review

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White paper peanut allergy—part 2: Diagnosis of peanut allergy with special emphasis on molecular component diagnostics

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Summary
Background Peanut allergy is an immunoglobulin E (IgE)-mediated immune response that usually manifests in childhood and can range from mild skin reactions to anaphylaxis. Since quality of life maybe greatly reduced by the diagnosis of peanut allergy, an accurate diagnosis should always be made.
Methods A selective literature search was performed in PubMed and consensus diagnostic algorithms are presented.
Results Important diagnostic elements include a detailed clinical history, detection of peanut-specific sensitization by skin prick testing and/or in vitro measurement of peanut (extract)-specific IgE and/or molecular components, and double-blind, placebo-controlled food challenge as the gold standard. Using these tools, including published cut-off values, diagnostic algorithms were established for the following constellations: 1) Suspicion of primary peanut allergy with a history of immediate systemic reaction, 2) Suspicion of primary peanut allergy with questionable symptoms, 3) Incidental findings on sensitization testing and peanut ingestion so far or 4) Suspicion of pollen-associated peanut allergy with solely oropharyngeal symptoms.
Conclusion The most important diagnostic measures in determining the diagnosis of peanut allergy are clinical history and detection of sensitizations, also via component-based diagnostics. However, in case of unclear results, the gold standard—an oral food challenge—should always be used.

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Abbreviations

BAT	Basophil activation test
DBPCFC	Double-blind, placebo-controlled food challenge
NPV	Negative predictive value
PPV	Positive predictive value
Sens	Sensitivity
sIgE	Specific immunoglobulin E
Spec	Specificity
SPT	Skin prick test

Introduction

Accurate diagnosis of a primary, systemic peanut allergy is of crucial importance for affected individuals and their families. A confirmed diagnosis can protect those affected from future allergic and even severe life-threatening events and support them in their ability to cope with the disease. Likewise, past allergic reactions can be causally assigned and, if necessary, differentiated from secondary, pollen-associated reactions.

In the case of a negative diagnosis, anxiety is reduced and the patient is protected from unnecessary or even harmful dietary restrictions. Even in the case of a positive diagnosis, it has been shown that this can improve the quality of life, e.g., by achieving clarity with regard to the diagnosis or by knowing the reaction threshold of severe allergic reactions, which can lead to stress reduction [1, 2].

The diagnosis of IgE-mediated peanut allergy is based on several key diagnostic elements. Building on a thorough history (including dietary and symptom diary if necessary), a key element is the detection of peanut-specific sensitization. This can be done by skin prick tests or in vitro by determining the specific IgE against peanut extract or against individual proteins of peanut in the serum (component diagnostics). Finally, oral provocation testing is still considered the gold standard of diagnosis and "clinical proof" of peanut allergy [5]. In this context, the double-blind, placebo-controlled food challenge (DBPCFC) remains the reference standard despite numerous in vitro diagnostic advances.

Medical history as well as nutritional and symptom protocol

A central building block in suspected peanut allergy is a careful allergologic history.

The history includes, but is not limited to:

- The patient's own medical history,
- The specific nutritional history, and
- Family history.

Infobox 1 Potential augmentation factors [3, 4]

- Physical activity
- Infections
- Medication intake (e.g., nonsteroidal anti-inflammatory drugs)
- Sleep deprivation
- Alcohol consumption

The reported symptoms should be recorded with their local, temporal and situational occurrence. For this the last 2–3 h before the allergic reaction in relation to food consumption and augmentation factors are crucial. In the case of multiple reactions, the individual reactions should be described in detail and, if possible, independently of each other. Potentially occurring augmentation factors should also be considered, as these may influence the reaction severity and threshold (Infobox 1).

In addition, the past and current history of other diseases of the atopic spectrum should be inquired about, such as atopic dermatitis, allergic rhinoconjunctivitis, allergic bronchial asthma, and other food allergies. Especially children with atopic dermatitis and/or chicken egg allergy seem to be predisposed to peanut allergy [6, 7]. If peanut allergy is suspected in infants and young children, the child's past diet, including any history of peanut consumption, should be inquired about. It should be emphasized that peanut allergy may be present in the infant without previous reactions or peanut intake being known to the parents. If, on the other hand, peanuts have already been eaten regularly and are well tolerated, a primary peanut allergy can be largely excluded.

Based on the exact description of the symptoms, an assessment can already be made as to whether the diagnosis fits more to a primary (directed against the storage proteins of the peanut) or a rare secondary (pollen-associated) peanut allergy. Coexistence is also possible [8]. The clinical picture of IgE-mediated food allergies includes a variety of symptoms that can affect all organ systems, from the skin (e.g., urticaria, flushing, angioedema), gastrointestinal tract (e.g., vomiting, nausea, abdominal pain, diarrhea), respiratory system (e.g., rhinorrhea, sneezing, coughing), to the cardiovascular system (e.g., cardiovascular collapse) [9]. Immediate-type skin reactions, as with most other food allergens, are common in primary systemic peanut allergy, especially in children. In contrast, however, respiratory and gastrointestinal symptoms are more often observed after peanut consumption compared to allergic reactions after the consumption of other food allergens. The severity of the reaction is very variable and can range from purely local or mild systemic allergic reactions (e.g., wheals, itching, vomiting) to anaphylaxis, e.g., with

Table 1 Summary of previous published data of possible cut-off values for peanut(extract)-specific IgE in regards to the diagnosis of primary peanut allergy

Reference	$N = x$ ($n_{tolerant} = x$, $n_{allergic} = x$)	Country	Age	Cut-Off (kU/l)	Sens (%)	Spec (%)	PPV (%)	NPV (%)
Peters et al. 2013 [14]	435 (290, 145)	Australia	Infants, mean: 1.5–1.7 years	≥ 15 ≥ 34	– 14	– 99	82 [12] 95	69
Dang et al. 2012 [36]	200 (100, 100)	Australia	Infants, mean: 1–1.2 years	≥ 0.35 ≥ 14.9	91 26	68 98	– –	– –
Sampson and Ho 1997 [13]	196 (60, 136)	USA	Children, mean: 5.2 years	≥ 0.35 ≥ 10.7	97 76	38 88	78 94	85 62
Nicolaou et al. 2010 [15]	81 (52, 29)	Great Britain	Children, 8 years	≥ 0.35 ≥ 15	95 58	93 100	31 92	100 99
Beyer et al. 2015 [12]	210 (120, 90)	Germany	Children, median: 4.5 years	≥ 0.35 ≥ 10	95 65	26 86	50 77	91 75

NPV negative predictive value, *PPV* positive predictive value, *Sens* sensitivity, *Spec* specificity, *SPT* skin prick test

involvement of the lungs or multiple organ systems at the same time [9].

Rare secondary pollen-associated peanut allergy may be influenced by the geographic pollen-distribution [10]. Pollen-associated food allergies usually manifest at school age and typically trigger mild local, (peri-)oral symptoms (e.g., tingling in the mouth or swelling of the lips) that may occur within minutes of food contact [8, 11]. Since peanuts are usually not eaten in a raw form, as for example hazelnuts are, with the exception of a few new vegan products, a secondary, pollen-associated peanut allergy occurs rather rarely, but cannot be completely excluded. A clear history may indicate a secondary, pollen-associated peanut allergy, but this is not sufficient to make a clear diagnosis [8]. Thus, in case of suspicion, further diagnostic steps should follow to detect specific sensitization (Fig. 4).

Peanut(extract)-specific IgE

The measurement of peanut(extract)-specific IgE in serum is an important component for the detection of peanut sensitization and offers the possibility to include molecular component diagnostics. Several studies have investigated cut-off values of peanut (extract)-specific IgE in relation to the presence of primary, systemic peanut allergy (Table 1). The negative predictive value (NPV) for a cut-off value of < 0.35 kU/l peanut(extract)-specific IgE ranges from 85 to 100% depending on the study and the population considered. If a patient has a peanut(extract)-specific IgE of < 0.35 kU/l, but there is a high likelihood due to the history that he or she sufferes from a primary, systemic peanut allergy, a prick test can also be performed. It is extremely unlikely that any sensitization present will not be detected in both sensitization tests. However, this approach has not yet been verified in any study.

Detection of peanut(extract)-specific IgE antibodies of ≥ 0.35 kU/l does not per se constitute evidence of clinically relevant peanut allergy. The 95% positive predictive value (PPV) ranges from 11 to 34 kU/l peanut(extract)-specific IgE, depending on the study population (Table 1). In Germany, the parameter "peanut(extract)-specific IgE" was also investigated for possible cut-off values [12]. A total of 210 children with suspected peanut allergy were evaluated at seven German centers for the diagnosis of a peanut allergy. All children received serological testing and oral peanut challenges. However, in this study only an 80% probability for a cut-off of 87.9 kU/l peanut(extract)-specific IgE could be defined, as the values for a 90% or 95% PPV were > 100 kU/l and consequently above the usual upper detection limit. Thus, no reliable cut-off value of peanut(extract)-specific IgE for the presence of a clinically relevant systemic peanut allergy could be determined in this study for the German population. In general, there is a large variability between the PPVs of the different studies. In comparison, Sampson and Ho found a 94% PPV at a peanut(extract)-specific IgE of ≥ 10.7 kU/l [13], whereas Beyer et al. achieved a much lower PPV of 77% at a similar peanut(extract)-specific IgE of ≥ 10.0 kU/l [12]. However, the time difference between the two studies must also be considered when results are compared.

Molecular component diagnostics

According to the WHO/IUIS Allergen Nomenclature Sub-Committee [16] peanuts (*Arachis hypogaea*) contain 18 proteins known to date, although the clinical relevance is only partially clear. Specific sensitization to six of the allergens classified as clinically relevant

Infobox 2 Food allergen families

Cupin superfamily: Ara h 1 and 3
Prolamin superfamily: Ara h 2, 6, 7 and 9
Profilin: Ara h 5
PR-10 protein: Ara h 8
Oleosin: Ara h 10, 11, 14 and 15
Defensin: Ara h 12 and 13

Table 2 Summary of previous published data on cut-off values for Ara h 2-specific immunoglobulin E (IgE) in regards to the diagnosis of primary peanut allergy

Reference	$N = x$ ($n_{tolerant} = x$, $n_{allergic} = x$)	Country	Age	Cut-Off (kU/l)	Sens (%)	Spec (%)	PPV (%)	NPV (%)
Beyer et al. 2015 [12]	210 (120, 90)	Germany	Median: 4 years	≥0.35 ≥10 ≥42.2	86 65 95% probability	86 86	80 77	88 75
Klemans et al. 2013 [24]	100 (53, 47)	The Netherlands	Median: 6 years	≥0.35 ≥5	91 55	72 98	74 96	90 71
Kansen et al. 2020 [32]	154 (59, 95)	The Netherlands	Median: 27 years	≥1.75	52	100	100	56
Codreanu et al. 2011 [33]	237 (71, 166)	France	Mean: 8.4 years	≥0.23	93	97	–	–
Eller and Bindslev-Jensen 2013 [34]	205 (30, 175)	Denmark	Mean: 5.6 years	≥1.28	76	97	–	–
Nicolaou et al. 2010 [15]	81 (52, 29)	Great Britain	Children, 8 years	≥0.35	100	96	–	–
Lieberman et al. 2013 [35]	167 (61, 106)	USA and Sweden	Median: 11.7 years	≥0.35	80	92	94	73
Dang et al. 2012 [36]	200 (100, 100)	Australia	Median: 1 year	≥0.35	81	93	–	–
Kim et al. 2016 [37]	48 (26, 22)	South Korea	>1 year	≥4	32	100	100	63

Sens sensitivity, *Spec* specificity, *PPV* positive predictive value, *NPV* negative predictive value, *SPT* skin prick test

(Ara h 1, 2, 3, 6, 8 and 9) can currently be investigated in Germany via commercial testing by molecular component diagnostics. The allergens can be classified into different food allergen families (Infobox 2). Currently, structural data exist for Ara h 1, 2, 3, 5, 6, and 8 [17–23].

Allergens in a food are considered major allergens if they are recognized by 50% of the allergic population via the specific serum- IgE antibodies. The major allergens in peanuts are Ara h 1 and Ara h 3 (members of the cupin superfamily) and Ara h 2 and Ara h 6 (members of the prolamin superfamily) [19, 20, 23]. Minor allergens are recognized in less than 50% of the allergic population. Minor allergens in peanuts include, for example, Ara h 5 from the profilin protein family and Ara h 8 from the Bet v 1 family [20–22].

Ara h 2-specific IgE

For the diagnosis of primary, systemic peanut allergy, mainly Ara h 2-specific IgE has been established as an important diagnostic marker prior to the determination of specific IgE against Ara h 1, Ara h 3 and Ara h 6. Several studies investigated cut-off values for Ara h 2-specific IgE, but these came to different results and—similar to the data for peanut(extract)-specific IgE—suggest age-related, geographical and/or also analytical differences (Table 2).

Studies on cut-off values of ≥0.35 kU/l Ara h 2-specific IgE on the prediction for a positive oral food challenge resulted in PPVs ranging from 77 to 100% for cut-off values between 4 to 10 kU/l Ara h 2-specific IgE [12, 24]. In a German study, univariate logistic regression was used to calculate estimated probabilities for positive oral food challenges in relation to Ara h 2-specific IgE diagnostics [12]. Thus, the 90% probability of a primary, systemic peanut allergy in children of this population was calculated to be 14.4 kU/l Ara h 2-specific IgE and a 95% probability was 42.2 kU/l Ara h 2-specific IgE [12].

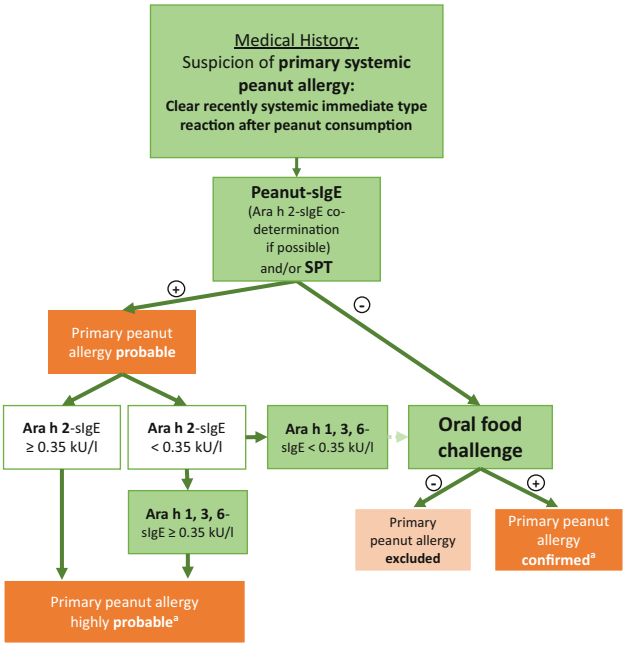

Fig. 1 Diagnostic algorithm for suspected primary systemic peanut allergy with recent immediate-type reaction after peanut consumption. [a]In case of falling specific IgE (peanut or Ara h 2), possibly future oral food challenge (e.g., 1 to 2 years of no accidental reaction and Ara h 2-specific IgE falling), *sIgE* specific immunoglobulin E, *SPT* skin-prick test. Modified after Krogulska and Wood [63]

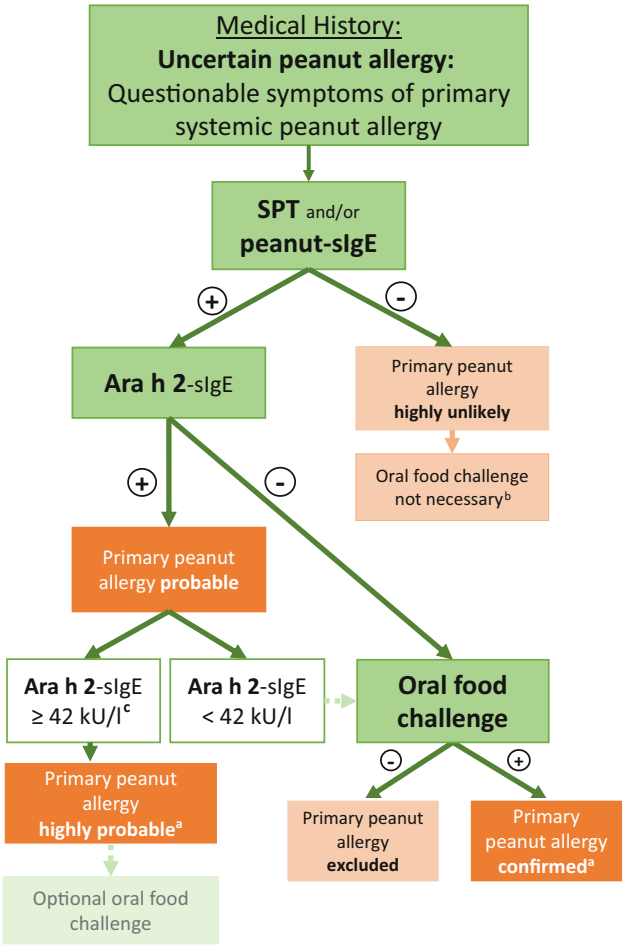

Fig. 2 Diagnostic algorithm for an uncertain peanut allergy—questionable symptoms. [a]If specific IgE (peanut or Ara h 2) is falling, possibly future oral food challenge (e.g., 1 to 2 years of no accidental reaction and Ara h 2-specific IgE falling). [b]Oral food challenge can be performed if desired for accurate diagnosis (e.g., patient/parent anxiety), [c]≥ 42 kU/l corresponds to a 95% probability of primary, systemic peanut allergy. *sIgE* specific immunoglobulin E, *SPT* skin-prick test. Modified after Krogulska and Wood [63]

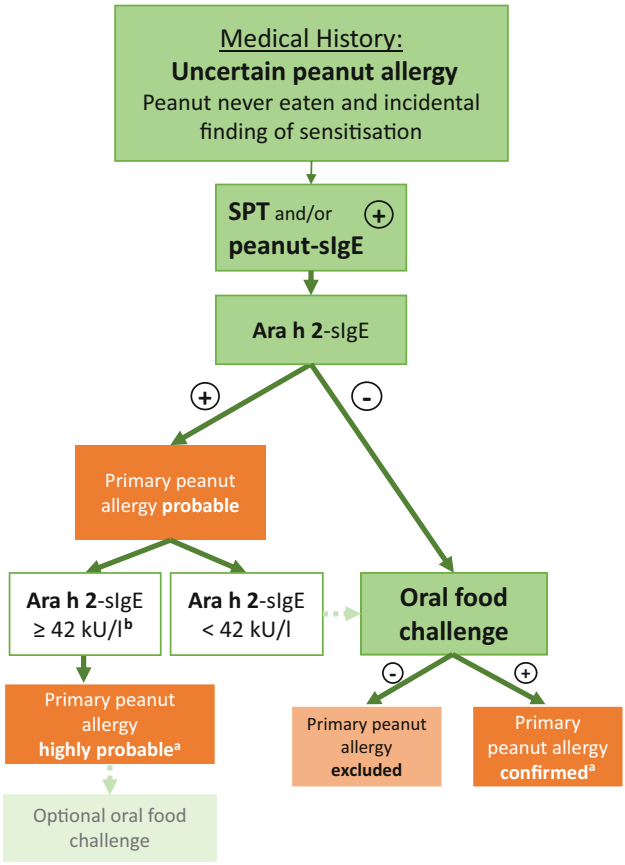

Fig. 3 Diagnostic algorithm for an uncertain peanut allergy—incidental finding of sensitization. [a]If specific IgE (peanut or Ara h 2) is falling, possibly future oral food challenge (e.g., 1 to 2 years of no accidental reaction and Ara h 2-specific IgE falling). [b]≥ 42 kU/l corresponds to a 95% probability of primary, systemic peanut allergy. *sIgE* specific immunoglobulin E, *SPT* skin-prick test. Modified after Krogulska and Wood [63]

An Ara h 2-specific IgE value of < 0.35 kU/l is falsely interpreted in clinical practice as an exclusion of a primary, systemic peanut allergy. However, this cut-off value does not have a sufficient NPV (range in studies: 73–90%, Table 2). This is due to the fact that some patients with a primary, systemic peanut allergy are not sensitized to Ara h 2, but form IgE antibodies against the other storage proteins such as Ara h 1, Ara h 3 or Ara h 6 exclusively [25]. Furthermore, sensitization to Ara h 2 suggests a primary systemic peanut allergy that begins in childhood. It appears that adolescents who become allergic to peanut after the age of 14 years are not sensitized to the storage proteins [25]. If molecular component-based diagnostics are used effectively, the need to perform oral food challenges can be reduced (Figs. 1, 2, 3 and 4). However, it is important that molecular component-based diagnostics are interpreted individually in each case, taking into account patient-intrinsic factors and the available medical history.

Peanut(extract)-specific IgE, Ara h 2-specific IgE, and skin prick test, if applicable, can be used to draw conclusions about the reaction dose, but not clearly about the severity of the reaction under food challenge [26]. For example, the wheal diameter or Ara h 2-specific IgE correlates inversely with the reaction dose under oral food challenge [26]. However, the severity of the allergic reaction under oral food challenge does not correlate with the wheal diameter of the prick test or the Ara h 2-specific IgE [8, 26]. However in contrast to this finding, two other studies from Denmark and Finland could demonstrate that Ara h 2-specific IgE alone, and also the combined measurement of Ara h 2- and Ara h 6-specific IgE can serve as possible predictive biomarkers for a severe allergic reaction [27, 28]. Furthermore, it appears that simultaneous sensitization to multiple peanut allergen components (e.g., to Ara h 1, 2, and 3) correlates with the severity of the allergic response under food challenge [29–31]. However, to date, there is no clear biomarker

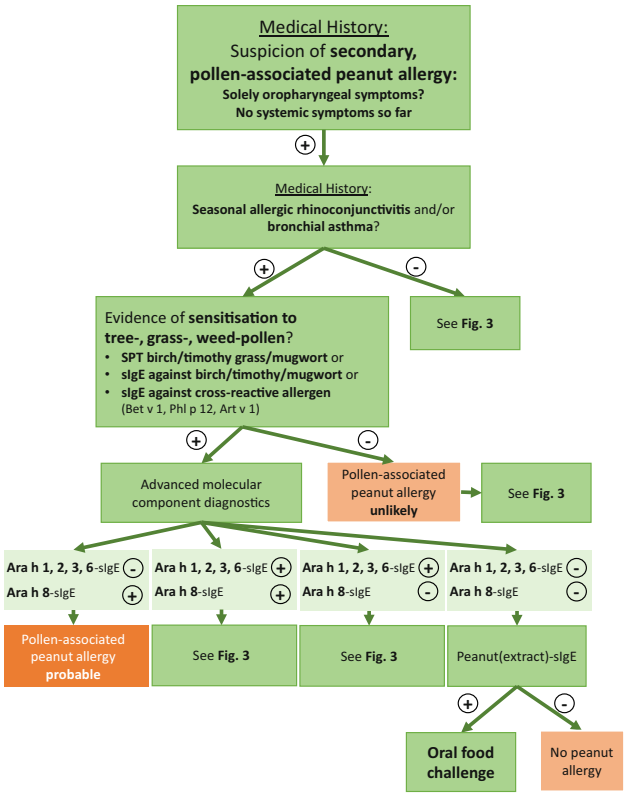

Fig. 4 Diagnostic algorithm for suspected secondary pollen-associated peanut allergy. *sIgE* specific immunoglobulin E. Modified after Krogulska and Wood [63]

that can predict the severity of the reaction under oral food challenge or even the severity accidental reaction in patients with primary, systemic peanut allergy.

Further component-based IgE diagnostics

Other peanut components, including Ara h 1, 3, and 6, may also provide diagnostic assistance [25]. Ara h 6 appears to have similar diagnostic significance to Ara h 2 [38]. Sensitization to Ara h 1, Ara h 2, and Ara h 3 usually occurs in childhood as markers of a primary systemic peanut allergy [25]. In contrast, Ara h 5 and Ara h 8 are cross-reacting proteins. Ara h 8 may be used as a marker protein for secondary pollen-associated peanut allergy (Fig. 4; [21, 22]). Thus, sensitization to Ara h 8, the Bet v 1- homolog, indicates concomitant birch pollen sensitization. In the EuroPrevall study, peanut tolerant subjects were frequently sensitized to Ara h 8 or Ara h 9 and showed no sensitization to the storage proteins Ara h 1, 2, or 3 [25]. In a Swedish study, 144 patients with sensitization to Ara h 8 (≥0.35 kU/l) but no sensitization to Ara h 1, Ara h 2, or Ara h 3 (<0.35 kU/l) were studied. Overall, only one study participant suffered from a systemic reaction, whereas 14 patients showed solely oropharyngeal symptoms at peanut challenge [11]. Ara h 9 is a lipid transfer protein (LTP). Sensitization to this LTP occurs more often in southern Europe and may be indicative of peanut allergy also with systemic, severe symptoms (25).

The presence of sensitization to oleosin components such as Ara h 10, 11, 14, or 15 also seems to indicate a more severe, systemic peanut allergy. Patients with only mild, oropharyngeal symptoms did not exhibit sensitization to oleosin components [39]. However, further studies with larger numbers of cases need to confirm this.

Peanut(extract)- prick testing

In practice, a "rule-out test" or also "search test" in the form of a skin prick test can also be performed at first, for example, in cases of moderate to severe atopic dermatitis or of questionable medical history. This has the advantage that the result is available during the patient´s visit and can be communicated at once. However, there might be absolute contraindications for performing a prick test [40], such as currently uncontrolled bronchial asthma, or a relative contraindication [41], such as severe anaphylaxis (requiring intensive care) in the past history, or the washout phase of medications, such as antihistamines, cannot currently be adhered to. In these cases a serological measurement of sensitization should take place in any case and prick testing should be not performed. Even if there is a clear history of primary, systemic peanut allergy, serological sensitization measurement can be performed in the first place (Fig. 1). In general, skin prick tests as a diagnostic tool for food allergy tend to have a high sensitivity and a high NPV [5, 8]. Thus, negative results usually have a better significance than positive test results, since there is often a low specificity and a low PPV or a meaningful result with a high PPV only occurs with large wheal diameters. Table 3 summarizes studies that have investigated the sensitivity, specificity, PPV and NPV of the prick test in relation to oral food challenges as the gold standard.

With a cut-off value of ≥3 mm wheal diameter for the presence (or absence) of peanut allergy, an NPV between 76 and 100% was obtained in the studies listed (Table 3). Thus, a negative test result (wheal size <3 mm) cannot always completely exclude a possible peanut allergy. In case of a discordance between a clear, recently positive history and a negative skin prick test result, serological sensitization diagnostics should always be performed and, if necessary, food challenge should be considered.

The larger the wheal diameter in the skin prick test, the higher the probability that a clinically relevant peanut allergy is present. Various studies have investigated whether a cut-off value can be defined in the prick test which can predict a positive oral food challenge with a high probability (Table 3).

In the studies summarized here, the PPV for a wheal diameter/cut-off value of, e.g., ≥8 mm ranged from 78 to 100%. The different values of the PPV in the various studies indicate different influencing factors, such as

Table 3 Summary of previous published data on possible cut-off values for peanut(extract) SPT in regards to the diagnosis of primary peanut allergy

Reference	$N = x$ ($n_{tolerant} = x$, $n_{allergic} = x$)	Country	Age	Cut-Off (mm)	Sens (%)	Spec (%)	PPV (%)	NPV (%)
Peters et al. 2013 [14]	435 (290, 145)	Australia	Infants, Mean: 1.5–1.7 years	≥ 8	54	98	95	80
Hill et al. 2004 [42, 43]	18 (3, 15)	Australia	Infants, < 2 years	≥ 3 ≥ 4 ≥ 8	100 93 73	67 100 100	94 100 100	100 75 43
	72 (18, 54)		Children, ≥ 2 years	≥ 3 ≥ 8	94 50	72 100	91 100	81 40
Sampson and Ho 1997 [13]	41 (21, 20)	USA	Children, Mean: 5.2 years	≥ 3	90	29	35	84
Roberts and Lack 2005 [44]	135 (68, 67)	Great Britain	Children, Mean: 7.3 years	≥ 3 ≥ 8	75 25	81 99	79 94	76 57
Nicolaou et al. 2010 [15]	81 (52, 29)	Great Britain	Children, 8 years	≥ 3 ≥ 8	79 32	98 99	47 86	100 99
Rance et al. 2002 [15]	363 (186, 177)	France	Children, median: 4 years	≥ 3 ≥ 16	100 15	66 100	74 100	100 55
Wainstein et al. 2007 [45]	85 (33, 52)	Australia	Children, Mean: 4.5 years	≥ 8 ≥ 15	75 6	67 100	78 100	63 40
Blumchen et al. 2014 [26] (personal communication)	67 (4, 63)	Germany	Children, median: 6.5 years	≥ 3 ≥ 8	100 52	25 75	95 97	100 9

NPV negative predictive value, *PPV* positive predictive value, *Sens* sensitivity, *Spez* specificity, *SPT* skin prick test

the age of the patients and/or the degree of cross-reactive sensitization to tree, grass, and weed pollen in the respective population. It should also be critically considered that different prick test solutions and needles were used in the studies and that methodological differences cannot be excluded. Thus, the significance of a "comparability" of the data is very limited.

For the German population and studied in a larger patient pool, data for clear cut-off values for the skin prick test with a 95% predictive value for a positive reaction after oral food challenge are lacking.

Cross-reactivity between peanut and other legume and tree nut allergens

Although peanut allergy may also involve serologic cross-reactivity with evidence of specific IgE to multiple tree nuts and/or legumes, this does not mean that such cross-sensitization is clinically relevant. In fact, approximately 50% of peanut allergic individuals have positive skin prick tests to other legumes, but less than 5% are clinically symptomatic after consumption of other legumes [46]. Without a good history and oral food challenge testing, it can be difficult to make accurate avoidance recommendations—possibly resulting in unnecessary, general elimination diets [47].

Previously, cross-reactivity was thought to occur only between proteins of the same family, mainly due to structural and sequence identity [46, 48]. In fact, cross reactivity often exists between proteins that have high homology in structure and sequence, but IgE cross reactivity also exists between nonhomologous protein families in food allergies [46, 49, 50]. These may be based on cross-reactive epitopes due to peptide sequences and other physical and chemical properties of an IgE binding site [50, 51]. A cross-reaction between known epitopes of Ara h 2 and a highly cross-reactive IgE epitope in walnut vicillin (Jug r 2) has been identified [50].

Oral food challenge testing

The gold standard of a diagnosis of primary peanut allergy is a standardized, double-blind, placebo-controlled oral food challenge (DBPCFC). Oral titrated peanut food challenges can also be performed openly. However, this option should only be considered if there is a very high probability of a negative result. Especially with increasing age and increased anxiety about the expected reaction, when assessing a late reaction (e.g., assessing worsening atopic dermatitis), or following an unclear open food challenge, double-blind placebo-controlled food challenge should be performed [52].

Although false-positive placebo reactions are rare (about 3%), one study showed that this affected younger children (age ≤ 1.5 years) more often (4%), as opposed to older children (age > 1.5 years; 1.5%) [53]. This again emphasizes the importance of DBPCFC testing also in infancy and toddlerhood.

For the standardized performance and evaluation of an oral food challenge, national [54] and interna-

Table 4 Quantities of a titrated oral food provocation to peanut. Modified after [54]

Stage	Peanut (mortared)	
	Quantity (g)	Protein amount
1	0.012	3 mg
2	0.04	10 mg
3	0.12	30 mg
4	0.4	100 mg
5	1.2	300 mg
6	4	1 g
7	12	3 g
Cumulative dose (on another day)	18 (about 15 pieces)	4.5 g

tional protocols such as the PRACTALL protocol [52] are available. The main goal is to unequivocally diagnose primary peanut allergy based on objective symptoms. The diagnostic algorithms to decide when an oral food challenge is appropriate and when it is not are shown in Figs. 1, 2, 3 and 4. Further indications for peanut challenges are, for example, determining a possible spontaneous tolerance development—even if it only occurs in approx. 20% of peanut allergy patients up to school age [55]. Another indication for a food challenge may be the start of an immunotherapy for peanut allergy to measure the success of the therapy in measuring the possible changes in the reaction dose [56].

Oral food challenge should always be performed under medical supervision and with trained personnel, as allergic reactions may occur. Before oral food challenge, the patient or parents should be informed about the procedure and give written consent. The patient should be free of an infection and should have no allergic symptoms as defined by food challenge stopping criteria, such as allergic rhinoconjunctivitis or urticaria. If comorbidities, such as atopic dermatitis or asthma, are present, this condition should be in a controlled state. In addition, antihistaminic agents should be discontinued at least 72 h prior to oral food challenge. Daily asthma therapy or proactive local steroid therapy for atopic dermatitis should be maintained. A plan of weight-adapted emergency medications should be established before food challenge begins, and intravenous access should be established depending on the indication.

In seven titrated steps, semi-logarithmically increasing doses of peanut are administered, e.g., in the form of peanut flour (Table 4). The time interval between each administration is 20 to 30 min. Placebo and allergen are given in a randomized and blinded order on different days. Neither the patient or parents nor the physicians or nurses know the exact sequence. If the seven titrated concentration levels are tolerated, a single cumulative dose should be given on a later day. The cumulative dose can thus prevent false-negative results, since about 13% of patients react only to a total cummulative amount of the allergen [57]. Clinical monitoring by trained personnel should take place during the entire food challenge as well as 2 hours after the last dose. Only after all food challenges—i.e., those with placebo or peanut allergen and, if applicable, the cumulative dose of the allergen—have taken place, the test is unblinded and the patient or parents are informed about the results [52].

As soon as symptoms occur during the food challenge, a decision is made on the basis of standardized clinical assessment criteria (symptom assessment form, for example, using PRACTALL [52]), a decision is made as to whether the food challenge should be discontinued and evaluated as positive or whether the symptoms are only questionable (subjective) and the test should be continued. In the case of questionable symptoms, for example, it is also possible to wait longer between doses before the next dose is administered. Questionable reactions include subjective symptoms such as tingling in the throat or mild nausea. If there are clear objective symptoms, the oral food challenge should be discontinued and considered positive. These symptoms primarily include immediate-type objective reactions such as generalized urticaria, marked angioedema, large-area flushing, persistent sneezing, constant eye rubbing, persistent cough, wheezing, hoarseness, stridor, dyspnea, vomiting (multiple times), drop in blood pressure or loss of consciousness [52, 58]. However, also late type reactions in atopic dermatitis, such as a 15-point worsening of the SCORAD, can also be considered a criterion for a positive food challenge. Despite the most accurate standardized stopping criteria [52] rarely false-positive (minimized by the placebo day) and false-negative food challenge results may occur [59].

Basophil activation test (BAT)

Another in vitro sensitization test currently under investigation is the basophil activation test (BAT), which measures, by flow cytometric analysis, activated CD63 and CD203c positive basophils after in vitro stimulation of whole blood with peanut extract.

In an English study of 43 peanut-allergic children compared to 61 peanut-tolerant children, an optimal cut-off of 8% CD63-positive cells upon stimulation of 100 ng/ml peanut extract for basophil activation was measured [60]. This cut-off value showed a PPV of 95% and an NPV of 98%. These data were recently verified by a Canadian/Austrian study of 129 peanut allergic children [61]. Again, a PPV of 96% and an NPV of 91% at the calculated optimal modeled cut-off for BAT was determined. Compared to Ara h 2-specific IgE (AUROC of 0.92), the BAT was even considered to be slightly more accurate (AUROC of 0.95) [61]. Although up to now only one study has shown that the BAT seems to correlate with the severity of the reaction under oral challenge [62]. Thus, the BAT could be another important part in the diagnosis of

peanut allergy in the future and possibly replace oral food challenges in defined cases. Compared to oral food challenges, the BAT is less invasive, less expensive and safer. The disadvantage of the BAT is the use of fresh whole blood, which has to be examined within a maximum of 24 h after blood collection. This requires great logistical effort, so that implementation in clinical practice is currently still difficult.

Diagnostic algorithm for suspected peanut allergy

The diagnosis of peanut allergy should always be made in the context of all diagnostic tools and in the individual context [63]. Only with the help of the interaction of all diagnostic tools can it be determined whether the diagnosis of a primary (systemic) or possibly secondary (pollen-associated) peanut allergy or exclusion of peanut allergy can be made. Above all the medical history is decisive for the procedure. All further diagnostic steps are based on this (Figs. 1, 2, 3 and 4, modified after [8, 63]). Thus, a detailed description of previous allergic reactions to peanut should first be available, so that differentiation into suspected primary, systemic immediate- or late-type peanut allergy or secondary, pollen-associated peanut allergy is possible. However, unclear cases also occur in clinical practice, such as patients with questionable symptoms or incidental findings of sensitization to peanut. The diagnostic algorithms presented here (Figs. 1, 2, 3 and 4) are based not only on existing scientific evidence but also on medical experience, especially in those areas that have not yet been fully scientifically proven. Since there is as yet no uniform diagnostic procedure for peanut allergy, the figures have been drawn up on the basis of consensus.

If a primary, systemic peanut allergy is suspected with a clear, recent systemic immediate-type reaction after peanut consumption (Fig. 1), the detection of specific sensitization should be performed by measuring specific peanut(extract)-IgE or an upstream prick test after exclusion of contraindications. An Ara h 2-specific IgE of ≥ 0.35 kU/L indicates a primary, systemic peanut allergy, so oral food challenge is not necessarily required. If Ara h 2-specific IgE is < 0.35 kU/L, Ara h 1, 3, and 6 should be also tested. If these values are negative, an oral food challenge is recommended. In case of sensitization to Ara h 1, 3 and/or Ara h 6 (possibly Ara h9 in patients from the mediterranean area) and concomitant presence of a positive peanut(extract)-specific IgE and/or prick test, a primary peanut allergy is very likely. However, the patient should possibly be challenged in the course of the next years, e.g., in case of a decreasing sensitization, in order not to miss a possible development of tolerance. In case of a clear immediate type reaction after ingestion of peanut-containing foods, but no sensitization evident in the prick test/peanut(extract)-specific IgE and no Ara h 2-specific IgE measurement, an oral food challenge should be performed (Fig. 1).

In case of inconclusive symptoms (Fig. 2) or evidence of sensitization with unclear clinical relevance (Fig. 3), an oral food challenge should be performed. If a positive peanut(extract)-specific IgE, and at the same time a negative Ara h 2-specific IgE, are present, it may be useful to test further components/storage proteins such as Ara h 1, Ara h 3 or Ara h 6 (possibly Ara h 9 for patients from the Mediterranean region), but oral food challenge is usually still necessary. Detection of sensitization witout oral provocation is sufficient for a well-founded diagnosis only in individual cases.

If a rare secondary, pollen-associated peanut allergy with symptoms of an oral allergy syndrome is suspected, sensitization testing to the cross-reactive, inhaled pollen allergens should be performed either by skin prick test or IgE measurement if comorbidity such as allergic rhinoconjunctivitis or bronchial asthma is also present (Fig. 4). If there is no comorbidity, we first assume questionable symptoms, so that both a primary, systemic and a secondary, pollen-associated peanut allergy may be present, and follow the algorithm in Fig. 2.

If solely oropharyngeal symptoms combined with one of the above-mentioned comorbidities and sensitization to pollen are present, a pollen-associated peanut allergy is likely, and an oral food challenge is not absolutely necessary in this case. Extended diagnostics by molecular component diagnostics (e.g., specific IgE against Ara h 8 positive, specific IgE against Ara h 1, 2, 3, 6 negative) can also be used in this case to obtain clarification about the presence of a secondary, pollen-associated peanut allergy (Fig. 4).

Conclusion

With suspected primary systemic peanut allergy, the quality of life of children and adolescents and their families can deteriorate significantly. Therefore, accurate diagnosis is very important before making the diagnosis. The most important diagnostic tools in determining the diagnosis of peanut allergy are clinical history, a sensitization test, and an oral food challenge. By now also other diagnostic procedures such as the basophil activation test (BAT) have been tested, which may improve the diagnosis but do not yet play a role for clinical practice and cannot replace oral food challenge as the gold standard.

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