Guidelines for the Prevention of Peanut Allergy and Emerging Peanut Allergy Immunotherapy

Executive Summary

Food allergy is defined as an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food[1]. Affecting up to 8.0% of children in the United States[2], food allergy represents a substantial public health concern. Annual estimates for food-related anaphylaxis cases treated in the nation's emergency rooms are 30,000, which result in 150-200 deaths[3]. Furthermore, the food-induced anaphylaxis hospitalization rate is on the rise[4]. The financial burden of food allergy has been estimated to be $24.8 billion annually, due to direct and indirect costs[5].

Of all the food allergies, peanut allergy is the most common cause of fatal food anaphylaxis in the United States[6,7]. The prevalence of peanut allergy in children has increased from 0.4% in 1999[8] to approximately 2% in 2010[2]. Fear of anaphylaxis, extreme dietary vigilance, and bullying from peers contributes to pronounced psychological stress and reduced quality of life for individuals with peanut allergy, and for their familes[9–11]. Moreover, peanut allergy continues as a lifelong problem for approximately 75% of those affected[12–14]. Despite its growing negative impact on individuals, their family, and our society, the current management of peanut allergy includes only peanut avoidance or treatment of symptoms[1]. The standard of care is characterized by a strict elimination diet and the timely administration of auto-injectable epinephrine when accidental exposure leads to an allergic reaction[1,15].

Vigilant avoidance of peanut-containing products is challenging for peanut-allergic individuals. Though product labeling in food manufacturing has improved, cross-contamination may still occur in many settings, such as in food service establishments[16]. Furthermore, voluntary precautionary allergen labeling lacks transparency and uniformity. Their widespread use eliminates many food choices for some allergic consumers, while others may question their accuracy and risk ingestion[16].

Consequently, anxiety and fears are engrained in everyday life of peanut-allergic individuals and their families[16]. These psychosocial issues stem from the variability of allergic reactions and the uncertainty regarding the risk of future reactions[17], resulting in a reduced quality of life for affected individuals[9,10]. In fact, the self-reported health-related quality of life for food allergic adolescents was poorer than their peers with diabetes[18].

In an attempt to alleviate the growing prevalence of peanut allergy, in 2000, the American Academy of Pediatrics (AAP) recommended delaying peanut introduction until at least 3 years of age for infants who had a family history of allergic disease[19]. However, following this recommendation, increased prevalence of food allergy was reported[20]. In fact, US prevalence of self-reported peanut allergy steadily increased from 0.4% in 1997, to 0.8% in 2002, to 1.4% in 2008 ($P < .0001$)[20].

More recently, studies have indicated that early introduction of peanut in infancy may protect against peanut allergy[21–23]. This concept originated from a 2008 study that observed the prevalence of peanut allergy in Jewish schoolchildren in Israel versus the United Kingdom[21]. Among the observed children, 1.85% of those in the UK had a peanut allergy, whereas peanut allergy affected only 0.17% of Jewish schoolchildren in Israel ($P < 0.001$). The observed

difference was associated with the introduction of Israeli children to peanut as infants and avoidance of peanut for the first year of life in the United Kingdom[21].

This data informed the Learning Early About Peanut Allergy (LEAP) study: a randomized, open-label controlled trial[22]. Among the 530 infants that were not pre-sensitized to peanut, peanut allergy at 60 months of age was 13.7% in the avoidance group and 1.9% in the consumption group ($P < 0.001$). Among the 98 infants that were pre-sensitized to peanut, 35.3% developed peanut allergy in the avoidance group, and 10.6% developed an allergy in the consumption group ($P = 0.004$). Infants in the consumption group had higher levels of protective peanut-specific IgG4, while infants in the avoidance group had higher titers of peanut-specific IgE (sIgE). As the first randomized trial to study early allergen introduction as a protective strategy, the LEAP study provided strong clinical and immunological evidence of the protective effect of early introduction of peanut in infancy[24]. A follow-up study demonstrated the persistence of the protective effect for 12 months after peanut avoidance[23]. Furthermore, early peanut introduction did not affect the duration of breastfeeding nor disrupt growth or nutrition[25].

These pivotal studies informed global changes in recommendations[26–29]. In the United States, the National Institute of Allergy and Infectious Diseases (NIAID) published an update to the guidelines for prevention of peanut allergy[26]. Three infant categories were defined, stratified by risk, with variable recommendations for testing and introduction of peanut for each group (Table 1). Following release of the new guidelines, many concerns emerged regarding the feasibility of their implementation due to their complexity, time restrictions, and other barriers[24,30,31].

Addendum Guideline	Infant Criteria	Recommendations	Earliest Age of Peanut Introduction
1	Severe eczema, egg allergy, or both	Strongly consider evaluation skin or blood testing for peanut-sIgE before introduction. Based on test results, introduce peanut-containing foods.	4-6 months
2	Mild-to-moderate eczema	Introduce peanut-containing foods	Around 6 months
3	No eczema or any food allergy	Introduce peanut-containing foods	Age appropriate and in accordance with family preferences and cultural practices

Table 1: Summary of NIAID 2017 Addendum Guidelines (adapted from[26])

Before the new guidelines, parents and pediatricians had been advised to delay exposure to allergenic foods. Now, the guidelines are promoting their prompt introduction to infants in conjunction with solid foods. Considering this drastic paradigm shift, public and medical education are critical for the required adjustment in parent guidance about early feeding practices[24].

For children with severe eczema and/or egg allergy, the indicated age of peanut introduction to reduce the risk of peanut allergy is a narrow time frame of 4 to 6 months of age. Procedures for peanut introduction in these high-risk cases depend on the results of peanut sIgE and/or skin prick testing (SPT), and may require rapid access to an allergist[24,32].

Given that there is currently no cure for food allergy, the primary goal of the majority of patients and caregivers is protection from an allergic reaction due to accidental ingestion[33]. Peanut allergy immunotherapy aims to increase the patient's reactivity threshold through desensitization[16], which is a reversible state induced by short-term exposure to an allergen[34]. Increased reactivity threshold translates to reduced risk of allergic reactions through unintentional exposure[16].

When the addendum was published, food allergy treatments, including oral immunotherapy (OIT) and epicutaneous immunotherapy (EPIT) were considered investigational. However, studies have since produced increasing evidence that these therapies offer safe and effective treatment of peanut allergy[35–37]. These immunotherapies involve exposing an allergic individual to an increasing amount of allergen to elevate the threshold that triggers a reaction. Currently, phase 3 developments of standardized forms of OIT and EPIT for peanut allergy are complete, and awaiting a formal decision from the Food and Drug Administration (FDA), according to the American Academy of Allergy, Asthma and Immunology (AAAAI)[38].

Clinicians may be unfamiliar with these new therapies considering they are not yet FDA approved and would benefit from education on the treatment options that may soon be available for peanut allergy, as well as the pros and cons of each treatment type. Further, a thorough review of the current guidelines regarding early introduction of peanut would increase familiarity among family practitioners, pediatricians, and allergists, and would ultimately increase adherence.

Gap #1:
Many clinicians are not adhering to the peanut allergy prevention guidelines and are not determining peanut allergy risk.

Learning Objective #1:
Assess peanut allergy risk based on national guidelines.

Outcome #1:
Clinicians will be better prepared to assess peanut allergy risk in patients.

Given the significant impact peanut allergies have on health and quality of life, accurate diagnosis and any means of prevention are invaluable. Despite the acceptance of the landmark studies[21–23] that informed the updated NIAID recommendations for prevention of peanut allergy[26], gaps have been identified in adherence to the new guidelines among general practitioners, pediatricians, allergists, and immunologists [39–45].

A recent survey indicated that, although pediatricians and allergists were aligned with the current NIAID guidelines, family physicians commonly recommended introduction of allergenic foods after 1 year of age[39]. Furthermore, preemptive screening of high-risk infants before peanut introduction was not routine for the majority of family physicians, pediatricians, or allergists that participated in the survey. The survey also highlighted an inconsistency in counseling regarding ongoing peanut exposure. The NIAID addendum states that following introduction, 6 to 7 grams of peanut should be given over 3 or more feedings per week. Though most allergists followed this recommendation, the majority of pediatricians and family practitioners had no advice for patients regarding ongoing peanut exposure[39].

A retrospective chart review before and after the release of the NIAID addendum indicated that the primary care physician rarely performed an initial evaluation for peanut allergy in either

case[40]. The authors of this study propose the introduction of time-efficient templates to allow quick documentation of a patient's peanut exposure status and allow the clinician to assess the need for an allergy referral rapidly.

Implementation of a quality improvement project at a large general pediatrics practice following the release of the new guidelines increased adherence after real-time clinic assistance by an allergist, suggesting that provider confidence in administering new counseling is a potential barrier[41]. The authors proposed that a change in workflow and further education are required to increase adherence.

Several studies presented at the 2019 American Academy of Allergy, Asthma and Immunology Annual Scientific Meeting demonstrate that non-adherence to the NIAID guidelines continues[42–45].

An online survey among pediatricians probed the awareness, barriers, and implementation of the NIAID guideline recommending assessment of peanut allergy risk for infants 4 to 6 months old before early introduction of peanut[42]. Less than one-third of participating pediatricians were fully adhering to the guidelines, though the majority of them reported awareness. For pediatricians that were fully or partially adhering to the guidelines, barriers included parental concerns regarding allergic reactions, lack of clinic time, the novelty of the guidelines, and conducting an in-office feeding of peanut. Of the 11% of pediatricians not adhering to the addendum, the majority reported insufficient knowledge of the guidelines[42].

Of specialists surveyed, 62.0% reported using all of the guidelines, and 33.5% reported using parts of the guidelines. However, 45.7% of survey respondents indicated they needed more education or training. The major identifiable barriers to implementation were parental concerns and lack of referrals. Therefore, improved education to parents and referring physicians is critical[43].

Retrospective chart reviews corroborate non-adherence to the new guidelines. A review of infants screened for peanut allergy in an allergy clinic after release of the new guidelines indicated that the majority of tested infants did not meet the NIAID guidelines[44]. Furthermore, challenges were often not performed on patients with an SPT of 3-7 mm, in opposition to the guidelines[44]. Another chart review of infants with a suspected diagnosis of eczema or egg allergy seen at an extensive primary care network revealed very few instances of discussions about early peanut introduction in the at-risk population[45]. Thus there were many missed opportunities to discuss early peanut introduction, which is partly due to a knowledge gap and lack of awareness of the guidelines[45].

Despite the challenges in adhering to the guidelines, family physicians, pediatricians, and allergists are willing to recommend introduction of allergenic foods before 6 months[40]. In fact, 96.7% of allergists and immunologists agreed that early introduction is effective in preventing peanut allergy[43].

When the guidelines are followed, supervised peanut introduction is safe, with a low risk of anaplylaxis[46]. Since guideline implementation has the potential to reduce peanut allergy incidence, improvements in adherence are critical[42].

Through additional access to educational materials, clinicians will be able to better assess peanut allergy risk based on national guidelines. Such educational materials would particularly benefit pediatricians and family practitioners, where substantial gaps exist in knowledge of the

new guidelines[39–45]. With educational programs, clinicians will be better prepared to assess peanut allergy risk in patients.

Gap #2:
Clinicians are not aware of recent clinical trial data on peanut allergy immunotherapies.

Learning Objective #2:
Describe the recent clinical data on emerging peanut immunotherapies.

Outcome #2
Clinicians will have a better understanding of the emerging peanut allergy immunotherapies.

Currently, there is no FDA-approved treatment for the prevention of food allergy. The current standard of care demands strict elimination diets and prompt symptom management with an epinephrine auto-injector in the case of allergic reaction[1]. In order to address the unmet need for peanut allergy therapeutics, OIT and EPIT have been granted FDA fast-track status. If approved, OIT and EPIT will represent the first approved treatments for peanut allergy[47].

The standardized form of OIT that is currently under FDA review was tested in a randomized, controlled, phase-3 trial, known as PALISADE (Peanut Allergy Oral Immunotherapy Study of AR101 for Desensitization)[35]. The oral biologic drug is defatted roasted peanut flour. Eligible participants had a clinical history of peanut allergy and at screening, had an allergic reaction to no more than 100 mg of peanut protein (~1/3 of a peanut kernel). Patients were randomly assigned (3:1) to receive the active drug or placebo in a dose-escalation period. At the end of the up-dosing phase, a dose of 300 mg of peanut protein (~1 peanut kernel) was reached and maintained for 24 weeks. The primary efficacy endpoint was the proportion of the participants 4 to 17 years of age who were able to ingest a single dose of at least 600 mg of peanut protein during the exit food challenge, without dose-limiting symptoms.

Among 496 participants between 4 and 17 years of age, 67.2% of those who received the active treatment, compared with 4.0% who received the placebo, were able to ingest a dose of at least 600 milligrams at the exit food challenge with no more than mild symptoms ($P < 0.001$). Furthermore, 50.3% of participants in the active drug group, compared with 2.4% in the placebo group, were able to tolerate 1000 mg of peanut protein at trial end ($P < 0.001$).

Adverse events were common during the intervention period. Severe reactions were reported in 4.3% of participants in the active-treatment group and in 0.8% of those in the placebo group. In the active drug group, 14.2% of participants had a systemic allergic reaction compared with 3.2% in the placebo group. Additionally, participants in the active drug group experienced adverse events affecting the gastrointestinal tract, respiratory tract, skin, and immune system at a higher rate than those in the placebo group.

The PALISADE investigators concluded that the active drug was an immunomodulatory treatment that resulted in desensitization in children and adolescents who were highly allergic to peanut[35].

The standardized form of EPIT that is currently under FDA review was tested in a randomized, controlled, phase-3 trial, known as PEPITES (Peanut EPIT Efficacy and Safety)[48]. The study aimed to assess the efficacy and adverse events of EPIT with a peanut patch in peanut-allergic children, aged 4 to 11 years. Eligible participants were diagnosed with a peanut allergy and

reacted with immediate hypersensitivity to 300 mg or less of peanut protein. Those that met these criteria were then randomized (2:1) to receive 250 µg of peanut protein, or placebo, through daily application of a patch; duration time gradually increased over 12 months. The primary outcome was the response rate difference between active and placebo groups following 12 months of treatment. Participants were considered responders if the posttreatment dose they reacted to was 300 mg or more, or 1000 mg or more, depending on their initial sensitivity.

Of 356 participants, 89.9% completed the trial. The responder rate was 35.3% with peanut-patch treatment compared with 13.6% with placebo. The 21.7% difference is statistically significant ($P < 0.001$). However, the pre-specified lower bound of the confidence interval threshold for a positive trial result was not met; the clinical relevance of not meeting this lower bound is unclear.

The results indicate that the peanut-patch treatment desensitized peanut-allergic children to peanut protein, with a high degree of adherence to the therapy and a low rate of serious adverse events. Longer-term outcomes of EPIT are under evaluation in an extension phase of this trial (PEOPLE clinical trial)[49].

Caregivers of participants in the OIT and EPIT trials expressed a motivation to establish a buffer against accidental peanut exposure and hoped the quality of life would improve by reducing anxiety concerning the severity of future reactions[13].

To address the clinical relevance of achieving thresholds of 300 mg and 1000 mg of peanut protein by peanut immunotherapy, a quantitative risk assessment modeled exposure through pairing US consumption data for various food product categories with potential peanut contamination levels previously observed in those foods[50]. Strikingly, increasing the threshold from 100 mg of peanut protein to 300 mg of peanut protein after immunotherapy reduced the risk of experiencing an allergic reaction by 95%[50].

In describing this clinical data to allergists and immunologists, these clinicians will have a better understanding of the emerging peanut allergy immunotherapies. With this knowledge, they will be prepared to discuss the benefits and limitations of the treatments upon impending approval. Many peanut-allergic individuals and their caregivers find the current standard of care to be burdensome and may be attracted to new therapy options and the potential for an improved quality of life[16,17,51].

Gap #3:
Clinicians may not understand how to integrate newer therapies into the ongoing clinical management of patients with peanut allergy.

Learning Objective #3:
Summarize selection considerations for emerging therapies.

Outcome #3:
Clinicians will have a better understanding of how to integrate emerging therapies into care and best practices for patient education.

The availability of the new treatment options for peanut-allergic individuals will introduce new considerations[16]. Understanding the benefit and burden of treatment, as well as the limitations of the available immunotherapies is essential for physicians, caregivers, and patients[16].

Allergists and immunologists should be prepared to select the most suitable treatment for individuals through shared-decision making with patients and caregivers.

Initially, it is essential that physicians, caregivers, and patients have a clear understanding of the goal of immunotherapy, which is to desensitize a patient to an allergen[16]. Desensitization is not a cure for peanut allergy; it is a reversible state that must be maintained[34]. Despite the predicted protection provided by an individual threshold dose of 300 mg of peanut protein, a strict peanut-product elimination diet should continue[16]. Emergency treatment plans should remain in place as accidental exposure to peanut protein may still occur at concentrations higher than the threshold obtained through immunotherapy.

Furthermore, those involved in the treatment plan should consider that there are still areas of uncertainty in the effectiveness of the treatment. For example, cofactors such as coexisting asthma, infection, and physical activity at the time of allergen exposure can influence an individual's allergen sensitivity and reaction severity[52]. Additionally, candidates for immunotherapy should understand that compliance with the therapy is essential for its success.

Many factors should be considered when selecting the best possible therapy for an individual with a peanut allergy in order to balance treatment safety and efficacy with patient goals, lifestyle, and commitment level.

Patient age will likely be the first consideration. Based on the phase-3 trial inclusion criteria, OIT will be approved for patients 4 through 17 years of age, while EPIT will be approved for children aged 4 to 11 years[53]. For patients that have a choice in treatment, there are several advantages and disadvantages to consider for each product.

The main advantage of OIT is that patients tolerating the daily maintenance dose of 300 mg will also likely tolerate accidental ingestion of at least 1 peanut[53]. Disadvantages to the OIT treatment regimen include the inconvenience of office visits for up-dosing and the risk of allergic reactions to any dose of the active-drug[53]. Furthermore, OIT may be challenging for a very active patient as it requires downtime after each treatment. Exercise and hot showers immediately before or after dosing increase the risk of adverse reactions[53]. Other factors that increase this risk include viral respiratory infections, menses, and nonsteroidal anti-inflammatory drug use[54]. Finally, a subset of patients will not tolerate the maintenance dose and be required to discontinue or modify the OIT therapy[53].

With EPIT, advantages include convenience and safety. The treatment protocol is much simpler and frequent office visits are unnecessary[53]. Because the daily dose of peanut is only 250 µg, adverse reactions are rare. Local side effects at the site of the patch are common but tend to be mild and dissipate over time[53]. Downtime is not required after application, which may be attractive for a very active patient. The major disadvantage of the patch treatment is that the average degree of desensitization after 12 months of treatment appears to be less than patients experience with OIT[35,48,53].

Despite all of the limitations associated with immunotherapy, food-specific quality of life improves following both OIT and EPIT treatment[55,56]. However, for some patients, immunotherapy may not be an attractive option, and the current standard of care involving strict avoidance of peanut remains a practical choice. Understanding the goals of the patient's family will be essential in starting an appropriate treatment for peanut allergy. Through summarizing the selection considerations for emerging therapies, clinicians will have a better understanding of how to integrate these therapies into care and best practices for patient education.

Conclusion:

A rapid and sustained increase in peanut allergy prevalence has occurred in the United States over the last two decades without the availability of any FDA-approved therapy options[53]. Research has indicated that early introduction to peanut decreases the rate of peanut-allergy, facilitating a change in the NIAID guidelines for prevention of peanut allergy. Furthermore, upon impending FDA-approval, OIT and EPIT will represent the first available treatment options for peanut allergy. These advances in the field have elicited a substantial shift in the treatment of peanut allergy in the clinical setting. Consequently, education is essential to supply clinicians with the knowledge and confidence necessary to provide the best possible care for peanut-allergic individuals.

References:

1. Boyce JA, Assa'ad A, Burks AW, et al. Guidelines for the Diagnosis and Management of Food Allergy in the United States: Summary of the NIAID-Sponsored Expert Panel Report. *J Allergy Clin Immunol*. 2010;126(6):1105-1118. doi:10.1016/j.jaci.2010.10.008

2. Gupta RS, Springston EE, Warrier MR, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. *Pediatrics*. 2011;128(1):e9-17. doi:10.1542/peds.2011-0204

3. Sampson HA. Anaphylaxis and emergency treatment. *Pediatrics*. 2003;111(6 Pt 3):1601-1608.

4. Lin RY, Anderson AS, Shah SN, Nurruzzaman F. Increasing anaphylaxis hospitalizations in the first 2 decades of life: New York State, 1990 -2006. *Ann Allergy Asthma Immunol Off Publ Am Coll Allergy Asthma Immunol*. 2008;101(4):387-393. doi:10.1016/S1081-1206(10)60315-8

5. Gupta R, Holdford D, Bilaver L, Dyer A, Holl JL, Meltzer D. The economic impact of childhood food allergy in the United States. *JAMA Pediatr*. 2013;167(11):1026-1031. doi:10.1001/jamapediatrics.2013.2376

6. Bock SA, Muñoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. *J Allergy Clin Immunol*. 2001;107(1):191-193. doi:10.1067/mai.2001.112031

7. Bock SA, Muñoz-Furlong A, Sampson HA. Further fatalities caused by anaphylactic reactions to food, 2001-2006. *J Allergy Clin Immunol*. 2007;119(4):1016-1018. doi:10.1016/j.jaci.2006.12.622

8. Sicherer SH, Muñoz-Furlong A, Burks AW, Sampson HA. Prevalence of peanut and tree nut allergy in the US determined by a random digit dial telephone survey. *J Allergy Clin Immunol*. 1999;103(4):559-562.

9. Primeau MN, Kagan R, Joseph L, et al. The psychological burden of peanut allergy as perceived by adults with peanut allergy and the parents of peanut-allergic children. *Clin Exp Allergy J Br Soc Allergy Clin Immunol*. 2000;30(8):1135-1143.

10. Sicherer SH, Noone SA, Muñoz-Furlong A. The impact of childhood food allergy on quality of life. *Ann Allergy Asthma Immunol Off Publ Am Coll Allergy Asthma Immunol*. 2001;87(6):461-464. doi:10.1016/S1081-1206(10)62258-2

11. Shemesh E, Annunziato RA, Ambrose MA, et al. Child and parental reports of bullying in a consecutive sample of children with food allergy. *Pediatrics*. 2013;131(1):e10-17. doi:10.1542/peds.2012-1180

12. Skolnick HS, Conover-Walker MK, Koerner CB, Sampson HA, Burks W, Wood RA. The natural history of peanut allergy. *J Allergy Clin Immunol*. 2001;107(2):367-374. doi:10.1067/mai.2001.112129

13. Greenhawt M, Marsh R, Gilbert H, Sicherer S, DunnGalvin A, Matlock D. Understanding caregiver goals, benefits, and acceptable risks of peanut allergy therapies. *Ann Allergy Asthma Immunol*. 2018;121(5):575-579. doi:10.1016/j.anai.2018.06.018

14. National Academies of Sciences, Engineering, and Medicine, Health and Medicine Division, Food and Nutrition Board, Committee on Food Allergies: Global Burden, Causes, Treatment, Prevention, and Public Policy. *Finding a Path to Safety in Food Allergy: Assessment of the Global Burden, Causes, Prevention, Management, and Public Policy*. (Oria MP, Stallings VA, eds.). Washington (DC): National Academies Press (US); 2016. http://www.ncbi.nlm.nih.gov/books/NBK435943/. Accessed April 6, 2019.

15. Sampson HA, Aceves S, Bock SA, et al. Food allergy: a practice parameter update-2014. *J Allergy Clin Immunol*. 2014;134(5):1016-1025.e43. doi:10.1016/j.jaci.2014.05.013

16. Shreffler WG, Baumert JL, Remington BC, et al. The importance of reducing risk in peanut allergy: Current and future therapies. *Ann Allergy Asthma Immunol Off Publ Am Coll Allergy Asthma Immunol*. 2018;120(2):124-127. doi:10.1016/j.anai.2017.10.038

17. Luccioli S. Food allergy guidelines and assessing allergic reaction risks: a regulatory perspective. *Curr Opin Allergy Clin Immunol*. 2012;12(3):323-330. doi:10.1097/ACI.0b013e3283535aaf

18. Blok BMJF, Dubois AEJ, Vlieg-Boerstra BJ, et al. Health-related quality of life of food allergic patients: comparison with the general population and other diseases. *Allergy*. 2010;65(2):238-244. doi:10.1111/j.1398-9995.2009.02121.x

19. American Academy of Pediatrics. Committee on Nutrition. Hypoallergenic infant formulas. *Pediatrics*. 2000;106(2 Pt 1):346-349.

20. 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;125(6):1322-1326. doi:10.1016/j.jaci.2010.03.029

21. 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;122(5):984-991. doi:10.1016/j.jaci.2008.08.039

22. 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;372(9):803-813. doi:10.1056/NEJMoa1414850

23. Du Toit G, Sayre PH, Roberts G, et al. Effect of Avoidance on Peanut Allergy after Early Peanut Consumption. *N Engl J Med*. 2016;374(15):1435-1443. doi:10.1056/NEJMoa1514209

24. Chen M, Welch M, Laubach S. Preventing Peanut Allergy. *Pediatr Allergy Immunol Pulmonol*. 2018;31(1):2-8. doi:10.1089/ped.2017.0826

25. Feeney M, Du Toit G, Roberts G, et al. Impact of peanut consumption in the LEAP Study: Feasibility, growth, and nutrition. *J Allergy Clin Immunol*. 2016;138(4):1108-1118. doi:10.1016/j.jaci.2016.04.016

26. Togias A, Cooper SF, Acebal ML, et al. Addendum guidelines for the prevention of peanut allergy in the United States: Report of the National Institute of Allergy and Infectious Diseases–sponsored expert panel. *World Allergy Organ J*. 2017;10(1). doi:10.1186/s40413-016-0137-9

27. Fleischer DM, Sicherer S, Greenhawt M, et al. Consensus communication on early peanut introduction and the prevention of peanut allergy in high-risk infants. *J Allergy Clin Immunol*. 2015;136(2):258-261. doi:10.1016/j.jaci.2015.06.001

28. Fewtrell M, Bronsky J, Campoy C, et al. Complementary Feeding: A Position Paper by the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) Committee on Nutrition. *J Pediatr Gastroenterol Nutr*. 2017;64(1):119-132. doi:10.1097/MPG.0000000000001454

29. Greer FR, Sicherer SH, Burks AW, COMMITTEE ON NUTRITION, SECTION ON ALLERGY AND IMMUNOLOGY. The Effects of Early Nutritional Interventions on the Development of Atopic Disease in Infants and Children: The Role of Maternal Dietary Restriction, Breastfeeding, Hydrolyzed Formulas, and Timing of Introduction of Allergenic Complementary Foods. *Pediatrics*. March 2019. doi:10.1542/peds.2019-0281

30. Wood RA, Burks AW. LEAPing forward with the new guidelines. *J Allergy Clin Immunol*. 2017;139(1):52-53. doi:10.1016/j.jaci.2016.11.005

31. Turner PJ, Campbell DE. Implementing Primary Prevention for Peanut Allergy at a Population Level. *JAMA*. 2017;317(11):1111-1112. doi:10.1001/jama.2017.0922

32. Addendum Guidelines for the Prevention of Peanut Allergy in the United States: Summary for Clinicians. :2.

33. Anagnostou K, Stiefel G, Brough H, du Toit G, Lack G, Fox AT. Active management of food allergy: an emerging concept. *Arch Dis Child*. 2015;100(4):386-390. doi:10.1136/archdischild-2014-306278

34. Lanser BJ, Wright BL, Orgel KA, Vickery BP, Fleischer DM. Current Options for the Treatment of Food Allergy. *Pediatr Clin North Am*. 2015;62(6):1531-1549. doi:10.1016/j.pcl.2015.07.015

35. PALISADE Group of Clinical Investigators, Vickery BP, Vereda A, et al. AR101 Oral Immunotherapy for Peanut Allergy. *N Engl J Med*. 2018;379(21):1991-2001. doi:10.1056/NEJMoa1812856

36. 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. doi:10.1016/j.jaip.2018.10.048

37. Vickery BP, Berglund JP, Burk CM, et al. Early oral immunotherapy in peanut-allergic preschool children is safe and highly effective. *J Allergy Clin Immunol*. 2017;139(1):173-181.e8. doi:10.1016/j.jaci.2016.05.027

38. The Current State of Oral Immunotherapy | AAAAI. The American Academy of Allergy, Asthma & Immunology. https://www.aaaai.org/conditions-and-treatments/library/allergy-library/oit. Accessed April 7, 2019.

39. Abrams EM, Singer AG, Soller L, Chan ES. Knowledge gaps and barriers to early peanut introduction among allergists, pediatricians, and family physicians. *J Allergy Clin Immunol Pract*. 2019;7(2):681-684. doi:10.1016/j.jaip.2018.07.035

40. McNamara KB, Schroer BC, Bjelac JA. Practice patterns among allergists on the early introduction of peanut. *J Allergy Clin Immunol Pract*. 2019;7(2):711-713.e1. doi:10.1016/j.jaip.2018.10.040

41. Russo CL, Shih JA. Implementing the Addendum Guidelines for the Prevention of Peanut Allergy in a Primary Care Practice: A Quality Improvement Project. *J Allergy Clin Immunol*. 2018;141(2):AB189. doi:10.1016/j.jaci.2017.12.599

42. Gupta RS, Jiang J, Bozen A, et al. Implementation, Practices, and Barriers to the 2017 Peanut Allergy Prevention Guidelines Among Pediatricians. *J Allergy Clin Immunol*. 2019;143(2):AB84. doi:10.1016/j.jaci.2018.12.260

43. Johnson J, Gupta RS, Bilaver LA, et al. Implementation of the 2017 Addendum Guidelines for Peanut Allergy Prevention Among AAAAI Allergists and Immunologists. *J Allergy Clin Immunol*. 2019;143(2):AB421. doi:10.1016/j.jaci.2018.12.945

44. Volertas S, Coury M, Sanders GM, McMorris MS, Gupta M. Infant Peanut Allergy Testing in the Post-LEAP World. *J Allergy Clin Immunol*. 2019;143(2):AB266. doi:10.1016/j.jaci.2018.12.814

45. Tapke DE, Stukus DR, Prince BT, Scherzer R, Mikhail I. Implementation of Early Peanut Introduction Guidelines Among Pediatricians. *J Allergy Clin Immunol*. 2019;143(2):AB273. doi:10.1016/j.jaci.2018.12.835

46. Stukus DR, Prince BT, Mikhail I. Implementation of guidelines for early peanut introduction at a pediatric academic center. *J Allergy Clin Immunol Pract*. 2018;6(5):1784-1786. doi:10.1016/j.jaip.2018.01.036

47. Wood RA. Food allergen immunotherapy: Current status and prospects for the future. *J Allergy Clin Immunol*. 2016;137(4):973-982. doi:10.1016/j.jaci.2016.01.001

48. 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. *JAMA*. February 2019. doi:10.1001/jama.2019.1113

49. Follow-up of the PEPITES Study to Evaluate Long-term Efficacy and Safety of Viaskin Peanut in Children - Full Text View - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03013517. Accessed April 7, 2019.

50. Baumert JL, Taylor SL, Koppelman SJ. Quantitative Assessment of the Safety Benefits Associated with Increasing Clinical Peanut Thresholds Through Immunotherapy. *J Allergy Clin Immunol Pract*. 2018;6(2):457-465.e4. doi:10.1016/j.jaip.2017.05.006

51. Salvilla SA, Dubois AEJ, Blok BMJF, et al. Disease-specific health-related quality of life instruments for IgE-mediated food allergy. *Allergy*. 2014;69(7):834-844. doi:10.1111/all.12427

52. Turner PJ, Baumert JL, Beyer K, et al. Can we identify patients at risk of life-threatening allergic reactions to food? *Allergy*. 2016;71(9):1241-1255. doi:10.1111/all.12924

53. Tilles SA, Petroni D. FDA-approved peanut allergy treatment: The first wave is about to crest. *Ann Allergy Asthma Immunol Off Publ Am Coll Allergy Asthma Immunol*. 2018;121(2):145-149. doi:10.1016/j.anai.2018.06.005

54. Parrish CP, Har D, Andrew Bird J. Current Status of Potential Therapies for IgE-Mediated Food Allergy. *Curr Allergy Asthma Rep*. 2018;18(3):18. doi:10.1007/s11882-018-0772-z

55. Factor JM, Mendelson L, Lee J, Nouman G, Lester MR. Effect of oral immunotherapy to peanut on food-specific quality of life. *Ann Allergy Asthma Immunol Off Publ Am Coll Allergy Asthma Immunol*. 2012;109(5):348-352.e2. doi:10.1016/j.anai.2012.08.015

56. Lewis M, Brown-Whitehorn T, Rooney C, Spergel J. P273 What happens when epicutaneous peanut immunotherapy ends? *Ann Allergy Asthma Immunol*. 2016;117(5):S103. doi:10.1016/j.anai.2016.09.286