

Managing Cross-Reactivity in Those with Peanut Allergy



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Peanut is an allergenic legume that can cross-react with other plant-based foods, notably other legumes and tree nuts. Peanut-allergic individuals can be both cosensitized and coallergic to such items, requiring foresight when eliciting a clinical history of a reaction, in the diagnostic evaluation of such allergies, and in the counseling of patients as to food avoidances after a diagnosis is made. Legume allergens belong to the Fabaceae family and encompass the cupin, prolamin, PR-10, and lipid transfer protein families, which mediate cross-sensitization including that between peanut and tree nut. Among legumes, the most

common patterns of clinical cross-reactivity are between peanut and lupine, peanut and soy, as well as chickpea and lentil, though this is highly dependent on geography and prevalence of these foods in the diet. Issues of cross-sensitization may exist between peanut and certain tree nuts, as well as among tree nuts though such patterns do not always result in clinically relevant allergy. Molecular diagnostic testing may be a future tool to help parse out the aforementioned patterns, but oral food challenges are still the gold standard for accurate diagnosis. Although potential desensitization treatments have emerged for peanut allergy, these have not been developed for other legumes and most tree nuts, and desensitization to peanut has not proven to have an effect on legume cross-sensitization. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:381-6)

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CASE PRESENTATION

SR is a 7-year-old boy who you, his allergist, diagnosed with peanut allergy during infancy based on a history of immediate, generalized urticaria and vomiting after his initial ingestion of peanut butter at 7 months of age. He underwent evaluation and testing at 12 months, revealing peanut skin prick test (SPT) measuring 8 × 13 mm, and peanut sIgE of 15.63 kU/L. The family has since restricted peanut from his diet, an anaphylaxis action plan has been provided, and he carries an epinephrine autoinjector at all times. Last year, he had an accidental exposure to peanut butter, and he developed immediate and bothersome urticaria on his face and torso. He has never eaten any tree nuts before, as his older brother has tree nut allergy and their home is tree nut free.

In the past year, SR has noticed new onset of an itchy throat with repeated ingestion of soy milk as well as with chickpea (in salad), both of which were previously tolerated with impunity. He continues to tolerate cooked peas, but has never tried lentils, green, black, kidney, pinto, or lima beans, or foods made with lupin.

Past medical history includes atopic dermatitis during infancy, which has been very mild since 3 years of age. He had viral-induced asthma between 1 and 6 years of age, managed with low-dose inhaled corticosteroids for several years, but he has done well off inhaled corticosteroids in the past year, requiring albuterol only a few times intermittently during viral upper respiratory illnesses. This past spring and summer, he developed persistent nasal congestion and rhinorrhea, requiring management with nasal corticosteroids, with which he has difficulty

Abbreviations used

Ana o- *Anacardium occidentale*
Ara h- *Arachis hypogaea*
Bet v- *Betula verrucosa*
Car I- *Carya illinoensis*
Cic a- *Cicer arietinum*
Cor a- *Corylus avellana*
CRD- *Component-resolved diagnostics*
Gly m- *Glycine max*
Jug r- *Juglans regia*
Len c- *Lens culinaris*
LTP- *Lipid transfer protein*
Lup an- *Lupinus angustifolius*
OFC- *Oral food challenge*
OIT- *Oral immunotherapy*
Pis s- *Pisum sativum*
Pis v- *Pistacia vera*
SPT- *Skin prick test*

adhering. He is otherwise healthy. On physical examination, he appears well apart from allergic shiners and edematous nasal turbinates bilaterally.

WHAT IS THE RATE OF CLINICAL CROSS-REACTIVITY (TRUE CLINICAL ALLERGY TO THE RELATED FOOD) BETWEEN PEANUT AND OTHER LEGUMES? HOW DIFFERENT IS THIS COMPARED WITH THE RATE OF CROSS-SENSITIZATION (POSITIVE SPT OR sIgE BUT FOOD IS TOLERATED)?

Legumes as a class belong to the Fabaceae family.¹ Peanut is perhaps the most notorious allergenic legume. Legumes are plant-based foods that grow from the ground and are surrounded by a pod. Peanut, soy, chickpea, and lupin appear to be the most clinically relevant, but family members also include alfalfa, clover, peas, beans, lentils, mesquite, carob, red gram, mung bean, and red kidney bean.¹ Legume allergens encompass the cupin, prolamin, PR-10, and lipid transfer protein (LTP) families. Legume sensitization may frequently be detected in pollen-sensitized individuals.¹

Lupine is a potential rising concern outside the United States as a new major allergen, in particular in the Mediterranean region.² Rates of lupine sensitization in Europe in 2 large studies has been noted to range from 1.6% in Northern Europe to 4.1% in Southern Europe. Another study estimated that 14.5% of adults and 17% of children also allergic to peanut were lupine sensitized.³⁻⁵ The degree to which lupine cross-sensitization in peanut is clinically relevant is harder to determine. In one Danish study of 39 peanut-allergic subjects, 89% were lupine sensitized, including 35% who had clinically relevant symptomatology.⁴ Lupine is typically ingested as milled flour, which has been noted to be a “hidden” ingredient in many breads using lupine as a supplement. Lupine flour can also be inhaled. The major lupine allergy is *Lupinus angustifolius* (Lup an) 1.¹

Soy is one of the 8 most common food allergies affecting approximately 0.4% of the population. Soy cross-sensitization with peanut is a well-documented issue, given homology between multiple soy and peanut allergens. In a study from several years ago, 31% (10/32) of peanut-allergic children had

positive SPTs to soy, but only 3% (1/32) had soy clinical reactivity.⁶ Given the lack of data for clinical cross-reactivity between peanut and soy, patients should not be routinely tested for soy or advised to avoid soy based on peanut allergy and soy cross-sensitization without a history of known soy symptomatology on ingestion.⁷

In Spain, chickpea and lentil are the most frequent legumes associated with clinical allergy (approximately 20% of the reported food allergy in Spain), and there are well-documented rates of cross-reactivity between the two.⁸ Chickpea is also a known allergen in India.⁹ Pea is an allergen in the Mediterranean region as well as some parts of Asia, having cross-reactivity with lentil. Although structural homology exists between peanut and lentil, there is lack of evidence of clinical cross-reactivity.

AT THE MOLECULAR LEVEL, WHICH LEGUME PROTEINS ARE ASSOCIATED WITH ANAPHYLAXIS? WHICH LEGUME PROTEINS ARE ASSOCIATED WITH POLLEN-FOOD SYNDROME?

There is promise that molecular-level diagnostics, identifying key components within a particular allergen representing IgE binding epitopes, may be able to provide greater specificity for phenotypes of reactivity.¹⁰ To date, this has been best explored in peanut, though this remains quite hypothetical.^{10,11} Figure 1 demonstrates the known components that can be commercially recognized for peanut, as well as their familial relationship with other legume components. Table 1 describes homology between legume components and plant panallergens.

For peanut, a few key patterns have been identified. There are emerging data that suggest that *Arachis hypogaea* (Ara h) 2, a 2s albumin seed storage protein, may have an association in peanut-allergic individuals who manifest severe/systemic reactivity, as opposed to mild oropharyngeal symptoms that may be more likely to be associated with Ara h 8.¹¹ Individuals with known *Betula verrucosa* (Bet v) 1 sensitization will recognize Ara h 8 (a PR-10 protein with homology to Bet v 1) based on cross-reactivity with inhalants.¹² Klemans et al¹³ calculated 100% positive and negative predictive values with sIgE to Ara h 2 at >5.17 and <0.07 kU/L, predicting the outcome of double-blind placebo-controlled food challenges with 50% accuracy (in 24 tolerant and 26 allergic patients) and providing data for peanut-tolerant individuals who are not sensitized to Ara h 2. In areas where birch pollen is endemic, it has been observed that testing with crude peanut extract (skin or serum) can be irrelevantly positive based on this pollen cross-sensitization alone. Ara h 9, an LTP, may be associated with anaphylaxis in LTP-endemic areas such as the Mediterranean, though in the United States, Ara h 9 may represent a marker of pollen (such as olive tree) sensitization and not be associated with clinically relevant disease.¹⁴

Soy components have been identified as well. *Glycine max* (Gly m) 5 and 6 are 7s albumin seed storage proteins, and there can be cross-sensitization to other similar 7S cupin family proteins such as Ara h 1 in peanut, *Pisum sativum* (Pis s) 1 and 2 in pea, Lup an 1 in lupine, and *Lens culinaris* (Len c) 1 in lentil.^{1,15} Gly m 4 is a PR-10-related protein, which can have cross-sensitization with Ara h 8 in peanut. There are multiple LTPs within the legume family that can be cross-sensitized with peanut Ara h 9, including Len c 3 in lentil, Pis s 3 in pea, and *Phaseolus vulgaris* 3 in green bean. However, clinical reactivity among legumes is far less common, and most of the resultant

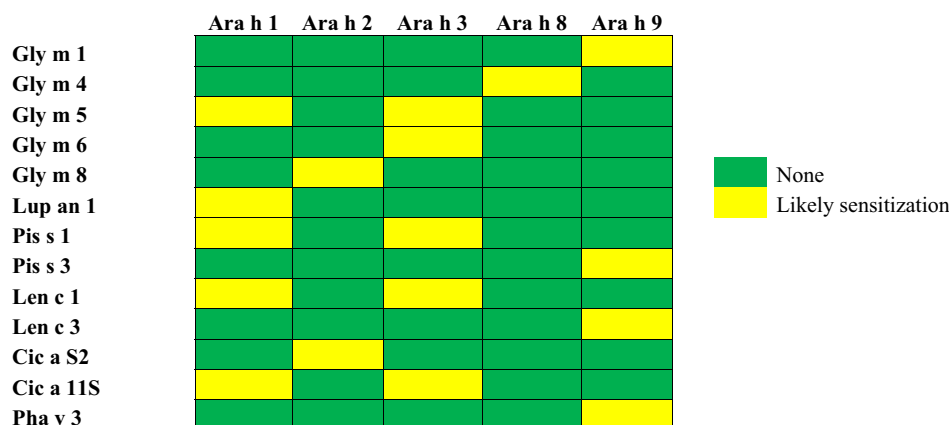


FIGURE 1. Peanut to other legume cross-sensitization heat map. *Ara h*, *Arachis hypogaea*; *Cic a*, *Cicer arietinum*; *Gly m*, *Glycine max*; *Len c*, *Lens culinaris*; *Lup an*, *Lupinus angustifolius*; *Pha v*, *Phaseolus vulgaris*; *Pis s*, *Pisum sativum*.

TABLE I. Legume family protein homology

Legume	2S albumin seed storage protein (prolamins)	7S albumin seed storage proteins (cuprins)	PR-10 protein	Lipid transfer protein	Other
Peanut	Ara h 2, Ara h 6	Ara h 1, Ara h 3	Ara h 8	Ara h 9	Ara h 5 (profilin)
Soy	Gly m 8	Gly m 5, Gly m 6	Gly m 4		Gly m 3 (profilin)
Lupine		Lup an 1, Lup a vicillin, Lup an 11S			Lup a 5 (profilin)
Pea		Pis s 1, Pis s 2		Pis s 3	
Chickpea	Cic a 2S	Cic a 11S			
Lentil		Len c 1		Len c 3	Len c 2
Green bean				Pha v 3	

Ara h, *Arachis hypogaea*; *Cic a*, *Cicer arietinum*; *Gly m*, *Glycine max*; *Len c*, *Lens culinaris*; *Lup an*, *Lupinus angustifolius*; *Pha v*, *Phaseolus vulgaris*; *Pis s*, *Pisum sativum*.

cross-sensitization is clinically irrelevant. No other legume components have been commercially developed.^{1,15}

IN PATIENTS WITH PEANUT ALLERGY, WHAT CLINICAL INVESTIGATIONS CAN HELP DISTINGUISH BETWEEN PHENOTYPES SUCH AS ANAPHYLAXIS VERSUS POLLEN-FOOD SYNDROME? WHAT CLINICAL INVESTIGATIONS ARE AVAILABLE FOR SOY AND OTHER LEGUMES?

For the clinical practice of food allergy in general, and more specifically legume allergy such as soy and chickpea, whole allergen commercial SPT and sIgE blood tests are commonly available, but poorly distinguish between clinically irrelevant sensitization, potentially anaphylactic IgE-mediated food allergy, and pollen-food syndrome.¹⁵ Component-resolved diagnostics (CRD) is widely available and used with frequency in Europe, but has had weaker availability in North America.¹⁶ In patients with a history of clinical symptoms on ingestion of specific foods, CRD test result patterns (*relative* levels of different components) have led to enthusiasm regarding the potential to distinguish anaphylactic food allergy versus pollen-food syndrome.

Allergen component testing (CRD) has been studied extensively for peanut (eg, Ara h 1, 2, 3, 6, 8, and 9), as per the above section, and is increasingly commercially available.¹¹ Although it is widely accepted that positive Ara h 2 levels appear to be most associated with peanut anaphylaxis, threshold values (eg, 95%

positive predictive value cutoffs) for component tests have varied widely depending on the population/geographic area studied, leading to confusion as to what cutoff level a clinician should use to assist with a diagnosis of peanut allergy, especially when the clinical history is remote or unclear.¹⁷ More worrisome is how positive values to various components that do not demonstrate a specific pattern (or “low” positive values) should be interpreted clinically, as these simply could be a consequence of clinically irrelevant sensitization in the setting of remote or unconvincing histories. In those scenarios, the oral food challenge (OFC) is still the gold standard for proper diagnosis.

For legumes other than peanut, commercial CRD for soy is available in certain areas of the world. Although definitive prospective studies are lacking, the most clinically relevant soy component tests appear to be Gly m 4, 5, 6, and 8.¹⁵ Gly m 4 cross-reacts with Bet v 1 birch pollen, or presumably other pollen allergens. Patients sensitized to both Gly m 4 and Bet v 1 typically have mild oropharyngeal symptoms on ingestion of unprocessed soy products (eg, soy drinks or soy protein powder), consistent with pollen-food allergy syndrome, and are mostly older children, adolescents, or adults (systemic or anaphylactic reaction is possible but the risk is low). In contrast, Gly m 5, 6, and 8 are stable seed storage proteins that do not cross-react with Bet v 1.¹⁸ Because of their stability, highly processed or refined soy products still have the potential to elicit reactions. IgE-mediated allergy to Gly m 5, 6, and 8 results in systemic, potentially anaphylactic reactions, and this affects infants and

young children more than older children or adults as it is typically outgrown in early childhood. Commercial CRD testing for legumes other than peanut and soy is typically unavailable.¹⁶

WHAT IS SR's FUTURE RISK OF ANAPHYLAXIS TO SOY AND CHICKPEA?

SR's parents ask you what SR's future risk of anaphylaxis is to soy and chickpea. You explain that this is a very difficult if not impossible question to answer without OFCs, and mention new tests that have emerged to help with this, though the availability of CRD testing is limited in your practice area to the research setting. You point out that you can more easily offer whole allergen SPT (including commercial vs fresh extracts) and sIgE tests, and OFCs if necessary. SPTs to environmental allergens are performed at today's visit and positive to tree (including birch) pollen and grass pollen. SPTs to foods are positive to peanut (9×10 mm), fresh soy (12×15 mm), fresh chickpea (11×12 mm), and negative to soy extract (chickpea extract unavailable). sIgE blood tests are positive to peanut (15.72 kU/L), and weakly positive to soy (0.73 kU/L) and chickpea (0.54 kU/L). Your impression is pollen-food allergy syndrome to soy and chickpea due to cross-reactivity with birch pollen. You inform SR's parents that the vast majority of patients with this have localized symptoms in the oropharyngeal mucosa (pruritus most commonly and sometimes perioral urticaria and lip angioedema), and that although he might develop anaphylaxis to soy or chickpea in the future, the risk is low. You offer supervised OFCs to assess SR's current clinical response because it has been several months since his last ingestion of soy or chickpea, but SR's parents decline as they feel they have already retried both foods at home several times with reproducible mild symptoms. You explain that for isolated pollen-food syndrome, those with a history of severe reactions should be prescribed an epinephrine autoinjector, but coincidentally SR is carrying an epinephrine autoinjector anyways due to his peanut allergy.

SHOULD SR RECEIVE SPTs TO LEGUMES HE HAS NOT TRIED BEFORE, FOR EXAMPLE, LUPIN, LENTILS, AND CERTAIN BEANS? WHAT WOULD BE THE SIGNIFICANCE OF POSITIVE SPTs TO LEGUMES HE HAS NEVER TRIED BEFORE?

With both legumes and any food under consideration, SPT or sIgE blood testing to foods that patients have never ingested before has poor predictive value due to an absent pretest probability of food allergy in addition to the potential for false positives (clinically irrelevant sensitization) or false negatives (less common in general but possible for certain foods).¹⁹ In this situation, the lack of history is the overwhelming factor for why someone should not be "screened" for cross-reactivity, and such screening would not obviate the need for an OFC to verify the significance of any positive test. The false-positive rate for food testing where there is lack of a convincing, recent supportive history for an IgE-mediated reaction can be high (eg, 50% to 80%), whereas the false-negative rate is variable based on the particular extract in question and its stability/allergen content.⁷ Peanut-allergic patients with positive SPT or sIgE testing to various other legumes should be told that the rate of clinically irrelevant cross-reactivity causing sensitization is high (approximately 90%), but the rate of true clinical reactivity (ie, allergic reaction) is low (approximately 5% to 10%).²⁰ Because of these

pitfalls, the OFC is the most important investigation for accurate diagnosis of irrelevant sensitization versus IgE-mediated allergy with potential for anaphylaxis, in the setting of positive SPT or sIgE testing to a legume never before consumed.⁷

With SR, you explain the pitfalls of SPT or sIgE testing before first ingestion for legumes SR has never tried before, but parents prefer not to take time from their busy schedules for OFCs to each individual legume he has not tried before. They understand the potential for false-positive or -negative results, but are absolutely insistent that they will not introduce these foods without testing, and their preference is to bring fresh foods for SPT in your office at one single follow-up visit. In the spirit of shared decision making, after again explaining the limitations of testing and the lack of standardized extracts for testing, you agree to work with the family to help facilitate introduction. At the follow-up, SPT is negative to fresh extracts of lentil and kidney bean, and lupin sIgE is positive (7.90 kU/L). You explain to the family that SR may have lupin allergy, but a formal diagnosis could only be made if a lupine OFC was performed (which you again offer). You describe that SR's risk of allergy to lentil and kidney bean is very low given both the low chance of clinical reactivity and the more sensitive (although potentially irritant) nature of SPT with fresh foods, and agree that it would be reasonable for him to try eating lentil and kidney beans for the first time at home.

WILL ORAL IMMUNOTHERAPY (OIT) TO PEANUT HELP TO DESENSITIZE SR TO SOY AND CHICKPEA AS WELL?

There is no evidence in the literature to suggest that peanut OIT treats allergy to other legumes, and there are no published data regarding the experience of OIT to these foods. There is limited evidence that pollen immunotherapy may result in desensitization to raw fruits/vegetables for those with pollen-food allergy syndrome, but this is limited to a paucity of data mainly with apple.^{21,22} There is also limited evidence that OIT to one tree nut may result in cross-desensitization to another tree nut.²³ Overall, there is too little evidence in the literature at present to suggest that peanut OIT helps with desensitization to other legumes, or provides any outcome beyond a dose-limited desensitization to peanut itself.

SHOULD SR RECEIVE SKIN TESTING TO TREE NUTS BEFORE FIRST INGESTION?

In vitro cross-sensitization between peanut and tree nuts has been found to be high in some studies, up to 86%.²⁴ These results are explained in part by the presence of similar (or closely related) epitopes, particularly in phylogenetically closely related nuts. For example, for pistachio and cashew, rPis v 3 and rAna o 1 have been found to have a high degree of cross-sensitization and reactivity. Similarly, pecan and walnut have a high degree of cross-sensitization and reactivity due to similarity between rCar I 4 and rJug r 4.^{25,26} In addition, cross-sensitization can occur between nuts belonging to phylogenetically distant species. Thus, extensive cross-sensitization has been demonstrated between the PR-10 proteins as well as between profilins, which are pan-allergens.¹⁵ Although *in vitro* cross-sensitization between storage proteins of unrelated nuts has been shown (ie, vicilins), clinical cross-reactivity resulting in allergy appears limited.²⁷ Most providers are aware of the risk of cosensitivity (positive

test results without demonstrated clinical reactivity), which has been commonly described.^{7,28} Peanut and tree nut allergy can coexist; based on a questionnaire and serologic testing, Sicherer et al²⁹ found that 37% of children allergic to peanut or tree nuts had a reaction to more than 1 nut, though this did not include OFC to validate these data. Similar data were found in the United Kingdom with one-third of patients reacting to multiple nuts, the most common being peanut, Brazil nut, almond, and hazelnut.³⁰

Thus, only a subgroup of patients allergic to peanut will have a concomitant allergy to one or several tree nuts. Correct identification of those at risk of systemic reaction to tree nuts is important, but particularly challenging. Indeed, indications for when to test in this context and the interpretation of the standard diagnostic workup (ie, SPT and sIgE to the whole nut extract) are hampered by cross-sensitization and it might be difficult to evaluate the clinical relevance of a positive test. Particularly, concomitant pollen sensitivity adds to diagnostic uncertainty by leading potentially to false-positive allergy tests. The development of CRD has been viewed as a major step forward for aiding the diagnostic evaluation of tree nut allergy. For example, European patients with positive sIgE to *Corylus avellana* (Cor a) 1 (PR-10), who have been primarily sensitized to tree pollen, are more likely to have mild reactions,³¹ whereas those sensitized to Cor a 9 and/or Cor a 14 are more likely to develop systemic reaction to hazelnut.¹⁵ Similarly, diagnosis of walnut and cashew allergy has been improved by measurement of sIgE to Jug r 1 and Ana o 3, respectively.^{32,33} Sensitization to LTPs such as Cor a 8 has been associated with systemic reactions mainly in the Mediterranean region, but positive tests to LTP are most of the time associated with localized or no symptoms.^{34,35} There is large geographical variation not only of tree nut allergy prevalence, but also sensitization profiles.^{36,37} For example, patients in Southern Europe are more likely sensitized to LTP (Cor a 8), whereas patients in Northern Europe or other birch-endemic regions are mainly sensitized to PR-10 (Cor a 1).³⁸ However, a significant proportion of patients are sensitized to different protein families at the same time, leading to difficulties in interpreting tests. In addition, allergen components are not commercially available everywhere, and not for all protein families in all tree nut.¹⁶ Thus, standard diagnostic workup does not always allow differentiation between clinically relevant sensitization and cross-reactivity/nonsignificant cross-sensitization.²⁸ The basophil activation test may be an emerging diagnostic laboratory tool, having recently shown promising results as a potential additional test to SPTs.³⁹ However, validation is still required, and this test is not available routinely outside of the research setting. Thus, the OFC remains the gold standard and plays a key role in management. Several recent studies based on OFCs report a lower rate of coexistent tree nut allergy (ie, less than 30%), compared with studies based on SPTs and/or sIgE results.³⁹⁻⁴¹ A recent study performed in Finland (birch-endemic region) showed that only 67.6% of the patients with suspected tree nut allergy based on current diagnostic criteria (peanut SPT ≥ 8 mm or peanut sIgE ≥ 15 kU/L) had an allergy confirmed by positive OFC.⁴² Of note, those studies were retrospective, and prospective studies based on OFC are ongoing to more accurately evaluate the rate of coexistent allergy between peanut, tree nut, and sesame.

The OFC is associated with potential for high medical costs and requires a safe setting with trained and experienced medical

staff. The decision to perform an OFC should be based on the clinical history, the results of the SPTs, and/or sIgE results, especially to different allergen components taking into account the geographical region. In case of positive SPT or sIgE tests, a specific tree nut should be introduced via physician-supervised OFC.⁴³ Some authors recommend home introduction if both SPT and sIgE are negative and there is no history of ingestion/reaction.⁴³

A concern associated with the decision to introduce tree nuts in patients allergic to peanut is the potential for cross-contamination, and some patients are not able to distinguish between different tree nuts.²⁸ Also, it cannot be excluded that recent recommendations to introduce peanut early in infancy might lead to increased rates of tree nut sensitization, for infants with positive peanut SPT, sIgE, and/or reaction on first peanut ingestion who thereafter are not given the opportunity to eat tree nuts regularly. It remains unclear if the introduction of a tree nut will prevent the development of allergy to that tree nut or not, particularly if the tree nut is not consumed regularly after its introduction. However, these concerns should be balanced with the potential risk of developing tree nut allergy in patients with peanut allergy due to the lack of exposure. Indeed, it has been shown that the rate of multisensitization and multiallergy increases with patient age.⁴⁴ In addition, it has been suggested that children sensitized to peanut are more likely to develop tree nut sensitization if they are not exposed.⁴⁵ Moreover, an over-restrictive diet has a clear impact on nutritional status and quality of life. All these factors need to be taken into account when making an individualized decision whether to introduce tree nuts in peanut-allergic patients. Further studies are urgently needed to answer these questions.

After a discussion of the pitfalls of testing to tree nuts before first ingestion, SR's parents decide to forego tree nut SPTs or sIgE testing, explaining that even if the tests are negative, they would not introduce SR to tree nuts because the older brother is tree nut allergic and the home is tree nut free. They also state that if testing is positive, both SR and his parents would not have any interest in pursuing an OFC due to difficulty in having him consume them regularly. Based on SR's relatively recent history of peanut reaction and continued convincing evidence of peanut sensitization (as assessed by you at his recent follow-up), you describe that his likelihood of outgrowing peanut allergy is low (and that the natural history of allergy to other legumes is unclear in the literature). You also suggest a repeat discussion of the family's comfort level with introducing SR to tree nuts at his next peanut allergy reassessment.

CONCLUSION

Although peanut-allergic patients may develop allergy to other legumes, the rate of clinically irrelevant cross-sensitization is much higher than the rate of clinical cross-reactivity. Caution is needed in both interpreting the literature and explaining this phenomenon to families, to clearly delineate when studies are describing only cross-sensitization as opposed to cross-reactivity. Although CRD may be helpful in some cases, this is not universally available clinically and does not replace the gold standard that remains the OFC. More research is needed to determine whether peanut desensitization for peanut-allergic individuals has any effect for concomitant allergy to other legumes. For peanut-allergic patients who have never ingested

tree nuts, it is recognized that there may be hesitancy to introduce tree nuts for the first time at home, but SPT and/or sIgE before tree nut introduction remains equally problematic and susceptible to false-positive results, with the OFC again representing the most ideal outcome as long as regular ingestion after passing the challenge is discussed before the procedure.

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