

LEAPing forward with the new guidelines



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In this month's issue of the *Journal*, the much anticipated product of the National Institute of Allergy and Infectious Diseases–sponsored expert panel on the “Guidelines for the prevention of peanut allergy” have been published.¹ We strongly commend the expert panel on this thoughtful, clear, evidence-based document, which is obviously the result of a significant amount of time and discussion. There is no doubt that these recommendations will prevent the development of lifelong peanut allergy in countless numbers of children. However, although this represents a major advance in our field, there is still much to learn in the realm of food allergy prevention related not just to peanut but to other foods as well.

Although our comments are in no way meant to criticize these well-constructed guidelines, we believe that there are several areas worthy of ongoing discussion related to both clinical care and the need for additional research. These include issues related to the definition of the “at-risk” population, the feasibility and implementation of the guidelines, and the potential, as with virtually any guideline, that unintended consequences could occur.

As we have learned in the past, there is a risk in developing guidelines on food allergy prevention if they are not based on solid evidence. Therefore the expert panel was appropriately cautious in limiting their recommendations to those based on high-quality evidence rather than relying heavily on expert opinion, as did the 2000 American Academy of Pediatrics' guidelines, which in retrospect provided incorrect advice.² Unfortunately, however, although there is extraordinarily high-quality evidence from the Learning Early About Peanut Allergy (LEAP) study³ and supporting evidence from a second study,⁴ the expert panel was to some degree constrained in the

recommendations they could make with a high level of confidence, and these constraints might have led to a few specific recommendations that could be construed as too conservative.

Most importantly in this regard, they chose to define the at-risk population for early peanut introduction based largely on the very narrowly defined and extremely high-risk population enrolled in the LEAP study, which included only infants with severe eczema, egg allergy, or both. Although the expert panel did suggest an approach for babies with less severe eczema and at least noted the potential effect of family history on the risk of peanut allergy, it is likely that infants who are allergic to foods other than egg are also at high risk of peanut allergy. This might be especially important if the benefit of peanut introduction is truly greatest at 4 to 6 months of age, as the guidelines strongly recommend. At that age, very few children are given a diagnosis of egg allergy, not because it does not exist but simply because it is not a common component of the infant diet, whereas clear diagnoses of young infants with allergy to other foods, especially milk, are very common. Furthermore, to our knowledge, there is no evidence that egg allergy is more highly associated with the development of peanut allergy than is allergy to other foods, such as milk, soy, or wheat. In support of this, in the observational study conducted by the Consortium of Food Allergy Research, early milk and egg allergy were equally likely to be associated with likely peanut allergy.⁵

The feasibility and implementation of these guidelines raises other specific concerns. For example, in a recent publication from Australia by Koplin et al.,⁶ they estimated that screening all infants with early-onset eczema, egg allergy, or both could require testing 16% of the population; that this would still miss 23% of peanut allergy cases; and that 29% of screened infants would require clinical follow-up because of positive skin test results. They went on to conclude that this approach “would pose major cost and logistic challenges that need to be carefully considered,” which is similar to the conclusion from another feasibility study conducted in an unselected Irish birth cohort that concluded that “community implementation would demand huge additional resources at all levels of health care.”⁷

In an apparent effort to maximize feasibility, especially in areas where there are too few allergists to perform the skin testing and oral peanut challenges necessary to implement the guidelines, the current recommendations differ from the preliminary “post-LEAP” consensus communication⁸ by now including the option of using IgE testing in lieu of skin testing. Although the purpose of this recommendation was to “minimize a delay in peanut introduction for children who may test negative,”¹ it is also important to recognize that this approach has the potential to do more harm than good. In fact, the LEAP study taught us that peanut IgE testing is far from a perfect screening tool, given that 22% of all participants, not even including screening failures, had a positive baseline IgE level to peanut, of whom only 2% had

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positive challenge results. In that study there was also no statistically significant relationship between the peanut IgE level and the baseline challenge outcome, so that even infants with higher peanut IgE levels usually had negative challenge results.

It is here where unintended and potentially harmful consequences could arise. Many babies without peanut allergy will have positive IgE test results, sometimes at high levels, and will be declared to have peanut allergy if they are not able to access the specialty care for further testing, as advised by the guidelines. A very rough estimate of the potential scope of this problem could be extrapolated from the Irish birth cohort study noted above, in which about 5% of babies had severe eczema or egg allergy. In the United States, even if only babies with severe eczema are screened, this would translate to about 200,000 infants per year for whom screening would be recommended and at least 40,000 who would have a positive peanut IgE level based on the LEAP data. Therefore the feasibility of guideline implementation might actually be complicated rather than facilitated by this approach. Even more importantly, unless these infants with positive IgE test results can access specialty care in a timely manner, they have a true risk of receiving a diagnosis of peanut allergy, unnecessarily avoiding peanut, and being placed at higher risk of peanut allergy, such as those in the avoidance group in the LEAP study.

Additional concerns regarding both feasibility and possible harm were expressed in the recent commentary by Levin et al,⁹ who objected to the recommendation that complementary foods be introduced before 6 months of age. This recommendation clearly contradicts those of the World Health Organization, which are based on clear evidence regarding the health benefits of exclusive breast-feeding for the first 6 months of life.¹⁰ The guidelines note this concern, as well as the publication by Feeney et al¹¹ demonstrating that early introduction of peanut in the LEAP cohort did not affect the duration or breast-feeding or overall nutrition. However, Levin et al⁹ make a compelling argument that LEAP and other studies on the early introduction of allergenic foods have been conducted only in high-income countries, with no data yet available on the medium- to long-term health effect of these practices. They advise that global consensus would clearly be desirable but strongly recommend that infant feeding guidelines be cognizant of the medical and socioeconomic realities of different settings. It is interesting to note that in comparison with the initial consensus communication, the words “in the United States” were added to the title of these guidelines, presumably in response to these and other concerns from around the world.

Two final comments relate to the approach to infants without risk factors and the early introduction of foods other than peanut. Given the absence of evidence, the expert panel suggested that infants without eczema or food allergy have age-appropriate peanut-containing foods freely introduced in the diet, together with other solid foods, in accordance with family preferences and cultural practices. Given that many children without known risk factors go on to have peanut allergy, one could argue for more

clear guidelines for early introduction in all children. This would also likely make it easier for primary caretakers to simply recommend early introduction as a universal practice. It should also be noted that they chose to not make recommendations regarding early introduction of other allergenic foods, although data are clearly emerging to suggest the benefit of early egg introduction to both low- and high-risk infants, including a recent meta-analysis.^{4,12-14} This is not a criticism of the guidelines but more an example of the rapidly evolving nature of this field.

In summary, we thank and commend the expert panel on this enormous task but caution readers that this is not the final story. It will likely be a decade or more before a more complete story has unfolded, and we anxiously await results of upcoming studies to address some of the questions posed here, as well as many, many others.

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