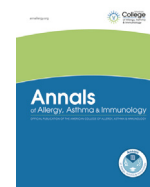




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Characteristics of tree nut challenges in tree nut allergic and tree nut sensitized individuals

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ABSTRACT

Background: Characteristics and outcomes of tree nut (TN) oral food challenges (OFCs) in patients with TN allergy or sensitization alone are poorly studied.

Objective: To determine the relation between TN sensitization levels and OFC outcomes.

Methods: Open TN OFCs performed from 2007 through 2015 at a referral center were analyzed to compare outcome based on skin prick test (SPT) wheal size, food-specific immunoglobulin E (sIgE), peanut co-allergy, and TN sensitization only vs TN allergy with sensitization to other TNs. Delayed OFC was defined as longer than 12 months from the time of an sIgE level lower than 2 kUA/L.

Results: Overall passage rate was 86% for 156 TN OFCs in 109 patients (54 almond, 28 cashew, 27 walnut, 18 hazelnut, 14 pecan, 13 pistachio, and 2 Brazil nut). Passage rates were 76% (n = 67) in patients with a history of TN allergy who were challenged to another TN to which they were sensitized and 91% (n = 65) in those with TN sensitization only (mean sIgE 1.53 kUA/L; range 0.35–9.14). Passage rates were 89% (n = 110 of 124) for a TN sIgE level lower than 2 kUA/L and 69% (11 of 16) for a TN sIgE level of at least 2 kUA/L. In 44 challenges in patients with peanut allergy and TN co-sensitization, the TN OFC passage rate was 96%. In 41 TN OFCs with a TN SPT wheal size of at least 3 mm, 61% passed, with a mean wheal size of 4.8 mm (range 3–11) in those passing vs 9 mm (range 3–20) in those failing.

Conclusion: TN challenges are frequently passed in patients with TN sensitization with or without a history of TN reactivity despite a TN SPT wheal of at least 3 mm or a TN sIgE level of at least 2 kUA/L. Nearly all patients with peanut allergy and TN co-sensitization passed the TN challenge, questioning the clinical relevance of “co-allergy.”

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Introduction

Food allergy to tree nut (TN) is estimated to affect approximately 1% of children in the United States based on self-report survey, and this rate has tripled over a 10-year period.¹ Compared with other foods, TN and peanut immunoglobulin E (IgE)-mediated reactions

are particularly associated with a higher degree of potential severity and are attributed as leading causes of fatal food allergy-induced anaphylaxis.^{1,2} Similar to peanut allergy (PA), TN allergy tends to persist into adulthood.³ Resolution rates for TN allergy might be lower than those for PA, although few longitudinal data

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Immunology, the European Academy of Allergy and Clinical Immunology, and the UCLA-Harbor Medical Center; and is a member of the Joint Task Force on Allergy Practice Parameters. Dr Couch and Dr Franxman report no relevant conflicts of interest.

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on TN allergy exist. In 1 study of 101 children with a history of clinical reactions to TN, resolution of TN allergy was reported for only 9% of patients,⁴ whereas recent data regarding PA reported that 22% of children regained tolerance based on a diagnosis established by an oral food challenge (OFC).⁵ In another large, nationally representative study, 14.3% of those who at one time self-reported TN allergy later reported tolerance.¹

In the setting of suspected TN reaction, skin prick testing (SPT) and serum-specific IgE (sIgE) help confirm an IgE-mediated food allergy and could serve as predictive measurements to assess the necessity of an OFC to confirm diagnosis. SPT and sIgE levels also have potential longitudinal utility to assess patient readiness to undergo OFC to determine whether they are still allergic. In peanut, egg, and milk allergies, an sIgE level lower than 2.0 kUA/L is a proposed 50% negative predictive value (NPV) at which patients can pass an OFC, and this should be offered.^{3,6} In TN allergy, a higher threshold has been proposed based on a study that examined 39 TN OFCs performed in children 4 to 19 years of age at a referral center, noting a 58% NPV with a TN sIgE level lower than 5.0 kUA/L and a 63% NPV with an sIgE level lower than 2.0 kUA/L.⁴ Given the limited published data on TN allergy, additional studies are needed to help better guide clinical decision making.

In clinical practice patients with PA are often screened for TN allergy. TNs are drupaceous fruits and peanuts are legumes, but they share certain cross-reactive IgE-binding epitopes.⁷ It is common for patients with PA to demonstrate some degree of TN co-sensitization and vice versa. Patients allergic to a particular TN often demonstrate co-sensitization to other TNs.^{8,9} In patients with PA, TN co-sensitization can occur in up to 86% of patients, although only 34% might display clinical reactivity TN (eg, symptom development after ingestion).¹⁰ Furthermore, many providers instruct children with PA to avoid TNs because of TN sensitization, despite no history of any TN reaction or low or absent sensitization. It is unclear whether this cross-reactivity is clinically relevant, and an OFC might be necessary to confirm a suspected IgE-mediated TN allergy.

There are no specific recommendations regarding the timing of when to perform an OFC in relation to low-positive or negative TN test results.^{3,11} It has been postulated that the OFC can be safely performed when sIgE test results are below the published 50% NPV cutoffs, although such values for TN are poorly established.¹² It is unclear whether decreasing or low sIgE levels and/or skin test results are superior predictors of being ready for an OFC, or what to do when these values are somewhat discrepant. Delaying an OFC can lead to additional, possibly unneeded, costs to the families and the health care system.¹¹ The objectives of this study were to provide additional data on the characteristics and outcomes of TN OFCs in patients with TN sensitization with and without a history of allergy to another TN and to further examine TN OFC characteristics and outcomes in individuals with PA and TN sensitization.

Methods

Study Design

A retrospective analysis was performed for all open TN OFCs conducted at the University of Michigan Division of Allergy and Clinical Immunology clinics (Ann Arbor) from 2007 through 2015. Patients undergoing TN OFC were identified from the allergy division database using *International Classification Diseases, Ninth Revision* coding and *Current Procedural Terminology* coding for OFC. Patients who had TN SPT and/or corresponding TN sIgE testing before the challenge were included in the study. Patients with a history of non-IgE-mediated food allergy were excluded. TN SPT wheal size, TN sIgE level, coexisting food allergy, comorbid allergic disease, and features of the patient's initial and any subsequent reactions were abstracted through chart review, and National

Institutes of Allergy and Infectious Diseases and Food Allergy & Anaphylaxis Network anaphylaxis criteria were used to assess the severity of documented reaction symptoms.¹³ In addition, timing of OFC in relation to testing results was assessed, with delayed OFC defined as occurring longer than 12 months from the time of an sIgE level lower than 2 kUA/L. The number of additional visits with testing from the time of an sIgE level lower than 2 kUA/L, age at time of OFC, and OFC outcome also were explored. Reasons for delaying OFC were not explored. Subjects were classified as allergic to TN (chart-documented clinical symptoms after TN ingestion), sensitized to TN (positive test results alone without lifetime TN exposure), or avoiding TN despite no sensitization or reaction history. Subjects with TN allergy in the study were not challenged to any TN to which they had demonstrated previous symptomatic reactivity upon ingestion. These individuals were challenged only to the TN to which they were sensitized and were being effectively managed as allergic to that item with avoidance recommended but without having ever ingested it.

Statistical Analysis

The primary outcome was to investigate the passage rates of TN OFCs in relation to SPT and sIgE results. Secondary outcomes included time to challenge (months), differences in OFC outcome based on sensitization vs allergy, age at the time of OFC, number of additional visits, history of anaphylaxis, and allergen type between the 2 groups. Descriptive statistics were analyzed to characterize the population, and Fisher exact tests and logistic regression were used to assess bivariate relations. Adjusted multiple regression models were used to determine predictive associations, and the STATA margins command was used to determine predictive values for challenge outcomes. An a priori determined α value of 0.05 was used for significance. All analyses were performed using STATA SE 13 (STATA Corp, College Station, Texas). The study was approved by the institutional review board of the University of Michigan.

Results

There were 156 TN OFCs identified for analysis; these were performed in 109 patients from 2007 through 2015. Patient characteristics are listed in [Table 1](#). Comorbid atopy was prominent. Half the patients in the population had TN allergy (defined as reporting clinical symptoms with TN ingestion and having positive skin or serum test results; $n = 54$), whereas 40% were only sensitized to TN (positive TN allergy test result only, without known symptoms attributable to ingestion; $n = 43$). The remaining ($n = 13$) had been avoiding TN because of another food allergy, despite negative TN test results, for unclear reasons (eg, presumed parent or provider preference that was poorly documented in the medical record). Most patients in the population (60%) had an additional food allergy, most commonly to peanut (42%). The most common presenting symptoms to any TN ingestion at initial diagnosis in those with TN allergy were skin manifestations including hives, itching, flushing, and/or rash and 28% had chart-documented symptoms consistent with anaphylaxis.

Overall Characteristics of TN Challenges in the Population

Challenge characteristics are listed in [Table 2](#). The overall OFC passage rate was 86%. Almond challenge was most commonly performed ($n = 54$), with a 100% passage rate. Of 67 TN challenges in patients with a prior reaction to TN (who were challenged to another TN to which they were sensitized), the passage rate was 76%, whereas the passage rate was 91% in 65 TN sensitized challenges (eg, no history of TN ingestion). The successful challenge rate (eg, "pass") was 71% in those with a history of anaphylaxis ($n = 21$) at initial diagnosis ([eTables 1.1–1.3](#)). Passage rate was the lowest (56%) in patients with facial swelling at initial presentation, and the

Table 1
Study Population Characteristics (N = 109)

Boys, n (%)	58 (53)
Age at tree nut allergy or sensitization diagnosis (y), mean (median)	4.5 (2.5)
Age at initial tree nut oral food challenge (y), mean (median)	11.2 (10.3)
Tree nut allergy (any symptom at initial presentation), n (%) ^a	54 (50)
Anaphylaxis	15 (28)
Skin symptoms (hives, itching, flushing, rash)	36 (67)
Facial swelling	16 (30)
Oropharyngeal symptoms (tongue or throat pruritus or swelling)	13 (24)
Respiratory symptoms (cough, wheezing, shortness of breath)	11 (20)
Vomiting	13 (24)
Tree nut sensitization (no clinical symptoms), n (%)	43 (40)
Tree nut avoidance owing to other food allergy (despite negative test results), n (%)	13 (12)
Concurrent food allergy, n (%)	65 (60)
Peanut allergy	46 (42)
Egg allergy	10 (9)
Milk allergy	4 (4)
Other food allergy	15 (14)
Atopic dermatitis, n (%)	42 (39)
Allergic rhinitis, n (%)	78 (72)
Asthma, n (%)	44 (40)

^aThese represent the most commonly reported symptoms and not necessarily an isolated single presenting symptom.

highest passage rate was 83% in patients with skin symptoms or vomiting. Most challenges were performed in patients with a TN sIgE level lower than 2 kUA/L (n = 124), and these had an 89% passage rate.

Of 101 challenges in patients with a TN SPT wheal smaller than 3 mm, the passage rate was 96%. Of OFCs in 47 patients with a TN sIgE level of at least 2 kUA/L (mean 6.41; range 2.23–19.7) and/or a TN SPT wheal of at least 3 mm (mean 6.5; range 3–20), the passage rate was 64% (partial data presented in Table 2). Passage rate was 61% for 41 TN OFCs with a wheal size of at least 3 mm, with a mean SPT wheal of 4.8 mm (range 3–11) in those passing vs 9 mm (range 3–20) in those failing the challenge. Passage rate was 69% for 16 OFCs with a TN sIgE level of at least 2 kUA/L near or at the time of the OFC, with mean a TN sIgE level of 5.12 kUA/L (range 2.23–9.14) in those passing the OFC vs 9.27 kUA/L (range 2.38–19.7) in those failing the OFC. In 65 TN OFCs in subjects sensitized to TN, 59 of 65 challenges were successful, including 10 in patients with an sIgE level of at least 2 kUA/L (median 4.49; mean 5.24; range 2.23–9.14) and 11 in patients with an SPT wheal size of at least 3 mm (median 4; mean 4.8; range 3–11). As presented in Figure 1, the NPV was 50% for TN skin test wheal size and sIgE level for all subjects in the entire sample (combined TN allergic and TN sensitized), adjusted for age, asthma, eczema, sex, and comorbid PA. Of the 156 TN OFCs, 94 were delayed (60%), with mean time to OFC for those that were delayed of 50 months (range 14–108) compared with 3.6 months

for those that were not delayed. The mean number of additional visits with testing until OFC was performed in the delayed group was 2.1 (range 0–7).

Table 2 presents data on the characteristics of failed challenges. Of the 22 failed OFCs, 14 had an sIgE level lower than 2 kUA/L and 4 had an SPT wheal size smaller than 3 mm. Most failed challenges (73%) had a recent SPT wheal size of at least 3 mm, whereas only 23% had an sIgE level of at least 2 kUA/L. Most patients failing OFC were allergic to TN (73%). Cashew was the most frequently failed challenge (n = 6), followed by walnut (n = 5) and pistachio (n = 4). No one failed almond challenge. Combining data, the OFC passage rates were 96% in OFCs with an SPT wheal smaller than 3 mm and 89% with an sIgE level lower than 2 kUA/L.

TN Challenges in Clinically Reactive vs Sensitized Individuals

Of 67 challenges in patients with TN allergy, there were 25 OFCs undertaken in individuals with a wheal size of at least 3 mm, with a passage rate of 56%. There were only 3 OFCs with an sIgE level of at least 2 kUA/L in this subgroup (all presented with anaphylaxis), with 1 that was passed (3.92 kUA/L). In 2 of these failed challenges, the sIgE level was 12.8 and 19.7 kUA/L respectively.

Table 3 presents TN sIgE and SPT results obtained in closest proximity to the time of OFC. For all TN challenges, mean sIgE level was higher in failed OFC (2.88; median 0.35; range <0.35–19.7) vs passed OFC (0.89; median 0.35; range <0.35–9.14; *P* = .01). This trend also was seen with SPT wheal size, with a mean of 7.4 mm (median 7.5; range 0–20) in failed OFC vs 1.1 mm (median 0; range 0–11) in passed OFC (*P* < .001). There was a higher mean sIgE level (1.53 kUA/L; median 0.35; range 0.35–9.14) for challenges in the TN-sensitized subset compared with the TN-allergic subset (0.99 kUA/L; median 0.35; range 0.35–19.7). However, mean SPT wheal size was slightly larger in patients with TN allergy (2.4 mm; 95% confidence interval 1.5–3.3) vs patients sensitized to TN (2.1 mm; 95% confidence interval 1.1–3.1). In the 6 failed challenges in subjects sensitized to TN, mean sIgE was 3.44 kUA/L (median 2.38; range 1.57–7.90), and mean SPT wheal size was 10.3 mm (median 10; range 2–20). In comparison, in 16 failed challenges in subjects with TN allergy, the mean TN sIgE level was 2.68 kUA/L (median 0.35; range 0.35–19.7), and mean SPT wheal size was 6.1 mm (median 5; range 0–16). The 50% NPVs for the TN challenge in subjects with TN sensitization and those with TN allergy are displayed in Figures 2 and 3, respectively. The 50% NPVs for the cashew and pistachio and the walnut, hazelnut, and pecan challenges are displayed in eFigure 1.

TN Challenges in Peanut and TN Co-Allergic Population

In this sample, 56 of 109 had a positive peanut SPT or sIgE result (n = 46 with PA, n = 10 with peanut sensitization). Characteristics

Table 2
Characteristics of TN OFCs^a

	n	Pass rate, %	OFC with sIgE <2 kUA/L, n (%)	OFC with sIgE ≥2 kUA/L, n (%)	OFC with SPT wheal <3 mm, n (%)	OFC with SPT wheal ≥3 mm, n (%)
All TN challenges	156	86	124 (79)	16 (10)	101 (65)	41 (26)
TN allergic	67	76	60 (90)	3 (4)	39 (58)	25 (37)
TN sensitized	65	91	47 (72)	13 (20)	45 (69)	16 (25)
Avoiding owing to other FA	24	100	17 (71)	—	17 (71)	—
Almond	54	100	42 (78)	6 (11)	37 (69)	11 (20)
Cashew	28	79	28 (100)	0 (0)	18 (64)	9 (32)
Walnut	27	82	19 (70)	3 (11)	15 (56)	10 (37)
Hazelnut	18	83	12 (67)	4 (22)	13 (72)	2 (11)
Pecan	14	79	10 (71)	1 (7)	11 (79)	3 (21)
Pistachio	13	69	11 (85)	2 (15)	8 (62)	4 (31)
Brazil nut	2	50	2 (100)	0 (0)	0 (0)	2 (100)

Abbreviations: FA, food allergy; OFC, oral food challenge; sIgE, specific immunoglobulin E level; SPT, skin prick test; TN, tree nut.

^aNinety-two percent of TN challenges had sIgE and SPT performed, 9% had only SPT performed, and 9% had only sIgE performed.

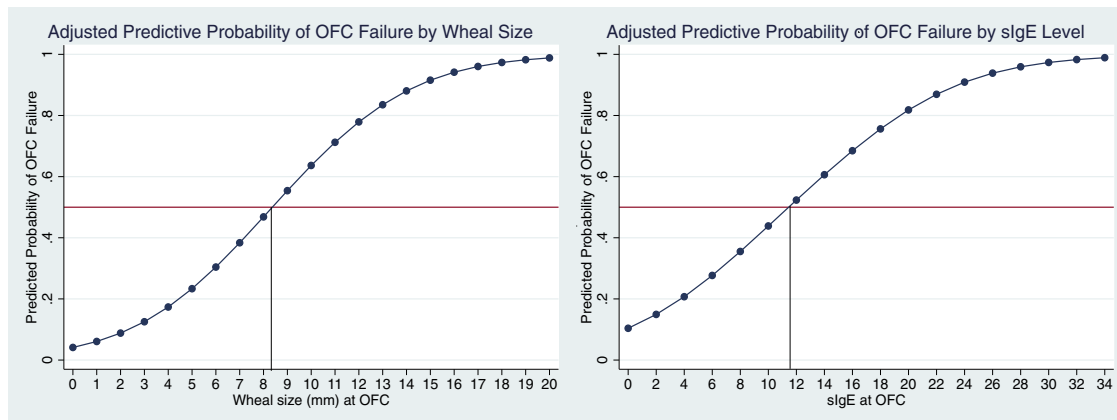


Figure 1. Fifty percent negative predictive values for an oral food challenge (OFC) to tree nut in subjects with tree nut allergy and sensitization. Values were adjusted for patient age, eczema, asthma, sex, and peanut allergy. Left panel displays wheal size curve and right panel displays tree nut specific immunoglobulin E (sIgE) curve.

of subjects with PA and those with peanut sensitivity are listed in Table 4. The initial peanut mean SPT wheal size was 9.7 mm and the initial mean sIgE level was 31.4 kUA/L, and 26% presented with symptoms constituting anaphylaxis. Sixty-five percent of patients with PA were sensitized to TN, 20% were allergic to TN, and 15% were avoiding TN despite negative TN test results and no exposure. There were 68 TN OFCs performed in the 46 patients with PA, with a passage rate of 96% (eTable 3). There were only 3 failed challenges occurring in 3 different patients (to walnut, hazelnut, and pistachio, respectively). Of those with PA, only 13% who were allergic to TN were challenged compared with 65% of those with TN sensitization and 22% of those who had been avoiding TN despite negative test results. Most TN challenges in these subjects with PA or peanut sensitization were performed in subjects with negative TN test results at the time of challenge, including 51 patients with an sIgE level lower than 2 kUA/L and 49 patients with an SPT wheal smaller than 3 mm. Fourteen TN OFCs were performed in the peanut-allergic population with a TN sIgE level of at least 2 kUA/L and/or an SPT wheal of at least 3 mm.

Discussion

In one of the largest series of TN OFCs to date, in this population there was a high TN challenge passage rate for subjects with TN allergy (challenged to a TN to which they were sensitized) and those with only TN sensitization, despite increased TN sensitization levels as noted by the 50% NPVs calculated for the population. These levels might provide reassurance that there is a larger margin of SPT or sIgE sensitization within which to strongly consider offering

an OFC, irrespective of whether the patient reacted to another TN or had PA, because these challenges were very well tolerated. Most subjects had TN allergy to at least 1 nut (50%), although a large subgroup was sensitized only to TN without any prior TN exposure (40%), and this sensitized group might have leveraged an overall high passage rate (86%). However, of subjects with allergy to TN, OFC pass rates to another TN to which they were sensitized remained relatively high at 76%. It is notable that most challenges took place with a recent SPT wheal smaller than 3 mm and/or an sIgE level lower than 2 kUA/L, which could suggest that, at this particular center, there might have been a bias toward challenging individuals with absent or minimal sensitization or a strong parental or provider preference for waiting until this scenario occurred. This is a limitation of the study. Because the study was retrospective, we could not assess these motivations. However, such a scenario might be relatively commonplace in clinical practice, given little guidance to influence decision making on the optimal timing and sensitization level for OFCs and a general overall confusion of how to manage TN sensitization.

Fleischer et al.⁴ noted a 45% pass rate in 20 TN challenges (median sIgE 0.84 kUA/L). Our pass rate was higher at 76% in 67 TN OFCs performed in subjects with TN allergy (median sIgE 0.35 kUA/L; mean 0.99), and at least half our challenges took place with an sIgE level lower than 0.35 kUA/L, which also could account for the higher pass rate, although our intent was not to directly compare these populations. It is noteworthy that in this study the median sIgE level was lower than 0.35 kUA/L in 16 failed challenges (mean 2.68), demonstrating that nondetectable sIgE levels do not necessarily infer success. SPT wheal size in this subgroup was better associated

Table 3
TN-specific IgE and Skin Prick Test Characteristics Near Time of Oral Food Challenge

	Pass rate, %	sIgE all (kUA/L), mean (median)	sIgE passed (kUA/L), mean (median)	sIgE, failed (kUA/L), mean (median)	Wheal size all (mm), mean (median)	Wheal size passed (mm), mean (median)	Wheal size failed (mm), mean (median)
All TN challenges (n = 156)	86	1.14 (0.35)	0.89 (0.35)	2.88 (0.35)	1.9 (0)	1.1 (0)	7.4 (7.5)
TN allergic (n = 67)	76	0.99 (0.35)	0.51 (0.35)	2.68 (0.35)	2.4 (0)	1.4 (0)	6.1 (5.0)
TN sensitized (n = 65)	91	1.53 (0.35)	1.36 (0.35)	3.44 (2.38)	2.1 (0)	1.2 (0)	10.3 (10.0)
Avoiding owing to other FA (n = 24)	100	0.35 (0.35)	0.35 (0.35)	—	0 (0)	0 (0)	—
Almond (n = 54)	100	1.18 (0.35)	1.18 (0.35)	—	1.27 (0)	1.27 (0)	—
Cashew (n = 28)	79	0.49 (0.35)	0.40 (0.35)	0.80 (0.38)	3.0 (0)	0.7 (0)	11.0 (10.5)
Walnut (n = 27)	82	1.36 (0.37)	0.74 (0.35)	4.16 (1.75)	2.5 (0)	1.4 (0)	7.4 (7)
Hazelnut (n = 18)	83	1.31 (0.54)	1.22 (0.54)	1.96 (1.96)	1.0 (0)	0.9 (0)	2.0 (2.0)
Pecan (n = 14)	79	2.15 (0.35)	0.40 (0.35)	10.03 (10.03)	1.4 (0)	0.5 (0)	4.7 (5.0)
Pistachio (n = 13)	69	1.13 (0.35)	0.64 (0.35)	2.24 (0.35)	3.4 (0)	1.9 (0)	8 (4.0)
Brazil nut (n = 2)	50	0.35 (0.35)	0.35 (0.35)	0.35 (0.35)	3.0 (3.0)	3.0 (3.0)	3.0 (3.0)

Abbreviations: FA, food allergy; sIgE, specific immunoglobulin E; TN, tree nut.

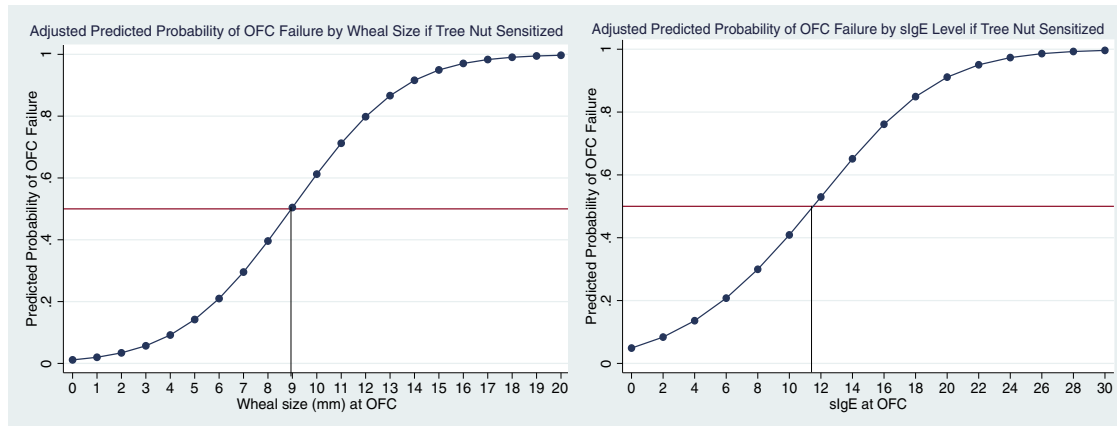


Figure 2. Fifty percent negative predictive values for an oral food challenge (OFC) to tree nut in subjects sensitized to tree nut. Values were adjusted for patient age, eczema, and peanut allergy. Left panel displays wheal size curve and right panel displays tree nut specific immunoglobulin E (sIgE) curve. Data reflect the relation of tree nut sensitization in subjects with no history of tree nut allergy.

with failure, although 56% passed OFCs with an SPT wheal of at least 3 mm.

The discovery of TN sensitization in individuals who have never ingested any TN or might be reactive to another TN but have never ingested the particular TN in question has become problematic in clinical practice. Sensitization in this context is difficult to interpret, is poorly specific, and can lead to potentially unnecessary food avoidance through conservative management.^{14,15} We found that 91% of 42 patients with sensitivity to TN undergoing 65 TN OFCs were successful, and OFC in these scenarios might have high utility.

Tree nut sensitization found while screening individuals with PA is equally problematic and can lead to unnecessary TN avoidance. Peters et al⁵ recently reported that in a population with OFC-proved PA, the TN sensitization rate was 61% for cashew, almond, or hazelnut. Another study using sIgE levels reported a higher rate of TN sensitization (88%) in patients with PA, but clinical TN allergy was present in only 34% of patients.¹⁰ We found that 42% of patients had PA, with 65% of these patients sensitized to TN and 20% allergic to TN. However, in the group with PA and TN sensitization, almost all TN OFCs were successful (96%), exceeding a prior study with a 69% passage rate in a similar clinical population.¹⁶ These data demonstrate that the success rate of TN OFCs in individuals with PA is potentially much higher than presumed and can lend to the consideration for a more proactive management of such patients. These aggregate data also question the utility of the common practice of screening for TN IgE sensitivity in individuals lacking

any TN exposure, given that most pass these challenges. This is particularly key for almond, for which all 54 OFCs were successful, 67% of which had PA. These findings could suggest that a more aggressive introduction approach might be possible with almond, although further study is necessary to validate this possibility.

In exploring the timing of TN OFC, 60% of such OFCs were delayed longer than 12 months. Fleischer et al⁴ reported a 63% NPV with a TN sIgE level lower than 2 kUA/L and recommended offering OFC given the relative likelihood of passing. We found that 89% of 124 challenges with an sIgE level lower than 2 kUA/L passed, further validating a high likelihood of passing an OFC below this threshold in a larger sample. Twelve months is a reasonable timeframe to perform an OFC if there is mutual intent to do so and believe this is an appropriate, if not conservative, time marker to use. We previously demonstrated that delaying OFC can lead to additional economic costs to families and the health care system.¹¹ The high rate of success from these data provide further lack of justification that such a delay is indicated or improves outcomes.

There were several limitations to this study. It was retrospective in nature, with all data obtained from electronic medical record review. All challenges were open and not double blinded, although open challenge is the standard for clinical practice but can be associated with subjective failure. In addition, this study was performed in a single institution at a food allergy referral center, and the study population can include subjects with “higher risk” food allergy and thus be viewed as clustered data that might not

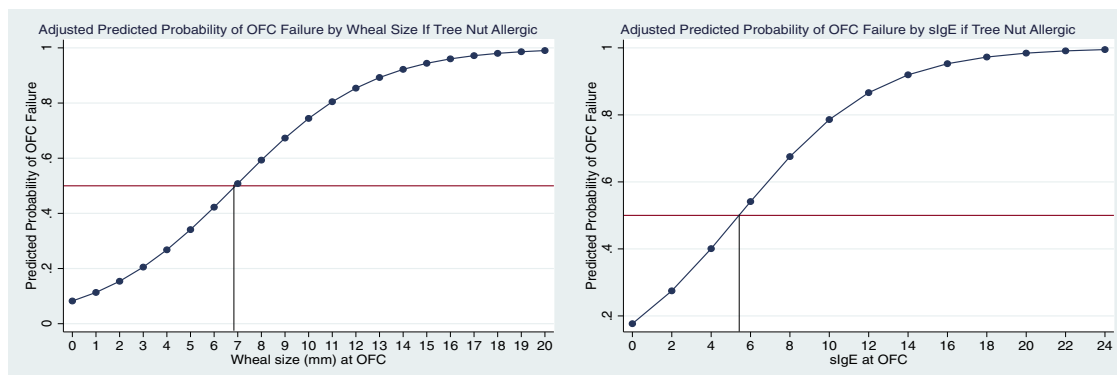


Figure 3. Fifty percent negative predictive values for an oral food challenge (OFC) in subjects with allergy to tree nut. Values were adjusted for patient age, eczema, and peanut allergy. Left panel displays wheal size curve and right panel displays tree nut specific immunoglobulin E (sIgE) curve. Data reflect the relation of tree nut sensitization in subjects with a primary allergy to a tree nut other than the one tested.

Table 4
Peanut-allergic Population Characteristics Challenged to Tree Nut (N = 46)

Boys, n (%)	24 (52)
Age at peanut allergy diagnosis (y), mean (median)	2.5 (2.0)
Age at initial tree nut oral food challenge (y), mean (median)	10.2 (10.4)
Symptom at initial peanut allergy presentation, n (%)	
Anaphylaxis	12 (26)
Skin symptoms (hives, itching, flushing, rash)	43 (93)
Facial swelling	13 (28)
Oropharyngeal symptoms (tongue or throat pruritus or swelling)	6 (13)
Respiratory symptoms (cough, wheezing, shortness of breath)	7 (15)
Vomiting	14 (30)
Tree nut allergic, n (%)	9 (20)
Tree nut sensitized (no clinical symptoms), n (%)	30 (65)
Avoiding tree nut despite negative test result, n (%)	7 (15)
Atopic dermatitis, n (%)	21 (46)
Allergic rhinitis, n (%)	33 (72)
Asthma, n (%)	20 (43)
Initial peanut SPT wheal size (mm), mean (median)	9.7 (10.0)
Most recent peanut SPT wheal size (mm), mean (median)	9.0 (9.0)
Initial peanut sIgE (kUA/L), mean (median)	31.4 (3.0)
Most recent peanut sIgE (kUA/L), mean (median)	39.3 (8.0)

Abbreviations: sIgE, specific immunoglobulin E; SPT, skin prick test.

generalize to other populations. Although we highlight the 50% NPV for when these OFCs were passed, these are applicable to our study population and might not necessarily generalize to other populations. Thus, caution should be used in interpreting those data. Most challenges were passed (86%), but most were performed with an sIgE level lower than 2 kUA/L and/or an SPT wheal smaller than 3 mm, indicating a possible selection bias in the baseline sample available for analysis for performing OFC in patients who would likely pass an OFC and provider and/or parent preference for an OFC with minimal or absent sensitization. It is unclear whether this occurred, because preferences for what patients were offered an OFC (and why) were not explored. As stated earlier, we could not determine the motivations of the provider or child's caregiver with respect to why the challenge was not performed before sensitization levels decreased to low or absent levels in some cases or why avoidance was recommended with no evidence of TN sensitization. Furthermore, it is unclear whether this pattern would actually be an outlier compared with other academic centers or community practices, given limited data on trends in TN challenges, including provider preferences for offering an OFC. Nevertheless, there were still a number of challenges performed in sensitized patients, including those with a history of PA and allergy to another TN, which are described risk factors for TN allergy.³ Despite these limitations, the study provides useful TN data that might be of use to help guide clinical decisions regarding OFC and the need for TN avoidance in individuals with TN allergy or sensitization, including the peanut-allergic co-sensitized population.

In conclusion, patients with TN allergy (being challenged to a TN to which they were sensitized) or TN sensitization in this population frequently passed TN OFCs despite an sIgE level of at least 2 kUA/L and/or an SPT wheal of at least 3 mm. We propose that positive TN SPT results (wheal size ≥ 3 mm) might be a better predictor of OFC outcome than sIgE levels in individuals with TN

allergy when the 2 tests are available. Outcomes of TN OFCs in patients with TN sensitization are difficult to predict using sIgE and/or SPT results, and we recommend that an OFC should be performed despite sensitization to further clarify the clinical relevance of positive test results. Given the high success rate of TN OFCs in individuals with PA, regardless of positive TN test results, we question the value of performing screening TN SPT or sIgE in patients without lifetime TN exposure. More specifically, we found that almond might be introduced into the diet of patients with PA without the need to perform SPT, sIgE, and/or OFC because 100% passed the almond challenge in our sample. Although this study contributes valuable data on TN allergy and TN sensitivity, additional studies are needed to help guide clinical decision making in this area.

Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.jana.2017.02.010>.

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eTable 1.1Characteristics of Tree Nut OFCs Near the Time of OFC in Individual Allergic to Tree Nut by Presenting Symptoms^a

	n	Pass rate, %	OFC with sIgE <2 kUA/L, n (%)	OFC with sIgE ≥2 kUA/L, n (%)	OFC with SPT wheal <3 mm, n (%)	OFC with SPT wheal ≥3 mm, n (%)
Anaphylaxis	21	71	17 (81)	3 (14)	11 (52)	8 (38)
Skin symptoms	46	83	41 (89)	1 (2)	33 (72)	13 (28)
Facial swelling	18	56	16 (89)	2 (11)	8 (44)	8 (44)
Oropharyngeal symptoms	15	73	12 (80)	2 (13)	10 (67)	5 (33)
Respiratory symptoms	15	67	14 (93)	1 (7)	8 (53)	6 (40)
Vomiting	18	83	17 (94)	1 (6)	10 (56)	7 (39)

Abbreviations: OFC, oral food challenge; sIgE, specific immunoglobulin E; SPT, skin prick test.

^aSkin symptoms were hives, itching, flushing, or rash. Oropharyngeal symptoms were tongue or throat pruritus or swelling. Respiratory symptoms were cough, wheezing, or shortness of breath. Ninety-three percent of tree nut challenges in individual allergic to tree nut had sIgE and SPT performed, 6% had only SPT performed, and 1% had only sIgE performed.**eTable 1.2**Testing Characteristics at Time of Initial Diagnosis for Tree Nut OFCs in Individual Allergic to Tree Nut by Presenting Symptoms^a

	n	sIgE <2 kUA/L, n (%)	sIgE ≥2 kUA/L, n (%)	SPT wheal <3 mm, n (%)	SPT wheal ≥3 mm, n (%)
Anaphylaxis	21	17 (81)	3 (14)	8 (38)	11 (52)
Skin symptoms	46	40 (87)	2 (4)	23 (50)	23 (50)
Facial swelling	18	16 (89)	2 (13)	6 (33)	10 (56)
Oropharyngeal symptoms	15	12 (80)	2 (13)	7 (47)	8 (53)
Respiratory symptoms	15	14 (93)	1 (7)	5 (33)	9 (60)
Vomiting	18	16 (89)	2 (11)	9 (50)	8 (44)

Abbreviations: OFC, oral food challenge; sIgE, specific immunoglobulin E; SPT, skin prick test.

^aSkin symptoms were hives, itching, flushing, and rash. Oropharyngeal symptoms were tongue or throat pruritus or swelling. Respiratory symptoms were cough, wheezing, or shortness of breath. Ninety-three percent of tree nut challenges in individual allergic to tree nut had sIgE and SPT performed, 6% had only SPT performed, and 1% had only sIgE performed.**eTable 1.3**Testing Characteristics at Time of Initial Diagnosis in Tree Nut Allergic Individuals by Presenting Symptoms^a

	n	sIgE <2 kUA/L, n (%)	sIgE ≥2 kUA/L, n (%)	SPT wheal <3 mm, n (%)	SPT wheal ≥3 mm, n (%)
Anaphylaxis	15	12 (80)	3 (20)	7 (47)	7 (47)
Skin symptoms	36	31 (86)	2 (6)	19 (53)	17 (47)
Facial swelling	16	15 (94)	2 (13)	5 (19)	10 (63)
Oropharyngeal symptoms	13	10 (77)	2 (15)	7 (54)	6 (46)
Respiratory symptoms	11	10 (91)	1 (9)	5 (45)	5 (45)
Vomiting	13	12 (92)	2 (15)	7 (54)	6 (46)

Abbreviations: sIgE, specific immunoglobulin E; SPT, skin prick test.

^aSkin symptoms were hives, itching, flushing, and rash. Oropharyngeal symptoms were tongue or throat pruritus or swelling. Respiratory symptoms were cough, wheezing, or shortness of breath. Ninety-three percent of tree nut challenges in individual allergic to tree nut had sIgE and SPT performed, 6% had only SPT performed, and 1% had only sIgE performed.

eTable 2Characteristics of Failed Tree Nut OFCs^a

	n	OFC with sIgE <2 kUA/L, n (%)	OFC with sIgE ≥2 kUA/L, n (%)	OFC with SPT wheal <3 mm, n (%)	OFC with SPT wheal ≥3 mm, n (%)
All failed tree nut challenges	22	14 (64)	5 (23)	4 (18)	16 (73)
Tree nut allergic	16	12 (75)	2 (13)	3 (19)	11 (69)
Tree nut sensitized	6	2 (33)	3 (50)	1 (17)	5 (83)
Almond	0	—	—	—	—
Cashew	6	6 (100)	0 (0)	0 (0)	6 (100)
Walnut	5	2 (40)	2 (40)	0 (0)	5 (100)
Hazelnut	3	1 (33)	1 (33)	0 (0)	2 (67)
Pecan	3	1 (33)	1 (33)	1 (33)	2 (67)
Pistachio	4	3 (75)	1 (25)	1 (25)	2 (50)
Brazil nut	1	1 (100)	0 (0)	0 (0)	1 (100)

Abbreviations: OFC, oral food challenge; sIgE, specific immunoglobulin E; SPT, skin prick test.

^aSeventy-seven percent of failed tree nut OFCs had sIgE and SPT performed, 14% had only SPT, and 9% had only sIgE performed.**eTable 3**

Tree Nut OFC Characteristics in Patients Allergic to Peanut With Tree Nut Co-sensitization

	n	Pass rate, %	OFC with sIgE <2 kUA/L, n (%)	OFC with sIgE ≥2 kUA/L, n (%)	OFC with SPT wheal <3 mm, n (%)	OFC with SPT wheal ≥3 mm, n (%)
Tree nut OFCs in patients allergic to peanut	68	96	51 (75)	8 (12)	49 (72)	8 (12)
Tree nut allergic	9	89	9 (100)	0 (0)	6 (67)	2 (22)
Tree nut sensitized	44	95	31 (70)	8 (18)	34 (77)	6 (14)
Tree nut avoidance despite negative test result	15	100	11 (73)	—	9 (60)	—
Almond	36	100	21 (58)	4 (11)	24 (67)	6 (17)
Cashew	5	100	5 (100)	0 (0)	3 (60)	1 (20)
Walnut	10	90	8 (80)	0 (0)	8 (80)	1 (10)
Hazelnut	11	91	7 (64)	4 (36)	9 (82)	0 (0)
Pecan	4	100	3 (75)	0 (0)	4 (100)	0 (0)
Pistachio	2	50	2 (100)	0 (0)	1 (50)	0 (0)

Abbreviations: OFC, oral food challenge; sIgE, specific immunoglobulin E; SPT, skin prick test.

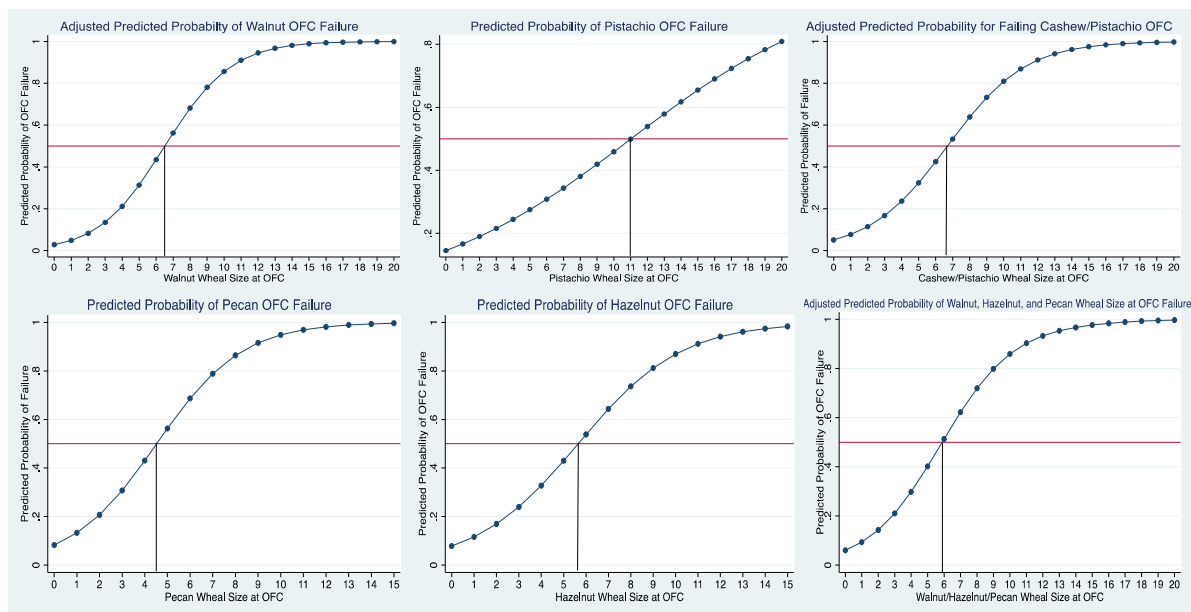


Figure 1. Fifty percent negative predictive values for an oral food challenge (OFC) to subjects with tree nut allergy and sensitization. Walnut is adjusted for peanut allergy. Curves for hazelnut and pecan are unadjusted because of power issues. Combined curves for cashew and pistachio and for walnut, pecan, and hazelnut curves are adjusted for age.