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Recent advances in the management of nut allergy

Elise Midun[a]*, Suzana Radulovic[b], Helen Brough[b] and Jean-Christoph Caubet[c]

ABSTRACT

Peanut/tree nut allergy is common and has been associated with particularly severe reactions. Epidemiological data have shown that the prevalence ranges between 0.05% and 4.9% for tree nut and between 0.5% and 3% for peanut. These large variations can be explained by differences in the age of included patients and the geographical region. In addition, the food consumption modality (ie, raw versus roasted) plays a major role, as heat treatment has the capacity to modify the allergenicity of nuts and legumes. Nut allergies tend to persist into adulthood and consequently have a high impact on quality of life.

Recently, it has been demonstrated that a significant proportion of nut allergic patients are able to tolerate other nuts. As opposed to the avoidance of all nuts, this approach is currently proposed in several tertiary allergy centers. However, diagnosis of nut allergy is particularly difficult due to co-sensitization leading to high rate of false positive skin prick tests and/or specific IgE to whole allergen extracts. The use of component resolved diagnosis leads to major improvement of diagnosis, particularly to distinguish between primary and secondary nut allergies. The basophil activation test has been suggested to be useful but is still used mainly as a research tool. Thus, diagnosis remains mainly based on the oral food challenge, which is considered as the gold standard.

Regarding treatment, avoidance remains the cornerstone of management of nut allergy. Oral immunotherapy is increasingly proposed as an alternative management strategy.

Keywords: Food allergy, Tree nut, Peanut, Cross reactivity, Oral immunotherapy

INTRODUCTION

Peanut and Tree nut (TN) allergies are one of the most common food allergies worldwide and constitute a major public health problem. The estimated prevalence of peanut/tree nut allergies is approximatively 2%.[1–4] There is a large variation in prevalence reported in different countries, ie, from 0.05% to 4.9% for tree nut and between 0.5% and 3% for peanut.[1,3,5–7] Peanut allergy is the most common nut allergy. The allergy prevalence for each tree nut seems to vary in different parts of the world.[1,7–10] Indeed, hazelnut allergy is the most frequent tree nut allergy in continental Europe; Brazil nut, walnut and almond are most commonly reported in the United Kingdom;[1,11] and walnut and cashew nut allergy are the most common tree nut allergies in the United States.[1,12] These differences are

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	Proportion of co-sensitization	Proportion of self-reported co-allergy	Proportion of co-allergy confirmed by OFC
Sicherer et al.[21]		34%	
Maloney et al.[24]	86%	34%	
Anagnostou et al.[25]	80%		
Cousin et al.[26]	87,1%		43,2%
Ball et al.[27]	23,4% of peanut-allergic patients are sensitized to nuts. 25,4% of patients allergic to nuts are sensitized to peanuts or other nuts.		32% of peanut-allergic patients are sensitized to nuts. 38% patients allergic to nuts are allergic to peanuts or other nuts.
Yang et al.[28]	51% of patients allergic to nuts are sensitized to peanut 73% of patients allergic to peanut are sensitized to nuts		
Clark et al.[29]	At 2 yr of age: 19% of children were multi-sensitized At 5-14 yr: 86% were multi sensitized	2% of children were multi allergic At 14yr: 47% of children were multi-allergic	
Elizur et al.[30]	60,6 %to 96,7%		<30%
Couch et al.[31]			12%
Brough et al.[11]			60,7%

Table 1. *OFC: oral food challenge, yr: year.*

mainly due to the variation of nuts consumed in different countries. However, prevalence variations have also been reported within the same country, highlighting the possible influence of environmental factors such as pollen exposure.[1,4]

An important aspect of nut allergy is the risk of potentially life-threatening allergic reactions. Indeed, nut allergies have been associated with severe allergic reactions more commonly than the majority of other foods. Recent studies reported that peanut/TN allergies account for 70–90% of fatalities from food-induced anaphylaxis, with TN alone accounting for 18–40%.[13] Peanut and TN allergies also tend to persist, and the acquisition of natural tolerance to peanut/TN occurs in only 9%–20% of peanut/TN allergic patients.[4] Despite years of research and clinical efforts, strict avoidance of the incriminated nut (peanut/TN) remains the cornerstone of management. Thus, quality of life (QoL) is reduced with increasing stress and anxiety due to the need for constant vigilance.[14,15]

Although other treatment options, such as oral immunotherapy, have been largely investigated for peanut and TN allergic patients, their use currently remains limited.[16]

Management of patients with peanut/TN allergy is often quite complex. The distinction between cross-sensitization and clinically relevant cross-reactivity between TN and also peanut can be difficult and often requires multiple investigations and oral food challenges (OFC). While avoidance of all nuts has been the rule for a long time in patients allergic to one nut, the possible

introduction of other nuts has recently been investigated in several studies.[17–20]

For the purpose of this review, we will discuss these different aspects constituting advances in the management of nut allergies.

Proportion of patients reacting to multiple nuts

Prevalence of co-sensitization and co-allergy

Co-existent allergy peanut and TN have been described for many years. Initially, in the 90s, Sicherer et al reported that 34% of patients allergic to peanut or 1 TN may present with multiple nut allergy.[21] However, further studies reported a large variation in the proportion of patients reacting to multiple nuts, ranging from 12% to 96.7%.[4,15,21–28] These data have been summarized in Table 1.

The influence of pollen allergy, the population studied as well as its ethnicity are all confounding factors that might influence the results. In addition, these differences can be explained by differences in the methodology of the studies.

Thus, studies that reported on specific IgE found that the co-sensitization rate among TN and peanut ranged between 60.6% and 96.7%.[24–26,28–30]

When a positive clinical history is required to diagnose nut allergy, but without a confirmatory OFC, the proportion of patients with multiple nut allergy is lower than expected, ranging between 23% and 68%[4,21–25] (Table 1).

Studies including OFCs to prove co-existent peanut/TN allergy, considered as the gold standard, report a rate co-existent allergy of 12%–38.8% and confirmed initial data by Sicherer[4,15,26,27] (Table 1). However, a recent prospective multicenter study in Europe (Pronuts study) based on 122 patients that underwent sequential OFC to determine allergy versus tolerance, showed a higher rate of co-existent peanut/TN or sesame seed allergy at 60.7%.[11] These results could be explained by the fact that the Pronuts study was prospective as opposed to retrospective in the previous studies,[27,31] assessed all 9 TNs (compared to other studies testing less TNs),[27,30] and included sesame seed which belongs to the Pedaliaceae (seeds) family. The NutCracker study which was also a prospective study including OFCs, reported a lower prevalence of multiple nut allergy below 30%,[30] however, this study (based on a cohort of 83 children with TN allergy in Israel) included only OFCs to a subset of TN (walnut, pecan, cashew, pistachio, hazelnut, and almond), which could potentially underestimate the rate of co-existent allergy.[30] Couch et al in a recent retrospective study, found similar results; 67 patients with a history of TN allergy underwent an OFC to another TN to which they were sensitized, but not exposed to before. Interestingly, only 14% of the included patients had a positive OFC to another TN. However, this study was retrospective and patients in this study had relatively low levels of specific IgE (90% of these patients had a sIgE <2 kU/L and at least half had a level <0.35 kU/L); thus, these patients were probably selected for OFC based on lower IgE tests to confirm non-allergy by OFC and this would have contributed to an underestimation of co-existent peanut/TN allergy.[31]

Development of peanut/TN allergy

The age of participants may also play a role in the rate of co-existent peanut/TN allergy. Indeed, although most TN allergies become apparent when a patient is young, many studies have shown that the rate of co-existent allergy between peanut and TN increases with age. The HealthNuts study showed that children who had peanut allergy at 1 year old had a 27% chance of having an OFC-confirmed TN allergy at 6 years of age.[15] Brough et al in a retrospective study reported similar results.[32] This increase can be explained particularly by the fact that nuts are introduced later than other foods. Indeed, Clark and Ewan showed that the number of nut consumption increased with age (23% eating more than one nut at 2 years, versus 73% by 10 years); they postulated that this could lead to higher rates of multisensitization (19% at 2 years, 86% at 5–14 years) and multiallergy (2% at 2 years to 47% at 14 years).[29] Conversely, Elizur et al proposed the opposite hypothesis, that elimination of TN in multiple-food-allergic patients could promote the development of sensitization and allergy to TN years later.[33] Peanut/TN co-sensitizations are

	Component	Protein Family	Co Sensitization/Cross Reactivity
Tree nut			
Hazelnut[18,36]	Cor a 1	PR-10	
	Cor a 2	Profilin	
	Cor a 8	LTP	Ara h 9, Jug r 3
	Cor a 9	legumin	
	Cor a 11	Vicilin	
	Cor a 12	Oleosin	
	Cor a 13	Oleosin	
	Cor a 14	2S albumin	
Cashew[18,36]	Ana o 1	Vicilin	Pis v 5
	Ana o 2	Legumin	Pis v 2
	Ana o 3	2S albumin	Pis v 1
Pistachio[18,36,155]	Pis v 1	2S albumin	Ana o 3
	Pis v 2	Legumin	Ana o 2
	Pis v 3	Vicilin	
	Pis v 4		
	Pis v 5	Legumin	Ana o 1
Walnut[36,107]	Jug r 1	2S albumin	Car i 1
	Jug r 2	Vicilin	
	Jug r 3	LTP	Cor a 8, Arah 9
	Jug r 4	Legumin	Car i 4
	Jug r 5	PR-10	
	Jug r 6	Vicilin	
	Jug r 7	Profilin	
Pecan[18,36]	Car i 1	2S albumin	Jug r 1
	Car i 2	Vicilin	
	Car i 4	Legumin	Jug r 4
Almond[122]	Pru du 1	PR-10	
	Pru du 2	PR-5	
	Pru du 3	LTP	
	Pru du 4	Profilin	Ara h 9, Cor a 8, Jug r 3
	Pru du 5		
	Pru du 6	Legumin	

(continued)

	Component	Protein Family	Co Sensitization/Cross Reactivity
Brazil nut[18,36]	Ber e 1	2S albumin	
	Ber e 2	Legumin	
Legumes			
Peanut[40,156,157]	Arah 1	Vicilin	Gly m 5
	Arah 2	2S albumin	Gly m 8
	Arah 3	Legumin	Gly m 6
	Arah 4	Legumin	Gly m 6
	Arah 5	Profilin	Gly m 3, lup a 5
	Arah 6	2S albumin	
	Arah 7	2S albumin	
	Arah 8	PR-10	Gly m 4
	Arah 9	LTP	Glym 1, Cor a 8, Jug r 3
	Arah 10	Oleosin	
	Arah 11	Oleosin	
	Arah 12	Defensin	Gly m 2
	Arah 13	Defensin	Gly m 2
	Arah 14	Oleosin	
	Arah 15	Oleosin	
	Arah 16	LTP	
	Arah 17	LTP	
	Gly m 1	LTP	Ara h 9
	Gly m 2	Defensin	Arah 12, 13
	Gly m 3	Profilin	Arah 5, Lup a 5
	Gly m 4	PR-10	Arah 8
	Gly m 5	Vicilin	Ara h1
	Gly m 6	Legumin	A ra h 3-4
	Gly m 7		
	Gly m 8	2S albumin	Ara h 2
Lupin[40,156,157]	Lup a 1	Vicilin	
	Lup a vicilin	Vicilin	
	Lup a 5	Profilin	
	Lup an 11S	Vicilin	

(continued)

	Component	Protein Family	Co Sensitization/Cross Reactivity
Seed			
Sesame seed[158]	Ses i 1	2 S albumin	No available data
	Ses i 2	2 S albumin	No available data
	Ses i 3	Vicilin	No available data
	Ses i 4	Oleosin	No available data
	Ses i 5	Oleosin	No available data
	Ses i 6	Legumin	No available data
	Ses i 7	Legumin	No available data

Table 2. (Continued) *PR-10: pathogenesis related protein type 10, LTP: lipid transfer protein.*

common and distinguishing asymptomatic sensitization from clinical food allergy is currently based on OFCs, whicht may lead to life-threatening reactions. The clinical relevance of serological cross-reactivity between peanut/TN therefore needs to be better defined.

Peanut/TN allergy has 2 main dimensions. One is the cross-reactivity for the components, and another is severity. Recent advances in the field of component resolved diagnostics (CRD) provides the clinician with more information as to whether the patient has secondary nut allergy due to pollen food syndrome (also known as oral allergy syndrome) or primary nut allergy, more likely to lead to systemic symptoms.

Co-allergy and co-sensitization

Indeed, there are different sensitization profiles in peanut/TN allergy. Patients can be, therefore, sensitized to different families of proteins within the nut. The physico-chemical properties of the proteins to which peanut/TN allergic patients may be sensitized are responsible for allergic reactions of varying severity. The most well-known protein family is the seed storage protein family (eg, Ara h 2, Cor a 9, Cor a 14) responsible for severe anaphylactic reactions, explained in part by their thermostability and digestive resistance. Other families of proteins that are also responsible for severe reactions are the oleosins, defensin and LTP family.

Other sensitization patterns can lead to less severe symptoms in the majority of cases, such as the reprensented sensitization to PR-10 and profilins family. This is due to the fact that these protein families are degraded by heat and digestion.[34]

Components, protein families and cross-reactivity between components are referenced in Table 2.

Structural homology

Allergies to certain well-defined combinations of nuts may be due to the presence of similar or closely related epitopes. Such closely related epitopes are more common in phylogenetically closely related nuts such as cashew and pistachio, walnut and pecan,[13,24,35,36] peanut and soybean.[34,37–40]

Thus, the Pronuts and NutCracker studies found that 97%–100% of pistachio and pecan allergic children were allergic to cashew nut and walnut, respectively.[11,30] Moreover, 64.2%–83.3% of patient allergic to cashew or walnut were respectively co-allergic to pistachio and pecan.[11,30] In a retrospective study, Andorf and al reported similar results.[35] Pistachio and cashew nuts belong to the same Anarcadiaceae family (homology 79% between rPis v 3 and rAna o 1, and homology 66% between Pis v 1 and r Ana o 3).[13,41] High homology between pecan and walnut protein sequences, which belong to the same botanical family (the Juglandaceae family), have also been described. Indeed, 2S albumin allergens in walnut (Jug r 1) and pecan (Car i 1) have 88% sequence identity and legumin allergens in walnut (Jug r 4) and pecan (Car i 4) have 95% sequence identity.[13]

Other studies have reported lower prevalence of co-allergy between cashew nut and pistachio. Indeed, Van der Valk et al and the HealthNut studies found that only 31%–36% of the cashew-allergic patients reacted to pistachio.[15,42] There is an uni-directionality of the co-existent allergies, as a lower proportion of patients allergic to walnut and cashew are allergic to pecan and pistachio, respectively. This suggests that some allergenic proteins are shared while others are unique to cashew and walnut and therefore result in mono-allergy.[30]

For peanut and soybean, studies have demonstrated similarities between both legumes allergens, such as Ara h 1, Ara h 3, and Ara h 8 with Gly m 5, Gly m 6, and Gly m 4, respectively, between 38,4%–70%[34,37–40] (Table 2). Despite this homology, studies show a low rate of cross sensitization and cross reaction. Indeed, in a study from several years ago, 31% of peanut-allergic children had cosensitization with soy, and only 3% had clinical reactivity to soy.[43] In other studies, the cross-reactivity rate has been estimated to be between 6.5% and 15%.[44,45] Another study by Savage et al reported that 98% of patients with a soy allergy also had a peanut allergy.[46] As with nut allergies, these data suggest that some proteins are common to peanut and soybean and some are specific to soybean and peanut.

Protein families

Different families of proteins such as the seed storage protein families (vicillins, 2 S albumins and legumes), the family of lipid transfer proteins (LTP) family, and pathogenesis-related protein type 10 (PR-10) family also help explain the cross-reactivity among peanuts and other legumes (eg, peanut-lupine). In addition, they also help explain, in part, why unrelated nuts such as TN and peanuts may exhibit serological and clinical cross-reactivity.[3,26,27]

Seed storage protein family

Peanut and lupine have a high degree of cross-reactivity; therefore, risk associated with cross reaction is also high as compared to other legumes. Studies show that 14.5%–89% of peanut allergic patients were sensitized to lupine however this cross sensitivity is clinically significant in only 4%–35% of cases.[47–52](Table 2). Cross-reactivity has been reported to be mediated by Lup a 1 (vicilin-like protein)[40,48] (Table 2). In 2017, the lupine profilin Lup a 5 was registered, which is highly cross-reactive to other profilins (eg, Ara h 5) and which is recognized by the sera of both lupine and peanut-allergic patients (www.allergome.org).

Lipid Transfer Protein family

Due to structural homology, lipd transfer proteings (LTPs) from different allergen sources are generally IgE cross-reactive; however, sensitization profiles are extremely heterogeneous, and individual cross-reactivity patterns may range from a single LTP to many different LTPs (from food or pollens).[53,54]

Some studies report a significant number of peanut/TN allergies associated with LTP sensitization, which may be responsible for severe systemic reaction.[55,56] The peach LTP Pru p 3 has been shown to be the primary sensitizing allergen for cross-reactivity with other LTP, including peanut (Ara h 9), hazelnut (Cor a 8), walnut (Jug r 3), and almond (Pru du 3)[57] (Table 2). It has been shown that sensitization to LTP leads to a large variety of clinical manifestations; although oral allergy syndrome (OAS) is probably the most frequent clinical expression, LTPs can be also responsible for severe systemic reactions.[54,55] Thus, it is the most frequent cause of primary food allergy in the Mediterranean area.[58,59]

LTP sensitization can occur via the gastrointestinal tract, but the predominant presence of the LTP syndrome only in the Mediterranean region suggests that environmental factors play a major role. Indeed, Vereda et al showed that in peanut allergic patients, LTP sensitization rate varied by country: in Spain, 60% of patients are sensitized to peanut LTP (Ara h 9) while these proportions were 7.7% and 14.3% in the United States and in Sweden, respectively.[56] The reasons for these geographical distributions are still poorly defined. Studies hypothesize that these distributions are in part due to variations in environmental homologous pollen allergens exposures in LTP-endemic areas such as Art v 3 from mugwort, or Pla a 3 from plane tree.[53,55] In agreement with Pastorello,[60] Scala et al reported that, in LTP allergic patients, co-sensitization with PR-10 proteins, is associated with milder symptoms.. In addition, the higher the levels of

birch pollen in a certain area, the lower the prevalence of LTP hypersensitivity.[61]

PR-10 family

TN and peanut allergy may display serological as well as clinical cross-reactivity with pollens.[62] The majority of these patients suffer from OAS. Patients initially allergic to birch pollens through sensitization to a PR-10 protein, may develop a secondary allergy (pollen-food syndrome) to peanuts or TN (OAS);[62,63] they develop mainly mild symptoms limited to the oropharynx, with pruritus, tingling, erythema, and mild edema of the mouth upon ingestion of peanut or TNs(67). Pollen food syndrome (PFS) is triggered by a cross-reaction between allergens in pollen and allergens in peanuts/TN.[62,63] Homologous proteins have been identified between hazelnut, walnut, peanut, and soybean and have been shown to cross-react with Bet v 1.[65–67]

The prevalence of PFS ranges from 4.7% to greater than 20% in children sensitized to pollens.[63,64] The PR-10 family also plays a significant role in PFS. Bet v 1 from birch pollen is well known of these proteins[64] and is one of the major panallergens in PFS.[63] Uotila et al in a retrospective study found that among subjects with birch sensitization, 84% were cosensitized to hazelnut, 71% to almond, and 60% to peanut; amongst these nut-sensitized patients, 40% of patients sensitized to hazelnut, 34% of those sensitized to almond, and 36% of those sensitized to peanut reported typical symptoms of PFS.[62] A retrospective review from Northern France, where there is a high level of birch pollen exposure, reported a 43.2% co-existent TN allergy rate amongst patients with peanut allergy (43,2%), with hazelnut being the most common TN allergy observed.[26]

Symptoms associated with PR-10 sensitivity are mainly mild.[66,68–70] However, the thermostability of the proteins in this family are variable. Heat processing such as roasting significantly reduces the rosacea fruit protein allergenicity in patients with birch-pollen allergy, but some sensitized individuals can still experience positive reactivity toward roasted peanut, soy, and TNs.[69]

Diagnostics for peanut and tree nut allergy

Peanut and TN allergy is typically diagnosed based on a combination of a convincing history of a IgE mediated allergic reaction, SPT, serum-specific IgE and, if necessary, an OFC.[71–74] For example, peanut allergy is diagnosed based on the clinical history of reaction, the presence of risk factors (severe atopic dermatitis) and if needed additional tests such as SPT, sIgE, and component resolved diagnosis (CRD). Although the cut-off points for determining allergy vary in different regions/clinical settings, these tests have led to a major improvement of the diagnosis of peanut allergy. If history and allergy tests are discordant, the gold standard for diagnosis of food allergies is the double-blind, placebo-controlled, food challenge (DBPCFC).[34]

One of the major issues in clinical practice is the difficulty in distinguishing asymptomatic sensitization (false positives) from primary allergy and from secondary allergy (PFS); this is particularly complex for nut allergies due to the high prevalence of pollen co-sensitization.[18]

Double-blind, placebo-controlled, food challenge

Although the DBPCFC is the gold standard for diagnosis of food allergies, this is costly, resource and time-consuming, and carries the risk of potentially life-threatening reactions. Some patients or their parents refuse to perform an OFC due to the fear of triggering a severe reaction. In the Pronuts study, Brough et al reported that 8.2% of children did not perform an OFC due to fear of reaction or history of previous severe reaction on exposure to the incriminated nut.[11] In this clinical setting, not performing an OFC can potentially lead to unnecessary and prolonged peanut/TN avoidance, which may have the unintended risk of increasing peanut/TN allergy risk.[75] However, it is necessary to find new, less invasive diagnostic tools for the diagnosis of peanuts/TN allergies. Studies have shown that combination of SPT, sIgE, and basophil activation test (BAT) improved the ability to identify allergic and tolerant patients. In the case of peanut allergic patients, this approach could potentially lead to a reduction of OFC of 76.6%–97%.[30,76]

SPT and specific IgE to whole extract allergen

As for other allergies, it is of major importance to interpret peanut/TN SPT and sIgE in the context of the clinical history. The diagnostic value of SPT and specific IgE to whole allergen extracts has been found to vary significantly among studies. Indeed, those different results might be explained by differences in the population studied, prevalence of pollen allergy, and the methodology used in the study.[30,62,77,78] These data have been summarized in Table 3. As an example, while a SPT <3 mm has a good negative predictive value;[79-82]SPT<3 mm still requires further investigations in the context of a convincing clinical history of nut allergy. In contrast, a SPT ≥3 mm to a specific nut, without an appropriate clinical context has a poor predictive value and is associated with high rate of false positives.[80,83,84] Clark et al showed that amongst patients with a history of reaction to peanut or TN, a SPT ≥8 mm had a predicted clinical reactivity greater than 95% accuracy.[85] Ho et al confirmed this threshold value for cashew, hazelnut, and walnut.[86]

Specific IgE to whole allergen extracts of peanut/TN are more widely available than SPTs and improve the management of patients with a suspicion of nut allergy. However, similarly to SPT, there is a large variation regarding the reported diagnostic values of sIgE.[24,30,87-89] Data are summarized in Table 3. As an example, Sampson et al showed in the 1990s that a peanut sIgE ≥15kU/L could predict clinical reactivity with greater than 95% certainty.[90] Clark et al confirmed and extended this result to TN allergy.[85,91] Fleisher et al reported that only 63% of patients with a history of clinical TN allergy and TN sIgE levels <2 kU/L passed their OFC.[4] In a retrospective study, Couch et al reported a higher proportion of patients with a negative OFC (89%) with similar levels of sIgE (<2kU/L).[31]

Specific IgE and SPT are routinely performed as a first-line procedure to support the diagnosis of allergy; however, false negatives can occur. These false negatives can be explained in part by the fact that commercial extracts (SPT and sIgE) do not contain extracts of oleosins (lipid-bound allergens) that are responsible for some allergic reactions. Modified skin prick testing (using the actual nut or nut butter), or the use of CRD to measure oleosins (e.g Ara h 10 and 11 for peanut) or in the basophilic activation test would therefore be valuable diagnostic tools, but these data need to be confirmed by further studies.[92]

Component resolved diagnosis

During the last decade, the introduction of CRD has led to a major improvement in the diagnosis of nut allergies.[18,75,93]

It is now possible to identify patients who have developed sIgE against seed storage proteins that are associated with a high risk of systemic reactions. The most well-known example is sIgE to Ara h 2, which is a peanut seed storage protein. It has been shown that 80%–100% of patients with primary peanut allergy are sensitized to Ara h 2.[59,94-97] Cut-off decision points for Ara h 2 sIgE have been determined in multiple studies, but there is a large variation of the reported values (Table 3). Hazelnut also contains seed storage proteins, ie, Cor a 9 and Cor a 14, and sIgE to these proteins have also been associated with systemic reactions.[98,99] These tests have been found to be highly specific and more sensitive than sIgE and SPT to whole allergen extract to diagnose a primary hazelnut allergy.[98] However, there is again a large variation of reported diagnostic values, particularly for sIgE to Cor a 14.[95,98-103] In addition, some studies have highlighted specific factors affecting the variation of the diagnostic values of sIgE to Cor a 9 and Cor a 14. Particularly, the age of the child may affect the diagnostic value of these tests. Thus, it has been found that Cor a 9-sIgE specificity decreases with age, while Cor a 14-sIgE specificity increases with age.[99,104,105] Specific IgE to seed storage proteins found in other TNs (ie, Jug r 1, Jug r 4 in walnut or Ana o 3 in cashew nut) have also been found to improve diagnostic accuracy of allergy to these nuts.[106-109] Regarding walnut, sIgE to Jug r 1 and Jug r 4, were reported to provide the best distinction between walnut allergy and sensitization.[110,111] Indeed, sIgE to Jug r 1 and Jug r 4 have been found to be positive in 75% and in 56.7–66% of walnut allergic patients, respectively.[112,113] The NutCracker study found that IgE levels ≥0.35kU/L to Jug r 1 and Jug r 4 provided the best diagnosis method for identifying walnut allergic

Food	Cutoffs for sIgE to extract allergen	Cutoffs for specific IgE to main components	Cutoffs for specific skin prick test
Peanut	≥15 kU/L, 95% PPV[159-161]		≥4 mm–15mm, 95%–100% PPV[80]
		Ara h 2 sIgE: 0.35–42.2 kU/L had 90%–95% PPV[76,95,96,162-165]	
		Arah 8 : 0.6 kU/L to 100 kU/L[66]	
		Arah 9: no available values	
Hazelnut	≥0,7kU/L- 15 kU/L or greater 57%-92%PPV[89,99]		≥8 mm–17mm or greater, 74%-100% PPV[86,166]
	≤0,35kU/l, 95%NVP[99]		
		Cor a 9 sIgE: 1 kU/L had 83% accuracy[99]	
		Cor a 14 sIgE: 0.72–47.8 kU/L had 87%–90% accuracy[95,100]	
		Cor a 1: no available values	
		Cor a 8: no available values	
Walnut	≥5.07 kU/L −18,5kU/L or greater, 95%–99% PPV[24,78]		≥8 mm, 95%PPV[30,86]
		Jug r 1 sIgE: 0.1 kU/L had 91% PPV(113), ≥0,35kU/l, accuracy 0,93(81)	
		Jugr 4 ≥ 0,35kU/L, accuracy 0,93(81)	
		Jug r 3: no available values	
Pecan			≥7 mm, 75% PPV[86]
Cashew	≥8 kU/l – 149.5kU/L or greater: 95%PPV[86,167]		≥8 mm, 95%PPV[86] ≥10–12 mm, 95% PPV[30,168]
		Ana o 3 sIgE: 0.16 kU/L had 97.1% accuracy for cashew and/or pistachio nut allergy[106]	
Pistachio	≥88 kU/l, 90% accuracy[24]		
Almond			
		Pru du 1 (PR-10)	
Brazil nut	≥3,5kU/l 100% PPV[88]		≥6 mm, PPV 100%[88] ≥9 mm, accuracy ≥95%[85]
		Ber e 1 sIgE: 0.25 kU/L had 94% PPV[169]	

Table 3. *PPV: positive predictive value, NPV: negative predictive value, PR-10: Pathogenesis related protein type 10.*

patients (accuracy 0,93) (Table 3). In addition, the NutCracker study reported that patients with walnut and pecan dual allergy were more frequently sensitized to Jug r 4 compared to patients with isolated walnut allergy.[78] Regarding cashew nut, 2 European studies have shown that up to 93% of children with cashew allergy are sensitized to Ana o 3.[106,114] Ana o 3 sIgE level ≥0.16kU/L had 97.1% accuracy for cashew and/or pistachio nut allergy.[106,114,115] (Table 3). Specific IgE to Ana o 3 have been reported as a highly accurate diagnosis marker also for pistachio allergy.[36,106]

Peanut/TN allergies may be the expression of a sensitization to LTP family (eg, Arah 9, Cor a 8, Jug r 3). Hazelnut has received the most extensive evaluation. Studies reported that sensitization to a hazelnut LTP (eg, Cor a 8) is a risk factor for objective symptoms in children from a Mediterranean region.[116–118] Hansen et al, in a multicenter study performed in Switzerland, Spain, and Denmark, reported that amongst patients with hazelnut allergy, 28% had positive sIgE to rCor a 8. The highest rate of sensitization to the LTP rCor a 8 was reported in Spain (71%), followed by Switzerland (15%), then Denmark (5%). LTP sensitization was present in 5 out of 7 patients (71%) with severe symptoms to hazelnut and in 11 out of 52 patients (21%) with milder reactions.[119] Diagnostic values of sIgE vary significantly between studies and cut-offs have not been clearly established. There are many confounding factors such as pollen influences, patterns of sensitization (food or pollen) and geographic distribution.

Distinction between primary and secondary allergy is a challenge and use of CRD can help differentiate phenotypes of peanut/TN allergy and co-sensitization. Uotila et al found that in a birch pollen endemic region, patients with peanut sensitization without associated symptoms and peanut allergic patients were equally sensitized to PR-10 proteins (Bet v 1 90%). In this cohort, over 90% avoided TNs but only 6%–44% presented with specific sensitizations to seed storage protein to TNs.[120] Hence, an accurate diagnosis based on CRD might have helped to decrease the rate of unnecessary avoidance. Proteins of the PR-10 family have been identified for walnut (Jug r 5),[107] hazelnut (Cor a 1),[121] almond (Pru du 1),[122] and peanut (Ara h 8).[66] As with primary allergies, the clinical expression of sensitization to PR-10 might be dependant on the specific IgE levels.[123]

Basophil activation test

The BAT is another promising diagnostic tool for nut allergy.[20,61] This test is not yet largely available in the clinical setting, because it requires appropriate equipment and trained personnel. Thus, Santos et al proposed to restrict the use of BAT to selected cases, for which the results of routinely used tests do not allow a precise diagnosis.[76] Several studies reported that in the diagnosis of peanut/TN allergies, BAT had a sensitivity ranging between 81.3% and 98%, and a specificity ranging between 77 and 100%.[30,104,124] However, cut-offs determined for the BAT can vary according to the population studied, the design of the study, and the methodology adopted for the BAT procedure and data analyses.[76]

Regarding peanut allergy, Santos et al and Ocmant et al determined optimal cut-off points for CD63 at 4.78% and 9.1%, respectively.[76,125] Basophil reactivity in peanut-allergic subjects was found to be associated with the severity of allergic reaction, and it has also been shown that BATs may be useful in monitoring patients undergoing OIT.[125–127] However, studies are still needed to confirm these results.

Studies evaluating the diagnostic value of the BAT for TN allergy are limited. Regarding hazelnut allergy, it has been found that the BAT has a sensitivity ranging between 85% and 100% and specificity ranging between 80% and 97%.[124,128–130] Recently, it was suggested that the use of the BAT in combination with SPT was useful for the diagnosis of TN allergies. Preliminary results report that the combination of BAT with SPT and clinical co-existent allergy knowledge enable the differentiation of co-allergenicity patterns in patients sensitized to walnut, pecan, cashew and pistachio.[30] However, these data should be examined in a prospective study with a larger patient population. In addition, BAT has been also shown to be potentially useful in identifying the culprit allergen in cases of PFS.[128,131–133]

MANAGEMENT

The basic approach to peanut/TN allergy management does not defer from current management approaches to other food allergies. It includes short-term, immediate treatment of symptoms after the exposure and long-term strategies assuring strict avoidance of culprit nut and minimising risk of any future reactions.[16]

The management of mild reactions has been based on the same therapies for many years, namely non-sedating antihistamines.[134] Epinephrine is the cornerstone and first-line treatment for anaphylaxis.[135] Early recognition of signs of anaphylaxis and prompt administration of epinephrine are absolutely key, and patients with potential anaphylaxis to peanut/TN should have easy access to epinephrine autoinjectors in the community.

Improved understanding of the pathophysiological mechanisms involved in allergic reactions may give rise to additional useful treatments. Vadas et al reported on the role of PAF and the activity of PAF acethylhydrolase in anaphylactic reactions.[136] Arias et al, in an experimental study in peanut-sensitized mice, reported that PAF antagonists significantly decrease the duration and severity of the anaphylactic reaction compared to other therapeutics (histamine receptor antagonist, 5 lipooxygenase inhibitor). Indeed 83% of PAF-treated versus 43% of untreated mice reached recovery within 120 min after peanut challenge. In addition, they also report that the combination of PAF receptor antagonists and histamine receptor antagonists allows for better management and an even more significant reduction in the severity and duration of the reaction.[137]

Long-term strategies assuring avoidance of index nut are quite complex and require a multidisciplinary approach, involving good education of patients and their families. This education involves teaching parents and their children to read food labels and recognise their allergen appropriately. Identifying and clearly listing the most common food allergens has become a legal requirement in many countries, but practices differ throughout the world. Many food companies also choose to add Precautionary Allergen Labels (PAL), such as "may contain", but it is not always clear what these labels mean, and consumers often do not fully understand this.[6]

Historically, the main management approach to nut allergy was strict, blanket avoidance of all nuts in all peanut and TN allergic patients. Although avoiding all nuts simplifies the management and may decrease the risk of reactions secondary to cross-contact or misidentification, it has many pitfalls. As peanut/TN are long-term allergies, patients must avoid all nuts (ie,. peanuts and TN) even if they might be clinically tolerant to selective nuts, which puts an additional and unnecessary restriction on patients' diet and social activities, which in turn reduces quality of life[138] and increases anxiety levels.[14] Strict avoidance of all nuts may lead to development of new allergies, as well as nutritional consequences, and influence growth, particularly in children with other food allergies.[33,139–141]

On the other hand, introducing selective nuts in the diet of patients allergic to some types of nuts can be complicated, requires multiple investigations, and often multiple in-hospital OFCs, which are limited not only by the available resources and time, but also carry risk, as reactions occurring during these OFCs can be severe.[11] Another important safety aspect of selective nut consumption is patients' and their families' ability to correctly recognise and distinguish the correct nuts themselves. A study involving 1105 participants conducted by Hostetler et al investigated the ability of children and adults to appropriately identify peanut/TNs. Participants were shown 19 different pictures of peanuts and TNs, and the mean number of correct responses was only 8.4. There was a significant difference between children and adults, but parents with nut allergic children did not perform any better than parents of children without a known nut allergy.[142]

Healthcare professionals' approach to the matter of nut avoidance in peanut/TN allergies management has changed; patient populations and their preferences have also changed. Patients and their families prefer having more freedom in making choices and tend to get more involved in their management decisions and wish dietary restriction to have less repercussions on their daily life. Management of their peanut/TN allergies

should be tailored to each patient, taking into consideration many aspects in addition to test results, such as age, history of previous reactions, concomitant conditions, patients' and families' understanding of their allergies, tendency towards risk taking, anxiety level, quality of life, and ultimately, what our patients and their families want as part of shared decision making.[143]

Building up immune tolerance in mainly peanut but also TN allergies has been a major focus of food allergy research over the past decade. The number of double-blind placebo controlled trials (with several trials including large numbers of participants) investigating oral, sublingual, and epicutaneous routes have showed this treatment approach to be efficacious in desensitizing the individual (increasing their threshold dose of reactivity), with quite a good safety profile.[144–146] However, the question of safety of different routes of peanut/TN immunotherapy and the benefit/risk ratio of this type of treatment remains a concern. A systematic review and meta-analysis published by Chu. et al showed that patients undergoing peanut oral immunotherapy (OIT) had a significant increase in anaphylaxis risk and frequency.[147] Authors concluded that peanut OIT achieved a modest degree of desensitization but caused more allergic and anaphylactic reactions in participants receiving treatment with peanut (albeit mostly during the updosing phase in hospital), when compared with the placebo group. On the other hand, as much as other routes such as epicutaneous or sublingual might have a better safety profile, they might not be as effective as the oral route.[148] This question will not be answered accurately unless large double-blind multiple arm studies comparing different routes of peanut/TN immunotherapy are performed.

Another approach to TN OIT would be using nut clusters such as cashew/pistachio,[11,19] walnut/pecan,[11,19] and pecan/walnut/hazelnut/macadamia nuts[11] as a treatment approach. Indeed, Elizur et al showed in their open label study investigating efficacy of walnut oral immunotherapy in 73 participants in which 55 participants received active treatment, all children with co-existing pecan allergy were also desensitised to pecan and 93% of children who were co-allergic to hazelnut were desensitised after their course of OIT with walnut.[19] Although these results seem promising, there is a lack of substantial evidence, and this might be quite an interesting and large area for future research.

Lastly, the question of TN allergy prevention still remains open. There is quite substantial evidence for the early introduction of peanuts being protective against development of peanut allergy in high risk infants. The LEAP (Learning Early About Peanut Allergy)randomised controlled trial showed a relative reduction in school-aged peanut allergy prevalence of 86.1% in peanut skin prick test negative and 70% in skin prick positive infants who started eating peanuts by the age of 11 months, when compared with the group who avoided peanut.[149] This finding was sequentially supported by the results from the EAT (Enquiring about tolerance) study in the per protocol group and in children with positive sIgE >0.1kU/L.[150,151] In addition, as the follow up LEAP-On Study showed, this protective effect remained beyond time of intervention, and 1 year of peanut avoidance was not associated with an increase in peanut allergy.[152]

It is not known whether a similar approach to tree nut allergy prevention would be effective, but previous data looking into development of sensitization/allergies to TN suggested this is likely. Unfortunately, as the LEAP study has shown, early introduction of peanut seems to be allergen specific and early peanut introduction was not effective in prevention of TN allergies.[153] There might be a practical limitation to this approach. As the prevention strategy requires an early intervention, families might find it difficult to introduce the required amounts of multiple TNs into the child's daily diet, which could greatly influence the success of prevention strategy. Other areas targeting the skin for the prevention of food allergies may be an alternative approach.[154] This is certainly a very interesting field for future research.

CONCLUSION

The specific difficulty with peanuts and TN allergies is the presence of cross-reactivity between them, and with pollens, making diagnostic and therapeutic management complex. Many diagnostic tools such as SPT, sIgE, CRD, and BAT are available to help make an accurate diagnosis, but

the OFC remains at the present time the gold standard despite the drawbacks that this entails. Healthcare practitioners often propose the avoidance of the index nut or of all nuts, as decided with the parent and child where appropriate. Peanut specific immunotherapy has shown benefits for desensitization but not tolerance induction once the treatment is stopped;[123] however, it is not widely available clinically. Recently, studies have also shown a benefit of immunotherapy with hazelnuts.[124–126] Regarding the primary prevention of TN allergy, data are missing; however, given the clear evidence for prevention for peanut allergy through early peanut introduction, it seems legitimate to also research this area. Targeted research is still required to answer some controversies in peanut and TN allergy treatment and prevention.

Abbreviations

Tree nut: TN; Oral allergy syndrome: OAS; Component-resolved diagnostic: CRD; Skin prick test: SPT; Pathogenesis related protein type 10: PR-10; Lipid transfer protein: LTP; Oral food challenge: OFC; Double-blind, placebo-controlled, food challenge: DBPCFC; Oral induction tolerance: OIT; Platelet-activating factor: PAF; Pollen-food syndrome: PFS; Precautionary Allergen Labels: (PAL)

Author's contribution

Elise Midun wrote the chapters: introduction, Proportion of patients reacting to multiple nuts, Co-allergy and co-sensitization, Diagnostics for peanut and tree nut allergy, and Conclusion, Suzana Radulovic wrote the chapter: Management. Helen Brough read and corrected the review, Jean-Christoph Caubet read and corrected the review.

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REFERENCES

1. McWilliam V, Koplin J, Lodge C, Tang M, Dharmage S, Allen K. *The Prevalence of Tree Nut Allergy: A Systematic Review*. Current Allergy and Asthma Reports; 2015 Sep [cited 2020 Jan 12];15(9). Available from: http://link.springer.com/10.1007/s11882-015-0555-8.
2. Sicherer SH, Muñoz-Furlong A, Godbold JH, Sampson HA. US prevalence of self-reported peanut, tree nut, and sesame allergy: 11-year follow-up. *J Allergy Clin Immunol*. 2010 Jun;125(6):1322–1326.
3. Du Toit G, Katz Y, Sasieni P, et al. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. *J Allergy Clin Immunol*. 2008 Nov;122(5):984–991.
4. Fleischer DM, Conover-Walker MK, Matsui EC, Wood RA. The natural history of tree nut allergy. *J Allergy Clin Immunol*. 2005 Nov;116(5):1087–1093.
5. Rona RJ, Keil T, Summers C, et al. The prevalence of food allergy: a meta-analysis. *J Allergy Clin Immunol*. 2007 Sep;120(3):638–646.
6. Hourihane JO, Dean TP, Warner JO. Peanut allergy in relation to heredity, maternal diet, and other atopic diseases: results of a questionnaire survey, skin prick testing, and food challenges. *BMJ*. 1996 Aug 31;313(7056):518–521.
7. Osborne NJ, Koplin JJ, Martin PE, et al. Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and predetermined challenge criteria in infants. *J Allergy Clin Immunol*. 2011 Mar;127(3):668–676. e1-2.
8. Prescott SL, Pawankar R, Allen KJ, et al. A global survey of changing patterns of food allergy burden in children. *World Allergy Organ J*. 2013 Dec 4;6(1):21.
9. Nwaru BI, Hickstein L, Panesar SS, et al. Prevalence of common food allergies in Europe: a systematic review and meta-analysis. *Allergy*. 2014 Aug;69(8):992–1007.
10. Moneret-Vautrin D-A. Épidémiologie de l'allergie alimentaire. *Rev Fr Allergol Immunol Clin*. 2008 Apr;48(3):171–178.

11. Brough HA, Caubet J-C, Mazon A, et al. Defining challenge-proven coexistent nut and sesame seed allergy: a prospective multicenter European study. *J Allergy Clin Immunol*. 2019 Dec;145(4):1231–1239. https://doi.org/10.1016/j.jaci.2019.09.036.
12. Marchisotto MJ, Harada L, Kamdar O, et al. Food allergen labeling and purchasing habits in the United States and Canada. *J Allergy Clin Immunol Pract*. 2017 Apr;5(2):345–351.e2.
13. Smeekens JM, Bagley K, Kulis M. Tree nut allergies: allergen homology, cross-reactivity, and implications for therapy. *Clin Exp Allergy*. 2018;48(7):762–772.
14. King RM, Knibb RC, Hourihane JO. Impact of peanut allergy on quality of life, stress and anxiety in the family. *Allergy*. 2009 Mar;64(3):461–468.
15. McWilliam V, Peters R, Tang MLK, et al. Patterns of tree nut sensitization and allergy in the first 6 years of life in a population-based cohort. *J Allergy Clin Immunol*. 2019 Feb;143(2):644–650. e5.
16. Muraro A, Werfel T, Hoffmann-Sommergruber K, et al. EAACI Food Allergy and Anaphylaxis Guidelines: diagnosis and management of food allergy. *Allergy*. 2014 Aug;69(8):1008–1025.
17. Eigenmann PA, Lack G, Mazon A, et al. Managing nut allergy: a remaining clinical challenge. *J Allergy Clin Immunol: In Pract*. 2017 Mar;5(2):296–300.
18. Weinberger T, Sicherer S. Current perspectives on tree nut allergy: a review. *J Asthma Allergy*. 2018;11:41–51.
19. Elizur A, Appel MY, Nachshon L, et al. Walnut oral immunotherapy for desensitisation of walnut and additional tree nut allergies (Nut CRACKER): a single-centre, prospective cohort study. *The Lancet Child & Adolescent Health*. 2019 May;3(5):312–321.
20. Wasserman RL, Hague AR, Pence DM, et al. Real-world experience with peanut oral immunotherapy: lessons learned from 270 patients. *J Allergy Clin Immunol Pract*. 2019;7(2):418–426. e4.
21. Sicherer SH, Burks AW, Sampson HA. Clinical features of acute allergic reactions to peanut and tree nuts in children. *Pediatrics*. 1998 Jul;102(1):e6.
22. Sicherer SH, Furlong TJ, Muñoz-Furlong A, Burks AW, Sampson HA. A voluntary registry for peanut and tree nut allergy: characteristics of the first 5149 registrants. *J Allergy Clin Immunol*. 2001 Jul;108(1):128–132.
23. McWilliam VL, Koplin JJ, Field MJ, et al. Self-reported adverse food reactions and anaphylaxis in the SchoolNuts study: a population-based study of adolescents. *J Allergy Clin Immunol*. 2018;141(3):982–990.
24. Maloney JM, Rudengren M, Ahlstedt S, Bock SA, Sampson HA. The use of serum-specific IgE measurements for the diagnosis of peanut, tree nut, and seed allergy. *J Allergy Clin Immunol*. 2008 Jul;122(1):145–151.
25. Anagnostou A. Insights into tree nut and sesame consumption from a cohort of 80 peanut-allergic children. *Pediatr Allergy Immunol*. 2019 May;30(3):389–392.
26. Cousin M, Verdun S, Seynave M, et al. Phenotypical characterization of peanut allergic children with differences in cross-allergy to tree nuts and other legumes. *Pediatr Allergy Immunol*. 2017 May;28(3):245–250.
27. Ball H, Luyt D, Bravin K, Kirk K. Single nut or total nut avoidance in nut allergic children: outcome of nut challenges to guide exclusion diets. *Pediatr Allergy Immunol*. 2011 Dec;22(8):808–812.
28. Yang L, Clements S, Joks R. A retrospective study of peanut and tree nut allergy: sensitization and correlations with clinical manifestations. *Allergy & Rhinology*. 2015 Jan 1;6(1):39–43.
29. Clark AT, Ewan PW. The development and progression of allergy to multiple nuts at different ages. *Pediatr Allergy Immunol*. 2005 Sep;16(6):507–511.
30. Elizur A, Appel MY, Nachshon L, et al. NUT Co reactivity - ACquiring knowledge for elimination recommendations (NUT CRACKER) study. *Allergy*. 2018;73(3):593–601.
31. Couch C, Franxman T, Greenhawt M. Characteristics of tree nut challenges in tree nut allergic and tree nut sensitized individuals. *Ann Allergy Asthma Immunol*. 2017 May;118(5):591–596. e3.
32. Brough HA, Costa J, Penagos M, et al. Increase in multiple nut reactivity with increasing age is not an artefact of incomplete allergy testing. *J Allergy Clin Immunol*. 2011 Feb;127(2):AB186. AB186.
33. Elizur A, Bollyky JB, Block WM. Elimination diet and the development of multiple tree-nut allergies: this work was done as part of Dr. Elizur's sabbatical from Sackler School of Medicine, Tel Aviv University, Israel. *Pediatr Res*. 2017 Oct;82(4):671–677.
34. Matricardi PM, Kleine-Tebbe J, Hoffmann HJ, et al. EAACI molecular allergology user's guide. *Pediatr Allergy Immunol*. 2016;27(Suppl 23):1–250.
35. Andorf S, Borres MP, Block W, et al. Association of clinical reactivity with sensitization to allergen components in multifood-allergic children. *J Allergy Clin Immunol Pract*. 2017 Oct;5(5):1325–1334. e4.
36. Geiselhart S, Hoffmann-Sommergruber K, Bublin M. Tree nut allergens. *Mol Immunol*. 2018 Aug;100:71–81.
37. Chruszcz M, Maleki SJ, Majorek KA, et al. Structural and immunologic characterization of Ara h 1, a major peanut allergen. *J Biol Chem*. 2011 Nov 11;286(45):39318–39327.
38. Hurlburt BK, Offermann LR, McBride JK, Majorek KA, Maleki SJ, Chruszcz M. Structure and function of the peanut panallergen Ara h 8. *J Biol Chem*. 2013 Dec 27;288(52):36890–36901.
39. Beardslee TA, Zeece MG, Sarath G, Markwell JP. Soybean glycinin G1 acidic chain shares IgE epitopes with peanut allergen Ara h 3. *Int Arch Allergy Immunol*. 2000 Dec;123(4):299–307.
40. Verma AK, Kumar S, Das M, Dwivedi PD. A comprehensive review of legume allergy. *Clin Rev Allergy Immunol*. 2013 Aug;45(1):30–46.
41. Willison LN, Tawde P, Robotham JM, et al. Pistachio vicilin, Pis v 3, is immunoglobulin E-reactive and cross-reacts with the homologous cashew allergen, Ana o 1. *Clin Exp Allergy*. 2008 Jul;38(7):1229–1238.
42. van der Valk JPM, Bouche RE, Gerth van Wijk R, et al. Low percentage of clinically relevant pistachio nut and mango co-sensitisation in cashew nut sensitised children. *Clin Transl Allergy*. 2017;7:8.

43. Bock SA, Atkins FM. The natural history of peanut allergy. *J Allergy Clin Immunol*. 1989 May;83(5):900–904.

44. Skolnick HS, Conover-Walker MK, Koerner CB, Sampson HA, Burks W, Wood RA. The natural history of peanut allergy. *J Allergy Clin Immunol*. 2001 Feb;107(2):367–374.

45. Bernhisel-Broadbent J, Sampson HA. Cross-allergenicity in the legume botanical family in children with food hypersensitivity. *J Allergy Clin Immunol*. 1989 Feb;83(2 Pt 1): 435–440.

46. Savage JH, Kaeding AJ, Matsui EC, Wood RA. The natural history of soy allergy. *J Allergy Clin Immunol*. 2010 Mar;125(3):683–686.

47. Gayraud J, Mairesse M, Fontaine JF, et al. The prevalence of sensitization to lupin flour in France and Belgium: a prospective study in 5,366 patients, by the Allergy Vigilance Network. *Eur Ann Allergy Clin Immunol*. 2009 Feb;41(1):17–22.

48. Moneret-Vautrin DA, Guérin L, Kanny G, Flabbee J, Frémont S, Morisset M. Cross-allergenicity of peanut and lupine: the risk of lupine allergy in patients allergic to peanuts. *J Allergy Clin Immunol*. 1999 Oct;104(4 Pt 1):883–888.

49. Shaw J, Roberts G, Grimshaw K, White S, Hourihane J. Lupin allergy in peanut-allergic children and teenagers. *Allergy*. 2008 Mar;63(3):370–373.

50. Reis AM, Fernandes NP, Marques SL, et al. Lupine sensitisation in a population of 1,160 subjects. *Allergol Immunopathol*. 2007 Aug;35(4):162–163.

51. Peeters KABM, Koppelman SJ, Penninks AH, et al. Clinical relevance of sensitization to lupine in peanut-sensitized adults. *Allergy*. 2009 Apr;64(4):549–555.

52. Fiocchi A, Sarratud P, Terracciano L, et al. Assessment of the tolerance to lupine-enriched pasta in peanut-allergic children. *Clin Exp Allergy*. 2009 Jul;39(7):1045–1051.

53. Asero R, Piantanida M, Pinter E, Pravettoni V. The clinical relevance of lipid transfer protein. *Clin Exp Allergy*. 2018;48(1):6–12.

54. Egger M, Hauser M, Mari A, Ferreira F, Gadermaier G. The role of lipid transfer proteins in allergic diseases. *Curr Allergy Asthma Rep*. 2010 Sep;10(5):326–335.

55. Zuidmeer L, van Ree R. Lipid transfer protein allergy: primary food allergy or pollen/food syndrome in some cases. *Curr Opin Allergy Clin Immunol*. 2007 Jun;7(3):269–273.

56. Vereda A, van Hage M, Ahlstedt S, et al. Peanut allergy: clinical and immunologic differences among patients from 3 different geographic regions. *J Allergy Clin Immunol*. 2011 Mar;127(3):603–607.

57. Mothes-Luksch N, Raith M, Stingl G, et al. Pru p 3, a marker allergen for lipid transfer protein sensitization also in Central Europe. *Allergy*. 2017 Sep;72(9):1415–1418.

58. Asero R, Antonicelli L, Arena A, et al. EpidemAAITO: features of food allergy in Italian adults attending allergy clinics: a multi-centre study. *Clin Exp Allergy*. 2009 Apr;39(4):547–555.

59. Flinterman AE, van Hoffen E, den Hartog Jager CF, et al. Children with peanut allergy recognize predominantly Ara h2 and Ara h6, which remains stable over time. *Clin Exp Allergy*. 2007 Aug;37(8):1221–1228.

60. Pastorello EA, Farioli L, Pravettoni V, et al. Pru p 3-sensitised Italian peach-allergic patients are less likely to develop severe symptoms when also presenting IgE antibodies to Pru p 1 and Pru p 4. *Int Arch Allergy Immunol*. 2011;156(4):362–372.

61. Scala E, Till SJ, Asero R, et al. Lipid transfer protein sensitization: reactivity profiles and clinical risk assessment in an Italian cohort. *Allergy*. 2015 Aug;70(8):933–943.

62. Uotila R, Kukkonen AK, Pelkonen AS, Mäkelä MJ. Cross-sensitization profiles of edible nuts in a birch-endemic area. *Allergy*. 2016 Apr;71(4):514–521.

63. Price A, Ramachandran S, Smith GP, Stevenson ML, Pomeranz MK, Cohen DE. Oral allergy syndrome (pollen-food allergy syndrome). *Dermatitis*. 2015 Apr;26(2):78–88.

64. Carlson G, Coop C. Pollen food allergy syndrome (PFAS): a review of current available literature. *Ann Allergy Asthma Immunol*. 2019 Oct;123(4):359–365.

65. Wangorsch A, Jamin A, Lidholm J, et al. Identification and implication of an allergenic PR-10 protein from walnut in birch pollen associated walnut allergy. *Mol Nutr Food Res*. 2017;61(4).

66. Mittag D, Akkerdaas J, Ballmer-Weber BK, et al. Ara h 8, a Bet v 1-homologous allergen from peanut, is a major allergen in patients with combined birch pollen and peanut allergy. *J Allergy Clin Immunol*. 2004 Dec;114(6):1410–1417.

67. Hofmann C, Scheurer S, Rost K, et al. Cor a 1-reactive T cells and IgE are predominantly cross-reactive to Bet v 1 in patients with birch pollen-associated food allergy to hazelnut. *J Allergy Clin Immunol*. 2013 May;131(5):1384–1392.e6.

68. Kleine-Tebbe J, Vogel L, Crowell DN, Haustein U-F, Vieths S. Severe oral allergy syndrome and anaphylactic reactions caused by a Bet v 1- related PR-10 protein in soybean, SAM22. *J Allergy Clin Immunol*. 2002 Nov;110(5):797–804.

69. Hansen KS, Ballmer-Weber BK, Lüttkopf D, et al. Roasted hazelnuts–allergenic activity evaluated by double-blind, placebo-controlled food challenge. *Allergy*. 2003 Feb;58(2): 132–138.

70. Ortolani C, Ballmer-Weber BK, Hansen KS, et al. Hazelnut allergy: a double-blind, placebo-controlled food challenge multicenter study. *J Allergy Clin Immunol*. 2000 Mar;105(3): 577–581.

71. Sicherer SH, Sampson HA. Food allergy: a review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. *J Allergy Clin Immunol*. 2018;141(1):41–58.

72. NIAID-Sponsored Expert Panel, Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol*. 2010 Dec;126(6 Suppl):S1–S58.

73. Burks AW, Jones SM, Boyce JA, et al. NIAID-sponsored 2010 guidelines for managing food allergy: applications in the pediatric population. *Pediatrics*. 2011 Nov;128(5):955–965.

74. Sampson HA, Aceves S, Bock SA, et al. Food allergy: a practice parameter update–2014. *J Allergy Clin Immunol*. 2014 Nov;134(5):1016–1025. e43.

75. McWilliam VL, Perrett KP, Dang T, Peters RL. Prevalence and natural history of tree nut allergy. *Ann Allergy Asthma Immunol*. 2020 May;124(5):466–472.

76. Santos AF, Douiri A, Bécares N, et al. Basophil activation test discriminates between allergy and tolerance in peanut-sensitized children. *J Allergy Clin Immunol*. 2014 Sep;134(3): 645–652.

77. Eigenmann PA, Sampson HA. Interpreting skin prick tests in the evaluation of food allergy in children. *Pediatr Allergy Immunol*. 1998 Nov;9(4):186–191.

78. Elizur A, Appel MY, Nachshon L, et al. Clinical and molecular characterization of walnut and pecan allergy (NUT CRACKER study). *J Allergy Clin Immunol: In Pract*. 2020 Jan;8(1):157–165.e2.

79. Randhawa I, Morphew T, Marsteller NL. Correlation of negative skin-prick test results for tree nuts and successful tree nut challenges among children with peanut allergy. *Allergy Asthma Proc*. 2018 Nov 1;39(6):456–460.

80. Stiefel G, Anagnostou K, Boyle RJ, et al. BSACI guideline for the diagnosis and management of peanut and tree nut allergy. *Clin Exp Allergy*. 2017 Jun;47(6):719–739.

81. Sampson H. Comparative study of commercial food antigen extracts for the diagnosis of food hypersensitivity. *J Allergy Clin Immunol*. 1988 Nov;82(5):718–726.

82. Sporik R, Hill DJ, Hosking CS. Specificity of allergen skin testing in predicting positive open food challenges to milk, egg and peanut in children. Clinical <html_ent glyph="@amp;" ascii=. *Experimental Allergy*. 2000 Nov;30(11):1541–1546.

83. Rancé F, Abbal M, Lauwers-Cancès V. Improved screening for peanut allergy by the combined use of skin prick tests and specific IgE assays. *J Allergy Clin Immunol*. 2002 Jun;109(6):1027–1033.

84. Eigenmann PA, Sicherer SH, Borkowski TA, Cohen BA, Sampson HA. Prevalence of IgE-mediated food allergy among children with atopic dermatitis. *Pediatrics*. 1998 Mar;101(3):E8.

85. Clark AT, Ewan PW. Interpretation of tests for nut allergy in one thousand patients, in relation to allergy or tolerance. Clinical <html_ent glyph="@amp;" ascii=. *Experimental Allergy*. 2003 Aug;33(8):1041–1045.

86. Ho M, Heine R, Wong W, Hill D. Diagnostic accuracy of skin prick testing in children with tree nut allergy. *J Allergy Clin Immunol*. 2006 Jun;117(6):1506–1508.

87. Baker MG, Kattan JD. Review of 400 consecutive oral food challenges to almond. *Ann Allergy Asthma Immunol*. 2019 Feb;122(2):189–192.

88. Ridout S, Matthews S, Gant C, Twiselton R, Dean T, Arshad SH. The diagnosis of Brazil nut allergy using history, skin prick tests, serum-specific immunoglobulin E and food challenges. *Clin Exp Allergy*. 2006 Feb;36(2):226–232.

89. Ortolani C, Ballmer-Weber BK, Hansen KS, et al. Hazelnut allergy: a double-blind, placebo-controlled food challenge multicenter study. *J Allergy Clin Immunol*. 2000 Mar;105(3):577–581.

90. Sampson HA, Ho DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents★. *J Allergy Clin Immunol*. 1997 Oct;100(4):444–451.

91. Du Toit G, Santos A, Roberts G, Fox AT, Smith P, Lack G. The diagnosis of IgE-mediated food allergy in childhood. *Pediatr Allergy Immunol*. 2009 Jun;20(4):309–319.

92. Jappe U, Schwager C. Relevance of lipophilic allergens in food allergy diagnosis. *Curr Allergy Asthma Rep*. 2017 Aug 9;17(9):61.

93. Treudler R, Simon JC. Overview of component resolved diagnostics. *Curr Allergy Asthma Rep*. 2013 Feb;13(1):110–117.

94. Koppelman SJ, Wensing M, Ertmann M, Knulst AC, Knol EF. Relevance of Ara h1, Ara h2 and Ara h3 in peanut-allergic patients, as determined by immunoglobulin E Western blotting, basophil-histamine release and intracutaneous testing: Ara h2 is the most important peanut allergen. *Clin Exp Allergy*. 2004 Apr;34(4):583–590.

95. Beyer K, Grabenhenrich L, Härtl M, et al. Predictive values of component-specific IgE for the outcome of peanut and hazelnut food challenges in children. *Allergy*. 2015 Jan;70(1):90–98.

96. Nicolaou N, Poorafshar M, Murray C, et al. Allergy or tolerance in children sensitized to peanut: prevalence and differentiation using component-resolved diagnostics. *J Allergy Clin Immunol*. 2010 Jan;125(1):191–197.e13.

97. Dang TD, Tang M, Choo S, et al. Increasing the accuracy of peanut allergy diagnosis by using Ara h 2. *J Allergy Clin Immunol*. 2012 Apr;129(4):1056–1063.

98. Beyer K, Grishina G, Bardina L, Grishin A, Sampson HA. Identification of an 11S globulin as a major hazelnut food allergen in hazelnut-induced systemic reactions. *J Allergy Clin Immunol*. 2002 Sep;110(3):517–523.

99. Masthoff LJN, Mattsson L, Zuidmeer-Jongejan L, et al. Sensitization to Cor a 9 and Cor a 14 is highly specific for a hazelnut allergy with objective symptoms in Dutch children and adults. *J Allergy Clin Immunol*. 2013 Aug;132(2):393–399.

100. Kattan JD, Sicherer SH, Sampson HA. Clinical reactivity to hazelnut may be better identified by component testing than traditional testing methods. *J Allergy Clin Immunol: In Pract*. 2014 Sep;2(5):633–634.e1.

101. Eller E, Mortz CG, Bindslev-Jensen C. Cor a 14 is the superior serological marker for hazelnut allergy in children, independent of concomitant peanut allergy. *Allergy*. 2016 Apr;71(4):556–562.

102. Faber MA, De Graag M, Van Der Heijden C, et al. Cor a 14: missing link in the molecular diagnosis of hazelnut allergy? *Int Arch Allergy Immunol*. 2014;164(3):200–206.

103. Buyuktiryaki B, Cavkaytar O, Sahiner UM, et al. Cor a 14, hazelnut-specific IgE, and SPT as a reliable tool in hazelnut allergy diagnosis in eastern mediterranean children. *J Allergy Clin Immunol: In Pract*. 2016 Mar;4(2):265–272. e3.

104. Santos AF, Brough HA. Making the most of in vitro tests to diagnose food allergy. *J Allergy Clin Immunol Pract*. 2017 Apr;5(2):237–248.

105. De Knop KJ, Verweij MM, Grimmelikhuijsen M, et al. Age-related sensitization profiles for hazelnut (Corylus avellana) in a birch-endemic region: hazelnut allergy: sensitization profiles. *Pediatr Allergy Immunol*. 2011 Feb;22(1pt2):e139–e149.

106. Savvatianos S, Konstantinopoulos AP, Å Borgå, et al. Sensitization to cashew nut 2S albumin, Ana o 3, is highly predictive of cashew and pistachio allergy in Greek children. *J Allergy Clin Immunol*. 2015 Jul;136(1):192–194.

107. Costa J, Carrapatoso I, Oliveira MBPP, Mafra I. Walnut allergens: molecular characterization, detection and clinical relevance. *Clin Exp Allergy*. 2014 Mar;44(3):319–341.

108. Sordet C, Culerrier R, Granier C, et al. Expression of Jug r 1, the 2S albumin allergen from walnut (Juglans regia), as a correctly folded and functional recombinant protein. *Peptides*. 2009 Jul;30(7):1213–1221.

109. Robotham JM, Teuber SS, Sathe SK, Roux KH. Linear IgE epitope mapping of the English walnut (Juglans regia) major food allergen, Jug r 1. *J Allergy Clin Immunol*. 2002 Jan;109(1):143–149.

110. Blankestijn MA, Blom WM, Otten HG, et al. Specific IgE to Jug r 1 has no additional value compared with extract-based testing in diagnosing walnut allergy in adults. *J Allergy Clin Immunol*. 2017 Feb;139(2):688–690. e4.

111. Sato S, Yamamoto M, Yanagida N, et al. Jug r 1 sensitization is important in walnut-allergic children and youth. *J Allergy Clin Immunol Pract*. 2017 Dec;5(6):1784–1786.e1.

112. Mew R, Borres M, Sjölander S, du Toit G. A retrospect study into the utility of allergen components in walnut allergy. *Pediatr Allergy Immunol*. 2016 Nov;27(7):750–752.

113. Wallowitz M, Peterson WR, Uratsu S, Comstock SS, Dandekar AM, Teuber SS. Jug r 4, a legumin group food allergen from walnut (*Juglans regia* cv. Chandler). *J Agric Food Chem*. 2006 Oct;54(21):8369–8375.

114. Lange L, Lasota L, Finger A, et al. Ana o 3-specific IgE is a good predictor for clinically relevant cashew allergy in children. *Allergy*. 2017 Apr;72(4):598–603.

115. Reitsma M, Bastiaan-Net S, Sforza S, et al. Purification and characterization of *Anacardium occidentale* (cashew) allergens Ana o 1, Ana o 2, and Ana o 3. *J Agric Food Chem*. 2016 Feb 10;64(5):1191–1201.

116. Flinterman AE, Akkerdaas JH, den Hartog Jager CF, et al. Lipid transfer protein-linked hazelnut allergy in children from a non-Mediterranean birch-endemic area. *J Allergy Clin Immunol*. 2008 Feb;121(2):423–428.e2.

117. Schocker F, Lüttkopf D, Scheurer S, et al. Recombinant lipid transfer protein Cor a 8 from hazelnut: a new tool for in vitro diagnosis of potentially severe hazelnut allergy. *J Allergy Clin Immunol*. 2004 Jan;113(1):141–147.

118. Pastorello EA, Vieths S, Pravettoni V, et al. Identification of hazelnut major allergens in sensitive patients with positive double-blind, placebo-controlled food challenge results. *J Allergy Clin Immunol*. 2002 Mar;109(3):563–570.

119. Hansen KS, Ballmer-Weber BK, Sastre J, et al. Component-resolved in vitro diagnosis of hazelnut allergy in Europe. *J Allergy Clin Immunol*. 2009 May;123(5):1134–1141. e3.

120. Uotila R, Kukkonen AK, Blom WM, et al. Component-resolved diagnostics demonstrates that most peanut-allergic individuals could potentially introduce tree nuts to their diet. *Clin Exp Allergy*. 2018 Jun;48(6):712–721.

121. Hirschwehr R, Valenta R, Ebner C, et al. Identification of common allergenic structures in hazel pollen and hazelnuts: a possible explanation for sensitivity to hazelnuts in patients allergic to tree pollen. *J Allergy Clin Immunol*. 1992 Dec;90(6):927–936.

122. Costa J, Mafra I, Carrapatoso I, Oliveira MBPP. Almond allergens: molecular characterization, detection, and clinical relevance. *J Agric Food Chem*. 2012 Feb 15;60(6):1337–1349.

123. Webber CM, England RW. Oral allergy syndrome: a clinical, diagnostic, and therapeutic challenge. *Ann Allergy Asthma Immunol*. 2010 Feb;104(2):101–108.

124. Hoffmann HJ, Santos AF, Mayorga C, et al. The clinical utility of basophil activation testing in diagnosis and monitoring of allergic disease. *Allergy*. 2015 Nov;70(11):1393–1405.

125. Ocmant A, Mulier S, Hanssens L, et al. Basophil activation tests for the diagnosis of food allergy in children. *Clin Exp Allergy*. 2009 Aug;39(8):1234–1245.

126. Jones SM, Pons L, Roberts JL, et al. Clinical efficacy and immune regulation with peanut oral immunotherapy. *J Allergy Clin Immunol*. 2009 Aug;124(2):292–300. e1-97.

127. Thyagarajan A, Jones SM, Calatroni A, et al. Evidence of pathway-specific basophil anergy induced by peanut oral immunotherapy in peanut-allergic children. *Clin Exp Allergy*. 2012 Aug;42(8):1197–1205.

128. Erdmann SM, Heussen N, Moll-Slodowy S, Merk HF, Sachs B. CD63 expression on basophils as a tool for the diagnosis of pollen-associated food allergy: sensitivity and specificity. *Clin Exp Allergy*. 2003 May;33(5):607–614.

129. Brandström J, Nopp A, Johansson SGO, et al. Basophil allergen threshold sensitivity and component-resolved diagnostics improve hazelnut allergy diagnosis. *Clin Exp Allergy*. 2015 Sep;45(9):1412–1418.

130. Lötzsch B, Dölle S, Vieths S, Worm M. Exploratory analysis of CD63 and CD203c expression in basophils from hazelnut sensitized and allergic individuals. *Clin Transl Allergy*. 2016;6:45.

131. Glaumann S, Nopp A, Johansson SGO, Rudengren M, Borres MP, Nilsson C. Basophil allergen threshold sensitivity, CD-sens, IgE-sensitization and DBPCFC in peanut-sensitized children: CD-sens, IgE-ab and peanut allergy. *Allergy*. 2012 Feb;67(2):242–247.

132. Wölbing F, Kunz J, Kempf WE, Grimmel C, Fischer J, Biedermann T. The clinical relevance of birch pollen profilin cross-reactivity in sensitized patients. *Allergy*. 2017 Apr;72(4):562–569.

133. Mayorga C, Gomez F, Aranda A, et al. Basophil response to peanut allergens in Mediterranean peanut-allergic patients. *Allergy*. 2014 Jul;69(7):964–968.

134. Anagnostou K, Swan KE, Brough H. The use of antihistamines in children. *Paediatr Child Health*. 2016 Jul;26(7):310–313.

135. Shaker MS, Wallace DV, Golden DBK, et al. Anaphylaxis—a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis. *J Allergy Clin Immunol*. 2020 Apr;145(4):1082–1123.

136. Vadas P, Gold M, Perelman B, et al. Platelet-activating factor, PAF acetylhydrolase, and severe anaphylaxis. *N Engl J Med*. 2008 Jan 3;358(1):28–35.

137. Arias K, Baig M, Colangelo M, et al. Concurrent blockade of platelet-activating factor and histamine prevents life-threatening peanut-induced anaphylactic reactions. *J Allergy Clin Immunol*. 2009 Aug;124(2):307, 14, 314.e1-2.

138. Avery NJ, King RM, Knight S, Hourihane JO. Assessment of quality of life in children with peanut allergy. *Pediatr Allergy Immunol*. 2003 Oct;14(5):378–382.

139. Flammarion S, Santos C, Guimber D, et al. Diet and nutritional status of children with food allergies. *Pediatr Allergy Immunol*. 2011 Mar;22(2):161–165.

140. Brough HA, Turner PJ, Wright T, et al. Dietary management of peanut and tree nut allergy: what exactly should patients avoid? *Clin Exp Allergy*. 2015 May;45(5):859–871.

141. Christie L, Hine RJ, Parker JG, Burks W. Food allergies in children affect nutrient intake and growth. *J Am Diet Assoc*. 2002 Nov;102(11):1648–1651.

142. Hostetler TL, Hostetler SG, Phillips G, Martin BL. The ability of adults and children to visually identify peanuts and tree nuts. *Ann Allergy Asthma Immunol*. 2012 Jan;108(1):25–29.

143. Anagnostou A, Hourihane JO, Greenhawt M. The role of shared decision making in pediatric food allergy management. *J Allergy Clin Immunol Pract*. 2020 Jan;8(1):46–51.

144. Blumchen K, Trendelenburg V, Ahrens F, et al. Efficacy, safety, and quality of life in a multicenter, randomized, placebo-controlled trial of low-dose peanut oral immunotherapy in children with peanut allergy. *J Allergy Clin Immunol Pract*. 2019;7(2):479–491. e10.

145. Fink WR, Capucilli P, Lewis MO, Rooney CB, Brown-Whitehorn TF. Significantly increased threshold dose after long-term peanut epicutaneous immunotherapy and daily oral peanut intake. *Ann Allergy Asthma Immunol*. 2020;124(4):403–405. e1.

146. PALISADE Group of Clinical Investigators, Vickery BP, Vereda A, Casale TB, Beyer K, du Toit G, et al. AR101 oral immunotherapy for peanut allergy. *N Engl J Med*. 2018 Nov 22;379(21):1991–2001.

147. Chu DK, Wood RA, French S, et al. Oral immunotherapy for peanut allergy (PACE): a systematic review and meta-analysis of efficacy and safety. *Lancet*. 2019 01;393(10187):2222–2232.

148. Fleischer DM, Greenhawt M, Sussman G, et al. Effect of epicutaneous immunotherapy vs placebo on reaction to peanut protein ingestion among children with peanut allergy: the PEPITES randomized clinical trial. *J Am Med Assoc*. 2019 Mar 12;321(10):946.

149. Du Toit G, Roberts G, Sayre PH, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med*. 2015 Feb 26;372(9):803–813.

150. Perkin MR, Logan K, Bahnson HT, et al. Efficacy of the Enquiring about Tolerance (EAT) study among infants at high risk of developing food allergy. *J Allergy Clin Immunol*. 2019 Dec;144(6):1606–1614.e2.

151. Perkin MR, Logan K, Tseng A, et al. Randomized trial of introduction of allergenic foods in breast-fed infants. *N Engl J Med*. 2016 May 5;374(18):1733–1743.

152. Du Toit G, Sayre PH, Roberts G, et al. Effect of avoidance on peanut allergy after early peanut consumption. *N Engl J Med*. 2016 Apr 14;374(15):1435–1443.

153. du Toit G, Sayre PH, Roberts G, et al. Allergen specificity of early peanut consumption and effect on development of allergic disease in the Learning Early about Peanut Allergy study cohort. *J Allergy Clin Immunol*. 2018;141(4):1343–1353.

154. Brough HA, Nadeau KC, Sindher SB, et al. *Epicutaneous Sensitization in the Development of Food Allergy: What Is the Evidence and How Can This Be Prevented? Allergy* [Internet]. 2020 Apr 6. https://doi.org/10.1111/all.14304 [cited 2020 May 13]; Available from:.

155. Costa J, Silva I, Vicente AA, Oliveira MBPP, Mafra I. Pistachio nut allergy: an updated overview. *Crit Rev Food Sci Nutr*. 2019 Feb 21;59(4):546–562.

156. Cabanillas B, Jappe U, Novak N. Allergy to peanut, soybean, and other legumes: recent advances in allergen characterization, stability to processing and IgE cross-reactivity. *Mol Nutr Food Res*. 2018 Jan;62(1):1700446.

157. Chan ES, Greenhawt MJ, Fleischer DM, Caubet J-C. Managing cross-reactivity in those with peanut allergy. *J Allergy Clin Immunol: In Pract*. 2019 Feb;7(2):381–386.

158. Adatia A, Clarke A, Yanishevsky Y, Ben-Shoshan M. Sesame allergy: current perspectives. *J Asthma Allergy*. 2017 Apr;10:141, 51.

159. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol*. 2001 May;107(5):891–896.

160. Sicherer SH, Morrow EH, Sampson HA. Dose-response in double-blind, placebo-controlled oral food challenges in children with atopic dermatitis. *J Allergy Clin Immunol*. 2000 Mar;105(3):582–586.

161. Perry TT, Matsui EC, Conover-Walker MK, Wood RA. Risk of oral food challenges. *J Allergy Clin Immunol*. 2004 Nov;114(5):1164–1168.

162. Nicolaou N, Murray C, Belgrave D, Poorafshar M, Simpson A, Custovic A. Quantification of specific IgE to whole peanut extract and peanut components in prediction of peanut allergy. *J Allergy Clin Immunol*. 2011 Mar;127(3):684–685.

163. Bernard H, Paty E, Mondoulet L, et al. Serological characteristics of peanut allergy in children. *Allergy*. 2003 Dec;58(12):1285–1292.

164. Klemans RJB, van Os-Medendorp H, Blankestijn M, Bruijnzeel-Koomen CAFM, Knol EF, Knulst AC. Diagnostic accuracy of specific IgE to components in diagnosing peanut allergy: a systematic review. *Clin Exp Allergy*. 2015 Apr;45(4):720–730.

165. Lieberman JA, Glaumann S, Batelson S, Borres MP, Sampson HA, Nilsson C. The utility of peanut components in the diagnosis of IgE-mediated peanut allergy among distinct populations. *J Allergy Clin Immunol: In Pract*. 2013 Jan;1(1):75–82.

166. Masthoff LJ, Pasmans SG, Hoffen E, et al. Diagnostic value of hazelnut allergy tests including rCor a 1 spiking in double-blind challenged children. *Allergy*. 2012 Apr;67(4):521–527.

167. Inoue Y, Trapnell BC, Tazawa R, et al. Characteristics of a large cohort of patients with autoimmune pulmonary alveolar proteinosis in Japan. *Am J Respir Crit Care Med*. 2008 Apr 1;177(7):752–762.

168. McWilliam V, Peters RL, Allen KJ, et al. Skin prick test predictive values for the outcome of cashew challenges in children. *J Allergy Clin Immunol: In Pract*. 2020 Jan;8(1):141–148.e2.

169. Rayes H, Raza AA, Williams A, Matthews S, Arshad SH. Specific IgE to recombinant protein (Ber e 1) for the diagnosis of Brazil nut allergy. *Clin Exp Allergy*. 2016 Apr;46(4):654–656.