



How molecular allergology can shape the management of allergic airways diseases

Davide Caimmi^{a,b}, Enrica Manca^{a,c}, Elena Carboni^{a,d}, and Pascal Demoly^{a,b}

Purpose of review

In allergy, personalized medicine passes through the assessment of molecular allergens sensitization profiles. Such technique may help to better diagnose and treat patients suffering from allergic respiratory diseases.

Recent findings

Different laboratory tests are available today to assess sensitization to molecular allergens, from singleplex assays, to unspecific, screening multiplex assays, mainly performed through microarrays or macroarrays. It is important to collect both results from specific IgE toward allergen extracts and toward molecular allergens, to collect the most complete information on the patient's profile, and therefore to highlight genuine sensitization, and exclude cross-reaction and sensitization because of pan-allergens. Being able to know the exact molecular sensitization profile of the patient, also helps predicting the possible evolution of the disease, and targeting the most appropriate allergen immunotherapy treatment to prescribe.

Summary

Even though a cost-effective analysis of running multiple assays in allergic patients has not been performed yet, such technique proved to be more efficient in detecting the appropriate treatment in each patient and in analyzing the true sensitization profile in patients suffering from allergic rhinitis, conjunctivitis, and asthma.

Keywords

allergen immunotherapy (AIT), allergens, component-resolved diagnosis (CRD), molecular allergology, respiratory allergy

INTRODUCTION

Allergic rhinitis, conjunctivitis, and asthma are the most common respiratory allergic diseases [1]. Classically, the diagnosis of allergic symptoms is based on the patient's clinical history, and on the results of skin prick tests (SPT) and/or of specific serum IgE, utilizing allergen extracts [2]. The composition of the extracts strongly influences the identification of specific IgE, so the results may vary or even diverge when using IgE assays of different companies [3,4,5^{***}]. SPT or specific IgE with allergen extracts contain a complex mix of various allergens, some of which are specific allergens, whereas others may be cross-reactive allergens [6,7^{***}]. These methods are therefore not able to specifically identify the exact molecular component responsible for the allergic reaction, which could actually be particularly useful, especially in polysensitized patients [1,2].

Prescribed therapies may be either symptomatic, to simply control symptoms and possible exacerbations, or curative, to treat the allergic cause of the disease. Symptomatic treatments, mainly including

oral or topical antihistamines, intranasal corticosteroids, topical cromoglycate, and eyes drops, are not always effective, especially when patients present with severe symptoms, or when they are allergic to different allergens or sensitized to specific cross-reactants or pan-allergens [3,8^{***}]. The only disease-modifier treatment with potential curative effects available today is allergen immunotherapy (AIT). AIT, mainly subcutaneous (SCIT) or

^aAllergy Unit, Département de Pneumologie et Addictologie, Hôpital Arnaud de Villeneuve, CHU de Montpellier, Univ Montpellier, Montpellier,

^bEpidemiology of Allergic and Respiratory Diseases Department (EPAR), IPLESP, UMR 1136 INSERM - Sorbonne Université, Paris, France,

^cPediatric Unit, University Hospital of Foggia, Foggia and ^dPediatric Unit, University 'Magna Grecia' of Catanzaro, Catanzaro, Italy

Correspondence to Pascal Demoly, MD, PhD, Allergy Unit, Département de Pneumologie et Addictologie, Hôpital Arnaud de Villeneuve, CHU de Montpellier, Univ Montpellier, 371 Avenue du Doyen Gaston Giraud, 34090 Montpellier, France. Tel: +33467336112;

fax: +0033467330740; e-mail: pascal.demoly@inserm.fr

Curr Opin Allergy Clin Immunol 2020, 20:000–000

DOI:10.1097/ACI.0000000000000630

KEY POINTS

- Results from skin prick tests and specific IgE assays through allergen extracts may differ depending on the composition of the product.
- Component resolved diagnosis is a precise and standardized technique, particularly useful in polysensitized patients, that allows to highlight specific allergenic profiles, leading to a '*personalized medicine*' approach to the patient.
- Molecular allergens may be useful to assess the severity of airway diseases and identify potential predictive factors for the symptoms clinical evolution.
- Singleplex or multiplex (microarray or macro array) assays may be prescribed to evaluate the exact molecular components to which patients are allergic.

sublingual (SLIT), is associated to symptoms reduction and long-term desensitization to the allergen included in the product, providing long-lasting effects, even years after its cessation [5¹¹,8¹²].

The prescription of AIT, based on SPT results only, may lead to the prescription of extracts to which patients are not allergic to and may hamper its effectiveness [8¹¹,9]. Component-resolved-diagnosis (CRD), also known as molecular diagnosis, should guide '*personalized medicine*' and prescription of AIT to patients, based on their molecular sensitization profile. CRD is a precise and standardized technique, which may help in differentiating a genuine sensitization to a respiratory allergen from poly-sensitizations or cross-reactions through pan-allergens [1–3]. Indeed, this technique allows the detection of the specific allergenic components responsible for the patient's sensitization and is becoming more and more useful in targeting the exact AIT to prescribe to allergic patients [2].

The burden of respiratory allergic diseases is mainly associated with the impact they have on patients' quality of life and on their direct and indirect costs [10]. For such reason, the main therapeutic goal today is the control of the symptoms, and the reduction of the allergic inflammation, to eventually improve patients' quality of life [11]. A better understanding of patients' allergic profile through CRD may help therefore clinicians in choosing the best therapeutic option to control symptoms and improve their quality of life.

Through the present paper, we aim to discuss how molecular allergology may help clinicians in optimizing the diagnosis and therefore the treatment of allergic respiratory diseases.

MOLECULAR ALLERGOLOGY TO COMPLETE THE DIAGNOSTIC PROCESS

For almost a century, allergic disorders have been diagnosed and treated using allergens extracted from their natural sources. The precise composition of the extracts, that are obtained through different chemical and physical processes, and after supplementation of active agents, and the allergen concentration in each product, are difficult to define and may vary from batch to batch [5¹¹,12]. Such aspect is still an issue, even though several different standardization techniques have been proposed, and the World Health Organization, the International Union of Immunological Societies, and the European Union have produced a few standardized allergens. Thus, results from SPT and specific IgE assays utilizing allergen extracts may be different depending on the composition of the product used [3–5¹¹].

In 1988–1989, the duplication of cDNA encoding allergens from birch, hornet venom and house dust mites (HDM), represented the birth of molecular allergology. Since then, many recombinant and natural purified allergens have been isolated, standardized, and produced [5¹¹]. CRD improves the identification of the allergen responsible for the symptoms. For example, in birch allergic patients, a sensitization to peanut extract may simply be a nonclinically relevant cross-reaction because of the homology between the PR-10 proteins Bet v 1 (major birch allergen) and Ara h 8; however, a subject experiencing an oral syndrome to peach, may be sensitized to birch, without presenting respiratory symptoms, because of a cross-reaction between the profilins Pru p 4 and Bet v 2.

Nowadays, many different laboratory tests are available and physicians may adapt their choice on which one to prescribe to their patients, based on their clinical history, and, of course, on the cost and geographical availability of each test. The three main available options include the singleplex assay; the disease-oriented customized multiplex tests; and the microarrays and macroarrays [Table 1]. The Singleplex assay (ImmunoCAP) requires, to be cost-effective, an extensive knowledge of the patient's clinical history and of the allergen(s) that need to be investigated. An intermediate option may be the customized multiplex test (Euroline; Euroimmun, Lübeck, Germany), which associates extracts and their principal molecular allergens, chosen on the specific patient's clinical profile, in order to differentiate between cross-reactions and genuine sensitization [5¹¹,13,14¹⁵]. As for multiplex assays, they may be performed through microarrays (such as ISAC, and MeDALL) and nanoparticles

Table 1. Possible options for component resolved diagnosis: advantages and disadvantages of the different molecular assays

	Advantages	Disadvantages
Singleplex	Cost Absence of potentially irrelevant information	Collection of extensive clinical history Knowledge of the exact allergens to look for Limited investigation
Customized multiplex	Combination of extracts and their most relevant molecules Intermediate option between singleplex and multiplex	Cost Collection of extensive clinical history Knowledge of the clinical profile of the patient
Multiplex: microarrays/ macroarrays	Dosage of a wide range of extracts and molecules Very small amount of serum required (20 µL)	Cost Collection of extensive clinical history Evaluation of the clinical relevance of each positive result

(FABER) or macroarrays (ALX). Even though they may be more practical in patients who react to several allergenic sources, their use requires the same extensive knowledge of the patient's clinical history as the singleplex assay, but even greater knowledge of the allergens compared to the previous test, given the risk of false-positive results to various allergens (i.e. sensitizations without any clinical relevance). This is especially true for children, given the long list of aeroallergens and food allergens usually included in the multiplex panels.

Moreover, IgE assays based on extracts and those based on molecular allergens sometimes give different results. In 2019, Til-Pérez *et al.* reported a cross-sectional study where they also found that SPTs are not always concordant with results from molecular allergens results, especially when evaluating patients for HDM and pollens [1]. Possible explanations for such discrepancy include, first, the fact that some IgE molecules are not present or are very limited in the molecular assay and therefore it may be negative even if the extract-based test is positive. In the same way, IgE may react towards certain molecules, which are absent or in low concentration in the extract assay. Sometimes, IgE antibodies do not recognize the major component of an extract but may result positive for its minor and cross-reactive components. In this case, extract-based tests may be positive while all tested molecular assays are negative. Finally, IgE antibodies may react strongly towards molecular allergen of an extract but more feebly towards the extract itself leading to a positive molecular assay with a negative or low positive extract test [3].

In 2016, the European Academy of Allergy and Clinical Immunology (EAACI) suggested two possible strategies for the diagnosis of allergic diseases: collecting detailed symptoms and either deciding, based on the information, which SPT to perform and then which molecular allergens to look for ('from clinics to molecules'); or performing multiplex molecular allergens tests to then decide which SPT

should be assessed ('from molecules to clinic') [2]. In 2018, Motches-Luksch *et al.* [14[¶]] analyzed the accuracy of both strategies in a cohort of 202 patients with suspected type I allergy. In patients for whom the 'from molecules to clinic' approach was adopted, less SPTs were performed to complete the diagnostic process. SPT were positive, contrary to microarray results, in 19% of patients in the ISAC-first group and in 34% in the SPT-first group. However, ISAC detected additional sensitizations in 18% of patients from the ISAC-first group, and in 32% of the SPT-first cohort. The authors concluded that the 'from molecules to clinic' method offers a reliable diagnostic workup in shorter time, and is especially applicable for young children and seniors, in atopic patients, and whenever SPT get difficult or unreliable [14[¶]]. Nevertheless, a cost-effectiveness study of such approach was not carried out in the study.

MOLECULAR ALLERGOLOGY TO PREDICT THE CLINICAL EVOLUTION OF ALLERGIC AIRWAYS DISEASES

Evaluation of molecular allergens may be useful to assess the severity of airway diseases and identify potential predictive factors for clinical evolution of the symptoms.

CRD may also be beneficial to identify multi-sensitized patients at risk of developing allergic rhinitis and/or asthma. For example, in patients sensitized to animal dander, the allergy work-up is classically based on the results of whole extract SPT or IgEs. Nevertheless, cross-reactive molecules, such as serum albumin, are present in all animal extracts used, and may then lead to an overestimation of sensitization rates to a specific animal [15]. Through the assessment of molecular allergens, as reported in a study by Nwaru *et al.* [15], sensitization to specific furry animal allergen components proved to be strongly associated to allergy, and to be a good predictor of asthma, allergic rhinitis, and markers of asthma severity.

In an Italian pediatric study, the authors evaluated the results of a cohort of 401 children, and analyzed the association and the predictive value of biomarkers of atopic sensitization. They found that the sensitization to the major *Phleum pratense* molecular allergen Phl p 1, an important initiator of grass pollen allergy, was associated with persistence of allergic rhinitis. However, asthma persistence seemed to be related to the less common sensitization to Phl p 5, which is associated to more severe forms of pollen asthma. Sensitization to the lipid transfer protein Pru p 3, proved to be associated with late onset of asthma, even if the authors could not discriminate whether such profile was directly associated with asthma or if it is a marker of severe atopic propensity [16].

In another study, the authors compared the molecular sensitization pattern of 59 children with allergic rhinitis. They observed that grass pollen allergens Phl p 1, Phl p 2, Phl p 5, and Phl p 6 were significantly higher in patients with more severe symptoms [17].

In a study evaluating the sensitization profile of 101 patients suffering from allergic rhinitis and asthma, sensitization to group 1 HDM proteins (Der p 1, Der f 1), and to Lep d 2 was significantly more frequent in patients with rhinitis and asthma compared to patients with rhinitis only. Moreover, Der p 2 and Der f 2 were associated with moderate to severe rhinitis, whereas Lep d 2 with both severe asthma and severe allergic rhinitis [1].

In a German birth cohort, the evolution specific IgE directed against 12 HDM allergens was assessed over 20 years, in more than 700 patients. Children with early sensitization to Der p 1, Der p 2, and Der p 23, parental allergic rhinitis, and higher exposure to mites were associated with a broader polymolecular IgE sensitization pattern later in life. Also, the detection of IgE to Der p 1 or Der p 23 at 5 years of age or before was a good predictor of asthma at school age [18].

Another study evaluated the evolution of IgE sensitization to *P. pratense* in children affected by allergic rhinitis to grass pollen. They reported that IgE sensitization to grass pollen may be detected years before the onset of clinical manifestations and that it may then increase in serum concentration and complexity through a 'molecular spreading' process during preclinical and early clinical disease stages, with the recognition of not many molecules. In time, this sensitization progressed in complexity and strength. The authors suggested that AIT might therefore be more effective if started at the earlier stage of preclinical sensitization [19].

Evidence regarding the relationship between specific allergens and the severity or the evolution

of airway disease is still weak. The limited number of studies and the restricted number of included patients make it necessary to wait for further investigations to evaluate if CRD may indeed help clinicians to identify patients presenting with sensitizations that may lead to organ-specific respiratory allergic diseases or to potentially severe forms of allergic rhinitis and/or allergic asthma.

MOLECULAR ALLERGOLOGY AND PERSONALIZED TREATMENT UTILIZING ALLERGEN IMMUNOTHERAPY

Whenever a causative relationship is proven between exposure to an allergen and onset of symptoms, and *in vivo* and/or *in vitro* tests are positive, AIT may be prescribed, in patients whose symptoms are not completely controlled by symptomatic treatments. AIT consists in repeatedly administering standardized doses of an allergen extract to reduce allergic inflammation and symptoms because of allergen exposure: it is the only disease modifying treatment for IgE-mediated disorders [3,20,21]. It is mainly prescribed to treat allergic rhinitis and allergic conjunctivitis. Since 2017, the Global Initiative for Asthma Report (GINA) recommends sublingual AIT as an add on therapy in adults with mild-to-moderate asthma and HDM allergy, partially or not controlled by other 'classical' antiasthmatic treatments [20,22*].

In a context of personalized medicine, which pursues the objective of providing personalized treatment strategy, CRD may acquire a central role in improving diagnostic accuracy and subsequently in selecting the best therapy for allergic diseases, and therefore be especially important when prescribing AIT [13]. It has recently been shown that molecular diagnosis may help decide which allergen to choose for AIT, and lead to different conclusions than prescriptions based on SPT results [23]. Molecular allergology allows to identify the single molecular allergen responsible for the patient's sensitization and such feature may be particularly useful in polysensitized patients, in patients sensitized to pan-allergens and in patients who live in areas where pollination cycles overlap [1,9].

Thanks to the complete analysis of the patient's sensitization profile, the best allergen to administer may be selected and AIT efficacy may essentially improve.

In 2014, Stringari *et al.* conducted a study on 651 Italian children with allergic rhinitis to grass. They used four theoretic prescriptions and pragmatic models of AIT and asked for the opinion of 14 pediatric allergists about AIT prescription on each patient. They found that CRD results altered the AIT

prescription in 40% of the patients. They reported the highest rate of corrections for olive and Betulaceae AIT, whereas the least was for grass pollen AIT [24].

In a Spanish study, the authors compared AIT products prescribed based on clinical history and SPT results, to those prescribed after evaluating molecular profiles. They included 70 poly-sensitized children, and found that original prescription was modified in 53.4% of patients. Furthermore, using molecular diagnosis, single-allergen AIT prescription increased from 18% to 51%. However, in 9.3% of children, CRD results showed that AIT was not useful or necessary, because patients presented with low sensitization to major allergens and/or sensitization to un-specific pan-allergens [6].

Similar results were obtained by Burgos *et al.* [9] who included 281 Spanish children with a positive SPT to grass and olive pollen. Sensitization pattern to major grass (Phl p 1+5) and olive (Ole e 1) pollen allergens was determined with molecular diagnosis. After CRD results, 52.8% of patients needed to modify their AIT prescription, and 15.3% did not need any AIT.

In a Ukrainian study, 126 patients suffering from allergic rhinitis/conjunctivitis were evaluated through both SPTs and molecular diagnosis. Based on the results of SPT, 50% of them were eligible for treatment with a two-extracts AIT ('mixture of weeds' and 'mixture of grasses'). Nevertheless, molecular allergology showed that such combination was not appropriate for any of these patients: indeed, 20% had a genuine sensitization to allergens of grass pollen, including a marker of cross-reactive molecules, whereas 30% were genuinely sensitized to Artemisia and/or ambrosia [23].

In the paper by Passalacqua *et al.* [25] from the present issue of the Journal, the authors underlined that single-allergen AIT has proven to show a higher effectiveness when compared to poly-allergen formulations.

The previously mentioned studies not only highlighted a decrease in the need to use of allergen mixtures and an increase of single-allergen AIT, but also that the association of SPT and CRD may lead to a more accurate, personalized, and effective prescription of AIT [6,23,25].

CONCLUSION

Traditionally, the diagnosis of allergic diseases is based on clinical history and SPTs. Because of its introduction, molecular allergology has considerably developed. Unlike SPT, the capacity of CRD to recognize specific allergenic molecules allows the

identification of precise (genuine and cross-reactive) sensitization profiles.

The 'from molecules to clinic' approach may result too expensive and not always necessary but CRD seems essential in patients presenting with complex sensitization profile or multiple allergy or different and/or unexplained (by known environmental exposures) clinical symptoms: it allows to shorten the diagnostic process, to select a more accurate AIT prescription, and consequently to administer more effective treatment and avoidance measures. Also, CRD may play an important role in the prediction of the clinical evolution of the patient and of symptoms severity.

In conclusion, CRD adds a value in diagnosis and management of airways' allergic diseases and puts the decision-making process of allergy in the world of personalized medicine. Nevertheless, it is still debated whether the CRD in clinical daily practice has a cost-effective advantage for the management of respiratory allergies. Indeed, today, multiple assay tests are still quite expensive, but no study has investigated the possible cost reduction because of a more appropriate and targeted treatment of respiratory allergic diseases.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. WHO Collaborating Center for Asthma and Rhinitis. Bousquet J, Anto JM, Demoly P, *et al.* Severe chronic allergic (and related) diseases: a uniform approach—a MeDALL–GA2LEN–ARIA position paper. *Int Arch Allergy Immunol* 2012; 158:216–231.
 2. Small P, Keith PK, Kim H. Allergic rhinitis. *Allergy Asthma Clin Immunol* 2018; 14(Suppl 2):51.
 3. Til-Pérez G, Carnevale C, Sarria-Echegaray PL, *et al.* Sensitization profile in patients with respiratory allergic diseases: differences between conventional and molecular diagnosis (a cross-sectional study). *Clin Mol Allergy* 2019; 17:8.
 4. Matricardi PM, Kleine-Tebbe J, Hoffmann HJ, *et al.* EAACI molecular allergology user's guide. *Pediatr Allergy Immunol* 2016; 27(Suppl 23):1–250.
 5. Matricardi PM, Dramburg S, Potapova E, *et al.* Molecular diagnosis for allergen immunotherapy. *J Allergy Clin Immunol* 2019; 143:831–843.
- An updated paper showing how molecular testing for diagnosis and treatment of allergic diseases is becoming more and more important and is leading allergology towards a 'personalized medicine'.
6. Del-Rio Camacho G, Montes Arjona AM, Fernández-Cantalejo Padial J, *et al.* How molecular diagnosis may modify immunotherapy prescription in multi-sensitized pollen-allergic children. *Allergol Immunopathol (Madr)* 2018; 46:552–556.

7. Heffler E, Puggioni F, Descalzi D, *et al.* Microarray immunodiagnosics for aeroallergens. *Curr Allergy Asthma Rep* 2019; 19:10.
- An interesting review on the impact of molecular allergy diagnostics on the management of patients presenting with complex respiratory symptoms and allergies.
8. Roberts G, Pfaar O, Akdis CA, *et al.* EAACI guidelines on allergen immunotherapy: allergic rhinoconjunctivitis. *Allergy* 2018; 73:765–798.
- The European Guideline for the management of allergic rhinitis and allergen immunotherapy.
9. Martínez-Cañavate Burgos A, Torres-Borrego J, Molina Terán AB, *et al.* Molecular sensitization patterns and influence of molecular diagnosis in immunotherapy prescription in children sensitized to both grass and olive pollen. *Pediatr Allergy Immunol* 2018; 29:369–374.
10. Belhassen M, Demoly P, Bloch-Morot E, *et al.* Costs of perennial allergic rhinitis and allergic asthma increase with severity and poor disease control. *Allergy* 2017; 72:948–958.
11. Linneberg A, Dam Petersen K, Hahn-Pedersen J, *et al.* Burden of allergic respiratory disease: a systematic review. *Clin Mol Allergy* 2016; 14:12.
12. Matricardi PM, Dramburg S, Skevaki C, Renz H. 'Molecular extracts' for allergy diagnostics and therapy. *Pediatr Allergy Immunol* 2019; 30:55–58.
13. Melioli G, Puggioni F, Racca F, *et al.* Clinical outcomes related to molecular allergy diagnosis. *Curr Opin Allergy Clin Immunol* 2019; 19:204–208.
14. Mothes-Luksch N, Jordakieva G, Hinterhölzl L, *et al.* Allergy diagnosis from symptoms to molecules, or from molecules to symptoms: a comparative clinical study. *World Allergy Organ J* 2018; 11:22.
- A paper showing the two possible diagnostic pathways 'from symptoms to molecules' and 'from molecules to symptoms'.
15. Nwaru BI, Suzuki S, Ekerljung L, *et al.* Furry animal allergen component sensitization and clinical outcomes in adult asthma and rhinitis. *J Allergy Clin Immunol Pract* 2019; 7:1230–1238.e4.
16. Cipriani F, Tripodi S, Panetta V, *et al.* Early molecular biomarkers predicting the evolution of allergic rhinitis and its comorbidities: a longitudinal multicenter study of a patient cohort. *Pediatr Allergy Immunol* 2019; 30:325–334.
17. Douladiris N, Garib V, Piskou K, *et al.* Molecular allergy diagnosis: a potential tool for the assessment of severity of grass pollen-induced rhinitis in children. *Pediatr Allergy Immunol* 2019; 30:852–855.
18. Posa D, Perna S, Resch Y, *et al.* Evolution and predictive value of IgE responses toward a comprehensive panel of house dust mite allergens during the first 2 decades of life. *J Allergy Clin Immunol* 2017; 139:541–549.e8.
19. Hatzler L, Panetta V, Lau S, *et al.* Molecular spreading and predictive value of preclinical IgE response to *Phleum pratense* in children with hay fever. *J Allergy Clin Immunol* 2012; 130:894–901.e5.
20. Tosca MA, Licari A, Olcese R, *et al.* Immunotherapy and asthma in children. *Front Pediatr* 2018; 6:231.
21. Richter AK, Klimek L, Merk HF, *et al.* Impact of increasing treatment rates on cost-effectiveness of subcutaneous immunotherapy (SCIT) in respiratory allergy: a decision analytic modelling approach. *Eur J Health Econ* 2018; 19:1229–1242.
22. Agache I, Lau S, Akdis CA, *et al.* EAACI guidelines on allergen immunotherapy: house dust mite-driven allergic asthma. *Allergy* 2019; 74:855–873.
- The European guidelines for AIT in mites driven asthma.
23. Zubchenko S, Sharikadze O, Maruniak S. Allergen component testing: a new era in diagnostics of patients with pollen allergy. *Wiad Lek* 2019; 72:391–394.
24. Stringari G, Tripodi S, Caffarelli C, *et al.* The effect of component-resolved diagnosis on specific immunotherapy prescription in children with hay fever. *J Allergy Clin Immunol* 2014; 134:75–81.
25. Passalacqua G. Allergen immunotherapy for pediatric asthma: current evidence and knowledge gaps. *Curr Opin Allergy Clin Immunol* 2020. [In press]