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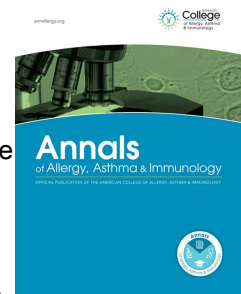
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Review Article: Unmet needs of children with peanut allergy: aligning the risks and the evidence

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Abbreviations/Acronyms: EPIT=epicutaneous immunotherapy; DNA=deoxyribonucleic acid; FDA=Food and Drug Administration; GI=gastrointestinal; HRQOL=health-related quality of life; LEAP=Learning Early About Peanut Allergy; NIAID=National Institute of Allergy and Infectious Diseases; OIT=oral immunotherapy; PALISADE= Peanut Allergy Oral Immunotherapy Study of AR101 for Desensitization

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Background: Peanut allergy is a potentially severe and lifelong allergy, with few effective treatments or preventative measures.

Objective : To convene an expert panel of allergists, pediatricians, and advocates to discuss and highlight unmet needs in the prevention and management of peanut allergies.

Methods: Literature searches of PubMed were performed. The panel evaluated published data on the prevention of peanut allergy, treatment of existing peanut allergy, and management of reactions following unintentional peanut exposures.

Results : Key unmet needs in the prevention and management of peanut allergy were identified, including: 1) enhancing and optimizing implementation of early peanut introduction as a means of preventing the development of peanut allergy; 2) developing knowledge translation strategies regarding the safety and efficacy data for current and emerging immunotherapies for peanut-allergic children to support their use in clinical practice; and 3) promoting understanding of true exposure risk in allergic individuals and ensuring access to epinephrine for accidental exposures that

provoke severe reactions. Clinicians should help educate caregivers about the actual risks associated with peanut allergy, and its prevention and management so that treatment decisions can be evidence based rather than fear based. Support tools are needed to help address caregiver goals, expectations, and psychological barriers, as well as identify facilitators for prevention and treatment strategies.

Conclusion : There are significant unmet needs in our understanding of peanut allergy; addressing these needs will help to enhance understanding of how to most effectively prevent and treat peanut allergy, as well as educate the food-allergic and nonallergic community regarding current evidence-based practices.

1 Introduction

2 Peanut allergy affects an estimated 1.0%–4.5% of US children.¹⁻⁵ Data suggest the
3 prevalence of peanut allergy has likely increased in the past 20 years⁶ and that severe reactions to
4 peanut have also increased. Most of the recent data are, however, indirect, assessing either
5 caregiver reports or discharge coding and medical claims.⁷⁻⁹ Only the Australian HealthNuts
6 study has prospectively measured prevalence using food challenge in a pediatric general
7 population.⁴

8 Beyond the physical burden of peanut allergy, there is increased recognition of impaired
9 health-related quality of life (HRQOL) for both patients and their parents.^{10,11} Anxiety can be a
10 significant burden for many peanut-allergic children and their parents, and potentially for new
11 parents, as well, who are contemplating the decision to introduce peanut early per new early
12 peanut introduction guidelines. In peanut allergy, HRQOL and self-efficacy (a measure of
13 empowerment and disease self-management) can be poor, and may contribute to self-imposed
14 lifestyle limitations and harm-avoidance behaviors that are disproportionate to the actual risk
15 related to peanut exposure.¹¹⁻¹³

16 Better education of parents and children may help to relieve unnecessary anxieties regarding
17 peanut allergy, while highlighting areas where to best focus concern. To that end, Allergy &
18 Asthma Network assembled a panel of experts on food allergies to identify potential unmet needs
19 in the prevention and management of peanut allergies with an emphasis on managing
20 consequences of accidental peanut exposures, as well as unmet research needs and knowledge
21 gaps.

23 Methods

An expert panel of 7 allergists (4 academic, 2 private practice, and 1 industry), 1 pediatrician, and 1 advocacy leader was chosen based on their prominence in the area of food allergies. The group had one telephone conference and a single face-to-face meeting between September and November 2018, with the intention of developing an agenda for discussing unmet needs in peanut allergy prevention and management.

Topics of discussion included peanut allergy prevention, peanut allergy management (including treatment options), and strategies for risk stratification to address allergic reactions after accidental or incidental exposure. A narrative review format was chosen, using a modified Delphi panel approach (75% agreement threshold) to achieve consensus on each unmet need.¹⁴ Based on author input, a medical writer performed targeted literature searches and helped support development of the first draft of the manuscript. Each author read and edited the manuscript draft in iterative fashion. Unanimous consensus was achieved on the unmet needs and recommendations.

Results

Current Unmet Needs in Managing Peanut Allergies

Prevention

What We Know

Data have demonstrated that early peanut exposure reduces the risk of developing peanut allergy in at-risk infants compared with delayed introduction,¹⁵⁻¹⁷ prompting a shift in guidelines in Australia/New Zealand, Canada, the United Kingdom, and the United States from recommending early peanut avoidance to an endorsement of early peanut ingestion to reduce the

risk of developing peanut allergy.¹⁸ Both observational and prospective data support this recommendation.

A 2008 observational study suggested a 10-fold increased risk of peanut allergy in Ashkenazi Jewish children living in London, United Kingdom, relative to a similar population of Ashkenazi Jewish children living in Tel Aviv, Israel, with the increase in London believed to be due to delayed peanut consumption until after age 3 years.¹⁵ This prompted the Learning Early About Peanut Allergy (LEAP) trial to prospectively examine whether early peanut introduction reduces the likelihood that a child will develop peanut allergy. The LEAP trial demonstrated that in infants not peanut sensitized at baseline, peanut allergy developed by month 60 in 14% of those randomized to delayed peanut introduction vs 2% of infants randomized to eat peanut between the ages of 4 and 11 months.¹⁷ Of children with low-level (1–4 mm) baseline peanut sensitization determined by skin testing, peanut allergy developed in 35% of those randomized to avoidance vs 11% randomized to consumption. These differences were all statistically significant, with the numbers needed to treat to prevent the development of peanut allergy being 8.5 in non-sensitized children and 4 in sensitized children, demonstrating heterogeneous risk reduction in both arms.¹⁹ In a 1-year follow-up study during which all subjects discontinued eating peanut, there were no differences in the rates of subsequent peanut allergy development during follow-up between the avoidance and consumption arms.

After publication of LEAP, the US National Institute of Allergy and Infectious Diseases (NIAID) assembled an expert panel to update guidelines on early peanut exposure to prevent the development of peanut allergy.¹⁸ The panel recommended early peanut-containing food introduction in infants aged 4–6 months with severe eczema or egg allergy, guided by results from additional screening tests. Similar guideline updates were implemented in Australia/New

Zealand, Canada, and the United Kingdom urging early peanut introduction, but without recommendation of any screening tests prior to introduction.^{20,21}

Unmet Needs

The NIAID guidelines provide a framework for early peanut introduction, but leave many questions unanswered about implementation, including whether it is necessary to screen children for risk prior to peanut introduction and the definition of a high-risk infant (**Table 1**).²²⁻²⁴ The NIAID guidelines recommend that moderate and low risk children should also have early introduction, but as with guidelines in other countries, do not endorse preliminary screening in these children.¹⁸

Secondary analysis of the primary LEAP data found that early introduction between months 6 and 11 was associated with a higher rate of tolerance (and a narrower confidence interval) than starting at months 4–6, which calls into question the need to prioritize peanut introduction as an initial key food in this narrow timeframe.²⁴

The LEAP trial only considered egg allergy and severe eczema as high-risk criteria, very narrow parameters that are different from preceding prevention studies.²⁵ Approximately 14% of all peanut-allergic children have no apparent risk factors prior to diagnosis,¹⁸ and more concerning in an Australian study, 23% with challenge-proven peanut allergy in a population-based cohort did not have severe eczema or egg allergy.²⁶ This may suggest poor specificity of the LEAP high-risk criteria and that other potential risk factors may need to be identified and studied.

More germane is the necessity for screening any infant, regardless of possible risk factors. Guidelines in Australia/New Zealand, Canada, and the United Kingdom do not

recommend any assessment of preexisting peanut sensitization before undertaking early introduction to an infant,^{22,27-28} a recommendation that is unique to the United States. Furthermore, the screening approach was found to not be cost-effective compared with not screening, with incremental costs of \$641,000,000 to prevent ~3200 fewer cases of peanut allergy over a 20-year horizon, although screening was cost-effective and prevented more cases of peanut allergy development compared with delayed introduction.²⁹

There are also needs to define caregiver preferences, clarify values regarding the desirability of medicalizing early peanut introduction, and assess potential caregiver-level barriers to guideline implementation. In a 2018 survey of 1000 expectant mothers and 1000 mothers of infants aged <1 year, 31% were willing to introduce peanut-containing products by age 6 months, with the proportion increasing to 40% after 11 months.³⁰ More than half of respondents were unwilling to allow in-office risk-assessment procedures before age 12 months to facilitate early introduction, including skin prick tests (51%) and oral peanut challenge (57%).

A cross-sectional, online survey of 369 pediatricians found that only 28% were fully following the NIAID recommendations for early peanut introduction and that 8% of the pediatricians surveyed were not even aware of them; 67% of respondents who had not implemented the guidelines were not familiar with the most recent version on early peanut introduction.³¹ A 2018 Canadian Society of Allergy & Clinical Immunology survey after introduction of the NIAID guidelines demonstrated low comfort in performing infant oral challenges, with only 42% of allergists performing them routinely and 11% not offering infant oral challenges despite offering skin prick testing them.²³ Anecdotally, there is also concern that infants are at high risk of severe reaction with early peanut introduction. Available data clearly show this to be unlikely, however, as food-related severe anaphylaxis in infancy is extremely

115 rare and no fatalities have been reported.³²⁻³⁴ As the LEAP study did not evaluate alternative
116 peanut ingestion schedules or durations, it is unknown whether shorter, less frequent, or smaller
117 amounts of peanut are equally efficacious for prevention of peanut allergy.³⁵

119 ***Emerging Treatments: Immunotherapies***

120 ***What We Know***

121 There has been increased research into food immunotherapies in the early 21st century,
122 with several viable therapies that increase the threshold dose at which reactions to ingested
123 allergen occur poised to become available.³⁶ Current food immunotherapies differ considerably
124 from traditional inhalant/venom immunotherapies, which are given every 1–4 weeks in an
125 observed office setting. In contrast, most food immunotherapy dosing occurs daily at home. With
126 oral immunotherapy (OIT), weekly to biweekly up-dosing occurs in the clinic until maintenance
127 is reached. In the clinical trials investigating epicutaneous immunotherapy (EPIT), daily dosing
128 after the initial patch application was done at home.

129 The US Food and Drug Administration (FDA) has not approved any food
130 immunotherapies, though this is anticipated to change in 2020 as the FDA has given two
131 products action dates for a decision regarding approval. The use of food as a therapy presents a
132 grey area, in particular if it is necessary for the FDA to approve use commercially available
133 foodstuff as OIT, which has been the subject of a 10-year debate.³⁷ While early- and late-stage
134 clinical trials of food OIT have been conducted in university settings under an FDA
135 investigational new drug approval mechanism, a parallel track of office-based OIT has evolved
136 using “regular” food in non-research settings in the United States and Canada.^{38,39} Oral
137 immunotherapy in such settings has been long described, historically,^{37,40-43} with multiple

studies and case series detailing successful real-world outcomes in children and young adults exposed to multiple forms of peanut across a wide range of ages, including very young children, though no randomized placebo-controlled trials in these settings exist.⁴²⁻⁴⁸ In 2014, a proprietary commercial peanut OIT product was developed to offer a standardized, allergen-characterized pharmaceutical-quality approach to OIT, using 12% light-roast peanut flour from the Golden Peanut Company, packaged in gelatin capsules with a binder and glider agent, technically constituting a device. The 12% light-roast peanut flour from Golden Peanut and Tree Nuts (Alpharetta, Georgia) had been used in previous CoFAR studies without the glider/binder and capsule.^{44,49,50} The capsule is not consumed; rather, it is opened and the flour contents are then mixed with another vehicle (e.g., pudding, applesauce) and eaten.

Irrespective of the particular OIT product used, published data on peanut OIT have noted a consistent pattern—strong efficacy, with the majority of participants reaching the desensitization goal, balanced by subjects experiencing anaphylaxis, reactions requiring epinephrine, and gastrointestinal (GI) adverse events.^{47,48,51} These reactions may be manageable for many, however, and overall published data indicate that 65%–85% of patients on any product form of OIT have progressed to reach a maintenance dose. There appears to be different safety (lower risk of anaphylaxis), efficacy, and adherence data in preschool-aged children, although more studies are needed to formally compare younger patients with other age groups.^{47,48}

Gastrointestinal and systemic hypersensitivity events, reported with both proprietary and nonproprietary OIT across multiple studies dating back 10 years, remain an unmet need in terms of enhancing peanut OIT safety.^{44,52-55} A *Lancet* meta-analysis of 12 peanut OIT clinical trials in children aged 4–17 years noted that peanut OIT significantly increased the relative risk and

frequency of anaphylaxis, epinephrine use, serious adverse events, vomiting, and angioedema vs no therapy, even after reaching maintenance dosing.⁵¹ This meta-analysis did not note any safety advantage in using commercial forms of immunotherapy (including the increased risk of anaphylaxis relative to no OIT). It is unclear if this risk is unique to older children apart from younger ones. However, this limitation has been well-recognized, and there are ongoing efforts to enhance OIT tolerability and efficacy have included ongoing studies that are exploring coupling OIT with anti-immunoglobulin E therapy, anti-IL-4/13, and probiotics, both with proprietary and non-proprietary products.^{52,56-59}

Epicutaneous immunotherapy is a desensitization strategy in which allergen is introduced into the immune system via the skin, bypassing the GI tract and absorption.⁶⁰⁻⁶² The EPIT dosing range is much reduced relative to OIT (micrograms vs milligrams), but has immunomodulatory effects that appear similar to those of other immunotherapy forms, although efficacy (specifically, timing of peak efficacy) may differ. In a 12-month phase 3 trial, 35% of patients receiving EPIT achieved the primary desensitization endpoint vs 13% of those on placebo, which while statistically significant missed a prespecified criterion for robustness of treatment effect, although a post-hoc analysis showed 63% in the peanut-patch group vs 28% in the placebo-patch group experienced an increased eliciting dose (any level of change) at 12 months.⁶⁰ In the EPIT trial, there were high rates of localized skin rash but there were no GI side effects reported, and a very low rate of anaphylaxis attributed to treatment.⁶⁰

Table 1 details some of the key comparisons of the two published phase 3 trials for both EPIT and the commercial OIT product. These trials had similar but distinct designs, making direct comparison of efficacy or safety difficult.^{60,63} While it is unclear when peak efficacy for either therapy is anticipated to occur, there were few known data for EPIT given limited previous

study, and a much clearer indication that desensitization occurs fairly rapidly for OIT within the first 6-12 months.^{60,63} Phase 2 data on biomarker changes and responder rates suggest peanut EPIT efficacy may continue to improve beyond 1 year of treatment,⁶² which is being explored in long-term follow-up in the EPIT Phase 3 trial, still ongoing (ClinicalTrials.gov identifier: NCT02916446). Long-term extensions of AR101 clinical trials are also ongoing (ClinicalTrials.gov identifier: NCT03292484) or have been completed (ClinicalTrials.gov identifier: NCT02993107), though results have yet to be published. Favorable data for changes in quality of life have been reported in abstract form for both OIT and EPIT, with a common (but not unexpected) finding that changes were not apparent with either trial until the second year of therapy, after unblinding and awareness of any treatment benefit occurred.

FDA approval of these potential therapies may provide important options for desensitizing individuals (i.e., increasing their triggering threshold dose) while reducing the risk of accidental exposure reactions. This may translate into improved confidence for patients to go out in the world and lead active lives, although more work needs to be done in this area. One simulation study of hypothetical exposure suggests increasing the threshold of a person's eliciting dose from <100 to ≥ 300 mg of peanut protein would reduce the risk of allergic reactions to accidental ingestions of various peanut-contaminated food products by $>95\%$,⁶⁴ while another study suggests that increasing the dose to 1000 mg would reduce the risk by 99%.⁶⁵ These are ranges that could be attained by either therapy, though these studies were not based on real-life data in patients desensitized by either product. Preliminary modeling suggests that both therapies can be cost-effective depending on the change in health utility (e.g., perceived treatment benefit) achieved, level of long-term sustained unresponsiveness attained, anaphylaxis risk reduction, and market price.⁶⁶

Unmet Needs

Treatment goals are poorly understood (**Table 2**). A 2016 survey of parents recruited from food allergy patient advocacy organizations reported that 56% of parents identified ad-lib allergen consumption as a treatment goal, with 28% identifying “protection from accidental ingestion” and 16% the “ability to consume limited amounts with caution.”⁶⁷ However, a qualitative study assessing parents of children enrolled in both phase 3 peanut trials noted that some parents are willing to trade reduced efficacy gains for lower therapy-associated risks.¹⁰ In their own words, these parents viewed commercial forms of peanut immunotherapy as a “seat belt” that provides additional safety on top of vigilant supervision (which would not be relaxed) and risk reduction behavior. Thus, what is being sought from therapy may vary by particular families, goals may evolve in the future once more parents experience their child achieving meaningful protection, and this area requires further study. Research is also needed to identify preferences for specific outcomes and treatment attributes that may influence treatment choice to help better tailor a particular choice to a family.

Work regarding value clarifications is needed to determine whether treatment goals are therapy specific, and differ with nonproprietary vs proprietary therapies, and between parents, children, and allergists. It is likely that a continuum of goals exists and varies between individuals, but it is important that some realistic, standardized outcome goals are provided for parents considering treatments.

Caregiver perceptions could be hindered by poor understanding of likely OIT/EPIT long-term risks and benefits. Post-marketing research, therefore, will likely be essential for any eventual commercial products, which may be approved after only a year of evaluation in

230 placebo-controlled, randomized, controlled trials plus short-term data from real-world safety
231 studies. Initial research characterizing caregiver and patient HRQOL, and patient peanut
232 consumption after completion of a long-term EPIT trial has been published and appears to note
233 favorable change with both products.⁶⁸ Longer term real-world feasibility, implementation, and
234 adherence data are needed, however, in particular regarding whether dosing interval interruptions
235 alter safety or efficacy. Further work is needed to help incorporate long-term, nonproprietary
236 OIT experience³⁷ (which is of longer duration and more robust than the proprietary data) into
237 real-world clinical settings.

238 There is also a need to define limits on acceptable risks of a reaction from treatment
239 itself, as well as to determine if immunotherapies have efficacy ceiling effects. A key unmet
240 need is to understand if reactions (including severe ones) related to treatment are perceived
241 differently (e.g., better accepted) than ones occurring from unintended exposures. Additional
242 research will be needed to determine whether sustained improvements in peanut tolerance are
243 achievable and in which patients. Based on limited long-term peanut OIT data, taste aversion to
244 peanut is potentially significant and may dissuade therapy adherence.⁴⁶ Moreover, it is unclear if
245 children put on OIT (or if EPIT reaches an indication up to age 17 years) will elect to continue
246 their parents started on their behalf once they become able to make medical decisions for
247 themselves. It is also unclear how immunotherapies may change health utility or HRQOL, so that
248 we can accurately determine the net benefits of treatment.

249 Further, outcome standardization is needed for assessment of tolerated doses. Two phase
250 3 clinical trials of immunotherapies evaluated different outcomes in their double-blind, placebo-
251 controlled food challenges, with EPIT using an eliciting dose at which objective symptoms
252 occurred and OIT using a tolerated dose (administered on a day when subjects did not receive

OIT) at which no more than mild symptoms occurred.^{60,63} Objectively, neither trial had a primary outcome defined with reference to unequivocally asymptomatic patients—this makes comparison different, and increases the difficulty for a parent to understand what level of protection their child may receive depending on product choice . Use of a single outcome standard would enhance comparative efficacy research and understanding of the heterogeneity of clinical response.^{53,69,70} Highly specific biomarkers are needed to monitor safety and efficacy as an alternative to relying on interim oral challenges and/or a maintenance dose to derive potential protection. A noted limitation of EPIT vs. OIT is that there is no daily ingestion of a specific mg dose, creating potential difficulty in knowing in “real time” if there is protection to a certain dose level. Conversely, day to day asymptomatic tolerance of OIT dosing is subject to a number of inflammatory cofactors (e.g., infection, menstruation, activity level) that may make the daily dose barometer less than 100% reliable. Therefore, for both therapies, there is urgent need to develop a biomarker that can help patients understand their threshold. The recently reported fatality of a French OIT patient who died during an entry food challenge further underscores the limitations and risks of using oral food challenge in the clinical setting as a surrogate for immunotherapy outcomes.⁷¹

Importantly, there are multiple other therapies in development for the treatment of peanut allergy, including DNA-based vaccines, peptide immunotherapy, subcutaneous immunotherapy, and monoclonal antibody-based therapy.⁷² Broader future options may eventually be available to provide patients with robust treatment choices to consider, some of which may be able to evolve around 1st generation therapies and offer protection against multiple food allergens, higher levels of threshold protection, offer alternatives to daily or even frequent dosing interval, or may be able to treat other allergic diseases beyond food allergy at the same time. The progress made to

this point in developing safe and effective treatment options for peanut allergy is remarkable.

However, this represents the start of the journey, and like any other space, efforts towards developing innovative and more efficient therapies will continue.

Accidental and Casual Exposures

What We Know

Parents often worry about their peanut-allergic children leaving an allergen-safe home for less controlled environments.⁷³ Some parents feel more secure having their children homeschooled or attending a peanut-free school,⁷⁴ and perceive they should remain hypervigilant of their children's surroundings.⁷⁵ Allergen-related anxiety can isolate children and impair HRQOL.⁷⁵ Casual environmental peanut exposure is, however, an unlikely threat unless there is a transfer to the mouth or mucus membrane. Several studies have demonstrated casual skin contact with peanut butter, touching washed surfaces, or inhaling shelled peanut dust or peanut butter vapors poses exceptionally rare risk of reaction, and no study has shown that peanut circulates on an airplane.⁷⁶⁻⁷⁹ Peanut is easily cleaned from surfaces and hands using soap and other common detergents, and there is no evidence that the volatile organic compounds that give peanut its characteristic smell carry any protein that can trigger a reaction.^{77,79-81}

Ironically, while families perceive a risk outside the home, studies have revealed that approximately one-third of accidental peanut reactions occurred at home.^{3,82} Although well intended, protective measures outside the house, such as allergen bans, do not guarantee that a public area can be reliably maintained as "peanut free." Worse, such restrictions may reduce vigilance and fail to teach children how to realistically interact with their environment. Few data on the efficacy of peanut bans are available. A Massachusetts study noted no significant

reduction in epinephrine use at peanut-free schools, or schools where peanuts were not served in the cafeteria or allowed in classrooms. While schools with peanut-free cafeteria tables had fewer epinephrine administrations than those without such tables, the absolute reduction in epinephrine administrations was small.⁸³ No data exists to show that not serving or otherwise restricting peanut on an aircraft improves outcomes as well. Although vigilance is necessary, overly restrictive environmental policies are no substitute for teaching avoidance and how to navigate a peanut-containing environment.

Multiple self-report food allergy surveys have noted severe reactions may occur in up to 50% of cases.^{3,84} Peanut-related fatalities are, however, exceptionally uncommon, ranging from 0.73 to 4.25/million person-years.⁸⁵ Nonetheless, given the potential for severe reactions, all peanut-allergic individuals should be trained to always carry self-injectable epinephrine and promptly treat reactions. Evidence suggests that epinephrine auto-injectors are dramatically underused and are often not even carried,^{82,86,87} and that fatality is disproportionately associated with these factors.^{88,89} Thus, a key focus of management should be to enhance adherence with anaphylaxis self-management planning and implementation. De-emphasizing fatality as a likely outcome is also important, but should be done in a way that does not inadvertently embolden patients to take unnecessary risks.

Unmet Needs

Anxiety related to peanut allergy and risk of reactions remains difficult to manage (**Table 1**). Past anaphylaxis is a significant moderator in worsening caregiver HRQOL and self-efficacy, and this may be further amplified by inaccurate perception of reaction severity.^{11,12,90} Health-related quality of life may also be worsened by using epinephrine to treat reactions when

anaphylaxis is not present, as some action plans and advocates have suggested.^{10-13,73,75,91} Other poorly characterized potential influences on HRQOL include conflicting provider management advice, as well as the inability to define and predict severe reactions, clinically phenotype patients, and characterize the long-term outlook for allergic patients.

Because accidental peanut exposures remain unpredictable events with variable consequences,^{82,92-95} management recommendations continue to stress a universal precaution approach centered around strict avoidance of peanut and caution that reaction severity can escalate. Few reliable models exist to characterize reaction severity and most are narrowly representative of a referral center population undergoing intentional challenge rather than the general allergic population who may experience accidental exposure.^{34,96} More reliable predictive models need to be developed to phenotype patients so we can better risk-stratify patients and tailor management.

Additional information gaps persist, such as the need to better understand the efficacy of restrictive policies/bans to ensure protective measures are effective and do not provide a false sense of security. Effort is needed to appropriately educate caregivers and patients about the varied peanut allergy myths, such as the belief that peanut can aerosolize and be harmful.⁷⁶ The field would be much better served, however, with attention focused away from low risks, like public casual contact/exposure, and emphasis placed on addressing a well-identified problem such as poor adherence with epinephrine carriage and use. Carriage rates must approach 100% and could be improved through public health endeavors such as the enhanced anaphylaxis education efforts of the past 15 years.

Discussion

Clinicians should be proactive in fostering a partnership with patients to keep them informed about the actual risks associated with their allergy. Informed patients will be better equipped to make evidence-based rather than fear-based contributions to decision-making about their own care. Clinicians should strive to emphasize evidence-based facts and reduce delivering well intended messages that over-emphasize fear and worst-case scenarios, which may lead to a misunderstanding of the actual degree of risk and be ineffective. Such messages are already highly pervasive in the community. It has been suggested that anxiety may be fueled by media reports referring to peanut allergy as an epidemic.⁹⁷ Such alarmism is the enemy of good care, and the medical disinformation that feeds it remains rampant, is rapidly spread online, and likely erodes the clinician-patient relationship to the detriment of care.

Improving care is, therefore, a multifaceted enterprise that involves not only developing and using preventive measures and treatments for peanut allergy, but also closing information gaps that foster peanut allergy misperceptions. With food allergy, the daily burden is uniquely psychological as affected children are generally otherwise healthy. Physicians can educate patients to help them live with less fear and anxiety and improved HRQOL and self-efficacy. Patients who are able to partner in the decision-making process for choosing the most appropriate treatment options will be better able to manage the actual risks they face each day.

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Table 1: Key Unmet Needs Related to Published Data for Anticipated Peanut Allergy Therapy Options

Commercial OIT	• Reducing the risk of treatment related anaphylaxis, epinephrine use, and adverse events • Reducing the risk of dose related adverse events related to doses taken on empty stomach, when sick or menstruating, when tired, or too close to exercising or a hot shower and enhancing convenience of dosing for the patient • Clarifying the true responder rate—how many tolerated 600mg without symptoms vs. with “no more than minimal symptoms” • Demonstrating real-life claims of reduced reaction severity outside of an exit oral food challenge • Understanding the risks for treatment related eosinophilic esophagitis • Understanding if dose interval can be stretched and the duration of therapy needed • Understanding if patients can be pushed to a higher maintenance dose than 300mg • Understanding if a 300mg daily maintenance dose is sufficient to produce sustained unresponsiveness • Understanding the effect that treatment will provide net benefit to a patient who still has to avoid eating peanut and carry self-injectable epinephrine • Real-world efficacy post-clinical trials where patients are unlikely to undergo entry oral food challenge before starting commercial OIT • Demonstrating using a characterized product is associated with significantly different safety and efficacy
EPIT	• Clarification about the efficacy of the product, with respect to both the number reaching the primary endpoint at a year, and the “super-superiority” margin vs. placebo of a 95% CI lower bound of 15 not being met • Clarification of the significance of the eliciting dose (vs. tolerated dose) in understanding to what protein level a patient may be protected • Understanding how to monitor treatment efficacy in the absence of daily oral product ingestion • Demonstrating efficacy in 12-17 year-old children • Reducing the risk of treatment related cutaneous reactions • Understanding if dose interval can be stretched and the duration of therapy needed • Understanding if a 250 mcg daily dose is sufficient to produce sustained unresponsiveness • Understanding the effect that treatment will provide net benefit to a patient who still has to avoid eating peanut and carry self-injectable epinephrine • Real-world efficacy post-clinical trials where patients are unlikely to undergo entry oral food challenge before starting EPIT
Non-Commercial OIT	• Understanding of the clinical significance of the lack of standardization/harmonization of multiple different products, dose ranges and protocol variations used • Reducing treatment-related adverse events such as anaphylaxis or reactions requiring epinephrine use, eosinophilic esophagitis and eosinophilic esophagitis like OIT-related syndrome (ELORS) • Reducing the risk of dose related adverse events related to doses taken on empty stomach, when sick or menstruating, when tired, or too close to exercising or a hot shower and enhancing convenience of dosing for the patient • Understanding the risks for treatment related eosinophilic esophagitis and/or ELORS • Understanding potential data quality issues—data are sparsely reported and come from case series without controls or research oversight, compared to registered and controlled clinical trials for commercial products • Understanding the effects of patient selection issues on outcomes—patients self-select for treatment, often do not undergo oral challenge prior to entry, and are not paying for therapy through insurance • Determining the difference in outcomes between the two OIT styles
Avoidance	• Understanding of why a patient or patient family may prefer avoidance over a therapy option • Reducing the risk and consequence of accidental exposure • Understanding if accidental exposure causing a reaction is viewed differently than therapy-associated exposure causing a reaction • Understanding how to enhance empowerment, self-efficacy, and quality of life of those who choose to not enter into therapy

Table 2

Key Unmet Needs and Knowledge Gaps

Area of Concern	Unmet Need/Knowledge Gap
Prevention of peanut allergy through early introduction	• What defines a high-risk infant? • Is screening necessary before introduction? • What are caregiver preferences surrounding early introduction? • Are infants undergoing early peanut introduction susceptible to anaphylaxis?
Treatment of peanut allergy	• Understanding of caregiver goals, preferences, and development of clinical decision-support tools • Long-term safety and efficacy data in a variety of age groups • Real-world translation for implementation, feasibility, and anticipated variation of practice • Comparative efficacy between proprietary and nonproprietary OIT methods • Comparative efficacy between OIT and EPIT • Standardization of clinical trial outcomes and endpoints • Discovery of biomarkers for both efficacy and safety • Role of other treatments for peanut allergy (eg, sublingual immunotherapy, vaccines, and

	biologics)
Unintended exposures and reaction management	• Knowledge translation of low risk of reacting to casual public peanut exposure through contact or airborne sources • Determinants of poor HRQOL and self-efficacy, and interventions to improve these • Predictors, phenotyping, and risk stratification of risk of severe reaction • Approaching 100% compliance with carrying injectable epinephrine and using it appropriately when indicated

EPIT, epicutaneous immunotherapy; HRQOL, health-related quality of life; OIT, oral immunotherapies.