Precision medicine in patients with allergic diseases: Airway diseases and atopic dermatitis—PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology

Antonella Muraro, MD,1,2 Robert F. Lemanske, Jr, MD,3 Peter W. Hellings, MD,4 Cezmi A. Akdis, MD,5 Thomas Bieber, MD,6 Thomas B. Casale, MD,7 Marek Jutel, MD,8 Peck Y. Ong, MD,9 Lars K. Poulsen, PhD,10 Peter Schmid-Grendelmeier, MD,11 Hans-Uwe Simon, MD,12 Sven F. Seys, PhD,13 and Ioana Agache, MD14

In this consensus document we summarize the current knowledge on major asthma, rhinitis, and atopic dermatitis endotypes under the auspices of the PRACTALL collaboration platform. PRACTALL is an initiative of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology aiming to harmonize the European and American approaches to best allergy practice and science. Precision medicine is of broad relevance for the management of asthma, rhinitis, and atopic dermatitis in the context of a better selection of treatment responders, risk prediction, and design of disease-modifying strategies. Progress has been made in profiling the type 2 immune response-driven asthma. The endotype driven approach for non-type 2 immune response asthma, rhinitis, and atopic dermatitis is lagging behind. Validation and qualification of biomarkers are needed to facilitate their translation into pathway-specific diagnostic tests. Wide consensus between academia, governmental regulators, and industry for further development and application of precision medicine in management of allergic diseases is of utmost importance.

Improved knowledge of disease pathogenesis together with defining validated and qualified biomarkers are key approaches to precision medicine. (J Allergy Clin Immunol 2016;137:1347-58.)

Key words: Precision medicine, personalized care, phenotype, endotype, biomarker, allergic rhinitis, allergic asthma, allergic skin disease

Since the beginning of medicine, patients with similar clinical characteristics, presently termed phenotypes, have been grouped and treated similarly according to the experience of the clinician and, subsequently, evidence-based medicine. However, many patients might not respond to therapy that is considered the standard of care, reinforcing the concept that “one size does not fit all.”

From 1Food Allergy Referral Centre Veneto Region, Department of Women and Child Health, Padua General University Hospital, Padua; 2the Department of Pediatrics, University of Wisconsin School of Medicine and Public Health, Madison; 3the Department of Otorhinolaryngology, University Hospitals Leuven; 4the Swiss Institute of Allergy and Asthma Research, University of Zurich, Christine Kühne-Center for Allergy Research and Education, Davos; 5the Department of Dermatology and Allergy, Christine Kühne-Center for Allergy Research and Education, Friedrich-Wilhelms-University, Bonn; 6the Department of Internal Medicine, University of South Florida, Tampa; 7the Department of Clinical Immunology, Wroclaw Medical University, and ALL-MED Medical Research Institute, Wroclaw; 8the Division of Clinical Immunology and Allergy, Children’s Hospital Los Angeles, and the Department of Pediatrics, Keck School of Medicine, University of Southern California, Los Angeles; 9Allergy Clinic Copenhagen University Hospital at Gentofte, Copenhagen; 10the Allergy Unit, Department for Dermatology, University of Zurich, Zurich, Switzerland, Christine Kühne-Center for Allergy Research and Education, Davos; 11the Institute of Pharmacology, University of Bern; 12the Laboratory of Clinical Immunology, University of Leuven; and 13the Department of Allergy and Clinical Immunology, Transylvania University, Brasov.

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Corresponding author: Antonella Muraro, MD, Food Allergy Centre Department of Women and Child Health, Padua General University Hospital, Padua, Italy. E-mail: muraro@centroallergicalimentari.eu.

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all” and encouraging the scientific community to unravel the pathophysiologic mechanisms causing the disease.

Currently, it is generally accepted that the clinical differences in treatment responses or disease course over time are related to underlying variations in genetic, pharmacologic, physiologic, biologic, and/or immunologic mechanisms that produce sub-classes of phenotypes termed endotypes. This endotype-driven observed heterogeneity in therapeutic response has led to the use of terms, such as precision or personalized medicine (among others), to direct therapy more specifically, when possible. For example, although the phenotype of anemia presents clinically with pallor related to low red blood cell indices, the underlying endotypes responsible for this phenotype are multiple (eg, iron deficiency, G6PD deficiency, and autoimmune disease among others). Thus, for anemia, defining the underlying endotype is critical in more precisely choosing any therapeutic intervention.

To evaluate the latest findings in precisely defining the endotypic profile of the allergic and/or asthmatic patient and the potential for the specialty of allergy/immunology to use this precision medicine approach, the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology have conducted a project focused on this topic. The previously successful PRACTALL approach, in which a panel of experts from these 2 geographic regions reviewed the literature and harmonized the evidence that supported the particular topic being analyzed, was used to conduct these analyses.

The focus for this PRACTALL was an examination of the potential benefits of applying the concepts of precision medicine to first airway and skin allergic diseases. A second PRACTALL paper soon to be published will cover the precision medicine approach for food allergy and anaphylaxis. Although a number of terms have been used to define this type of approach, the consensus of the writing groups was to use the term precision medicine. As such, according to the National Institutes of Health, precision medicine is an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person. A well-defined endotype should link the key pathogenic mechanism with a clinical phenotype of asthma through biomarkers. There are several benefits of endotyping in a clinical setting, such as stringent consideration of entry criteria for epidemiologic, genetic, or therapeutic trials.

### Defining asthma endotypes

Generally, it is considered that a type 2 immune response underlies atopic asthma. Eosinophilic airway inflammation and an increase in type 2 cytokine levels (eg, induced sputum, bronchoalveolar lavage fluid, and bronchial biopsy specimens) are characteristic of these patients. The type 2 immune response endotype has been related to response to inhaled corticosteroids and disease outcomes, such as exacerbations.

Several subendotypes can exist within the type 2 complex endotype, such as the IL-5–high, IL-13–high, or IgE-high endotypes. Aspirin-exacerbated respiratory disease is also a particular subtype of the type 2 complex endotype, where the hyperactive metabolic pathway shapes the type 2 immune response. In this view type 2 immune response endotypes are defined by subgroups of patients who have a beneficial response to treatment targeting the IL-5, IL-13, or IgE pathogenetic pathways (Fig 1, A). The type 2 complex endotype can also be identified in patients with allergic rhinitis (AR) as a fundamental for the unified airways disease concept (Fig 1, B).

Both the innate and acquired immune responses contribute to type 2 immune response endotypes (Fig 1, A). TH2 cytokines (eg, IL-4/IL-13) drive a pathophysiologic response in asthmatic patients. The type 2 complex endotype can also be identified in allergic rhinitis (AR) as a fundamental for the unified airways disease concept (Fig 1, B).

The mechanisms contributing to the non-type 2 immune response in asthmatic patients are less clear (Fig 2). Two major mechanisms leading to neutrophilic inflammation are postulated: (1) the dysregulated innate immune response, including neutrophil-intrinsic abnormalities, and (2) activation of the IL-17–dependent pathway. In addition, type 1 immune responses might contribute to asthma severity: high IFN-γ levels in sputum of asthmatic patients have been associated with severe asthma. Several factors, such as metabolic or epigenetic factors, or activation of the epithelial-mesenchymal trophic unit have been identified as modulators. The endotyping of non–type 2 immune response asthma lags behind that of type 2 immune response asthma, and until now, no endotype-driven interventions have been proved effective.

### Asthma biomarkers

Currently identified asthma biomarkers are used to predict treatment response in patients with type 2 immune response asthma. There are several benefits of endotyping in a clinical setting, such as stringent consideration of entry criteria for epidemiologic, genetic, or therapeutic trials.

**Abbreviations used**

AD: Atopic dermatitis

AR: Allergic rhinitis

CRTH2: Chemoattractant receptor-homologous molecule expressed on T\(_2\) cells

FENO: Fraction of exhaled nitric oxide

NO: Nitric oxide

TSLP: Thymic stromal lymphopoietin

**PRECISION MEDICINE AT THE LOWER AIRWAYS: ASTHMA**

The heterogeneity of asthma in relation to patients’ characteristics (phenotype), underlying pathogenic mechanisms (endotype), and clinically significant outcomes, including response to treatment, has been established beyond any doubt. Better asthma management needs a refined understanding of disease heterogeneity and mechanisms in relation to clinically significant outcomes.

Extended heterogeneous disease-related metabolic, inflammatory, immunologic, and remodeling pathways have been described, and a stable pattern is defined as a disease endotype.
A, Overview of the type 2 immune response in asthmatic patients. Three main phenotypes of type 2 immune response–driven asthma are described: eosinophilic inflammation; allergic sensitization, as depicted by the presence of antigen-specific IgE; and airway hyperreactivity and remodeling. Both the innate and acquired immune responses contribute to type 2 immune response endotypes. Endotype-driven asthma management targets most of the molecular pathways involved in type 2 immune response asthma: green, approved treatment targets for asthma; blue, under investigation; red, potential treatment targets.

B, Overview of the type 2 immune response in patients with rhinitis. Three main phenotypes of rhinitis are described, which are similar to those of asthma, with the exception of remodeling. Different cellular and molecular players contribute to type 2 immune responses in patients with rhinitis. In contrast to asthma, none of these molecular pathways are under investigation for targeted treatment. ILC, Innate lymphoid cell; NKT, natural killer T cell; PGD2, prostaglandin D2.

FIG 1. A, Overview of the type 2 immune response in asthmatic patients. Three main phenotypes of type 2 immune response–driven asthma are described: eosinophilic inflammation; allergic sensitization, as depicted by the presence of antigen-specific IgE; and airway hyperreactivity and remodeling. Both the innate and acquired immune responses contribute to type 2 immune response endotypes. Endotype-driven asthma management targets most of the molecular pathways involved in type 2 immune response asthma: green, approved treatment targets for asthma; blue, under investigation; red, potential treatment targets. B, Overview of the type 2 immune response in patients with rhinitis. Three main phenotypes of rhinitis are described, which are similar to those of asthma, with the exception of remodeling. Different cellular and molecular players contribute to type 2 immune responses in patients with rhinitis. In contrast to asthma, none of these molecular pathways are under investigation for targeted treatment. ILC, Innate lymphoid cell; NKT, natural killer T cell; PGD2, prostaglandin D2.
response–driven inflammation (Table 1). It should be noted that most asthma biomarkers are currently used in research settings and still need to be validated and qualified. A valid biomarker is defined as “a biomarker that is measured in an analytical test system with well-established performance characteristics and for which there is an established scientific framework or body of evidence that elucidates the physiologic, toxicologic, pharmacologic, or clinical significance of the test results.” Validation is the process of assessing the biomarker and its performance characteristics and determining the range of conditions under which the biomarker will produce reproducible and accurate data. Qualification is the evidentiary process of linking a biomarker with biological processes and clinical end points.

Blood eosinophilia is a well-demonstrated biomarker of type 2 immune response–driven inflammation in asthmatic patients and has been linked to response to corticosteroids and, more recently, anti–IL-4/IL-13–targeted and anti–IL-5–targeted treatment. Its correlation to sputum or bronchial eosinophilia cannot always be demonstrated; thus blood and airway eosinophils cannot be used interchangeably because they might reflect different type 2 subendotypes. Sputum eosinophil levels have also been useful for predicting response to inhaled steroids and anti–IL-13 and anti–IL-5 therapy.

The periostin gene has been identified as an IL-13–inducible gene in bronchial brushings from asthmatic patients. Periostin expression in bronchial tissue has been shown to be a biomarker of eosinophilic airway inflammation, whereas serum periostin levels have been related to the response to anti–IL-13 therapy in patients with mild-to-moderate asthma.

Serum dipeptidyl peptidase 4 has also been shown to predict responses to anti–IL-13 therapy. In another study sputum IL-13 levels were used to identify responders to anti–IL-13 treatment.

In a post hoc analysis a composite biomarker combining blood eosinophils, periostin, and fraction of exhaled nitric oxide (FeNO) identified anti-IgE mAb omalizumab responders. Recent data suggest that blood eosinophils alone might be a useful biomarker to predict responses to omalizumab.

Biomarkers measured in exhaled breath are of particular interest because of their noninvasive character. In steroid-naive asthmatic patients FeNO values correlated well with eosinophilic airway inflammation. Breath analysis by using eNose (volatile organic compounds in exhaled breath) can identify asthmatic patients and can be used to predict their response to steroids with greater accuracy than sputum eosinophil counts or FeNO values.

There are several biomarkers predicting poor steroid response in asthmatic patients, such as p38 and MSK1 phosphorylation status of blood monocytes, vanin-1 expression and CpG methylation, the presence of TH2/TH17 double-producing cells in bronchoalveolar lavage fluid, and airway expansion of specific gram-negative bacteria. A corticosteroid-responsive endophenotype was recently described.

Endotype-driven asthma treatment

Early clinical trials with anticytokine therapies in asthmatic patients were not successful because of inclusion of unselected patients. As an example, anti–IL-5 therapy in unselected patients
A recent tailored approach selecting patients for anti–IL-5–targeted treatment based on their blood or sputum eosinophil counts proved to be more rewarding (Table II).

Several steps need to be taken into account when considering tailored therapy for asthmatic patients (Fig 3). Before assessment of a patient’s phenotype and endotype, correct diagnosis of asthma should be ensured. Comorbidities need to be evaluated and treated properly. A crucial step is to unravel which pathophysiologic mechanism or mechanisms are driving the disease, thereby determining the patient’s endotype. Translation of biomarkers into pathway-specific diagnostic tests is essential and should guide the design of future large clinical trials incorporating both longitudinal and mechanism-tailored end points.

Many targeted treatments are in various stages of clinical development for patients with type 2 immune response–driven inflammation: anti–IL-4/IL-13, anti–IL-4, anti–IL-5, and anti-IgE antibodies, as well as CRTH2 antagonists (Fig 1 and Table II). At present, biomarkers are not sufficiently specific to select the subendotype of type 2 immune response asthma specifically responding to a targeted treatment (Table I). For example, blood eosinophils predicted response to anti–IL-4/IL-13, anti–IL-5, and anti-IgE antibodies, as well as CRTH2 antagonists, and the (lack of evaluation for blood or sputum eosinophilia) did not show significant effects on asthma exacerbations or lung function improvement. A recent tailored approach selecting patients for anti–IL-5–targeted treatment based on their blood or sputum eosinophil counts proved to be more rewarding (Table II).

### TABLE I. Asthma biomarkers guiding tailored treatment approaches

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Treatment expected to produce a response</th>
<th>Associations</th>
<th>Comments (point of care, variability/fluctuation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Eosinophils</td>
<td>Anti–IL-5</td>
<td>Exacerbations</td>
<td>Easily available</td>
</tr>
<tr>
<td></td>
<td>Anti-IgE</td>
<td>LF decrease</td>
<td>Significant fluctuation</td>
</tr>
<tr>
<td></td>
<td>Anti–IL-4/IL-13</td>
<td>Fixed airway obstruction</td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRTH2 antagonists</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specific IgE</td>
<td>Anti-IgE</td>
<td>Exacerbations</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AIT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Periostin DPP-4</td>
<td>Anti–IL-13</td>
<td>LF decline</td>
<td>Research type</td>
</tr>
<tr>
<td>Induced sputum</td>
<td></td>
<td>Exacerbations</td>
<td>Research type</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>Anti–IL-5</td>
<td></td>
<td>Research type</td>
</tr>
<tr>
<td></td>
<td>ICS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-13</td>
<td>Anti–IL-13</td>
<td>Unknown</td>
<td>Research type</td>
</tr>
<tr>
<td>Exhaled breath</td>
<td>Anti–IL-5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anti-IgE</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anti–IL-13</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ICS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolomics (VOC)</td>
<td>ICS</td>
<td>Unknown</td>
<td>Research type</td>
</tr>
</tbody>
</table>

There is significant overlap between biomarkers used to predict response to different endotype-driven strategies. In addition, few biomarkers are easily available, most are subject to significant fluctuation, and none are validated and qualified.


### TABLE II. Endotype-driven treatment in type 2 immune response–driven asthma

<table>
<thead>
<tr>
<th>Predictive biomarker</th>
<th>Drug</th>
<th>Target</th>
<th>Effects</th>
<th>Regulatory status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood eosinophils</td>
<td>Omalizumab</td>
<td>IgE</td>
<td>Reduces exacerbations, improves symptoms and quality of life</td>
<td>FDA and EMA approved</td>
</tr>
<tr>
<td>Periostin</td>
<td>Fexol</td>
<td>IL-13</td>
<td>Reduces eosinophil counts, exacerbations, and OCS improves FEV₁</td>
<td>FDA approved</td>
</tr>
<tr>
<td>Blood/sputum eosinophils</td>
<td>Mepolizumab</td>
<td>IL-5</td>
<td>Reduces eosinophil counts, exacerbations, improves FEV₁</td>
<td>EMA under consideration Tested for CRSwNP</td>
</tr>
<tr>
<td>FENO</td>
<td>Reslizumab</td>
<td>IL-5</td>
<td>Reduces eosinophil counts, exacerbations improves FEV₁</td>
<td>FDA under consideration</td>
</tr>
<tr>
<td>Blood eosinophils</td>
<td>Benralizumab</td>
<td>IL-5Rα</td>
<td>Reduces eosinophil and basophil counts, exacerbations improves FEV₁</td>
<td>Phase III</td>
</tr>
<tr>
<td>Blood eosinophils</td>
<td>Dupilumab</td>
<td>IL-4Rα</td>
<td>Reduces exacerbations, improves FEV₁, improves symptoms and quality of life</td>
<td>Phase III Tested for CRSwNP, AD, and EoE</td>
</tr>
<tr>
<td>Periostin DPP-4</td>
<td>Tralokinumab</td>
<td>IL-13</td>
<td>Reduces eosinophil counts and exacerbations improves FEV₁</td>
<td>Phase II</td>
</tr>
<tr>
<td>Periostin</td>
<td>Lebrikizumab</td>
<td>IL-13</td>
<td>Reduces exacerbations improves FEV₁</td>
<td>Phase III</td>
</tr>
</tbody>
</table>

The IgE, IL-5, and IL-4/IL-13 pathways can be targeted with mAbs. There is a remarkable overlap between the so-called predictive biomarkers and a significant heterogeneity in clinical response.

**CRSwNP**, Chronic rhinosinusitis with nasal polyps; **DPP-4**, dipeptidyl peptidase 4; **EMA**, European Medicines Agency; **EoE**, eosinophilic esophagitis; **FDA**, US Food and Drug Administration; **IL-4Ra**, IL-4 receptor α; **IL-5Ra**, IL-5 receptor α; **OCS**, oral corticosteroids.
After treatment. Rhinitis phenotypes have been the basis of evidence-based treatment algorithms for rhinitis. A phenotype-based strategy for rhinitis implies a trial-and-error approach, with guidance of treatment based on the severity and duration of symptoms. As a consequence, a significant percentage of patients with AR have uncontrolled disease, highlighting the need for precision medicine in patients with AR. Precision medicine implies endotype- rather than phenotype-driven treatment added to the prediction of successful therapy, prevention of disease, and participation of the patient.

The first step in the implementation of precision medicine in patients with rhinitis will be to characterize the endotype as a guide to a tailored therapeutic approach. It should be emphasized that patients with rhinitis might have a complex endotype and that the current understanding of cellular and molecular processes giving rise to a certain phenotype require further study. In addition, as described for asthma, there are several modulators of endotype expression, such as the environment, microbiome, lifestyle, and nasal anatomy.

The following endotypes of rhinitis are being proposed (Fig 4).

Type 2 immune response rhinitis

Mast cell–bound specific IgE is cross-linked by absorbed allergen molecules, leading to acute symptoms and influx into the nasal mucosa of eosinophils, basophils, and T and B lymphocytes. This is often accompanied by a systemic immune response dominated by type 2 cytokines produced by CD4+ T cells, type 2 innate lymphoid cells, and basophils, which is associated with blood and nasal eosinophilia. The type 2 immune response endotype usually is attributed to AR; however, occupational/ environmental low-molecular-weight substances leading to release of epithelially derived TSLP, IL-33, and IL-25, can initiate or aggravate a type 2 immune response.

Type 1 immune response rhinitis

An innate and adaptive type 1/IL-17 immune response leads to influx of neutrophils and IFN-γ–producing CD4+ T cells, usually as the background of infectious rhinitis.

Neurogenic rhinitis

This particular endotype is characterized by a relative overexpression of transient receptor potential potential channels on trigeminal nerves and high concentrations of substance P and neuropeptides and is linked to gustatory rhinitis, rhinitis of the elderly, and idiopathic rhinitis with nasal hyperreactivity.

Epithelial dysfunction

Epithelial dysfunction can be primary or secondary to type 2 or type 1 immune response–induced inflammation. It can be divided roughly into the ciliary dysfunctional pathway (primary vs secondary) and the barrier dysfunctional pathway, with reduced expression of zonula occludens 1 and occludin-1 facilitating subepithelial migration of exogenous immune-stimulating molecules.

Several other rhinitis phenotypes, such as drug-related, senile, and hormonal rhinitis, are poorly characterized by the lack of data on biomarkers and the molecular and cellular mechanisms involved.

In clinical practice efforts can be made in endotyping patients with rhinitis by measuring total and allergen-specific IgE levels.
Several other biomarkers are used in research settings, such as serum IL-5, nasal total and allergen-specific IgE, eosinophil-derived neurotoxin, eosinophil cationic protein, eosinophil peroxidase, IL-5, substance P, neurokinin 1, IL-33, and TSLP levels and staining of mucosal biopsy specimens for TRPV-1, zonula occludens 1, or occludin.

These biomarkers should ideally be supplemented by nasal function measurements, such as nasal flow measurement (to confirm nasal obstruction) and cold dry air provocation (to determine nasal hyperreactivity), nasal nitric oxide measurement (to measure nasal inflammation), nasal allergen provocation (to confirm the clinical relevance of allergens), and evaluation of smell performance (in patients mentioning reduced smell capacity).

The best example of an endotype-driven treatment in rhinitis is the use of allergen-specific immunotherapy in patients in whom an allergen-induced type 2 immune response endotype leads to a clinically relevant exposure-symptom relation. Another example of endotype-driven treatment is the highly successful intervention with capsaicin for the neurogenic endotype.

Precision medicine represents the future of rhinitis care in patients whose symptoms are not fully controlled despite evidence-based treatment. Essential steps toward precision medicine in patients with rhinitis are described in Table III.

**RHINITIS ENDOTYPES**

<table>
<thead>
<tr>
<th>NON-TYPE 2</th>
<th>TYPE 2</th>
<th>NEUROGENIC</th>
<th>EPITHELIUM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils</td>
<td>Eosinophils</td>
<td>Environment</td>
<td>TSLP</td>
</tr>
<tr>
<td>IFN-γ, IL-17, TNF</td>
<td>Mast cells</td>
<td>Life-style</td>
<td>IL-33</td>
</tr>
<tr>
<td></td>
<td>IL-5, IL-4/IL-13</td>
<td>Microbiome</td>
<td>Barrier / ciliary dysfunction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nasal anatomy</td>
<td>Remodeling</td>
</tr>
</tbody>
</table>

**SYMPTOMS**

- Congestion
- Rhinorrhea
- Hyposmia
- Sneezing
- Itch
- NHR

**COMMON COLD**

- rhinitis of the ELDERLY

**ALLERGIC**

- IR with NHR

**RHINITIS PHENOTYPES**

- severity / duration / sensitization pattern / co-morbidities

**FIG 4.** Overview of rhinitis phenotypes and endotypes. Similar to asthma, a type 2 immune response and non-type 2 immune response endotype can be described for rhinitis. Neurogenic and epithelial barrier dysfunction endotypes are particularly relevant for rhinitis. ILC, Innate lymphoid cell; IR, idiopathic rhinitis; NHR, nasal hyperreactivity; NK, neurokinin; SP, substance P; TRP, transient receptor potential.

**PRECISION MEDICINE AT THE SKIN: ATOPIC DERMATITIS**

Atopic dermatitis (AD) is a disease with a highly complex pathophysiology (Fig 5) and heterogeneous phenotypes, which are illustrated by different features, such as age of disease onset, variable response to allergens, spectrum of severity, potential of IgE auto-reactivity, and comorbidities (asthma, rhinitis, food allergy, and infections). In the field of AD, in contrast to asthma, we are just in the beginning of the development of precision medicine and the attempt to reach a biomarker-based molecular taxonomy. We expect that the complexity of the clinical phenotype is underlined by even more complex profiles of possibly different pathophysiological pathways from which we can learn and develop a strategy for discovery, validation, and qualification of biomarkers.

Precision medicine is of broad relevance for the management of AD, which is known to have a diverse natural history ranging from complete remission to relapsing flares to very severe and persistent forms variably associated with comorbidities, such as asthma and AR. Clearly, the discovery and validation of biomarkers with ideally prognostic and predictive value for AD represents a significant unmet need in this field.

The following endotypes of AD are being proposed (Fig 6 and Table IV): (1) type 2 immune response AD, covering the whole disease spectrum from background inflammation in nonlesional skin to acute disease flares to chronic disease, peaking during acute flares, and (2) non—type 2 immune response AD mixing TH1-, TH17-, and TH22-driven inflammation and epithelial dysfunction.

In addition to the attempt to identify possible provocative factors, the current approach in AD management is still “one size fits all” based on use of emollients and anti-inflammatory drugs in all patients, although the disease provides a number of...
opportunities for more personalized management.\textsuperscript{90,91} Thus far, there is no clear evidence for targeted therapy for any kind of approved anti-inflammatory treatment regimen in patients with AD. However, with the emergence of biologics targeting well-defined cytokines and pathways, such as anti–IL-4/IL-13 or anti–IL-31,\textsuperscript{92,93} the need for predictive biomarkers of therapeutic response has to be reconsidered.

Biomarkers could be useful in the management of early-onset disease at different time points throughout the natural history of AD (Fig 7).\textsuperscript{94} Some biomarkers, such as CCL17, have been shown to be a consistent measurement of AD severity in multiple clinical trials. Also, filaggrin deficiency as a potential candidate for prognosis and indoleamine 2,3-dioxygenase as a predictive marker for viral skin infections leading to eczema herpeticum have been demonstrated.\textsuperscript{95} It is also a common phenomenon to see multiple allergen-specific IgE sensitizations, particularly in patients with moderate-to-severe disease, but their clinical relevance is often questionable for avoidance strategies. It is highly probable that multiple biomarkers will be needed as a signature profile in AD to predict the severity, comorbidities, and treatment response.

Two recent proof-of-concept studies showed that 6 to 8 months of skin barrier therapy prevents the development of AD during this period of time in a significant portion (30\% to 50\%) of infants born to parents with a history of atopy.\textsuperscript{96,97} This suggests an opportunity for early intervention with a positive effect on the emergence of AD and possibly on the “atopic march,” thus...
representing a disease-modifying strategy. The selection of these high-risk patients was based solely on family history. The outcome could be substantially improved if we used validated biomarkers to select those infants (the right patient) with high risk assessed not only based on family history but also on biomarker signature. Moreover, it is expected that the early improvement (the right time) of the barrier dysfunction could be substantially enhanced if we have appropriate new emollients (the right drug), including ingredients able to support barrier function, given in the optimal frequency amount (the right dose). These new products and innovative ingredients could be based on the availability of biomarkers unraveling the individual pathophysiologic origin of the barrier dysfunction in a given patient subgroup.

CONCLUSION AND FUTURE PERSPECTIVES

Precision medicine is of broad relevance for the management of asthma, rhinitis, and AD from a better selection of responders to treatment and design of better clinical trials to risk prediction and disease-modifying strategies. In this PRACTALL we summarized the current knowledge on major asthma, rhinitis, and AD endotypes (Table IV).

For asthma, several steps have been taken in profiling the type 2 immune response–driven asthma, together with endotype-driven strategies. However, more information is needed to better target specific pathways in patients that will optimize patients’ therapeutic responses while avoiding adverse effects. Endotype-driven management of non–type 2 immune response asthma, rhinitis, and AD is clearly an unmet need in the field.

In addition, most biomarkers are currently used in research settings and still need to be validated and qualified. Asthma, rhinitis, and AD biomarkers are complicated by remarkable heterogeneity compared with specific cancer biomarkers. This complexity includes different patterns of onset and clinical presentation and marked variations in the rate of disease remission or progression, together adding to the considerable challenge both in determining the appropriate clinical outcome and in delineating efficacy biomarkers.

A strategy for biomarker validation and qualification needs to be created, including development of reference laboratories and clinical epidemiology and validation centers, as well as networks of cooperative human tissue banks or resources. Open interaction among steering committees of large trials and large cohort studies should be encouraged for the free exchange of ideas and specimens.

Improved knowledge of the pathogenesis of asthma, rhinitis, and AD and information-relating biomarkers with clinically relevant outcomes will permit a better means for assessment of the effects of new interventions. It is evident that there is a shared

### TABLE IV. Proposed endotypes of asthma, AR, and AD

<table>
<thead>
<tr>
<th>Asthma</th>
<th>AR</th>
<th>AD</th>
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<tbody>
<tr>
<td>Type 2 immune response</td>
<td>Type 2 immune response</td>
<td>Type 2 immune response</td>
</tr>
<tr>
<td>Non–type 2 immune response</td>
<td>Non–type 2 immune response</td>
<td>Non–type 2 immune response</td>
</tr>
<tr>
<td></td>
<td>Epithelial dysfunction</td>
<td>Epithelial dysfunction</td>
</tr>
<tr>
<td></td>
<td>Neurogenic</td>
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FIG 6. Proposed endotypes for AD. Three main phenotypes of AD are described: nonlesional skin, acute disease flares, and chronic remitting relapsing AD. A type 2 immune response is present in all 3 phenotypes, with a peak in acute disease flares. $T_{h2}$ and $T_{h17}$-driven inflammation adds to the type 2 immune response in the dysregulated immune response present in nonlesional skin, whereas $T_{h2}$ and $T_{h1}$-driven inflammation is prominent in patients with the chronic form of AD. Epithelial dysfunction is a key mechanism partnering with the dysregulated immune response in nonlesional skin and in patients with chronic AD and facilitates acute disease flares.
recognition between academia, government regulators, and industry regarding the need for both the development and application of precision medicine in patients with asthma, rhinitis, and AD.\textsuperscript{66} This is a path other disease areas have taken, and there are experiences, processes, and infrastructure mechanisms in existence on which we can build.

Clinical implications: Improved knowledge of the pathogenesis of asthma, rhinitis, and AD leads to the concept of disease endotypes, thus supporting the potential for the specialty of allergy/immunology to use the precision medicine approach. After a correct diagnosis and proper management of comorbidities, a crucial step is to unravel which pathophysiologic mechanism or mechanisms are driving the disease, thereby determining the endotype of the patient and providing validated pathway-specific diagnostic tests.

REFERENCES
VOLUME 137, NUMBER 5
J ALLERGY CLIN IMMUNOL


43. Wagner JA, Williams SA, Webster CJ. Biomarkers and surrogate end points for

42. Wagner JA. Overview of biomarkers and surrogate endpoints in drug develop-

44. Goodsaid FM, Frueh FW, Mattes W. Strategic paths for biomarker qualification.

35. Bullens DM, Truyen E, Coteur L, Dilissen E, Hellings PW, Dupont LJ, et al. IL-


23. Chambers ES, Nanzer AM, Pfeiffer PE, Richards DF, Timmo PM, Martinez AR, et al. Distinct endotypes of steroid-resistant asthma characterized by IL-


20. Rajan JP, Wineinger NE, Stevenson DD, White AA. Prevalence of aspirin-

19. Agache I, Sugita K, Morita H, Akdis M, Akdis C. The complex type 2 endotype in al-

18. Agache I, Sugita K, Morita H, Akdis M, Akdis C. The complex type 2 endotype in al-

17. Agache I, Sugita K, Morita H, Akdis M, Akdis C. The complex type 2 endotype in al-

16. Agache I, Sugita K, Morita H, Akdis M, Akdis C. The complex type 2 endotype in al-

15. Agache I, Sugita K, Morita H, Akdis M, Akdis C. The complex type 2 endotype in al-

14. Agache I, Sugita K, Morita H, Akdis M, Akdis C. The complex type 2 endotype in al-

13. Agache I, Sugita K, Morita H, Akdis M, Akdis C. The complex type 2 endotype in al-

12. Agache I, Sugita K, Morita H, Akdis M, Akdis C. The complex type 2 endotype in al-

11. Agache I, Sugita K, Morita H, Akdis M, Akdis C. The complex type 2 endotype in al-

10. Agache I, Sugita K, Morita H, Akdis M, Akdis C. The complex type 2 endotype in al-

9. Agache I, Sugita K, Morita H, Akdis M, Akdis C. The complex type 2 endotype in al-

8. Agache I, Sugita K, Morita H, Akdis M, Akdis C. The complex type 2 endotype in al-

7. Agache I, Sugita K, Morita H, Akdis M, Akdis C. The complex type 2 endotype in al-

6. Agache I, Sugita K, Morita H, Akdis M, Akdis C. The complex type 2 endotype in al-

5. Agache I, Sugita K, Morita H, Akdis M, Akdis C. The complex type 2 endotype in al-

4. Agache I, Sugita K, Morita H, Akdis M, Akdis C. The complex type 2 endotype in al-

3. Agache I, Sugita K, Morita H, Akdis M, Akdis C. The complex type 2 endotype in al-

2. Agache I, Sugita K, Morita H, Akdis M, Akdis C. The complex type 2 endotype in al-

1. Agache I, Sugita K, Morita H, Akdis M, Akdis C. The complex type 2 endotype in al-


87. Bieber T. Atopic dermatitis 2.0: from the clinical phenotype to the molecular taxonomy and stratified medicine. Allergy 2012;67:1475-82.


