed storage proteins (Ara h 1 to 3). These results also correlated with severity of outcomes, from the least severe being related to birch sensitization and most severe associated with reactivity to seed storage proteins, although it should be noted that individual patient outcomes deviate from observed correlations. A later onset of allergy in the Spanish and Swedish patients also suggests that route of sensitization was more likely respiratory. In another study of Spanish children, however, Ara h 2 sensitization was most common and best correlated with clinical reactions.⁵⁷ In a study of 31 peanut-sensitized children in Singapore, among whom 19 had significant clinical reactions and only 4 were tolerant, 87% reacted against Ara h 1 and 2 and 55% to Ara h 3.⁵⁸ Ara H 2 was the most important component that contributed to clinical PNA in Taiwanese children as well.⁵⁹

Persons living in birch pollen-rich regions may be expected to become sensitized to birch and subsequently test positive to peanut, perhaps with some degree of reactivity similar to patients with pollen-associated food allergy syndrome (oral allergy syndrome). In persons with pollen-cross-reactive sensitization, it may be helpful to define their pattern of sensitization to peanut proteins for prognosis. In a study of 74 patients in Sweden,⁶⁰ median age 23 years (range, 14 to 61 years) with known peanut sensitization and suspected PNA, component testing was evaluated against clinical history. Twenty-six (35%) showed no binding to Ara h 1 to 3 but had binding to Ara h 8 that was similar to the remainder of the group. Those positive to Ara h 1 to 3 had higher PN-IgE (median, 21 kU_A/L versus 0.73 kU_A/L; $P < .0001$), with most, 60%, having levels >15 kU_A/L compared with none in the group negative to Ara h 1 to 3. All those with positive Ara h 8 were positive to birch. Among 58 with reaction severity data, 56% positive to Ara h 1 to 3 reported severe reactions compared with 18% without binding ($P < .01$).

Using a nested study design from a Swedish birth cohort, 4 groups of 50 children at age 8 years were tested: (1) sensitized to peanut and not birch, (2) sensitized to both, (3) sensitized to birch and not peanut, and (4) sensitized to neither.⁶¹ Having sensitization to peanut without sensitization to birch was a marker for clinical reactivity (74% without versus 43% with), and only 8% who were only birch sensitized reported symptoms from peanut (22% sensitized to birch but with undetectable PN-IgE had detectable Ara h 8). Reactions were reported in 87%

reactive to Ara h 1 to 3 without sensitization to Ara h 8 versus 17% reactive to Ara h 8 and not Ara h 1 to 3 ($P < .001$). Of those with IgE sensitivity to Ara h 2, 83% reported clinical symptoms, which increased to $>95\%$ if there was also binding to Ara h 1 or 3. Particularly severe reactions (respiratory symptoms) were also more common when there was IgE binding to Ara h 2 plus Ara h 1 or 3 compared with binding to Ara h 2 alone (50% versus 9%; $P = .002$).

Presumably, many persons only sensitized to Ara h 8 can consume heated peanut. In evaluation of 144 Swedish children only sensitized to Ara h 8, all but one could tolerate peanut ingestion as reported from natural ingestion or during OFC to roasted peanut. The one who reacted was re-evaluated and had shown an increase in PN-IgE from 1.5 to 8.8 kU_A/L and detectable Ara h 6 (0.45 kU_A/L); the investigators made a similar observation in a patient outside of the study.^{62,63} Testing for anti-Ara h 6 IgE is not currently approved by the Food and Drug Administration and is not generally included in peanut component “packages” in the United States. Other helpful observations from these studies included that 14 children (9.7%) experienced transient oral symptoms that resolved with continued dosing, none of the participants had a PN-IgE >25 kU_A/L, one participant reacted to peanut only during the pollen season, and all were birch-sensitized even though not all reported allergic rhinitis.

Few studies include adults. Adults with late-onset disease (after age 10 years), compared with adults with early childhood onset, have milder symptoms, smaller peanut prick skin test wheals, and lower peanut IgE levels, possibly because late onset disease is related to sensitization to cross-reactive pollen allergens.⁶⁴ Mittag et al⁴⁸ evaluated 20 Swiss and Dutch adults (mean age, 26 years) sensitized to birch pollen and reporting reactions to peanut. During supervised OFCs, all had oral symptoms and 8 had systemic symptoms. Those with systemic symptoms had some binding to Ara h 1 to 3 (not all to Ara h 2). Three of their patients with isolated Ara h 8 sensitization reported systemic reactions in the past, but this was not observed during the OFC.

Obtaining component testing adds additional cost to the evaluation of peanut allergy and should be used judiciously. Table V summarizes clinical situations when component testing is more or less likely to be informative, based on the available data reviewed here.

COMBINING INFORMATION TO SECURE A DIAGNOSIS

Several studies have evaluated the potential for increased diagnostic value when simultaneously considering the results of

TABLE IV. Examples of outcomes of peanut food challenge (or convincing clinical reactions) against serum Ara h 2 results

Age (y)	No. in study	Serum specific Ara h 2 IgE (kU _A /L)	Probability of reaction/reaction rates	Comments	Reference
8	81	0.35	Sensitivity, 1.0 Specificity, 0.96 LR, 25	UK birth cohort focusing on sensitized participants, assumed allergic for reactions with IgE >15 kU _A /L, cohort allergy rate 2.1%, enriched with 12 additional children with peanut allergy	Nicolaou 2011 ⁵²
		0.55	Sensitivity, 0.93 Specificity, 1.0 LR, ∞		
Median, 1.16	158	0.35	Sensitivity, 0.81 Specificity, 0.88 LR, 6.7	Australian study, population-based, random from among peanut sensitized, 33% of sensitized subset were allergic	Dang 2012 ⁵³
		0.88	Sensitivity, 0.62 Specificity, 0.95 LR, 12		
		1.92	Sensitivity, 0.5 Specificity, 0.99 PPV, 0.96 LR, 50		
		3.51	Sensitivity, 0.43 Specificity, 1.0 LR, ∞		
Median, 6	100	0.2	PPV, 0.71 NPV, 0.92 LR, 2.1	Netherlands, suspected peanut allergy, 100 randomly selected from 200, allergy rate 47%	Klemans 2012 ⁵⁴
		0.35	PPV, 0.74 NPV, 0.90 LR, 3.3		
		1	PPV, 0.81 NPV, 0.79 LR, 4.9		
		2	PPV, 0.87 NPV, 0.77 LR, 7.8		
		5	PPV, 0.96 NPV, 0.71 LR, 27.5		
		10	PPV, 1.0 NPV, 0.66 LR, ∞		
Mean, 7	60	0.23	PPV, 0.63 NPV, 0.91 LR, 2.3	US study, referral population, 43% with reaction history, selected for challenge according to relatively low test results (mean PN-IgE 1.2 kU _A /L; range, 0.4-21.2 kU _A /L), allergy rate 43%	Keet 2013 ⁵⁵
		0.35	PPV, 0.70 NPV, 0.89 LR, 3.1		
		2	PPV, 0.75 NPV, 0.62 LR, 4.1		
Mean, 7-10	227	0.1	Sensitivity, 0.96 Specificity, 0.85 LR, 6.4	France, 2 groups culled from 2 centers with various risk factors: peanut allergic (n = 166), sensitized to pollen but tolerant of peanut (61 of whom 79% were peanut sensitized)	Codreanu 2011 ⁵⁶
		0.23	Sensitivity, 0.93 Specificity, 0.97 LR, 31		

TABLE V. Considerations in obtaining peanut component tests

Factors that make component testing LESS likely to be informative	Factors that make component testing MORE likely to be informative
A recent convincing clinical reaction	Mild reactions or no reaction history
A remote significant clinical reaction in a patient with PN-IgE ≥ 15	Remote clinical reaction with development of birch sensitization over time
PN-IgE >25 or <0.35 kU _A /L	PN-IgE 0.35-15 kU _A /L
Lack of birch sensitization	Birch sensitization
Younger children	Older persons

several tests. Wainstein et al³⁷ did not find increased utility of combining SPT, PN-IgE, and a contact test to peanut over using specific diagnostic levels of SPT or PN-IgE. Johannsen et al⁴⁰ (Tables I and II) noted that combining SPT and PN-IgE was helpful such that having both SPT <7 mm and PN-IgE <2 kU_A/L was associated with tolerance in 95% of their cohort, whereas having both above those parameters was associated with tolerance for only 11%, providing better accuracy than using each test alone, with sensitivity of 0.96 and NPV of 0.95. Rancé et al³⁸ (Tables I and II) considered applying the diagnostic values of SPT and PN-IgE in concert to increase accuracy and to reduce the need for OFCs. For their population, if at least the PST was ≥ 16 mm or PN-IgE ≥ 57 kU_A/L, sensitivity was 28% and specificity 100%, and when SPT (using raw peanut) was <3 mm and PN-IgE was <57 kU_A/L, NPV was 100% (overall, 47 of 177 positive OFCs would have been avoided).

A predictive model by DunnGalvin et al⁶⁵ combined sex, age, history (4 categories), SPT, PN-IgE, and total IgE with the use of data from 94 subjects (33% allergic), with validation in another 30 patients (42% allergic). Their “calculator” had better sensitivity (96%) and specificity (90%) than SPT alone, PN-IgE alone, or combining just the 2 tests.

Klemans et al⁵⁴ considered numerous clinical and laboratory parameters in a study of 100 patients with suspected PNA, but the model performed similarly to obtaining an Ara h 2 test and only reduced the need for OFC to approximately 50%. They also attempted to validate the model proposed by DunnGalvin et al⁶⁵ and noted a similar ability to discriminate positive and negative outcomes but a poor ability to replicate the predicted probabilities and observed frequency of allergies.

Nicolaou et al^{4,52} attempted to develop a model with the use of peanut components, sex, atopic dermatitis, sibling PNA, maternal atopic history, asthma, and allergic rhinitis, but the model did not perform better than component testing alone. Misclassification was highest when PN-IgE >15 kU_A/L was used (17.3%), or SPT >8 mm (15.0%), but Ara h 2 at 0.35 kU_A/L was lowest at 2.5%. *However, misclassification by Ara h 2 was much higher in the population assessed by Keet et al,⁵⁵ 21.3% at the same value of 0.35 kU_A/L for Ara h 2.*

Dang et al⁵³ considered the application of 5 approaches to diagnosis in 200 Australian children with a median age of 14 months where the test population was derived from a population-based study (randomly selected from among those peanut sensitized), where 33% of sensitized subset were allergic. They considered using high/low diagnostic values of PN-IgE >15 kU_A/L or <0.35 kU_A/L, PST >8 mm or <3 mm, or Ara h 2 >1.0 or <0.01 kU_A/L. Using PN-IgE alone would have resulted in 95 OFCs, SPT alone 50 OFCs, and Ara h 2 would have resulted in the need for 44 OFCs. However, a stepped approach of testing PN-IgE then Ara h 2 would have reduced the need for OFC to 32, and PST followed by Ara h 2 to only 21

OFCs. *Thus, a stepped approach, similar to considering retesting after determination of a post-test probability, favored skin testing and then component testing for their population.*

SEVERITY AND NATURAL COURSE

Patients are often under the impression that test results reflect the severity of their allergy. However, data on this supposition are mixed. Several studies suggest that the severity of a clinical reaction to peanut does not correlate well with the IgE test results.^{33,38} Hourihane et al⁶⁶ showed a modest association ($r = 0.6$, $P = .001$) of supervised food challenge outcome severity with PN-IgE concentrations (although correlation to community reactions was not apparent). van der Zee et al⁶⁷ found that greater clinical sensitivity to peanut, defined by the eliciting dose during blinded challenges, was associated with increasing age, higher peanut-specific IgE levels, and the absence of atopic dermatitis. Wainstein et al⁶⁸ also found that, although a history of anaphylaxis did not predict anaphylaxis on OFC, larger SPT and higher PN-IgE did. In the largest study to date, among children with persistent PNA in a referral population, initial PN-IgE >24.8 to 99.9 kU_A/L had an odds ratio of 2.0 and >100 kU_A/L had an odds ratio of 3.3 compared with having an initial PN-IgE of <4.8 kU_A/L for severe reactions.⁸ However, none of these data should be used to counsel individual patients as to their risk of severe reactions because these reactions may occur at any SPT or PN-IgE result. Presumably, the severity of a reaction in the community is even more affected by the amount consumed, as well as additional factors such as underlying disease and state of health (asthma).

With component testing, some additional insights to severity have been obtained. Peeters et al⁶⁹ used purified peanut proteins for testing (Ara h 1 to 3, Ara h 6) and found a correlation of clinical severity with recognition of Ara h 2 and 6 at low concentrations, and Ara h 1 and 3 at higher concentrations, indicating apparent increased potency of Ara h 2, also noted by Palmer et al.⁷⁰ Astier et al⁷¹ used recombinant peanut proteins, Ara h 1 to 3, and found binding was dominant to Ara h 2 but severity correlated with polysensitization. Indeed, a positive correlation of increased diversity of binding, whether to the allergens^{69,72} or specific regions on the allergens (epitopes)⁷³ is a common theme that may translate to future diagnostic tests that can predict severity, likelihood of current allergy, and resolution. However, studies have not yet specifically correlated severity against detectable Ara h 2 IgE and it would be wrong to conclude that any binding to Ara h 2 (or Ara h 1 to 3) denotes severe PNA (some children tolerate peanut with positive tests to these stable proteins), or that lack of anti-Ara h 2 IgE eliminates the risk of a severe reaction.

Regarding natural course, it is evident that approximately 20% of young children with peanut allergy will tolerate peanut by

TABLE VI. Clinical pearls for diagnosing peanut allergy

Key observation	Examples (as applicable)	Diagnostic implication
Epidemiologic factors provide an estimate of peanut allergy risk.	General population was tested (1%-2% allergic from 8% to 10% sensitized), sibling history (7%), personal atopy (25%-30%).	Prior probability estimates according to personal and family history of atopy can be used to improve diagnostic utility.
Medical history provides important information to estimate pretest probability.	Subjects never ingested peanut (relies on epidemiologic risks) versus a history of ingestion (details in text).	As above; the diagnostic meaning of a test result may vary depending on the prior probability estimated from the medical history.
Studies evaluating outcomes against diagnostic test results are often limited by small, selected samples with various methodologic limitations and wide confidence intervals for "diagnostic" results.	Results from unselected populations (birth cohort) may differ from selected ones (referral center). With 30 participants, a study calculating a result with 90% sensitivity has a 95% confidence interval of approximately 64%-95%.	Application of study results to predict outcomes for a patient requires caution.
Clinical reaction risk increases with increasing PST size or PN-IgE. PST wheal >8 mm and PN-IgE >15 kU _A /L often reflects clinical allergy.	See Tables I and II .	With some elevation of prior probability, these cutoff points are often BUT NOT ALWAYS diagnostic. More studies are needed.
Negative PST or undetectable PN-IgE usually rule out clinical allergy. <i>However, these results with a convincing clinical history warrant extreme caution.</i>	See Tables I and II .	"Negative" tests are associated with reactions in some patients in most studies. If prior probability is increased, consider additional tests (PST or PN-IgE if not performed, raw or roasted peanut PST, and/or OFC as indicated).
Higher PN-IgE correlates with severity in some studies.	In one study ⁸ PN-IgE >24.8-99.9 kU _A /L had an odds ratio of 2.0 and >100 kU/L had an odds ratio of 3.3 for severe reactions compared with having an initial PN-IgE of <4.8 kU _A /L.	Although higher results are associated with severity, a full spectrum of severity is observed for patients at all PN-IgE concentrations.
Ara h 2 may provide stronger predictive accuracy.	See Table IV .	May add diagnostic accuracy if PN-IgE and additional clinical data are not already highly predictive, but more studies needed to characterize diagnostic utility. See Table V .
Binding to Ara H 8 without binding to Ara h 1-3 is usually associated with no or mild reactions.	A small subset of patients has systemic reactions despite this profile.	Component testing may identify persons with low risk of systemic reactions.
Persons with isolated Ara H 8 sensitization typically have lower PN-IgE and are birch sensitized.	See text.	There may be little utility in testing components when PN-IgE >25 kU _A /L, or when it is known that there is no sensitization to birch pollen. See Table V .
Diagnostic accuracy and reduced need for OFC can be achieved by combination or serial use of tests.	Diagnostic accuracy after indeterminate results from history/SPT or history/PN-IgE may be improved with adding additional tests (SPT, PN-IgE, or component testing).	Pretest and post-test probability calculations may be used to incorporate adding additional tests to increase final diagnostic accuracy.

school age, suggesting the need for periodic retesting.^{74,75} Fleischer et al⁷⁶ evaluated their approach to young patients with the possibility of resolved PNA. Eighty children (median age, 6 years) with peanut-IgE concentrations of 5 kU_A/L or less were evaluated and 55% overall and 63% of those with levels of 2 kU_A/L or less passed OFCs. Prior studies reviewed in Sicherer⁷⁷ additionally suggest that persons with smaller PST results, less certain clinical history, mild reactions, and fewer additional allergies are more likely to experience resolution. Our clinical experience suggests that prognosis may be best predicted by the trend in peanut IgE levels over the first few years after diagnosis, with those children whose PN-IgE levels remain

low having a better prognosis than children whose levels rise sharply.

FUTURE DIAGNOSTIC TESTS

A variety of additional approaches are under study to improve PNA diagnosis. Evaluation of IgE binding to specific segments (epitopes) of individual proteins may provide additional diagnostic insights.⁷⁸ Flinterman et al⁷⁹ evaluated binding to specific epitopes on Ara h 1, 2, and 3 and found that children binding to a larger number of epitopes were more sensitive to peanut. Epitope mapping may therefore provide even more information

about clinical reactivity than component testing alone,⁸⁰ including identifying the most informative ones and creating predictive models that are based on statistical modeling.⁸¹ Evaluation of intensity and affinity of binding may add additional prognostic information.⁸² Evaluation of IgE binding is not the only method being evaluated. Differences in T-cell proliferative responses to whole peanut or components is another avenue under investigation.⁸³ Additional possibilities include components used for SPTs,^{69,71,84} metabolomics,⁸⁵ and basophil activation potentially using peanut components.⁸⁶ Although these future diagnostic tests hold promise for clinical or research purposes, much more investigation is needed.

SUMMARY

It appears from the data that are emerging that we may be close to a time when we can enter a small set of variables into a computer program and have an estimate of the probability of PNA spit back. However, the variability among the studies presented here may indicate that fine-tuning is still required and that the calculations may vary among regions and clinical settings. In addition, studies in adults are sorely needed.

Although the variation in results among studies is disheartening and sometimes confusing, a variety of observations provide a tangible means of improving diagnostic predictions for our patients, as summarized in Table VI. However, tests should be used judiciously, especially because costs may vary. More studies correlating test results to clinical outcomes measured by a "gold standard," the double-blind, placebo-controlled OFC, are needed. This also applies to Ara h 2 and other components. Performing such studies has become increasingly difficult as new knowledge biases future studies (presumed allergy based on testing precluding OFCs), and diagnostic studies are not easily funded. Until better characterization of the diagnostic utility of current tests is undertaken, and until new tests and novel uses of current tests arrive, the current findings can provide excellent diagnostic information. Results suggest, however, that OFCs will likely remain a mainstay of diagnosis for many patients presenting with possible PNA and that the history is still the most important test for all patients who have previously consumed peanut.

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