

Primary Prevention of Food Allergy

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Abstract Food allergy is estimated to affect approximately 8% of children in the USA. This is a disease without any known treatment or cure and, for some, a disease that can be quite severe, even life-threatening. While recent advances in potential treatment have made remarkable strides, with two food-targeted immunotherapy products now in phase III trials, perhaps the biggest gains in the field have come in the advent of potential preventative strategies to avoid the development of food allergy in high-risk individuals. There have been multiple, randomized, controlled trials (RCTs) performed in the past 5 years that have demonstrated significant risk reduction from early allergen introduction. These include two trials for early peanut introduction and five trials for early egg introduction in the first year of life. The results indicate that primary prevention of food allergy through early allergen introduction may represent a strategy that could potentially avert tens of thousands of children from becoming food allergic. In support of the data for peanut, the National Institute of Allergy and Infectious Diseases recently sponsored an addendum to the 2010 food allergy guidelines, specifically recommending peanut be introduced in both high- and standard-risk infants to reduce the risk of developing peanut allergy. To date, no formal recommendations have been made for egg, however. This review will focus on the latest evidence supporting early introduction as a strategy to prevent food allergy, as well as on practical aspects for its successful implementation.

Keywords Food allergy · Peanut allergy · Allergy treatment · Immunotherapy · Food allergy guidelines

Abbreviations

RCT	Randomized controlled trials
RPCT	Randomized, placebo-controlled trial
LISA	Influences of Lifestyle-Related Factors on the Immune System and the Development of Allergies in Childhood
RR	Relative risk
OFC	Oral food challenge
LEAP	Learning Early About Peanut Study
RRR	Relative risk reduction
ARR	Absolute risk reduction
NNT	Number needed to treat
EAT	Enquiring About Tolerance
STAR	Solids Timing for Allergy Reduction
STEP	Starting Time for Egg Protection
BEAT	Beating Egg Allergy Study
HEAP	Hen's Egg Allergy Prevention
PETIT	Prevention of Egg Allergy with Tiny Amount Intake
AAP	American Academy of Pediatrics
NIAID	National Institute of Allergy and Infectious Diseases
AAAAI	American Academy of Allergy, Asthma and Immunology
SPT	Skin prick test

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Introduction

Food allergy is estimated to affect approximately 8% of children in the USA [1]. This is a disease without any known

treatment or cure, and for some, a disease that can be quite severe, even life-threatening [2, 3]. There is some debate if the prevalence of food allergy is truly rising—US self-reported estimates indicate this is the case, but elsewhere this may be quite debatable [3, 4•]. While recent advances in potential treatment have made remarkable strides, to the extent that two food-targeted immunotherapy products are now in phase III trials, perhaps the biggest gains in the field have come in the advent of potential preventative strategies to avoid the development of food allergy in high-risk individuals. There have been multiple randomized controlled trials (RCTs) now that have demonstrated significant risk reduction from early allergen introduction, a strategy that could potentially avert tens of thousands of children from becoming food allergic [5••]. This review will focus on the latest evidence supporting early introduction as a strategy to prevent food allergy.

Setting the Table: Early Data Suggesting Food Allergy can Be Prevented

Multiple observational studies have shown either a protective association between food sensitization and early introduction of solid food or reported early solid introduction and reduced odds of developing food allergy.

Several large, observational cohorts have noted potentially protective relationships between earlier reported timing of food introduction and the risk of sensitization to that food [6]. Joseph et al., in an inner-city children cohort ($n = 594$), noted decreased odds of peanut and egg sensitization at age 3 years among children born to atopic mothers who had any solid food introduction before 4 months of life, but noted increased odds of both peanut and egg sensitization if solid food introduction was delayed past age 1 year [7]. In the Finnish Type I Diabetes national study ($n = 994$), delayed introduction of oat, wheat, and egg was associated with an increased risk of food sensitization [8]. Similarly, in the LISA birth cohort ($n = 2073$), delayed solid food introduction past 4–6 months was not protective of developing food sensitization at age 6 years and was more associated with food sensitization [9]. In a Finnish birth cohort, early introduction of fish in the first year of life was associated with a lower relative risk of developing rhinitis, eczema, asthma, and food/pollen sensitization [10]. The Finnish Diabetes Prediction and Prevention cohort noted that consecutive, early introduction of oat (<5.1 months), barley (<5.5 months), fish (< 6 months), and egg (<11 months) was associated with reduced risk of sensitization to wheat and egg (with oat, fish, egg, and barley introduction), milk (with oat introduction), and fish (with fish introduction) in Finnish children ($n = 3781$) followed to age 6 years [11]. Roduit et al. demonstrated that reduced diversity of foods introduced within the first year of life (none to three vs. six or more foods) was

associated with higher risk of both food sensitization at age 4.5 and 6 years and physician-diagnosed food allergy at age 6 years [12]. Lastly, data from another longitudinal Finnish cohort ($n = 3242$), children noted that more limited food diversity in the first 6 months of life was associated with development of allergic rhinitis at 5 years, and limited diversity in the first 12 months with the risk of developing asthma, allergic rhinitis, eczema, and wheeze [13].

While these studies strongly suggest that the timing of food introduction may moderate the development of allergen-specific IgE, there is still a cognitive dissonance between developing food sensitization and developing clinical food allergy [3]. A collective strength and weakness of these sensitization studies is the unclear influence of increased dietary diversity on the effects of any single food being introduced early.

Three prominent observational trials have noted a risk-reducing relationship between reported early allergen exposure and food allergy. In an observational cohort, DuToit et al. noted a tenfold difference in the rates of developing food allergy among Ashkenazi Jewish children in Tel Aviv, Israel with reported peanut exposure in the first year of life vs. similar children in London with reported delayed peanut introduction until after 3 years (relative risk (RR) 5.8 for developing allergy). Interestingly, the same findings were noted for both tree nut and sesame as well [14•]. In an Australian population infant-level cohort, Koplin et al. noted a significant 1.6 and 3.4 times increased odds of developing oral food challenge (OFC)-proven egg allergy at age 1 year among those with reported egg introduction after 10 and 12 months of life, respectively, compared to reported introduction before 6 months [15]. Katz et al. noted that among over 13,000 children in a single center Israeli birth cohort, the odds of developing milk allergy were 19.3 in infants with reported milk introduction between 105 and 195 days of life vs. within the first 14 days of life, independent of any breastfeeding association [16].

Proof Is in the Pudding: Interventional Trials and Demonstration of Risk Reduction

Seven RCTs to date have investigated a relationship between early allergen introduction and food allergy prevention, in both standard-risk and at-risk infants. In the Learning Early About Peanut (LEAP) allergy study, DuToit et al. demonstrated a statistically significant risk reduction (17% absolute risk reduction [ARR], 80% relative risk reduction [RRR]) in 4–11 month old at-risk infants (severe atopic dermatitis and/or egg allergy) randomized to consume 2 g of peanut thrice weekly for 5 years vs. avoidance for 5 years in both minimally peanut-sensitized (1–4 mm) and non-sensitized infants [17••]. In the Enquiring About Tolerance (EAT) study, Perkin et al. noted no significant difference in rates of

allergy development to any allergen (milk, peanut, fish, wheat, sesame, and egg) at 3 years in a RCT of multiple randomized, sequential allergen introduction beginning at either 3 months and before 6 months or after 6 months of life in exclusively breastfed standard-risk children. However, there were small, significant ARR differences in the per protocol population for egg (ARR 4.1) and peanut (ARR 2.5) favoring the earlier time of introduction [18••].

Studies for early egg introduction show different outcomes. In the Solids Timing for Allergy Reduction (STAR) study, Palmer et al. conducted a randomized placebo-controlled trial (RPCT) of raw, pasteurized powdered egg protein introduction (0.9 g/day) at 4 vs. 8 months of life in infants with moderate-to-severe eczema, demonstrating a trend towards reduced risk of egg allergy at 1 year (RR 0.65, $p = 0.11$). This trial was stopped prematurely as 15 out of 49 4-month olds enrolled were both egg-sensitized and egg-reactive upon first ingestion, suggesting possible increased risk in egg-sensitized children [19]. In the Starting Time for Egg Protection (STEP) RPCT study of non-eczematous infants born to atopic mothers, Palmer et al. noted a non-significant 3.3% ARR in the development of egg allergy at age 1 year between groups randomized to receive 0.9 g raw, pasteurized egg protein a day, favoring introduction at 4–6 vs. 10 months, as well as significant decreases in egg IgE and increases in egg IgG4 from baseline in this group. The STEP trial had a lower rate of baseline reactions vs. the STAR trial [20]. The Beating Egg Allergy Study (BEAT) RPCT study also noted no significant difference in egg allergy at age 1 year between groups randomized to raw, pasteurized egg introduction (2.5 g/week) at 4–6 vs. 8 months, but did show a 9.7% ARR in egg sensitization between groups favoring earlier introduction, and no differences between groups in peanut sensitization or eczema development. In BEAT, children with baseline egg skin test >2 mm were excluded, and 14 non-egg sensitized children experienced mild to moderate reactions in the first week but not on the initial dose, and all infants had an atopic primary relative [21••]. In the Hen's Egg Allergy Prevention (HEAP) RPCT, Bellach et al. noted no significant difference in rates of OFC-proven egg allergy at age 1 year between atopic infants randomized to thrice weekly raw, pasteurized egg introduction (vs. placebo) at 4–6 months (RR 3.3, $p = 0.35$), but noted that 3 out of 12 egg-sensitized children in the intervention group suffered severe reactions with initial introduction [22••]. Lastly, in the Prevention of Egg Allergy with Tiny Amount Intake (PETIT) trial, Natsume et al. conducted a DBRPCT of $n = 147$ Japanese 4–5 month olds with eczema. After screening but pre-randomization, participants had their eczema aggressively treated, and eczema care was maintained throughout the intervention period. Participants were then randomized to consume 50 mg a day of heated egg powder from 6 to 9 months of life, then 250 mg a day from 9 to 12 months,

vs. placebo. In the group given egg, 4/47 (9%) vs. 18/47 (38%) in the placebo group developed egg allergy (RR 0.22, 95% CI 0.08–0.61; $p = 0.0012$; NNT 3.4), favoring early introduction and prompting early cessation of the trial per protocol [23]. Adverse events were uncommon—19 events in occurred in 9 (15%) egg participants vs. 14 events in 11 (18%) placebo participants in the placebo group.

In a recent meta-analysis, Ierodiakonou et al. evaluated this collective body of recent work to further investigate the level of evidence supporting early allergen introduction [5]. These trials are summarized in Table 1. Ierodiakonou et al. noted “moderate certainty” of evidence that introducing peanut between 4 and 11 months reduced the risk of developing peanut allergy (RR 0.29; 95%CI 0.11–0.74) based on two RCTs (LEAP and EAT) investigating early peanut introduction inclusive of 1550 children; and introducing egg between 4 and 6 months reduced the risk of developing egg allergy (RR 0.56; 95%CI 0.36–0.87) based on five RCTs (STAR, STEP, BEAT, HEAP, PETIT) inclusive of 1915 children [17••, 18••, 19, 20, 21••, 22••, 23]. They furthermore noted low certainty evidence that early fish introduction was associated with reduced allergic sensitization, and no evidence that early introduction of milk or hydrolyzed formula was associated with any preventative effects. However, despite these positive findings, the authors urged caution in interpreting these data based on an additional analysis, using trial sequential analysis to determine how many additional patients would be necessary to have good certainty of a 30% effect size. For peanut, this actually could not be determined; and for egg, this estimated thousands of additional trial participants would be needed. Moreover, the authors also highlighted issues regarding generalizability and unknown effectiveness of their pooled findings in real-life populations [5].

Where Do We Go from Here? The Evolution of Guidance Regarding the Timing of Allergen Introduction

Formerly, in 2000, the American Academy of Pediatrics (AAP) recommended delayed allergen high-risk introduction in children at risk for allergic disease (based on having a first-degree relative with allergic disease). These recommendations included delayed introduction of cow's milk until age 1 year, egg until age 2 years, and peanut, tree nuts, and fish until age 3 years to prevent food allergy development. In addition, pregnant women and nursing mothers were additionally instructed to avoid these allergens in their diet [24]. The AAP then reversed this recommendation in 2008, given limited evidence delayed introduction was beneficial. Instead, the AAP recommended solid food introduction not be delayed past 4–6 months of life, though these recommendations did not actively recommend a specific timing for introducing foods such

Table 1 Summary of primary prevention randomized controlled trials (RCTs) to date.

Study acronym	Full title	Study type (sample size)	Population	Intervention	Primary outcome	Results
LEAP (UK) [17••]	Learning Early About Peanut Allergy	Non-blinded RCT (n = 640)	High-risk infants • Moderate to severe eczema and/or egg allergy	• <i>Thrice weekly consumption of 2 g of peanut protein vs complete avoidance of peanut after randomization at 4–11 months, through 60 months of life</i> • <i>Early introduction group (EIG) introduced 2 g of protein twice weekly at 3 months of peanut, cooked egg, cow's milk, sesame, whitefish, wheat • Standard introduction group (SIG) at 6 months of >6 foods</i>	• <i>IgE-mediated peanut allergy based on OFC at month 60</i>	• ITT analysis showed prevalence of peanut allergy 13.7% in the avoidance group vs 1.9% in the consumption group ($p < 0.001$)
EAT (UK) [18••]	Enquiring About Tolerance	Non-blinded RCT (n = 1303)	Standard risk: • Exclusively breastfed until allergenic foods introduced	• <i>Early introduction group (EIG) introduced 2 g of protein twice weekly at 3 months of peanut, cooked egg, cow's milk, sesame, whitefish, wheat • Standard introduction group (SIG) at 6 months of >6 foods</i>	• <i>IgE-mediated food allergy to at least 1 of the 6 allergens at 1 or 3 years of age based on OFC</i>	• ITT analysis showed no difference in food allergy between EIG vs SIG • PP analysis showed significantly less prevalence of peanut allergy ($p = 0.003$) and egg allergy ($p = 0.009$) in EIG vs SIG
STAR (Australia) [19]	Solids Timing for Allergy Reduction	Blinded RPCT (n = 86)	High-risk infants with moderate to severe eczema	• <i>Daily consumption of egg vs placebo powder from 4 to 8 months • 0.9 g raw whole egg powder daily (0.4 g protein/day) • Cooked egg at 8 months</i>	• <i>IgE-mediated egg allergy at 12 months based on positive SPT and egg OFC</i>	• Study terminated early: 1/3 of patients reacted to egg at entry OFC • At 12 months, 33% had egg allergy in egg group vs 51% in control (not significant)
STEP (Australia) [20]	Starting Time for Egg Protein	Blinded RPCT (n = 820)	Intermediate risk: • Atopic moms (allergic disease + positive enviro SPT) • Infants: no allergic dz	• <i>Daily consumption of egg vs placebo powder from 4 to 6.5 months • 0.9 g raw whole egg powder daily (0.4 g protein/day)</i>	• <i>IgE-mediated egg allergy at 12 months based on positive SPT and egg OFC</i>	• No significant differences in egg allergy between groups • No anaphylactic reactions at initial egg intro
BEAT (Australia) [23]	Beating Egg Allergy Trial	Blinded RPCT (n = 319)	Intermediate risk: • Infants with 1st degree relative with atopy • Infants: neg egg SPT	• <i>Daily consumption of egg vs placebo powder at 4 months • 350 mg protein daily raw whole egg powder • Cooked egg at 8 months</i>	• <i>Sensitization to egg by SPT at 12 months of age</i>	• Subjects in egg group vs placebo had significantly less egg sensitization (10.7 vs 20.5%, $p = 0.03$) • No harm with egg intro
HEAP (Germany) [21••]	Hen's Egg Allergy Prevention	Blinded RPCT (n = 406)	Normal risk general population • Infants with IgE <0.35 kU/L at enrollment	• <i>Thrice weekly 2.5 g egg protein from 4 to 6 months of age until 12 months</i>	• <i>Sensitization to egg based on egg IgE >0.35 kU/L at 12 months of age</i>	• No evidence of preventing egg sensitization or allergy • High rate of anaphylaxis at egg introduction at entry
PETIT (Japan) [22••]	Prevention egg allergy in infants with AD	Blinded RCT (n = 121)	High-risk infants with atopic dermatitis	• <i>Daily consumption of 50 mg heated egg from 6 to 9 months</i> • <i>Daily consumption of 250 mg heated egg from 9 to 12 months</i>	• <i>IgE-mediated egg allergy at 12 months of age based on OFC</i>	• Prevalence of egg allergy 37.7% in placebo vs 8.3% in egg group ($p = 0.0013$) • No SAEs

RPCT randomized placebo-controlled trial, OFC oral food challenge, SPT skin prick test, ITT intention to treat, PP per protocol

as peanut or associate the timing of introduction with any prevention benefits [25]. The AAP has not since updated these recommendations. The American Academy of Allergy, Asthma and Immunology (AAAAI) endorsed similar recommendations in 2013 [26].

Very recently, the 2008 guidance has changed. In direct response to LEAP, a 26-member expert panel of allergists, pediatricians, dermatologists, gastroenterologists, advocacy group leaders, and allied health professionals created a focused addendum to the 2010 National Institute of Allergy and Infectious Diseases (NIAID)-sponsored food allergy guidelines, specifically addressing early peanut introduction to prevent peanut allergy [27••]. The introduction of other allergens was not addressed, however. This addendum recommends that peanut should be introduced as early as 4–6 months of life in high-risk infants, with high-risk defined as children with severe eczema and/or egg allergy, with the following caveats (Table 2):

- High-risk infants are recommended to undergo assessment by a trained specialist with peanut skin prick test (SPT). Alternatively, serum peanut-specific IgE testing could be sent by any non-allergy provider assessing the child (to prevent any delay in access to specialty care), with referral to a trained specialist if the serum test is >0.35 kU_A/L.
- Infants undergoing skin testing who are noted to have 0–2 mm wheal size should be instructed to have peanut-containing foods introduced at home. The same applies for children who have serum-specific peanut <0.35 kU_A/L. Infants who tolerate introduction are recommended to consume 2 g of peanut protein thrice weekly.
- Infants undergoing skin testing who are noted to have a 3–7-mm wheal size are recommended to have in-office peanut introduction, either as a graded challenge or observed feeding. Infants who tolerate introduction are recommended to consume 2 g of peanut protein thrice weekly.

- Infants undergoing skin testing who are noted to have a ≥ 8 -mm wheal size (a size associated with probable peanut allergy) are not recommended to have peanut introduction, and these children should be managed as if they are allergic. However, it is understood that some parents and providers may still mutually wish to introduce peanut despite the large skin test, and these children should then also undergo in-office peanut introduction, either as a graded challenge or observed feeding. Infants who tolerate introduction are recommended to consume 2 g of peanut protein thrice weekly [27••].

Practical tips on how to facilitate introduction are included, as are recommendations on forms of age-appropriate peanut-containing foods (Table 3). The expert panel slightly modified the at-risk criteria from the LEAP study, but otherwise kept these largely intact. Severe eczema was defined as recalcitrant and persistent disease failing escalating skin care regimens, including diligent use of emollient-based moisturization and application of topical corticosteroid agents more potent than over-the-counter strength hydrocortisone. Subjective, parent-reported severity is not a criterion in these guidelines. Furthermore, egg allergy was defined as an objective history of symptomatic egg ingestion in egg-sensitized infants (but not egg-sensitized infants without a history of eating egg) [27••]. Realistically, given data suggesting egg is rarely introduced until much later in the first year of life, the egg-specific criteria may not contribute significantly. These criteria are meant to discourage haphazard inclusion of egg-sensitized individuals and reduce any egg screening. Like the LEAP study, a family history of allergic disease (including food allergy) and food allergies other than egg in the infant were not considered as high-risk factors [6, 17••, 27••, 28].

Where the new guidelines also differ from the LEAP study is expansion of infants who may benefit from early peanut

Table 2 Summary of the NIAID Addendum Guideline Recommendations

Summary of Addendum Guidelines			
Addendum Guideline	Infant criteria	Recommendations	Earliest recommended age of peanut introduction ^a
1	Severe eczema, egg allergy, or both	Strongly consider evaluation by sIgE and/or SPT and, if necessary, an oral food challenge. Based on test results, introduce peanut-containing foods	4–6 months
2	Mild to moderate eczema	Introduce peanut-containing foods at home	Around 6 months
3	No eczema or any food allergy	Introduce peanut-containing foods at home	Timing of introduction is age appropriate and in accordance with family preferences and cultural practices

Adapted from Ref [27••]

^a Peanut is not recommended to be the first solid food introduced into an infant's diet and should only be introduced after a child has demonstrated the ability to tolerate solid food, to rule out non-specific signs/symptoms that could be confused for possible food allergy

Table 3 Recommendations on how to introduce peanut to your child

Specific amounts, different types of peanut-containing foods that are safe for infants to eat, and instructions on how to introduce at home, in-office via a supervised feeding, or by graded OFC are provided in detail in the appendices of the Addendum Guidelines. General recommendations for home peanut introduction include the following:

- Do not feed your child peanut as the first solid food introduced into his or her diet.
- Only introduce peanut for the first time to your child on a day when he or she is healthy and has no concomitant illness such as an upper respiratory infection.
- Do not feed your child peanut for the first time outside the house (e.g., at daycare or a restaurant).
- At least one adult caregiver should be able to focus all of his or her attention on the infant.
- The caregiver should plan to have enough time after ingestion to watch the infant for signs of an allergic reaction for up to 2 h.
- Give the infant a small taste of peanut, then wait 10 min before giving a larger portion to make sure it is tolerated, then give the remainder. Avoid a full serving in one bite.
- Do not give children under 4 years whole peanuts or peanut butter directly from a spoon to avoid a choking risk.

introduction. The expert panel also recommends early peanut introduction for moderate-risk (mild/moderate eczema) and low-/no-risk infants, given no evidence of harm and expert consensus this would provide a benefit. For these infants, the recommendation states that peanut can be introduced starting around 6 months of life (with the same dose/frequency targets), but importantly, these groups can have introduction at home without specialist assessment. However, there is exception made for in-office assessment in cases of significant caregiver concern or reluctance for introduction, to facilitate adherence to the guidelines. Though data are mounting which support early egg introduction for similar benefits against developing egg allergy, the NIAID-sponsored panel deferred to make recommendations on early introduction of other allergens at this time [27••].

The Dog that Caught the Bus: Now What Do We Do?

Many viewed LEAP's results as sufficient to initiate new policy, but key questions remain about how comprehensively "at-risk" infants have been defined: if the effect sizes demonstrated in LEAP can be replicated in US populations, if adequate healthcare services resources to implement population-level pre-assessment in the USA actually exist, and what stakeholder preferences are towards accepting these new recommendations [29–31].

Exclusion of family history or other infant food allergies may be a major weakness in comprehensively determining which infants are at-risk [32, 33]. Recent secondary analysis of the LEAP dataset has demonstrated that peanut SPT size, eczema severity, and egg allergy had little overall impact on the probability of peanut tolerance so long as peanut was introduced early, but there are no data evaluating if milk or a grain allergy (more likely to be in the diet in this age than egg) may be relevant [34]. Most importantly, the necessity of allergy-testing peanut-naïve children before introduction—a practice

contradicting multiple clinical food allergy practice guidelines—remains completely unproven. Allergy testing is poorly predictive and has low specificity when assessing foods never previously eaten—not a new finding [3]. While LEAP was a RPCT, the use of skin testing was neither a randomized nor controlled aspect—there was no control group introduced to peanut early without pre-evaluation to compare the necessity of testing and subsequent in-office supervised peanut introduction [17••]. Lack of data to definitively demonstrate if the trial outcome would have been different further questions if the recommendation for pre-evaluation is based on actual medical necessity or simply driven by lack of physician comfort. In light of real-world experience from Israel and Australia, where early peanut introduction outside the office setting is recommended for all infants without screening (and occurs safely), it is fair to question the utility of in-office assessment [35].

Implementing these guidelines at a US population level will hopefully significantly lower the incidence of peanut allergy, assuming excellent adherence to these recommendations from parents and providers—a questionable assumption, given no data indicating such stakeholders either agree with the concept or are supportive of in-office pre-evaluation/introduction. Implementing such recommendations would require large numbers of supervised ingestions, which would serve as a barrier to care. Therefore, the feasibility of implementing guidelines, which essentially medicalizes peanut introduction, requires careful study of stakeholder preferences (both parent and provider), education regarding allergy testing pitfalls, reassurance that early peanut introduction is indeed safe, and assessment that the necessary healthcare resources to provide such service at a population level exist [36]. Key considerations include the number of infants potentially requiring timely access (infants on waitlists for testing and supervised introduction risk delayed introduction), parental comfort with the assessment, allergist access/willingness to conduct in-office peanut introduction (there are <5700 allergists in the USA and Canada, with <20% regularly offering OFCs) [37],

and justification of the cost-effectiveness of pre-assessment. It is unrealistic to expect that only those in the highest risk group (with severe eczema) will seek or be referred for in-office evaluation/introduction, and that providers of lesser-risk infants would not also request similar evaluation [38]. Resource prioritization and utilization within a small labor force may prove problematic and could result in disruption of access to care for other diagnoses requiring an allergist's care. One possible undesirable outcome would be iatrogenic creation of an infant cohort with 3–7-mm SPTs that are never offered in-office introduction due to the above reasons, excluding them from the possible benefits of early peanut introduction and increasing their risk of developing peanut allergy. Another concern is that peanut might not be the only food screened for by serum IgE testing or skin testing, resulting in possibly multiple positive tests that could require OFCs, further straining allergy access and care, or multiple foods being avoided based simply on possibly false-positive allergy tests.

Lastly, there are concerns about how accurately findings from a highly supervised, single-center UK study will generalize to the US population. Should there have been an obligation to replicate the LEAP findings before recommending a broad policy change based on a single study? Advocates for the policy change note LEAP was a costly study, and some may now view it unethical to randomize infants to delayed introduction given the potential harm associated with delay has been established—both valid points. However, replication may answer unresolved issues, specifically regarding other potential risk factors, if there is a narrower age window for introduction for maximal prevention, if office-based pre-assessment/introduction is necessary, and if there is an optimal dose/duration of peanut consumption for optimal treatment effect. Additional data could result in establishment of true best practice, determine healthcare service utilization needs, and maximize health and economic benefits of the policy. As a parallel, there has not been any hesitancy to conduct multiple trials in distinctly different populations for early egg introduction. Some argue that, in doing so, this has established early egg introduction as a far less certain concept, given three Australian trials (STAR, STEP, BEAT) noted no significant difference in rates of egg allergy development (despite trends towards benefits), a German trial (HEAP) noted distinct harm, and a Japanese trial (PETIT) noted smashing success and was halted early due to ethical concerns of doing harm through avoidance given establishment of benefit [19, 20, 21•, 22•, 23]. At present, despite strong evidence of risk reduction, we have no guideline specifically advocating early egg introduction to reduce the risk of developing egg allergy [5]. One could certainly theorize that additional peanut trials may have resulted in similar findings, potentially, and that perhaps equipoise in changing any policy would have resulted.

Future Recommendations

There continues to be data emerging that make a compelling case for early allergen introduction to prevent the development of specific food allergies. Such trials, to date, have not been conducted in the USA. At present, the largest groundswell of support, both in the USA and internationally, has been for the data surrounding early peanut introduction. The USA has recently joined Israel and Australia in formalizing early peanut introduction as part of a national infant feeding strategy. Published in January 2017, the NIAID addendum guidelines for early peanut introduction represent an expert consensus based on the best available data [26]. If successfully implemented, the guidelines should lead to a meaningful reduction in the future incidence of peanut allergy. However, to reach these lofty goals, the policy may require fine-tuning to better align with real-world practices, aspects which were difficult to anticipate in formulating the guidelines given limited data to inform such decisions. Thus, the next few years will be crucial for knowledge translation so that the full health and economic benefits of peanut allergy prevention can be actualized. While pooled data appear to demonstrate benefit for early egg introduction, this has not yet been formally incorporated into any infant feeding guidelines or strategy, though this may change in the near future.

Compliance with Ethical Standards

Conflict of Interest Matthew Greenhawt is supported by grant 1K08HS024599-01 from the Agency for Healthcare Quality and Research; was an Expert Panel member of the NIAID-sponsored Guidelines for Peanut Allergy Prevention; represented the American College of Allergy, Asthma and Immunology in the formation of the Consensus Communication on Early Peanut Introduction and the Prevention of Peanut Allergy in High-Risk Infants; has served as a consultant for the Canadian Transportation Agency and Aimmune Therapeutics; is a member of physician/medical advisory boards for Aimmune, Nutricia, Kaleo Pharmaceutical, Nestle, and Monsanto; is a member of the scientific advisory boards for the National Peanut Board; has received honorarium for lectures from Thermo Fisher, ReachMD, and the Kentucky/Pennsylvania/Aspen/New York allergy societies, the ACAAI, the EAACI, and UCLA/Harbor Medical Center; and is a member of the Joint Taskforce on Allergy Practice Parameters.

David Fleischer is a member of the scientific advisory council for the National Peanut Board, represented the American Academy of Allergy, Asthma and Immunology in the formation of the Consensus Communication on Early Peanut Introduction and the Prevention of Peanut Allergy in High-Risk Infants; was a Coordinating Committee and Expert Panel member of the NIAID-sponsored Guidelines for Peanut Allergy Prevention; is a member of physician/medical advisory boards for Aimmune, Kaleo Pharmaceutical, Nestle, and Monsanto; and received grant support from Nestle, Monsanto, DBV Technologies, and Aimmune Therapeutics.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of importance
- Of major importance

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