

Combining skin prick, immediate skin application and specific-IgE testing in the diagnosis of peanut allergy in children

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Previous studies have suggested various diagnostic cut-offs of allergy tests for the diagnosis of clinical peanut allergy in children. There are few data relating to the use of combinations of these tests in children. We aimed to determine the validity of previously reported diagnostic cut-off levels of peanut allergen skin tests and peanut specific-immunoglobulin (Ig) E, as well as the usefulness of combinations of these, for predicting clinical peanut allergy in our Allergy Clinic. Children attending the Allergy Clinic with a positive peanut skin prick test (SPT; $n = 84$) were included in the study. Immediate skin application food tests (I-SAFT) using 1 g of peanut butter (positive if any wheals were detected at 15 min), peanut specific-IgE levels and open-label peanut food challenges were performed. Fifty-two of 85 peanut challenges were positive. Skin prick test specificity was 67% at ≥ 8 mm and 100% at ≥ 15 mm. The I-SAFT was 82% specific. A peanut specific-IgE level of 0.37 kU/l was 98% sensitive but 33% specific. A level of 10 kU/l was 100% specific. Combinations of a SPT of ≥ 8 mm with a positive I-SAFT and a peanut specific-IgE ≥ 0.37 kU/l were 88% specific with a sensitivity of 38%. Using challenge outcomes as the standard, available *in vitro* and *in vivo* diagnostic tests for peanut allergy have poor sensitivity and specificity and combining them does not significantly improve their clinical usefulness. Previously described diagnostic cut-off levels do not have general applicability. Allergy practitioners may need to interpret results of allergy tests in the context of their own practices.

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Food allergy affects between 6% and 8% of children under 3 (1) and only about 20% of children who have peanut allergy can be expected to outgrow their allergy (2). Food allergies are not only important in terms of their potential danger with respect to anaphylaxis with its associated morbidity and mortality (3), but they also have a profound impact on quality of life for many children (4). Children with mild or consistently non-life-threatening reactions to food may be advised to follow inappropriately stringent management plans for the avoidance of the suspected food, which often results in more

distress for the child and their family than is caused by the allergy itself. For these reasons, it is important to be as certain as possible when making the diagnosis of peanut allergy. Many children presenting to a General Practitioner (GP), Paediatrician or Allergist do not have a previous history of a food reaction. During skin testing for other reasons many of these children are found to be skin test positive to foods, e.g. peanut that they have never eaten or have previously tolerated. Often these children are then diagnosed with food allergy if the results of their tests fit diagnostic cut-offs, usually

established elsewhere. However, at least some of these diagnoses may be incorrect if the diagnostic cut-offs are not valid for those locations. While it is important to offer the appropriate management to a child with a food allergy, it is equally important not to inappropriately diagnose and instigate management strategies for food allergy in a child who does not have it.

Double-blind, placebo-controlled food challenges (DBPCFC) are the 'gold standard for the diagnosis of food allergy' (1). But, they are time-consuming and potentially risky procedures to perform (5). More recently, skin prick testing (SPT) and *in vitro* measurement of peanut specific-immunoglobulin (Ig) E (radioallergosorbent assay or CAP) have been used to diagnose clinical peanut allergy. However, these tests only indicate sensitization and not clinical allergy (6, 7). Sporik et al. (7) have reported a SPT wheal diameter ≥ 8 mm to be 100% specific in predicting positive challenges to peanut in children attending an Allergy Clinic in Melbourne Australia.

Atopy patch tests with occlusion times of > 48 h have been investigated in the diagnosis of allergy relating to many foods (8–13). However, these studies have usually focused on children with mixed or delayed hypersensitivity reactions such as atopic dermatitis. The immediate skin application food test (I-SAFT; 14), often modified by applying a food to the skin (often the cheek) prior to a food challenge is sometimes used to identify children supposedly sensitive to very small quantities of allergen. If a wheal develops where the food is applied the challenge is usually terminated and deemed positive. While there is good evidence that ingestion of very small quantities of peanut may lead to systemic allergic reactions in some sensitive individuals (15, 16), we suspected that contact sensitivity may not predict the outcome of a food challenge. If so, abandoning the challenge based on a positive contact reaction may not be best practice.

Studies have investigated food specific-IgE as a method for predicting the outcome of a food challenge (17, 18). A peanut specific-IgE level of 15 kU/l was found to have a $> 95\%$ predictive value for a positive challenge in a study of children with atopic dermatitis by Sampson and Ho (1).

Whether combining these *in vivo* and *in vitro* diagnostic tests improves their predictive value for clinical peanut allergy has not been specifically assessed for immediate hypersensitivity to peanut in children. Roehr et al. (19) evaluated combinations of SPT, patch tests and food specific-IgE in predicting clinical food allergy,

but they evaluated both immediate and delayed reactions, did not evaluate SAFT and did not include peanut. Seidenari et al. (12) included peanut in their analysis of the combination of SPT and patch tests, but again did not evaluate SAFT and included both children and adults in their study.

There is a need for a reliable method for diagnosing immediate hypersensitivity reactions in children without the need for a food challenge. We aimed to determine the validity of peanut SPT, I-SAFT and peanut specific-IgE diagnostic cut-off levels, established elsewhere, in our Allergy Clinic. And we aimed to determine whether combining these tests improves their ability to diagnose clinical peanut allergy in children.

Methods

Study design

A case-control study was conducted at Sydney Children's Hospital, a tertiary referral children's hospital in Sydney, Australia, between June 2003 and December 2004. The Human Research Ethics Committee (HREC) of our area health service approved the study protocol.

Patients and controls

The study sample was recruited consecutively from those children attending the Allergy Clinic who had a positive peanut SPT, defined as a wheal 3×3 mm larger than a saline control, and whose parents agreed to participate after giving written informed consent. Children with a negative peanut SPT were excluded. Peanut SPT were not done specifically for inclusion in the study, but was always as part of the routine clinical investigation of the child. Occasionally, the children tested had a history or suspicion of food allergy (peanut and other foods) but many had been referred due to concerns about other atopic disease and had no history of food allergy. Others had no pre-existing history of atopy and some were believed to be tolerant of peanut but their parents were concerned usually because of another nut allergy. All children with a positive peanut SPT had a peanut I-SAFT and specific-IgE measurement performed. Those without a history of ingestion of peanut in the preceding 3 months underwent an in-hospital peanut challenge. Eighty-four children were recruited, 51 had a positive peanut challenge or recent reaction to peanut and were included in the study group, 33 had a negative challenge and were included in the control group.

Other atopic disease

Children were considered to have asthma if they fulfilled the following criteria (1). A doctor diagnosed history of wheeze on at least one previous occasion and (2) more than one previous occasion of use of an inhaled β -agonist or current regular use of an inhaled β -agonist and/or (3) current or previous regular use of an inhaled corticosteroid and (4) age over 2 yr. To increase the sensitivity of our criteria, they were not required to have had formal lung function testing to be considered asthmatic. Children were considered to have allergic rhinitis if they had clinical signs and symptoms consistent with allergic rhinitis, e.g. frequent nasal itch, congestion, rhinorrhea and pale, swollen inferior turbinates on rhinoscopy as well as a positive SPT for an aeroallergen, e.g. house dust mite.

Skin prick testing

Skin prick testing was performed using a commercial whole peanut extract 1:10 w/v (Hollister-Stier laboratories LLC, Spokane, WA, USA) with a negative control (glycero-saline) and a positive control (Histamine HCL). Usually the test was performed on the ventral surface of the child's forearm. Antihistamine medication was withheld for at least 72 h prior. The resulting wheal was measured with a tape measure after 15 min. The geometric mean of the SPT wheal size was then calculated and this value was used to determine the sensitivity and specificity at various sizes of SPT.

Immediate skin application food testing

The I-SAFT was a modification of an I-SAFT method described previously (14). One gram of peanut butter (Dick Smith's smooth peanut butter) on a 2.5 cm cardboard square was applied directly to the child's skin. One gram of emulsifying ointment BP on a 2.5-cm cardboard square was used as a negative control. The peanut butter patch was removed after 15 min and the result read. I-SAFT was scored as positive if any wheals were detected in the area under the patch. I-SAFT was interpreted by an investigator who was blinded to the placement of the peanut patch and placebo.

Measurement of peanut specific-IgE

Measurement of peanut specific-IgE (Pharmacia UniCAP system FEIA; Marmacki magnestics AG, Uppsala, Sweden) was carried out on all

subjects. The lower limit of measurement of the test was 0.35 kU/l and the upper limit was 100 kU/l. For analysis, values <0.35 kU/l were deemed to be 0.35 kU/l and values >100 kU/l were deemed to be 100.1 kU/l. Total IgE levels were usually not measured. In most cases the peanut specific-IgE level was not known prior to the peanut challenge. As the protocol provided that blood was drawn on the day of the challenge the result was not available prior to commencing the challenge in those cases.

Combinations of tests

We sought to determine if combining the SPT, I-SAFT and peanut specific-IgE level resulted in improved sensitivity and specificity compared with the individual tests, thus making a combination more clinically useful than each test used in isolation. We analysed two different combinations of the test data, the first was a SPT ≥ 8 mm, together with a positive I-SAFT and a positive peanut specific-IgE level (≥ 0.35 kU/l). A SPT ≥ 8 mm was chosen because it was the same as the SPT level we analysed in isolation, which was found not to be predictive of the outcome of a peanut challenge. Thus, we wondered if combining this level with other tests would improve its predictive value. The second was a SPT ≥ 8 mm together with a positive I-SAFT and a specific-IgE level that was ≥ 0.35 kU/l but <10 kU/l. This was carried out because a peanut specific-IgE level of ≥ 10 kU/l was found to be predictive of peanut allergy when used alone. So we sought to determine if combining lower levels of peanut specific-IgE with other tests was comparable.

Peanut challenges

In-hospital open-label peanut challenges were carried out on most children with a positive peanut SPT. Those with a recent (within 3 months) history of ingestion (with or without a reaction) of an amount of peanut that could easily be estimated were not re-challenged. Children with a history of anaphylaxis were also not re-challenged. All children undergoing challenges had been on a peanut-free diet prior to the challenge and were all free of symptoms such as urticaria, wheeze, etc. All challenges were performed as part of routine clinical assessment of the study subject; none was done exclusively for enrolment in this study.

For the peanut challenges, finely chopped peanut (containing 26% protein) was used. The children were given 0.02, 0.2, 2.0, 3.8 and 5.7 g

(11.7 g cumulative; approximately 12 peanuts) at 20- to 30-min intervals under medical supervision and with an intravenous cannula *in situ*. These doses were arbitrarily chosen because they represented stepwise increases in the peanut protein content, i.e. 0.005, 0.05, 0.5, 1 and 1.5 g. The peanut was usually disguised in a food that the child was known to tolerate to make it more palatable to the children. The children were observed in hospital for a period of 2 h after the last ingested dose.

The challenge was scored as positive if any cutaneous (urticaria; angioedema), gastro-intestinal (abdominal pain; nausea; vomiting; diarrhoea), respiratory (hoarse voice, cough, stridor, wheeze) or cardiovascular (hypotension, tachycardia, collapse, shock) reaction(s) occurred within 2 h of ingestion of the last dose. Anaphylaxis was classified as involvement of the cardiovascular and/or respiratory systems and at least one other system. Reactions involving two or more organ systems but not the respiratory or cardiovascular system were classified as multi-organ system reactions (20). Challenges were scored as negative if no objective reaction had occurred within 2 h of the last dose of peanut. Where necessary, treatment with antihistamine, hydrocortisone and/or adrenaline was administered.

Statistical methods

Statistical analysis of the mean values of the negative and positive peanut challenge groups for both SPT wheal size and peanut specific-IgE level was performed with a Mann-Whitney *U*-test for

non-parametric data. Chi-squared tests were used to analyse the association between demographic factors as well as the I-SAFT result and the challenge result. Standard binary logistic regression was used to analyse factors predictive of the outcome of a peanut challenge. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and 95% confidence intervals for the specified tests were calculated. GRAPHPAD PRISM version 4.00 for Windows (GraphPad Software, San Diego, CA, USA; <http://www.graphpad.com>) and SPSS for Windows (version 14) were used. A *p*-value of < 0.05 was considered statistically significant.

Results

Eighty children underwent 81 in-hospital open-label peanut food challenges. One child underwent two peanut challenges during the study period and the results of both were included. A further four children had a clear history of ingestion of a readily estimated amount of peanut within the preceding 3 months. Thus, a total of 85 challenges in 84 children, aged 11 months to 17 yr, were included in the study. The demographics of the study participants are given in Table 1. A previous reaction to peanut and asthma were significantly associated with a reaction on peanut challenge.

Fifty-two of 85 peanut challenges were positive and 33 were negative (prevalence 61.2%; Table 2). There were no reports of a child whose challenge was negative at 2 h developing symptoms of a delayed reaction in the hours or days following the peanut challenge. The minimum

	Patients (positive challenge; n = 52)	Controls (negative challenge; n = 32)	p-Value
Age (yr)			
Mean $\pm$ s.e.m.	4.49 $\pm$ 0.43	4.54 $\pm$ 0.39	0.94†
Sex (n)			
Boys	31	22	0.51‡
History of peanut allergy (N)			
Known previous exposure to peanut	40	24	0.84‡
Previous reaction to peanut§	40	16	0.007‡*
Other atopic disease (n)			
Asthma	21	6	0.028‡*
Eczema	37	23	0.78‡
Other food sensitivity/allergy¶	34	26	0.23‡
Allergic rhinitis	17	15	0.26‡
Any atopy**	48	31	0.97‡

Table 1. Demographics of enrolled subjects (n = 84)

**p* < 0.05.

†*t*-Test.

‡Chi-square test.

§History of an allergic reaction to peanut in children previously exposed to peanut.

¶Documented allergic reaction and/or positive skin prick test (SPT) to foods other than peanut.

**One or more of asthma, eczema or food sensitivity/allergy.

Table 2. Range of outcomes for all peanut challenges

Challenge outcome	n (%)
No reaction (negative challenge)*	33 (38.8)
Cutaneous†	21 (24.7)
GIT‡	6 (7.1)
Multiorgan system§	14 (16.6)
Anaphylaxis¶	11 (12.9)
Total	85 (100)

*No reaction noted within 2 h of challenge.

†Facial or generalized urticaria or angioedema only.

‡Abdominal pain, nausea, vomiting, diarrhoea only.

§Involvement of two or more systems without involvement of the cardiovascular or respiratory system.

¶Involvement of the cardiovascular or respiratory system and at least one other system.

cumulative dose of peanut needed to cause a reaction was 0.02 g (or less) and the maximum was 11.7 g (3 g peanut protein). No children had involvement of their respiratory or cardiovascular systems without involvement of another system. All reactions settled with appropriate treatment.

A SPT ≥ 8 mm was chosen for analysis because it has previously been reported to be 100% specific (7). The sensitivity, specificity, PPV and NPV of SPT, I-SAFT, peanut specific-IgE and combinations are shown in Table 3. No child reacted to the placebo cream used for the I-SAFT. Of the 11 children with a SPT ≥ 8 mm, two refused to ingest more than 2 g of peanut during the challenge and a further two developed mild perioral erythema early in the challenge that resolved spontaneously. Both went on to tolerate the remaining doses of peanut with no reaction and as such these challenges were considered negative by the investigators. One other child vomited while the final dose of peanut was in his mouth, this dose was repeated and no reaction occurred. This challenge too was considered negative. We were concerned that the two children who refused to complete the challenge may have reacted to a larger amount of peanut, and that other investigators may have stopped the

other three challenges at the first sign of a reaction and thus considered those challenges as positive. In order to ensure that this would not have made a significant difference to the analysis we repeated it with these five challenges considered to be positive. This did not significantly change the results as the sensitivity of an 8-mm SPT increased only modestly to 77% (95% CI: 64–87%) and the specificity increased to 79% (95% CI: 59–92%).

We observed that no child with a peanut SPT ≥ 15 mm in size or a peanut specific-IgE level ≥ 10 kU/l had a negative peanut food challenge thus making those levels 100% specific for the respective tests in our Allergy Clinic. The combination of a SPT ≥ 8 mm with both a positive I-SAFT and positive peanut specific-IgE (> 0.37 kU/l) was more specific than a SPT ≥ 8 mm, I-SAFT alone or positive peanut specific-IgE alone to predict a positive challenge but this was observed infrequently and the sensitivity was poor (Table 3).

The mean SPT wheal size for a negative peanut challenge was 7.3 mm (95% CI: 6.3–8.4 mm) which differed significantly from the mean SPT wheal size for a positive peanut challenge of 9.8 mm (95% CI: 9–10.5 mm; Mann–Whitney: $p = 0.0004$; Fig. 1). The mean peanut specific-IgE level for a negative challenge was 1.4 kU/l (95% CI: 0.8–2 kU/l) that also differed significantly from the mean peanut specific-IgE level for a positive challenge of 26.8 kU/l (95% CI: 17.4–36.2 kU/l; Mann–Whitney: $p < 0.0001$; Fig. 2). The I-SAFT was significantly associated with the outcome of the peanut challenge (χ^2 ; $p = 0.003$) but the specificity was not clinically useful (Table 3). When the factors significantly associated with the outcome of the peanut challenge, including the mean SPT wheal size, peanut specific-IgE level, I-SAFT result, a previous reaction to peanut and asthma were analysed using logistic regression, only the specific-IgE level was predictive of the outcome of the challenge ($p = 0.01$; OR: 1.39; CI: 1.08–1.78).

Table 3. Sensitivity, specificity, PPV and NPV for all tests at specified cut-off levels

	Sensitivity (%)	95% CI	Specificity (%)	95% CI	PPV (%)	NPV (%)
SPT ≥ 8 mm	75	62–86	66.7	48–82	78	62.9
SPT ≥ 15 mm	5.8	1–16	100	89–100	100	40.2
I-SAFT	50	36–64	81.8	65–93	81.3	50.9
CAP 0.37 kU/l	98.1	90–100	33.3	18–52	70	91.7
CAP 10 kU/l	54	39–67	100	89–100	100	58
Combination 1	38.5	25–53	88	72–97	83	47.5
Combination 2	19.2	10–32	88	72–97	71.4	40.9

PPV, positive predictive value; NPV, negative predictive value; SPT, skin prick test (mean wheal diameter); I-SAFT, immediate skin application food test; CAP, Pharmacia UniCAP peanut specific-IgE level.

Combination 1 = SPT ≥ 8 mm; positive I-SAFT; CAP: ≥ 0.37 kU/l.

Combination 2 = SPT ≥ 8 mm; positive I-SAFT; CAP: 0.37–10 kU/l.

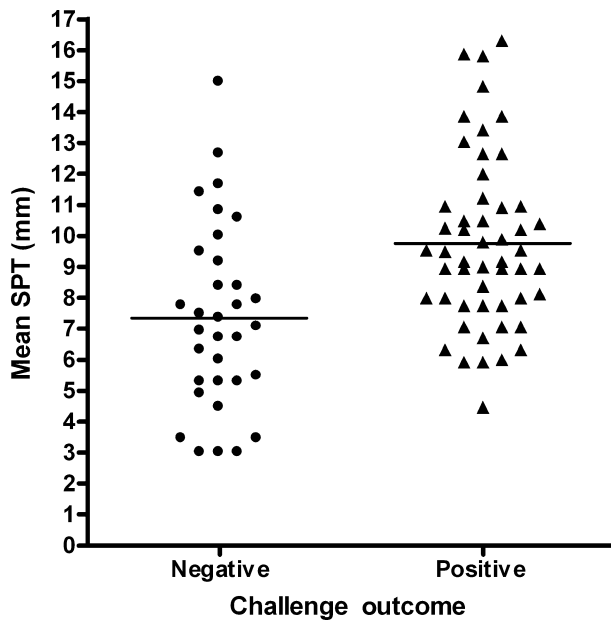


Fig. 1. Comparison between the outcome of the peanut food challenge and the mean peanut skin prick test (SPT) wheal size in millimetres. Horizontal bars show the mean SPT wheal size for both negative and positive peanut challenges (Mann-Whitney test: $p = 0.0004$).

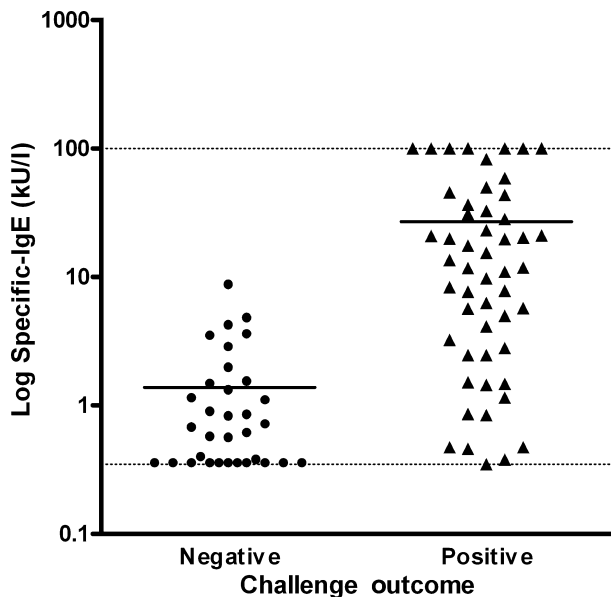


Fig. 2. Comparison between the outcome of the peanut food challenge and the mean peanut specific-IgE level in kU/l. Horizontal bars represent the mean peanut specific-IgE level for both negative and positive peanut challenges (Mann-Whitney test: $p < 0.0001$). Dotted lines represent the limits of detection of the assay.

Discussion

A negative SPT is known to be extremely sensitive for excluding food allergy (1). The

clinical usefulness of a positive SPT (3 mm larger than negative control) is more limited because of the poor specificity associated with a positive SPT result. Recently, Sporik et al. (7) found that a SPT of 8 mm was 100% specific for peanut allergy in a group of children with either a high index or suspicion of food allergy or a previous positive food challenge in the last 12 months presenting to an Allergy Clinic in Melbourne, Australia. They do comment that the SPT cut-off levels may be different according to the clinical context. A recent study by Roberts and Lack (21) in children with a history suggestive of peanut allergy reported a specificity of 98.5% for a SPT of ≥ 8 mm, supporting the findings of Sporik et al. (7). Eleven of 33 of the negative challenges occurred in children with a SPT ≥ 8 mm. We found a much larger mean SPT (≥ 15 mm) had a specificity of 100%. But as there were only three patients with SPTs of ≥ 15 mm these results are difficult to extrapolate to larger populations even if a SPT ≥ 15 mm is truly 100% specific. However, Rance et al. (22) found a SPT of > 16 mm using a raw peanut extract to be 100% specific in their study of 363 children with suspected allergy to foods other than peanut. Kagan et al. (23) evaluated 47 children with a positive peanut SPT but no previous peanut ingestion and found a SPT > 13 mm had a specificity of 100%. Therefore, a larger SPT value of at least 13 mm may be more useful as a predictive level across different allergy clinics with different patient populations. At this level, however, the sensitivity of a positive test will be low.

The sensitivity and specificity of a test are inherent properties of the test, are not dependent on the prevalence of a disease (unlike the PPV and NPV) and therefore should not be expected to vary from location to location. Why then is there such a wide variation in 100% specific levels from one study to another? The reason for this may be that the size of the SPT is affected by factors other than the presence of allergy such as using different skin test devices and techniques or different sources of allergen (24, 25) and many others including the ages of the children being tested (26). In fact three different commercial skin test reagents, and almost certainly different skin prick techniques were used in the studies mentioned above (7, 21, 23, 27) in which various predictive levels for SPT were found. A study by Hefle et al. (28) showed that peanut skin test extracts are difficult to standardize and frequently differ in their protein content, allergenicity and potency. The age distribution of our sample was similar to that of Sporik et al. In our study 13% of children who underwent SPT were

< 2 yr of age compared with 20% in the study by Sporik et al. (7). Nevertheless other extraneous factors may have been present which influence the size of the SPT and alter the sensitivity and specificity independently of the presence of peanut allergy.

As expected we found the mean SPT wheal size was significantly larger and peanut specific-IgE level significantly higher for a positive challenge compared with a negative challenge. Sampson has also shown that children with a higher peanut specific-IgE level will have a higher probability of a reaction to a food challenge (29) and the results of the logistic regression analysis in our study support this. Because SPT and specific-IgE are continuous variables the further to the right one chooses a value to use as a cut-off the higher the specificity will be and eventually one should find a value that has 100% specificity in all settings. However, these values may not be clinically useful as they may be too large to apply to the majority of patients undergoing allergy testing and are of very poor sensitivity.

In our study, a peanut specific-IgE level of 0.37 kU/l had a sensitivity of 98% and specificity of 33%. These results are similar to those of Sampson and Ho (1) who evaluated the usefulness of peanut specific-IgE levels in 196 children with atopic dermatitis. They found a >95% PPV level for peanut specific-IgE of 15 kU/l which is similar to the level of 10 kU/l that we found to be >95% predictive of clinical peanut allergy (Table 3). Our findings suggest that the predictive value of peanut specific-IgE may also be expanded to groups with a lower incidence of atopic dermatitis. Presumably the lower predictive level (10 kU/l) found in our study may be due to the very high total IgE levels in children with atopic dermatitis from Sampson's study; however, as we did not measure total IgE levels a direct comparison is difficult. Alternatively the difference may be due to interlaboratory variables in the assay that affect the sensitivity and specificity of the test similarly to the SPT. However, with improved quality control measures and the use of standardized allergen extracts (30) the variability between laboratories using assays from the same commercial source can be expected to be minimal. There will obviously always be some interlaboratory variability but perhaps the diagnostic cut-offs of the UniCAP specific-IgE level may be more universally applicable than the SPT cut-offs. Further studies will be required to determine this.

The combination of a SPT ≥ 8 mm, positive I-SAFT and positive peanut specific-IgE had

better specificity than any test used alone, except SPT ≥ 15 mm or peanut specific-IgE ≥ 10 kU/l, but did not help to achieve clinically useful sensitivity and specificity. This would suggest that combinations of tests are no more useful than many individual tests, a finding supported by other studies (21). In addition, as the combination of tests includes the SPT, the same factors as influence the size of the SPT when used alone would mean our results are unlikely to be valid in many other clinics.

In making diagnostic decisions clinicians should consider a patient's pre-test probability in assessing the likelihood that that individual patient has a disease (allergy) once the result of a diagnostic test (SPT) is known. Fagan's nomogram is a useful tool which uses the patient's pre-test probability for having allergy and the likelihood ratio (LR) of a given test result for calculating the post-test probability (31). But because the LR is dependent on the sensitivity and specificity of a test (31), which may differ from clinic to clinic as discussed above, it is possible that two patients with the same pre-test probability and the same test result, e.g. an 8 mm SPT would have different post-test probabilities if tested at two different allergy clinics. Thus, until a more universally applicable test is developed allergists will need to have an idea of the specificity and sensitivity of allergy tests used in their individual practices. As such most patients, especially those with no prior history of peanut ingestion, in whom the pre-test probability of peanut allergy is low and who have allergy tests with <95% post-test probability of allergy should undergo peanut food challenges.

In any study of peanut allergy it is vital that subjects are given doses of peanut adequate to induce a reaction in most peanut-sensitive people. This ensures that negative challenges occur only because the subject is truly not allergic to peanut and not because their threshold dose was not reached. The cumulative dose of peanut used in this study was similar to, or larger than, the amount generally used in other studies (7, 21, 23). Therefore, the percentage of subjects at risk of a reaction to more peanut than was used in this study appears extremely small.

Like other open-label studies of food allergy, observer bias may have played a role in this study. In order to minimize this only an objective reaction was denoted as positive and where possible the challenge was repeated if the reaction was unclear or equivocal. However, there were a few cases of a child developing mild transient perioral erythema after the second or third dose of peanut and then going on to

complete the challenge and tolerate the last dose with no reaction. Such challenges were deemed negative by the investigators.

The findings of this study suggest that previously reported 100% specific levels of skin tests for peanut allergy are not strictly reproducible from location to location. Using combinations of SPT, I-SAFT and peanut specific-IgE does not solve this problem. Perhaps measuring peanut specific-IgE is a more universally applicable test but it is evident that allergists need to know how to interpret skin test sizes in their individual practices and should not rely on levels determined elsewhere. Food challenges should be considered the diagnostic standard for patients with a post-test probability for allergy of <95% as calculated by the treating doctor considering the sensitivity and specificity of the allergy tests used in his or her own clinic. This is especially true if the patient only has a positive SPT and does not have a history of a reaction to an identified allergen. Otherwise an incorrect diagnosis of allergy may severely and unnecessarily impact on a patient's lifestyle (4, 32). In our own Allergy Clinic if a SPT cut-off of 8 mm were used alone for diagnosis approximately 1/3 of children tested who do not have peanut allergy would be assumed to have it and would need to implement the lifestyle and social changes associated with having a food allergy. This places an unnecessary and significant burden on the patients and their families, their schools and the health system. Finally, when applying these findings to clinical practice it is important to bear in mind that even tests that are predictive of a positive challenge do not predict the severity of the reaction. This may have important implications with regard to the prescription of emergency medication, e.g. Epi-Pen, and in advice to patients.

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