



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

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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

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Abbreviations used

AD:	Atopic dermatitis
AR:	Allergic rhinitis
CRTH2:	Chemoattractant receptor-homologous molecule expressed on T _H 2 cells
FENO:	Fraction of exhaled nitric oxide
NO:	Nitric oxide
TSLP:	Thymic stromal lymphopoietin

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 subclasses of phenotypes termed endotypes.¹ 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.²

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.¹

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.³⁻⁶ 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 well-defined endotype should link the key pathogenic mechanism with a clinical phenotype of asthma through biomarkers.^{7,8} 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.⁹ 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.¹⁰⁻¹⁵ The type 2 immune response endotype has been related to response to inhaled corticosteroids^{9,16} and disease outcomes, such as exacerbations.^{17,18}

Several subendotypes can exist within the type 2 complex endotype, such as the IL-5-high, IL-13-high, or IgE-high endotypes.¹⁹ 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.²⁰ 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 pathogenic pathways (Fig 1, A). The type 2 complex endotype can also be identified in patients with allergic rhinitis (AR) as a fundament for the united airways disease concept (Fig 1, B).

Both the innate and acquired immune responses contribute to type 2 immune response endotypes (Fig 1, A). T_H1/T_H17 inflammatory cells²¹⁻²⁵ and nonallergic mechanisms, such as environmental factors, psychosocial stress, activation of metabolic pathways,²⁶⁻²⁸ resident cells in the remodeled phenotype,^{29,30} or epithelial barrier dysfunction,³¹ further modulate the profile of type 2-driven inflammation. In addition, type 2-driven inflammation is characterized by a high cellular plasticity that enables the cells to adapt to a specific inflammatory milieu. Innate immune response cytokines, such as IL-33 and thymic stromal lymphopoietin (TSLP), modulate the mast cell-driven phenotype, whereas type 2 cytokines promote a particular phenotype involving smooth muscle cells and epithelial and endothelial cells in asthmatic patients. The latter also influence the permissiveness of the epithelium for allergens and of the endothelium for the recruitment of inflammatory cells to inflamed tissues and mucus production.³²⁻³⁴

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.^{15,16,35-39} 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.^{13,40} 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

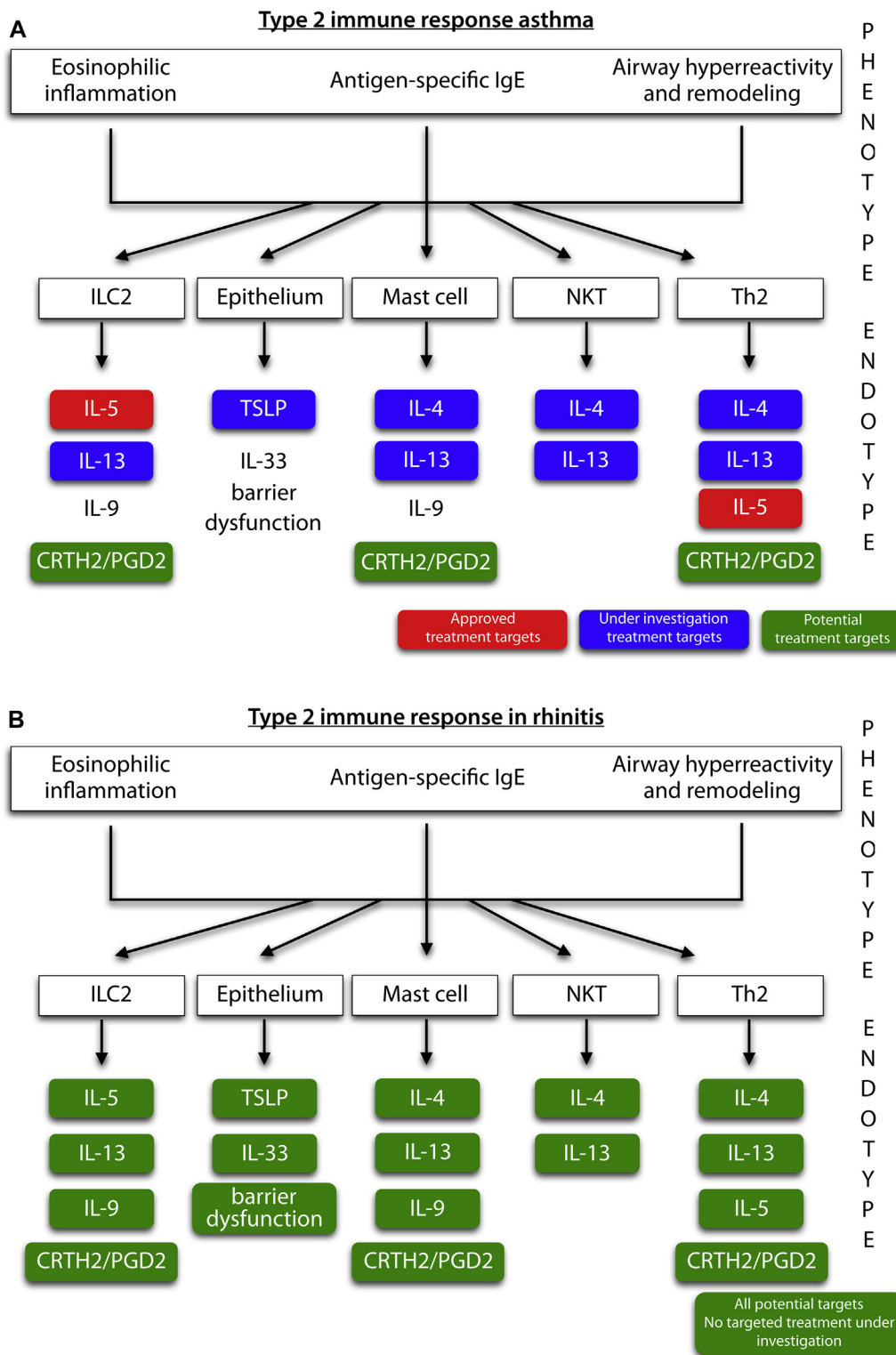


FIG 1. A, Overview of the type 2 immune response in asthmatic patients. Three main phenotypes of type 2 immune response–driven asthma are described: eosinophilic inflammation; allergic sensitization, as depicted by the presence of antigen-specific IgE; and airway hyperreactivity and remodeling. Both 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.

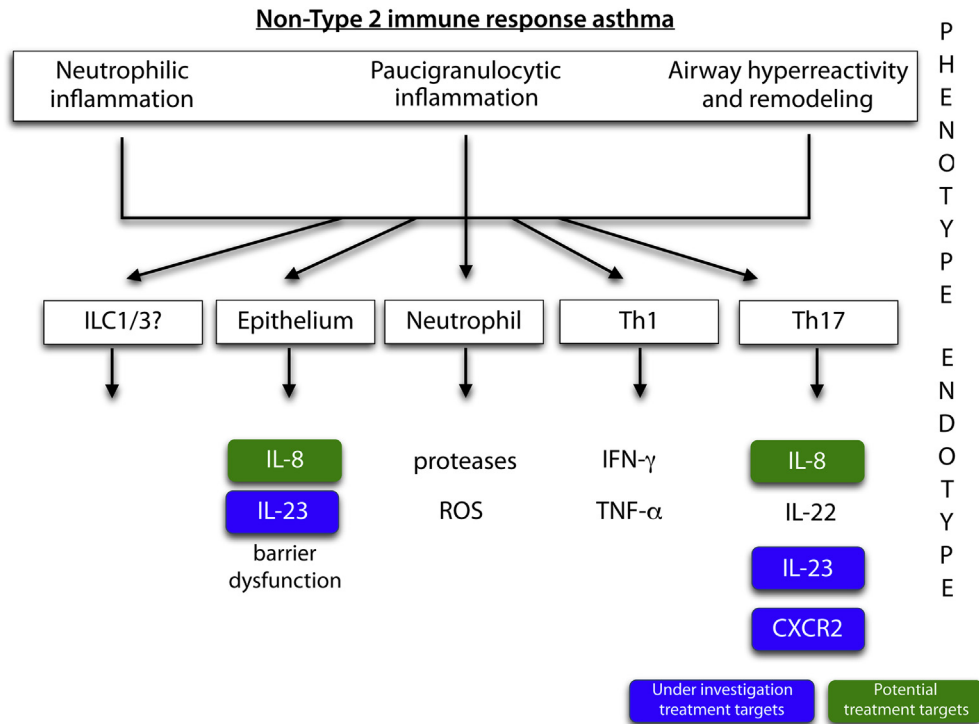


FIG 2. Overview of non-type 2 immune response in asthmatic patients. Three main phenotypes of non-type 2 immune response asthma can be described based on the inflammation pattern and the presence of airway hyperreactivity and remodeling. Some of the described molecular pathways are under investigation (blue) for an endotype-driven approach. Potential treatment targets are indicated in red. *ILC*, Innate lymphoid cell; *ROS*, reactive oxygen species.

response-driven inflammation (Table I). 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.”⁴¹ 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.⁴²⁻⁴⁴

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-targeted⁴⁵ and anti-IL-5-targeted^{46,47} 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 steroids¹⁶ and anti-IL-13 and anti-IL-5 therapy.^{17,18,46-48}

The periostin gene has been identified as an IL-13-inducible gene in bronchial brushings from asthmatic patients.^{9,49} Periostin expression in bronchial tissue has been shown to be a biomarker of eosinophilic airway inflammation,⁵⁰ whereas serum periostin levels have been related to the response to anti-IL-13 therapy in patients with mild-to-moderate asthma.⁵¹

Serum dipeptidyl peptidase 4 has also been shown to predict responses to anti-IL-13 therapy.⁵² In another study sputum IL-13 levels were used to identify responders to anti-IL-13 treatment.⁵³

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.⁵⁴ Recent data suggest that blood eosinophils alone might be a useful biomarker to predict responses to omalizumab.⁵⁵

Biomarkers measured in exhaled breath are of particular interest because of their noninvasive character. In steroid-naïve 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.^{56,57}

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 T_H2/T_H17 double-producing cells in bronchoalveolar lavage fluid, and airway expansion of specific gram-negative bacteria. A corticosteroid-responsive endophenotype was recently described.⁵⁸⁻⁶³

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

TABLE I. Asthma biomarkers guiding tailored treatment approaches

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

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.

AIT, Allergen immunotherapy; DPP-4, dipeptidyl peptidase 4; ICS, inhaled corticosteroids; LF, lung function; VOC, volatile organic compounds.

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

Predictive biomarker	Drug	Target	Effects	Regulatory status
Blood eosinophils	Omalizumab	IgE	Reduces exacerbations	FDA and EMA approved
Periostin			Improves symptoms and quality of life	
FENO				
Blood/sputum eosinophils	Mepolizumab	IL-5	Reduces eosinophil counts, exacerbations, and OCS	FDA approved
FENO			Improves FEV ₁	EMA under consideration Tested for CRSwNP
Blood eosinophils	Reslizumab	IL-5	Reduces eosinophil counts, exacerbations	FDA under consideration
			Improves FEV ₁	
Blood eosinophils	Benralizumab	IL-5R α	Reduces eosinophil and basophil counts, exacerbations	Phase III
			Improves FEV ₁	
Blood eosinophils	Dupilumab	IL-4R α	Reduces exacerbations	Phase III
			Improves FEV ₁	Tested for CRSwNP, AD, and EoE
			Improves symptoms and quality of life	
Periostin	Tralokinumab	IL-13	Reduces eosinophil counts and exacerbations	Phase II
DPP-4			Improves FEV ₁	
Periostin	Lebrikizumab	IL-13	Reduces exacerbations	Phase III
			Improves FEV ₁	

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-4R α , IL-4 receptor α ; IL-5R α , IL-5 receptor α ; OCS, oral corticosteroids.

(lack of evaluation for blood or sputum eosinophilia) did not show significant effects on asthma exacerbations or lung function improvement.^{64,65} 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).^{66,67} 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

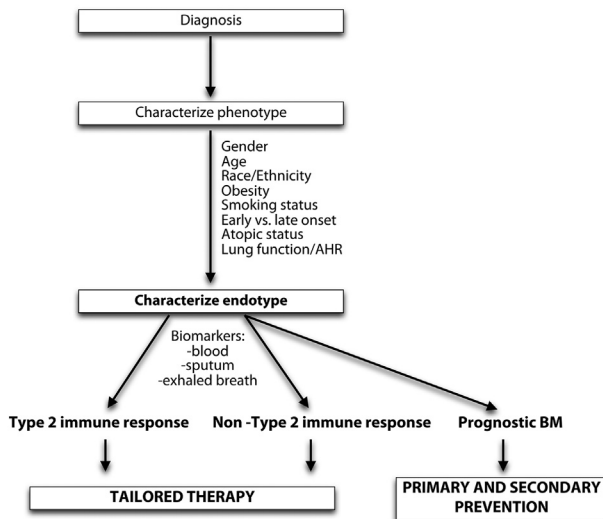
Suggested approach to precision medicine in asthma

FIG 3. Suggested approach to precision medicine in asthmatic patients. First, the correct diagnosis of asthma should be verified, and comorbidities should be treated properly. In a second step phenotype is established based on visible properties. Further characterization of the patient's endotype is crucial to ensure the optimum response to treatment and risk prediction, especially for those with severe and uncontrolled disease. Validation of prognostic biomarkers related to disease severity and risk prediction (including risk to develop asthma) open new pathways for primary and secondary asthma prevention. *AHR*, Airway hyperresponsiveness; *BM*, biomarkers.

clinician will face a conundrum of how best to treat patients with severe asthma with high blood eosinophil counts.⁶⁸

Limited data are available about the long-term efficacy of targeted treatment in asthmatic patients. For example, sputum eosinophil counts and exacerbation frequency increased as soon as 3 months after stopping treatment with the anti-IL-5 mAb mepolizumab.⁶⁹ Current targeted asthma interventions do not seem to influence the natural history of the disease or induce long-term remission.

Another limitation of targeted treatment in asthmatic patients is the interindividual and intraindividual variation in response, which is called the dissociated effect.⁷ This might be due to the (epi)genetic background, the predominant immune-inflammatory pathway, and the contribution from remodeled tissue. Drug efficacy at the target site adds to the observed variability in response.

In summary, recent therapeutic advances have unraveled some of the contributions of phenotype and endotype to the pathogenesis of asthma and the responses to specific therapies. However, more information is needed to better target specific pathways in subjects that will optimize the patient's therapeutic responses while avoiding adverse effects.

PRECISION MEDICINE AT THE UPPER AIRWAYS: RHINITIS

The current definition of rhinitis relies on the combination of history, clinical examination, and allergy diagnostic testing, which allows the distinction of 3 major subgroups: allergic, infectious, and nonallergic noninfectious rhinitis.^{70,71}

Rhinitis phenotypes were described in relation to the severity and duration of symptoms, major presenting symptoms, sensitization pattern, presence of comorbidities, and level of control

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,⁷² highlighting the need for precision medicine in patients with AR. Precision medicine implicates 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).^{73,74}

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,⁷⁵ 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 AR⁷⁶; 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.^{77,78}

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.⁷⁹

Neurogenic rhinitis

This particular endotype is characterized by a relative overexpression of transient receptor potential channels on trigeminal nerves and high concentrations of substance P and neurokinins and is linked to gustatory rhinitis, rhinitis of the elderly, and idiopathic rhinitis with nasal hyperreactivity.⁸⁰

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.⁸¹

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

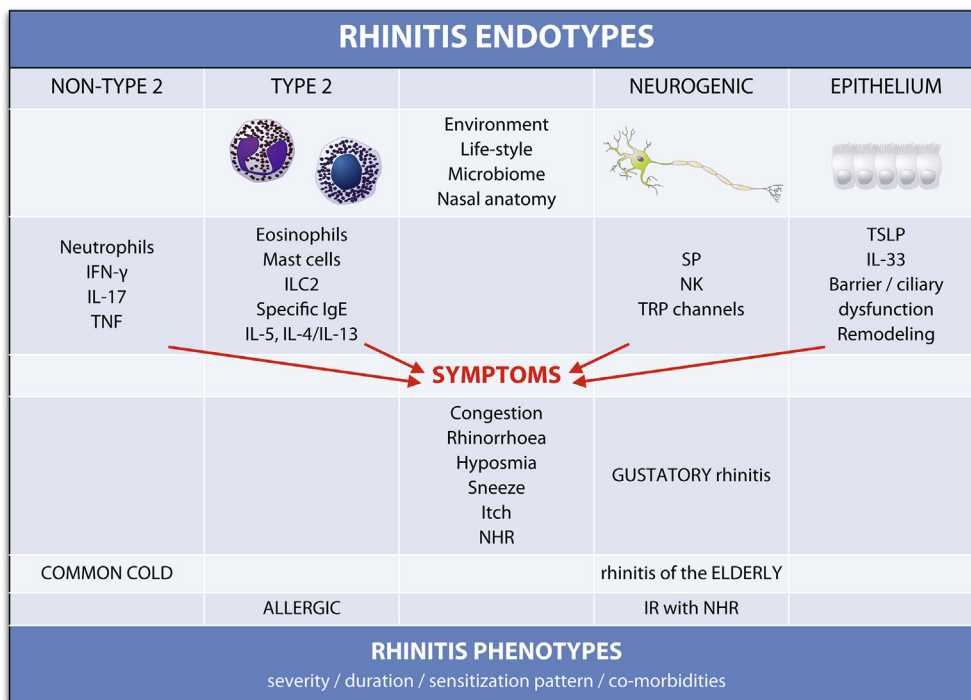


FIG 4. Overview of rhinitis phenotypes and endotypes. Similar to asthma, a type 2 immune response and non-type 2 immune response endotype can be described for rhinitis. Neurogenic and epithelial barrier dysfunction endotypes are particularly relevant for rhinitis. *ILC*, Innate lymphoid cell; *IR*, idiopathic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

and blood eosinophil, nasal eosinophil, and neutrophil counts. 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.^{82,83} Another example of endotype-driven treatment is the highly successful intervention with capsaicin for the neurogenic endotype.⁸⁰

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](#).

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 autoreactivity, and comorbidities (asthma, rhinitis, food allergy, and infections).⁸⁴

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 pathophysiologic pathways⁸⁴⁻⁸⁶ from which we can learn and develop a strategy for discovery, validation, and qualification of biomarkers.⁸⁷

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 T_H1 -, T_H17 -, and T_H22 -driven inflammation and epithelial dysfunction.^{84,86,88,89}

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

TABLE III. Essential steps for applying precision medicine in patients with rhinitis

- Precise evaluation of the patient's perception of disease severity and effect of the disease on the patient's quality of life, as well as the social and general environment of the patient
- Clear-cut dissection of nasal pathophysiology into mucosal and structural components
- Rigorous assessment of inflammatory components (eg, eosinophilic vs neutrophilic inflammation, IgE, cytokines, and neural mediators) and functional effects (nasal hyperreactivity, smell, and patency)
- Correct evaluation of the risk for disease progression
- Proper information for the patient on the treatment strategy (monotherapy vs combined therapy), involving information on treatment goals, expected benefits and adverse events, and effects of treatment in the long-term together with evaluation of the patient's preference for a particular therapeutic plan

Type 2 and non-type 2 immune responses are common pathogenic pathways and disease endotypes for asthma, rhinitis, and AD. Epithelial dysfunction is of particular relevance for describing disease endotypes in patients with rhinitis and AD, whereas the neurogenic pathway is most prominent for rhinitis.

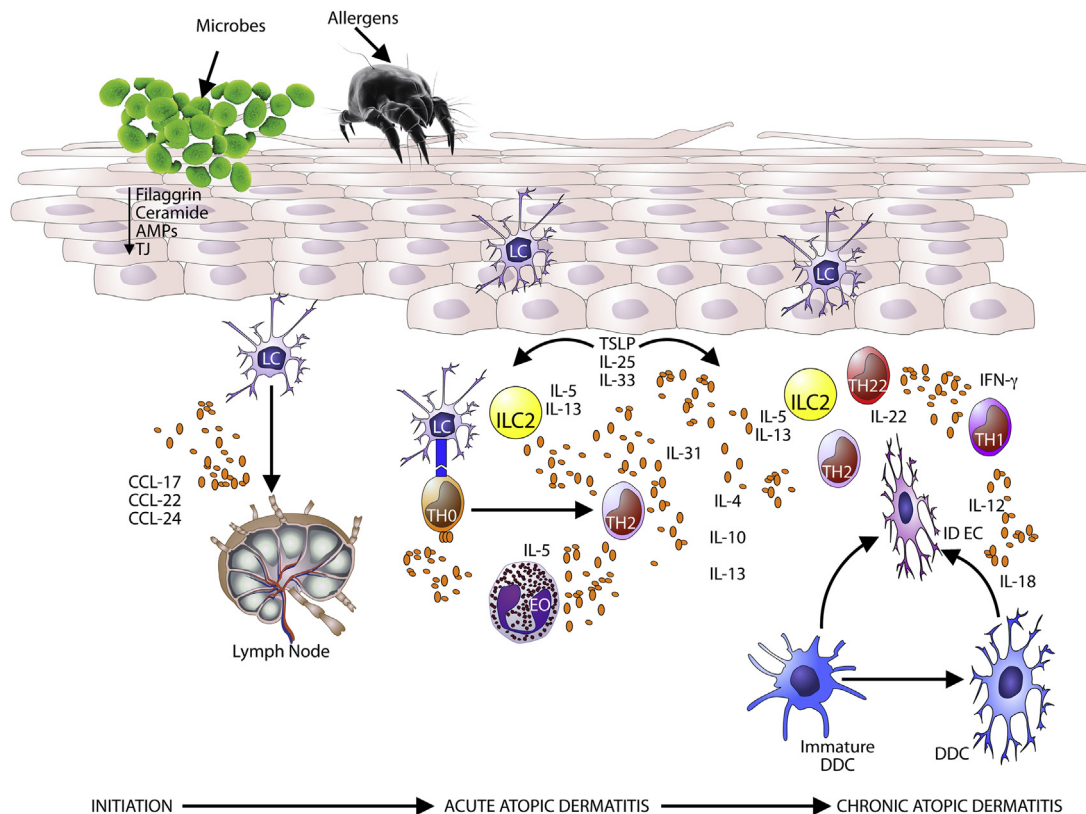


FIG 5. Pathogenesis of AD. The complexity of the clinical phenotype in patients with AD is underlined by complex profiles of different pathophysiologic pathways connecting the innate and the adaptive immune response with epithelial barrier dysfunction and allergic sensitization. *AMPs*, Antimicrobial peptides; *DDC*, dermal dendritic cell; *Eo*, eosinophil; *ID EC*, inflammatory dendritic epidermal cell; *ILC*, innate lymphoid cells; *LC*, Langerhans cell; *TJ*, tight junctions.

opportunities for more personalized management.^{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,^{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).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.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.^{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

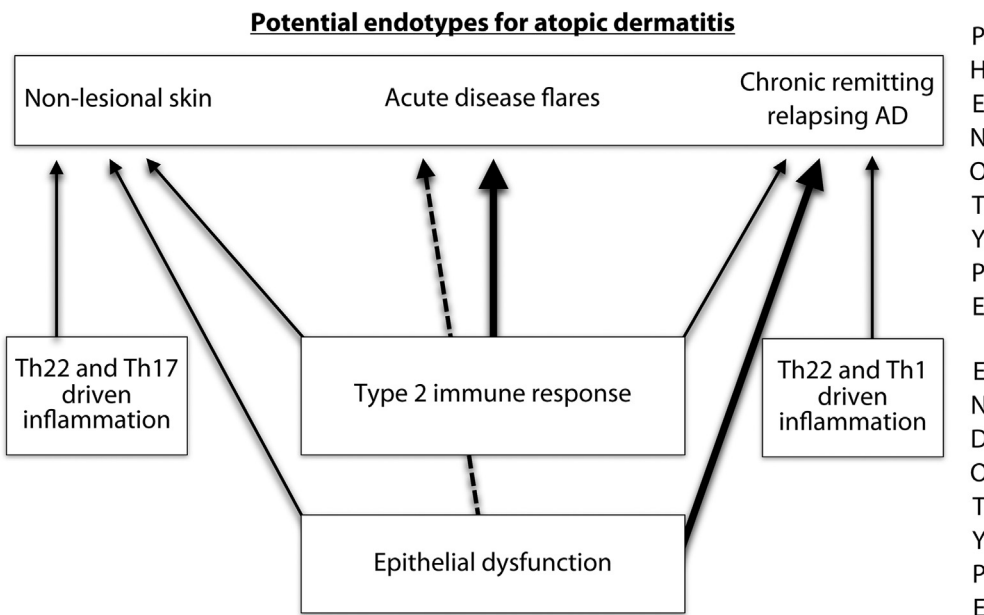


FIG 6. Proposed endotypes for AD. Three main phenotypes of AD are described: nonlesional skin, acute disease flares, and chronic remitting relapsing AD. A type 2 immune response is present in all 3 phenotypes, with a peak in acute disease flares. T_H22 - and T_H17 -driven inflammation adds to the type 2 immune response in the dysregulated immune response present in nonlesional skin, whereas T_H22 - 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.

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

Asthma	AR	AD
Type 2 immune response	Type 2 immune response	Type 2 immune response
Non-type 2 immune response	Non-type 2 immune response	Non-type 2 immune response
	Epithelial dysfunction Neurogenic	Epithelial dysfunction

representing a disease-modifying strategy.⁹⁰ 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.⁹¹ 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

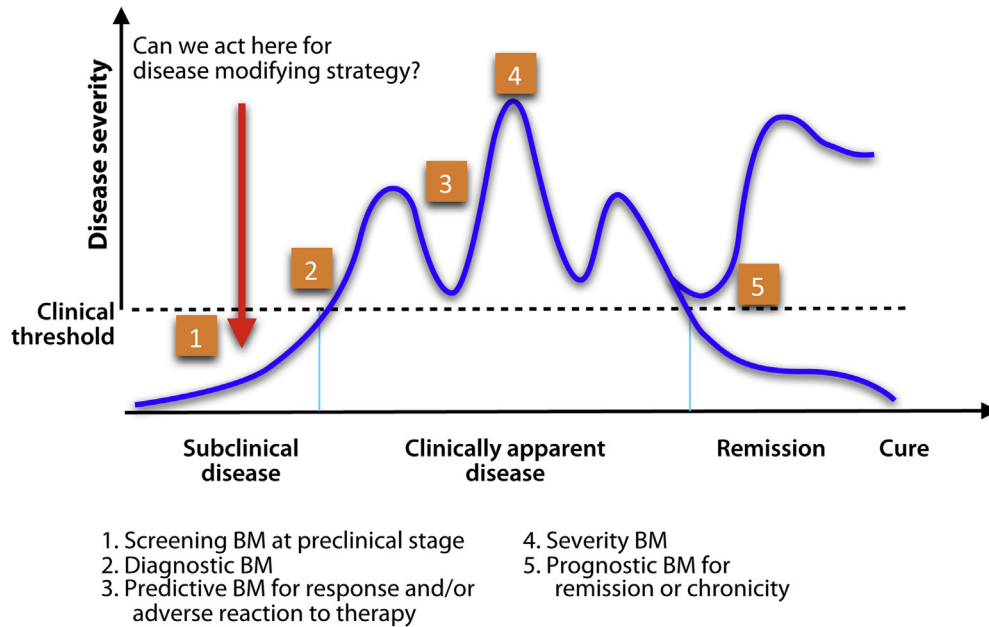


FIG 7. The concept of longitudinal biomarkers (BM) in the management of AD at different time points throughout the natural history of the disease. Early stage BM (stages 1 and 2) allows screening at the preclinical stage and primary prevention of the disease together with early diagnosis. During the clinical course of the disease, biomarkers can predict responses, adverse reactions, or both to treatment and can guide targeted, endotype-driven interventions with an improved safety profile. Prognostic biomarkers relate to disease severity, disease flares, or occurrence of remission.

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.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.

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