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REVIEW

WILEY

Early priming of asthma and respiratory allergies: Future aspects of prevention

A statement by the European Forum for Education and Research in Allergy and Airway Disease (EUFOREA) and the EAACI-Clemens von Pirquet Foundation

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Abstract

In order to summarize recent research on the prevention of allergies—particularly asthma—and stimulate new activities for future initiatives, a virtual workshop sponsored by the EAACI Clemens von Pirquet foundation and EUFOREA was held in October 2021. The determinants of the "allergic march" as well as the key messages from intervention studies were reviewed by an international faculty of experts. Several unmet needs were identified, and a number of priorities for future studies were proposed.

KEYWORDS

Allergy prevention, asthma prevention, prediction of asthma, risk factors for allergy

The workshop was sponsored and organized by the European Forum for Education and Research in Allergy and Airway Disease (EUFOREA) and the EAACI-Clemens von Pirquet Foundation. A honoraria was paid to each active participant.

1 | INTRODUCTION

Since the realization of allergies in childhood as a major public health problem in many parts of the world, prospective birth cohort studies have been initiated, that follow the incidence, prevalence, and persistence of IgE-mediated sensitizations as well as airway symptoms. Frequently, manifestations of the upper or lower airways appear with other atopic comorbidities such as eczema and food allergy. Longitudinal studies have led to a better understanding and phenotyping of the so-called "atopic march" from infancy to adolescence. Although some of the relevant genetic, environmental, and lifestyle determinants have been extensively studied, there are few encouraging messages from intervention studies aimed at prevention, particularly asthma prevention.

After a first workshop in 2012,[1] another follow-up virtual workshop was held in October 2021 sponsored by the European Forum for Research and Education in Allergy and Airway disease (EUFOREA) together with the EAACI-Clemens von Pirquet Foundation. The intention was to provide an updated platform for the presentation of recent research results by key researchers and stakeholders, to encourage the exchange of ideas and stimulate new activities for future initiatives.

Key Message

This article updates our current knowledge of the genetic and environmental determinants for allergy and asthma and discusses future options for primary and secondary prevention.

2 | NATURAL HISTORY AND DISEASE PREDICTION

The global period prevalence of several atopic phenotypes in childhood and adolescence such as atopic dermatitis, allergic rhinitis, asthma, and food allergy was initially assessed more than 20 years[2] ago by the International Study of Allergies and Asthma in Children (ISAAC), a large cross-sectional multicenter study. More detailed understanding of the disease development, natural course, and comorbidities was obtained from several longitudinal observational birth cohorts, which clearly demonstrated atopy and asthma to become frequently manifest during the first years of life (Figure 1). The annual incidence of most manifestations is higher in children than in adults, comorbidity with different atopic manifestations is common, and—more commonly than in adults—symptoms tend to improve or remit completely over time despite years of persistence.[3,4] However, high-risk groups in terms of progression and persistence could be identified by latent class analysis.[58,59]

The first sensitization is often induced by food proteins such as cow´s milk and hen´s egg, followed by tree nuts or peanuts in many countries. Differences may depend on regional variations and traditions of infant nutrition.[5]

Sensitization to environmental indoor or outdoor allergens may be rarely observed during the first months; in most cases, they develop during kindergarten- or school-age. Sequential following of molecular IgE development suggests that specific IgE antibody levels tend to increase and spread from one molecular signal to a whole spectrum of responses to multiple allergens. Usually, this process precedes the disease development by several years, as it was shown in grass pollen and dust mite studies. It evolves in the first decade of life, leading from a simple, mono-molecular, or oligo-molecular to a very complex poly-molecular IgE sensitization profile.[6–9] More recent cross-sectional studies have described a cluster of allergic patients characterized by several multi-morbidities and a remarkable polymolecular sensitization state.[10,11] A recent study suggested that variations in IgE responses might possibly explain some limited efficacy of therapeutic interventions in patients, particularly in polymolecular sensitizations.[60]

Early studies demonstrated that infantile eczema together with an atopic parental history increases the risk for subsequent allergic airway disease. This part of the "atopic march" attracted the interest of many researchers and stimulated early intervention studies in these high-risk groups, unfortunately without much success, suggesting that different atopic manifestations are probably sequentially co-expressed by a common genetic susceptibility rather than later phenotypes developing directly from infantile manifestations.[12,13]

Remarkably, there is a good chance of some manifestations going into complete remission: Infantile allergies to hen´s egg and cow´s milk have a good chance to be "outgrown" after some years, and also, atopic dermatitis in most cases will at least show considerably improvement, if not completely disappear. In contrast, allergic diseases of the upper or lower airways tend to persist, in many cases throughout adulthood.

3 | LUNG FUNCTION

Lung function development has been carefully assessed from early childhood to adulthood. Earlier studies suggested that atopic children with low lung function in early infancy had a higher risk of wheeze between the age of 4 and 11 years. In contrast, airway responsiveness in infancy was not associated with subsequent asthma. In the German MAS birth cohort, where longitudinal lung function development was followed up to the age of 20 years, lung function trajectories of atopic asthmatics were found to be reduced at the age of 13 and 20 years compared to those of other asthmatics. Data from the Copenhagen prospective birth cohort (children of mothers with asthma) on asthma in Childhood (COPSAC 2000) suggest that lung function of children with persistent asthma seems to be reduced from very early life and remains reduced throughout

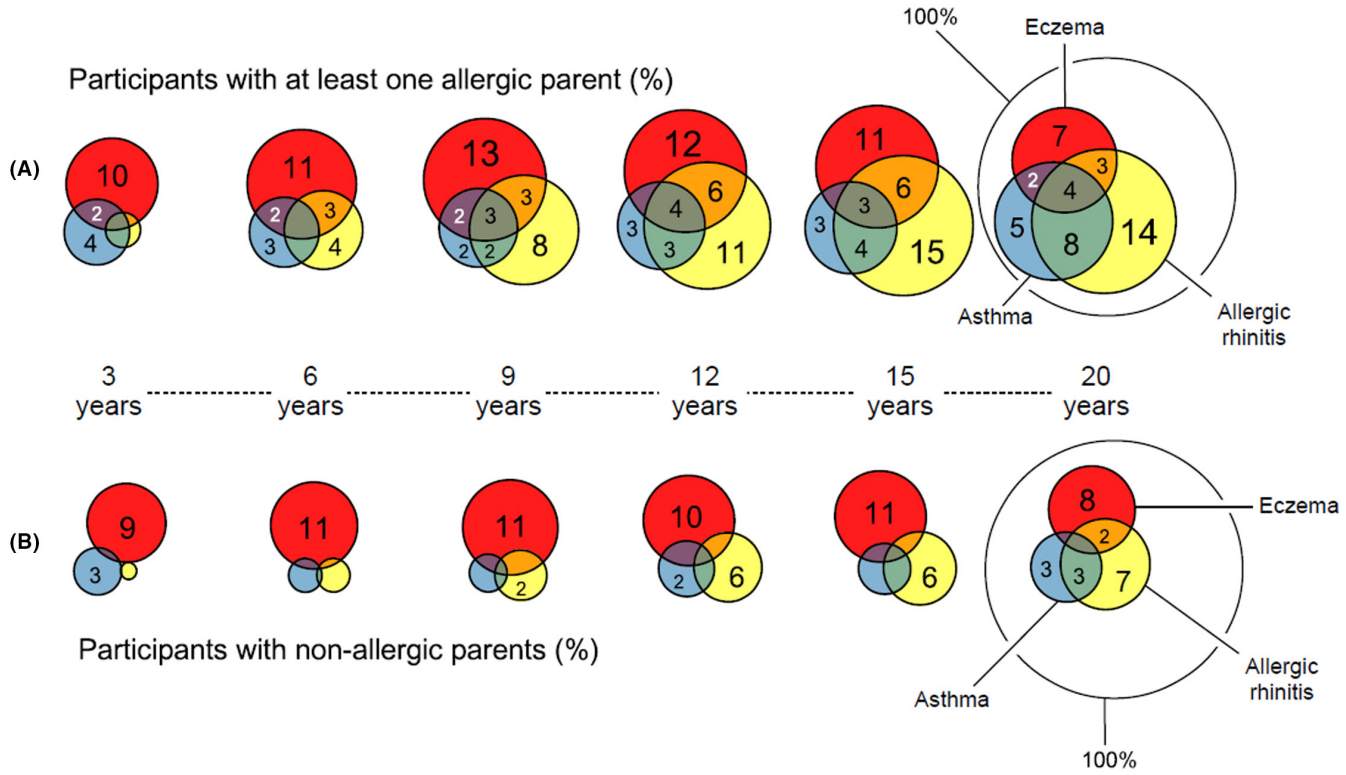

FIGURE 1 Comorbidity of asthma, rhinitis, and eczema over the first 20 years of life in children and adolescents with and without allergic parents. Data from the German multicenter birth cohort MAS (reproduced from 13 by authorization of the publisher)

childhood.[14,15] The investigators discuss whether the deficit might be congenital. Whether or not impaired lung function in early life in a given patient is predictive of COPD later in adulthood remains unclear, but the observation that lung function trajectories tend to track with age suggests that there is an important link that deserves further studies.[16]

4 | RISK AND PROTECTIVE FACTORS

Atopic manifestations are well-known to run in families, and having an affected family member constitutes a major risk factor.[15–19]

Hundreds of genes have been associated with disease, but more importantly, we now know that asthma, allergic rhinitis, and eczema partly coexist because they share many genes that are involved in immune-regulation and host-response mechanisms.[18,19]

One such example is the *TSLP* gene on chromosome 5q22, which encodes for a cytokine that may serve as a master regulator of type 2 immune responses in asthma and allergies. Other genes with broad disease associations are *HLAs*, *IL4/IL13*, and *IL33*.[20] In contrast, the most well-replicated gene region for childhood asthma, chromosome 17q12-21 including *ORMDL3* and *GSDMB*, seems primarily to be involved in airway dysregulation, for example, following a viral infection, rather than with allergy-related processes.[21] These insights may have broad implications for asthma and allergic disease diagnostics and treatment, especially in the era of precision medicine and biologics.

5 | RELEVANT DETERMINANTS IN THE ENVIRONMENT

The question of exposure to indoor allergens and its relevance for disease development has been addressed in early studies. Clearly, there were different dose–response relationships for children with and without a genetic atopy background, indicating that higher levels of domestic allergens like house dust mites have to be considered a risk factor for sensitization, which then would facilitate asthma and lung function impairment in school age.[24,25] Interestingly, as shown by the British MAAS cohort, the clear effect of early life exposure to pets may disappear in the second decade of life. The reasons for this observation are unclear.[26]

Large efforts have also been directed toward exploring DNA methylation and gene expression profiles in childhood asthma and allergy. Not surprisingly, altered levels have been observed for several genes in relation to allergic diseases, but also several environmental factors, such as tobacco smoke or air pollution exposure. In agreement with the shared genetics findings, a similar pattern has emerged also for methylation[22] and gene expression,[23] which suggest that allergic multimorbidity truly stems from shared molecular mechanisms. It can be anticipated that omics analyses will be incorporated into clinical allergy practice to guide diagnostics, treatment selection, and response.

The role of environmental as well as intrauterine tobacco smoke exposure has attracted the interest of researcher for decades. Postnatal passive tobacco smoke exposure (child is a "side stream

smoker") has been repeatedly found to be relevant for asthma development in childhood. Maternal smoking during pregnancy (when the fetus is a "mainstream smoker") has been studied in a large number of children from 5 birth cohorts and tends to be associated with an increased odds for asthma, but not for rhinitis during childhood and adolescence.[27]

In cord blood of children of smoking mothers, differences in DNA methylation have been found, which may persist even into adulthood.[75–77] E-cigarettes are often perceived as healthier alternative to common tobacco cigarettes, which is why increasing numbers of women switch from regular cigarettes to electronic delivery system during pregnancy. Along this line, the fruit fly has become an informative animal model to study how maternal exposures affect next generations: Maternal e-nicotine has not only been found to reduce growth in the F1-generation but also deregulate airway developmental pathways in a highly sex-specific manner.[28] More recently, paternal exposure—particularly during the father´s own adolescence—has also been suggested to play a role in the development of asthma risk in offspring.[78] Putative vectors of paternal epigenetic information include sperm noncoding RNAs, which may change first transcriptional programs in the early embryo.[79]

For more than 30 years, the "hygiene hypothesis" has been stimulating researchers with an interest in asthma prevention. It initially referred to a significantly decreased risk of allergic sensitization and hay fever in subjects having many siblings (Figure 2). While it was obvious that viral infections were causing and triggering asthma, there were reasons to speculate that day-care early in life, oro-fecal, and other infections, and also, farm exposure were having long-term protective effects against airway allergies[30,31,54,55,61,67–70] During the last years, it was demonstrated that—in this specific population—microbial exposure was an important modifier of the development of childhood allergies and asthma.[52]

The interactions of host, microbiota, and environment can well be studied in environments rich in microbial diversity such as the farming environment. Children living on farms are exposed to a wider range of microbes as compared to their rural peers.[29] This exposure explains a substantial share of the asthma-protective effect of growing up on a farm. Considerable agreement of bacterial richness between mattress dust samples and nasal samples of the same individuals suggests that environmental microbiota is transferred to the mucosa of the (upper) airways, where they may interact with the local mucosa-associated immune system.[30] Moreover, close contact with microbiota is self-evident for the mucosal surface of the largest immune organ, the gut. Adequate maturation of the gut microbiome in the first year of life is fostered by a farm environment and contributes to the prevention of asthma in the farm context.[31] Specifically, the capability of producing short-chain fatty acids such as butyrate and propionate characterizes a well-matured gut microbiome with favorable effects on asthma prevention. How immune maturation and microbial maturation follow an interactive process has to be in the focus of future research.

Several groups have tried to establish predictive scores for allergies and asthma, which might be used to improve allergy treatment and create a more targeted prevention in the future.[32]

Despite many open issues, recent data from three birth cohorts evaluated by the German research consortium CHAMP,[71] which is supported by the German Ministry of Research and Education (BMBF), investigated risk factors of asthma in childhood. In addition to classical risk factors such as sex and maternal asthma large genome-wide association studies and epigenetic analyses contributed to a better understanding about interactions between genetic, epigenetic, and environmental protective factors like farming.

6 | PROMISING INTERVENTION STRATEGIES

Early initial attempts to achieve prevention were focused on avoidance of allergen exposure, both to food allergens in infancy as well as to indoor allergens in subsequent years. Retrospectively, it has to be concluded that these interventions did not demonstrate sufficient evidence and probably were of limited, if any, effect at all.

One of the few examples, where consistent avoidance of neonatal exposure leads to effective prevention, is anaphylaxis induced by latex exposure particularly in babies born with spina bifida. Studies led to guidelines suggesting latex-free surgical theaters in all pediatric centers, which have turned out to be highly successful.[53]

7 | INFANT NUTRITION

Primary prevention by the avoidance of cow´s milk and prolonged breastfeeding was shown to have limited effect. Although some studies indicate that avoidance of regular cow´s milk-based formulas, the first day of life may reduce the risk of food allergy, the use of "hypoallergenic" milk hydrolysates still remains controversial. A recent communication by the investigators of the German GINI study reported a long-term reduction of the prevalence of asthma in high-risk teenagers.[47] However, messages from this study are still disputed controversially, and national guidelines in Europe and beyond differ in their recommendations regarding prevention by infant formulae.

Primary and secondary prevention trials focusing on early introduction of solids (EAT study) or early feeding of peanuts in infants with severe eczema and early egg sensitization (LEAP study) showed that early tolerance can be achieved by this strategy which may be mediated by the change in the gut microbiome and fermentation of high fiber containing foods by butyrate producing bacteria.[72–74]

8 | DOMESTIC ENVIRONMENT

Although allergen avoidance has become part of all guidelines for the treatment of symptomatic children, its advisement regarding primary prevention is disappointing for a number of reasons. The

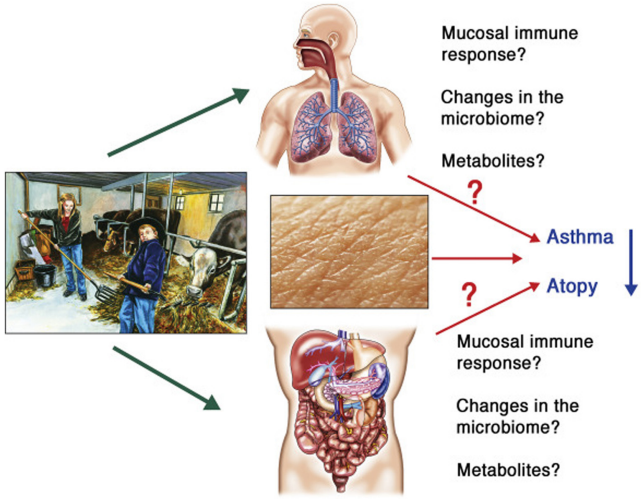

FIGURE 2 The microbial environment, its relevance for the host and for asthma prevention in early life (reproduced from Mutius E[81] by authorization of the publisher)

elimination of indoor allergens in the domestic environment has turned out to be either difficult (cat allergens will remain air-born even months or years after the elimination of the pet), almost impossible (dust mite allergens in mattresses or carpets) or ineffective (several intervention studies like the Dutch PIAMA-study have reported no robust effect on populations). Few intervention studies have reported encouraging results.[82,83]

9 | PHARMACOLOGICAL PREVENTION

A number of pharmacological interventions aiming at asthma prevention in high-risk cohorts of infants and toddlers have been performed, mostly in groups with parental atopy predisposition, unfortunately with negative results. Antihistamines (cetirizine, levocetirizine, and desloratadine), inhaled corticosteroids, and calcineurin inhibitors were investigated for their preventive potential. None of them proved to reduce the incidence of asthma or to modify the disease. These disappointing results support the hypothesis that the sequential manifestation of eczema and asthma in the pediatric population is rather the result of genetically determined coexpression of the phenotypes than development from one to another manifestation.

It is widely accepted that pharmacological treatment of asthma in childhood with drugs such as inhaled steroids, long-acting beta-agonists, and the long-acting muscarinic receptor antagonist tiotropium is crucial for achieving asthma control and preventing exacerbations.[33,34] However, so far, none of them has been proven effective in preventing the onset of asthma and modifying the natural history of the disease. After a broader use of biologics for the treatment of allergic diseases in pediatric populations became possible, the vision of a therapy more closely related to the underlying pathophysiology of an individual patient has come more into reach.[80] Until now, the application of biologics has been quite expensive (ie high direct costs) and for this reason limited to use in more severe patient groups. But it is more than a dream to postulate that biologics will emerge from the status of "reserve medications" for difficult-to-treat patients toward first-line treatment options especially for the younger patient group where the disease is still developing and progress into more severe and/or comorbid endotypes might be preventable. In children with both, atopic dermatitis and asthma, the use of the anti-IL-4-receptor-alpha antibody, dupilumab, has been shown to be very effective.[35–37] Oral abrocitinib, a Janus kinase (JAK) 1–selective inhibitor modulating the function of key cytokines, and the oral JAK-inhibitor, Upadacitinib, might become additional options for future interventions in early childhood in selected severe cases; however, side effects as having a broader impact on immune functions in the T-cell compartment have to be taken into consideration.

Anti-IgE therapy, which is effective in childhood asthma as well as in allergic rhinitis,[51] would simultaneously address all different IgE antibodies and therefore treat all the patient's multi-morbidities with one single and simple nonspecific therapeutic approach.[9] It will be intriguing to see if very early treatment with anti-IgE or other biologicals in even younger patients will be successful in changing the natural history of severe atopic diseases and maybe even show preventative effects against the development of respiratory allergies in young children with AD.[45] However, in chronic atopic eczema, IgE does not seem to play a central role, and approaches focusing on T2-inflammation may be more promising.

10 | ALLERGEN IMMUNOTHERAPY

Allergen immunotherapy applied to children from the 6th year of age onwards is available and registered as subcutaneous (SCIT) or sublingual (SLIT) long-term treatment. It is applied in order to achieve specific immune tolerance to the offered allergen and has been shown to achieve disease-modifying long-term effects for at least 2 years after stopping the treatment. Recently, it was demonstrated in placebo-controlled prospective as well as real-world trials that sublingual treatment with a grass pollen tablet for 3 years in children with allergic rhinitis will not only reduce seasonal symptoms and need for medication but also reduce the incidence of asthma and the need for asthma medication for up to 2 years beyond termination of treatment.[49,50,62,64,66] This allergen-specific disease-modifying effect will probably stimulate additional trials for primary asthma prevention in high-risk populations using other allergenic compounds.[63,65] Facing primary prevention in atopy-prone newborns and secondary prevention in IgE-sensitized children, the intervention effect of allergen immunotherapy remains controversial. For both strategies, the proof of concept remains to be determined in further trials.

11 | MICROBES

During the last decade, the roles of microbial exposure in the environment as well as mucosal microbial colonization in populations have attracted the interest of many researchers.[46,81]

Assuming that the exposure to microbes early in life has beneficial effects, investigators have applied microbial compounds to infants and young children to try to prevent atopic manifestations including asthma. Some of these studies appear to find encouraging results.[38]

A number of drugs containing bacterial lysates as well as probiotic additives to infant formulae have been studied. Some of them, sponsored by the American NHLBI, are still ongoing.[43]

The remarkable success of an intervention was published last year. In a randomized placebo-controlled study in Spain, 120 preschool children with at least 3 wheezing attacks were treated for a period of 6 months with a compound of 6 different dead whole gram-positive and gram-negative bacteria.[39,41,56] The primary outcome (number of wheezing episodes during 1 year) was highly significant and convincing as well as all of the secondary outcomes analyzed: Despite the fact that viruses play the key role in inception and triggering acute attacks of wheeze, the administration of the heat-inactivated whole bacteria preparation delivered to the oral mucosa showed a potent stimulus on the innate immunity, leading to a broader and more consistent host response to infections.[40,41]

Another approach to address the prevention of asthma is to target rhinoviruses (RV), known to induce wheeze in early life, which is strongly linked to childhood asthma. CDHR3 polymorphisms have been shown to be linked to an increased susceptibility to RV-C infections and a severe asthma phenotype in children. Therefore, it is of high interest to see if an RV-C vaccine applied in infancy may be useful in preventing asthma.[44,45] Similarly, it would be interesting to see if an RSV vaccine could reduce subsequent development of asthma in early childhood.

12 | PERSPECTIVES FOR THE FUTURE

Obviously, asthma inception is complex, resulting from interactions between host and environmental factors. The significant progress in our understanding of the disease pathogenesis in infancy and childhood as well as of parental exposures modifying offspring phenotypes and epigenetics has identified multiple promising approaches for prevention. Ongoing studies, integrating multiple -omics, are currently under way which might help to further unravel the mechanisms of the disease and thus have better identity biomarkers to especially address a population at risk with personalized measures.[57]

A few years ago, a workshop sponsored by the American National of Heart, Lung and Blood Institute (NHLBI) proposed research priorities for allergy and asthma prevention.[42] Some of these issues still seem to stand as top priorities among many researchers, for controversies which need clarifying, or for deficits in evidence and questions that should be addressed in the years to come. These unmet needs—among others—are listed in Table 1.

Exploration of the world of microbiomes has revitalized the debates around the "hygiene hypothesis"[48] and early priming of immune regulation, not only for atopy and allergy but also for other non-communicable diseases. Studies on farming families and religious traditional communities (Amish, Hutterites) suggest that early microbial exposure is important as a modulator of the development of childhood asthma and allergies.[48,52] So far, not one single component conferring protection has been identified, and it seems quite possible that several factors with a multitude of exposure routes might be relevant and that asthma preventive approaches will focus on more than one facet. As our understanding of the relationship between the developing infant microbiota and immune system grows, long-term protection from allergic diseases might yet become more than just a dream.

TABLE 1 Unmet needs for allergy and asthma prevention

Primary prevention of skin and airway manifestations through infant formulae (hydrolysates with pro- and prebiotics) and/or specific nutritional interventions.
Secondary prevention in high-risk infants (positive family history, allergic sensitization etc.) with anti-IgE or other novel biologicals (such as anti-IL5, anti-IL 4, and IL13).
Primary prevention of wheezing with various bacterial lysates (Orbex study, NHLBI)
Rhinovirus-C-vaccine in high-risk infants and young children, RSV vaccine
Allergen-specific immunotherapy using various preparations and application routes in high-risk infants and young children

CONFLICT OF INTEREST

UW reports lecture fee from Berlin-Chemie, Hipp, Engelhard/Germany, Nestle, ALK, StallergenesGreer, Roxall Medizin. SL receive honoraria for lectures and advisory boards from Sanofi-Aventis, DBV, ALK, Leti, and Allergopharma. PE reports lecture and consulting honoraria from Novartis, Nestlé, Danone, and Abbott. EM has received lecture and advisory board reimbursement from ALK, AstraZeneca, Chiesi, Novartis, and Sanofi outside the submitted work. SKE has nothing to disclose. CL has nothing to disclose. PM has nothing to disclose. BS has nothing to disclose. SH has nothing to disclose. ME reports two patents EP 1 964 570 B1 / US000009950017B2: Pharmaceutical compound to protect against allergies and inflammatory illnesses and EP 2 361 632 B1: Specific environmental bacteria for the protection from and/or the treatment of allergic, chronic inflammatory, and/or autoimmune diseases. DJ reports grant funding from NIAID, NHLBI, NIH Office of the Directors, and GlaxoSmithKline. Personal fees for consulting with GlaxoSmithKline, Sanofi, Regeneron, Vifor Pharma, and AstraZeneca. Personal fees for DSMB for Pfizer. EH has nothing to disclose. SZ has nothing to disclose. ANG reports personal fees from MSD, Novartis, Merck, Inmunotek, Diater, AstraZeneca, and research grants from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Merck, Novartis, Diater, Inmunotek. EvM reports grants from the Bavarian State Ministry of Health and Care, the German Federal Ministry of Education and Research, royalties from Elsevier GmbH, Georg Thieme Verlag, Springer-Verlag GmbH, Elsevier Ltd., consulting fees from the

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