

REVIEW ARTICLE

Precision medicine in united airways disease: A “treatable traits” approach

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Abstract

United airways disease (UAD) is the concept that the upper and lower airways, which are anatomically and immunologically related, form a single organ. According to this concept, upper and lower airway diseases are frequently comorbid because they reflect manifestations of a single underlying disease at different sites of the respiratory tract. Allergic asthma-allergic rhinitis is the archetypal UAD, but emerging data indicate that UAD is a heterogeneous condition and consists of multiple phenotypes (observable clinical characteristics) and endotypes (pathobiologic mechanisms). The UAD paradigm also extends to myriad sinonasal diseases (eg, chronic rhinosinusitis with or without nasal polyps) and lower airway diseases (eg, bronchiectasis, chronic obstructive pulmonary disease). Here, we review currently known phenoendotypes of UAD and propose a “treatable traits” approach for the classification and management of UAD, wherein pathophysiological mechanisms and factors contributing to disease are identified and targeted for treatment. Treatable traits in UAD can be analyzed according to a framework comprising airway inflammation (eosinophilic, neutrophilic), impaired airway mucosal defense (impaired mucociliary clearance, antibody deficiency), and exogenous cofactors (allergic sensitizers, tobacco smoke, microbes). Appreciation of treatable traits is necessary in advancing the effort to deliver precise treatments and achieve better outcomes in patients with UAD.

KEYWORDS

asthma, bronchiectasis, COPD, ENT (rhinitis, nasal polyps), united airways disease

1 | INTRODUCTION

The respiratory tract is divided into the upper and lower airways at the level of the vocal cords. Despite this artificial distinction, they are anatomically contiguous and immunologically related. United airways disease (UAD) is the concept that upper and lower airways form a single organ, with upper and lower airway diseases co-occurring frequently because they reflect different manifestations of a single underlying disease process.¹ Possible mechanisms linking the upper and lower airways include aspiration of nasal inflammatory cells and mediators into the tracheobronchial tree, hematogenous

propagation of inflammatory mediators from one part of the airway to another, stimulation of bone marrow progenitor cells, or the naso-bronchial reflex.²

The archetypal UAD is allergic asthma-rhinitis, but emerging data indicate that UAD is complex and heterogenous, and may present with other clinical phenotypes of sinonasal disease (eg, chronic rhinosinusitis with or without nasal polyps) and lower airway disease (eg, bronchiectasis, chronic obstructive pulmonary disease [COPD]). Even within a given clinical phenotype, there is further variability based on the underlying pathobiologic mechanisms, known as endotypes. Current guideline-based management approaches (summarized

in Table 1) stratify patients according to symptoms, disease control, future risk, and occasionally broad clinical phenotypes, but do not sufficiently consider complexity and variability in other important dimensions such as airway inflammation, airway mucosal defense, and exogenous cofactors. Failure to recognize this complexity or treat both upper and lower compartments of the airways inevitably leads to suboptimal outcomes for patients.

The treatable traits approach has been described for lower airway diseases,³ and in this review, we extend its application to combined upper and lower airway disease. We summarize the current evidence for known clinicopathobiologic subtypes ("phenoendotypes") of UAD. We have grouped the clinical manifestations of UAD according to the "treatable traits" of airway inflammation, airway mucosal defense dysfunction, and exogenous cofactors (Figure 1 and Table 2). These traits are not mutually exclusive and multiple traits may contribute to disease in an individual at any one point in time. Treatable traits may also vary over time. It is with the intention of drawing the readers' attention to traits that are common to both airway compartments that we have artificially classified the upper and lower airway conditions as presented in this review. We believe that targeting common disease processes, when used in combination with current patient stratification approaches, is likely to lead to clinical improvements at both sites of the respiratory tract.

2 | AIRWAY INFLAMMATION

Airway inflammation is important in the pathogenesis of many upper and lower airway diseases. It is a dynamic trait which varies over time and is modulated by factors such as treatment, infection, environmental exposures, and natural history of disease.⁴ Clinicians commonly assume that asthma and chronic rhinosinusitis with nasal polyps (CRSwNP) are stereotypically eosinophilic in nature, and that chronic rhinosinusitis without nasal polyps (CRSsNP) or COPD is stereotypically neutrophilic. As discussed below, while these generalizations may hold true for many cases there is substantial variability in the underlying pathophysiological mechanisms for each clinical phenotype or disease. Identification and quantification of airway inflammation can help to direct appropriate treatment. Current methods to assess upper and lower airway inflammation are summarized in Table 3.

2.1 | Allergic asthma-rhinitis

The link between allergic asthma and allergic rhinitis (AR) is well established. Up to 40% of AR patients have asthma and almost all patients with asthma have AR.⁵ Many patients with AR also exhibit nonspecific bronchial hyperresponsiveness.⁶

IgE-mediated hypersensitivity to aeroallergens results in type 2/eosinophilic inflammation in the respiratory tract, manifesting as rhinitis in the upper airways and asthma in the lower airways. Upon allergen exposure, sensitization occurs whereby specific IgE (sIgE)

are generated, circulate in the blood, and attach to the surface of mast cells and basophils, including those that reside in the airway mucosa. Subsequent exposure to allergen triggers mast cells degranulation, release of chemical mediators, and synthesis of leukotrienes and cytokines, resulting in an immediate allergic airway reaction. The late phase response involves Th2 lymphocyte recruitment with production of inflammatory cytokines such as IL-4, IL-5, and IL-13, as well as activation of eosinophils.

The central role of sIgE in allergic asthma-rhinitis is highlighted by a population-based birth cohort study showing that presence of peripheral blood sIgE directed against common allergens is associated with increased odds of asthma and rhinitis in childhood.⁷ In adults with AR, experimental nasal provocation with house dust mite allergens induces not only nasal eosinophilia but also bronchial eosinophilic inflammation, bronchoconstriction, and bronchial hyperresponsiveness,⁸ suggesting inflammatory crosstalk between upper and lower airways.

The allergic asthma-rhinitis phenoendotype usually begins in childhood and can be identified by measuring peripheral blood total IgE which is elevated, *plus* demonstration of atopy by the presence of raised sIgE levels in blood or skin prick test positivity. Omalizumab, an anti-IgE monoclonal antibody, is efficacious for both severe allergic asthma⁹ and uncontrolled AR.¹⁰ Therapeutic response to omalizumab is predicted by higher baseline periostin levels and reduced free serum IgE levels during period of treatment.¹¹

In some cases, specific causative allergens can be identified and targeted with allergen immunotherapy. In both AR¹² and allergic asthma,¹³ immunotherapy improves symptoms and reduces the need for pharmacotherapy in the short term, albeit with limited evidence for longer-term efficacy. Treatment of AR patients with grass pollen sublingual immunotherapy tablets was associated with slower AR progression, less frequent asthma onset, and slower asthma progression.¹⁴ Candidate biomarkers that can identify and/or predict response to allergen immunotherapy include the sIgE:total IgE ratio, specific IgG4 and IgE-FAB.¹⁵

2.2 | Local allergic rhinitis-non-allergic asthma: local mucosal IgE production

A subset of asthma and rhinitis patients demonstrate type 2/eosinophilic allergic airway responses mediated by sIgE which is produced and sequestered in the airway mucosa, with skin prick test non-reactivity and no detectable circulating sIgE in peripheral blood. In the upper airway, this phenoendotype is known as local allergic rhinitis (LAR), a distinct entity characterized by local production of sIgE in the nasal mucosa without evidence of systemic atopy. LAR does not appear to represent a *forme fruste* of AR,¹⁶ and is associated with increased risk of asthma compared to healthy individuals without LAR.¹⁷

The lower airway analog of LAR may correspond to a subtype of non-allergic asthma which is currently not well defined, but whose existence is supported by studies (Supporting Information: References S1-S4). In the aforementioned entity, intramucosal IgE

TABLE 1 Current guideline-based approaches for stratification and treatment of patients with airway diseases

Site	Disease	Approach to stratification of patients and selection of therapies	Patient stratification groups	Recommended treatments according to patient stratification	Other possible treatments
Upper airway	Allergic rhinitis	Depends on symptoms, time course, severity, control, patient preferences, availability of treatment, and cost. One approach is a step-up/step-down approach based on assessment of control	Step 1: mild symptoms	Intranasal or oral non-sedating H ₁ -antihistamines	Leukotriene antagonists Allergen and irritant avoidance Allergen immunotherapy Nasal filters or saline
			Step 2: moderate-to-severe symptoms or persistent AR	Intranasal corticosteroids	
			Step 3: uncontrolled at step 2 (current or historical)	Combination intranasal corticosteroids and intranasal H ₁ -antihistamines	
			Step 4: uncontrolled at step 3	Short course oral steroids	
Chronic rhinosinusitis	Chronic rhinosinusitis	Based on clinical phenotype	CRSsNP	Intranasal corticosteroids	Saline irrigation Sinus surgery for medically refractory disease
				Antibiotics (second line)	
			CRSwNP	Consider short course of oral steroids	
				Intranasal corticosteroids	
Lower airway	Asthma	Assessment of symptoms, exacerbations, and lung function followed by stepwise escalation/de-escalation of therapy	Step 1 Step 2 Step 3 Step 4 Step 5	Short course of oral steroids	Leukotriene receptor antagonists Theophylline Allergen avoidance Allergen immunotherapy for patients with allergic rhinitis and sensitized to house dust mites, frequent exacerbations, and FEV ₁ > 70% Vaccinations Weight reduction for obese asthma patients
				Antibiotic if suspicion of infection	
				Consider leukotriene receptor for acetylsalicylic acid sensitivity	
				Consider low-dose ICS	
				Low-dose ICS	
				Low-dose ICS + LABA	
				Medium-/high-dose ICS + LABA	
				Low-dose oral corticosteroids	
				Add-on treatments: tiotropium, anti-IgE, anti-IL5, bronchial thermoplasty	
				Patients may benefit from phenotyping and endotyping at Step 5	

(Continues)

TABLE 1 (Continued)

Site	Disease	Approach to stratification of patients and selection of therapies	Patient stratification groups	Recommended treatments according to patient stratification	Other possible treatments
	Chronic obstructive pulmonary disease	Assessment of symptoms (CAT, mMRC), exacerbations, airflow obstruction (FEV ₁)	Group A (CAT < 10, mMRC < 2, infrequent exacerbations)	Bronchodilator	Smoking cessation (including pharmacologic treatment) Education, self-management, and pulmonary rehabilitation
			Group B (CAT ≥ 10, mMRC ≥ 2, infrequent exacerbations)	LABA or LAMA Increase to LABA + LABA if persistent symptoms	Pneumococcal and influenza vaccinations Long-term oxygen therapy in the presence of severe resting hypoxemia
			Group C (CAT < 10, mMRC < 2, frequent exacerbations)	LAMA Increase to LABA + LABA or change to LABA + ICS if further exacerbations	Long-term noninvasive ventilation for patients with severe chronic hypercapnia and a history of hospitalization for acute respiratory failure
			Group D (CAT ≥ 10, mMRC ≥ 2, frequent exacerbations)	LAMA + LABA Increase to LABA + LABA + ICS if persistent symptoms/further exacerbations Consider macrolides Consider roflumilast if FEV ₁ < 50% predicted and patient has chronic bronchitis	Bronchoscopic or surgical lung volume reduction surgery for selected patients
Bronchiectasis	Assessment of microbial infection, exacerbations and airflow symptoms		<i>Pseudomonas aeruginosa</i> infection with frequent exacerbations	Long-term inhaled antibiotic treatment Escalate to combined oral and inhaled antibiotic treatment if inadequate response	Physiotherapy, pulmonary rehabilitation, and/or airway clearance
			Non- <i>Pseudomonas aeruginosa</i> infection with frequent exacerbations	Long-term macrolide treatment Escalate to combined oral and inhaled antibiotic treatment if inadequate response	Pneumococcal and influenza vaccinations Long-acting bronchodilators for patients with significant breathlessness
			Multiple sequential airway treatments	Short- or long-acting bronchodilators → Mucolytic/physiotherapy adjuncts → airway clearance → inhaled antibiotics	

AR, allergic rhinitis; CAT, COPD Assessment Tool; CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps; FEV₁, forced expiratory volume in one second; ICS, inhaled corticosteroids; ICS + LABA, combination inhaled corticosteroids and long-acting beta agonist; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; mMRC, modified Medical Research Council dyspnea score.

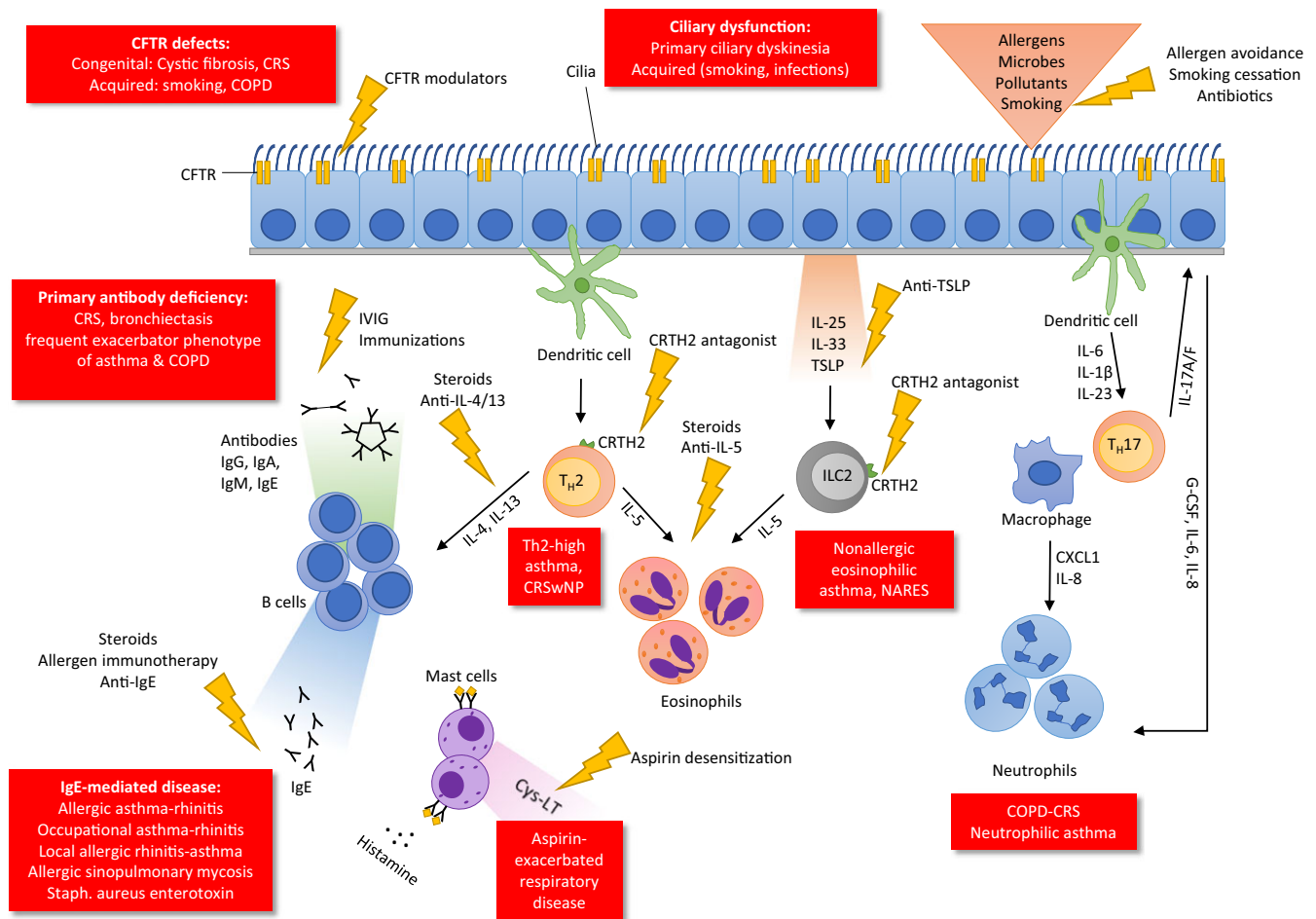


FIGURE 1 Treatable traits in global airways disease. Derangements in airway inflammation (allergic and non-allergic eosinophilic, neutrophilic, or leukotriene-mediated), airway mucosal defense (primary antibody deficiency, ciliary dysfunction, or cystic fibrosis transmembrane regulator [CFTR] dysfunction) and exogenous cofactors (specific allergens, microbes, or pollutants—depicted in the upper right triangle) are associated with specific upper and lower airway disease phenoendotypes, listed in the red boxes. Potential targeted treatments are depicted by the lightning bolts

synthesis is observed in the lower airways, and functional sIgE can be found in the sputum despite negative skin prick tests and blood sIgE levels. Bronchial inhalational challenge with allergen induces a clinical lower airway allergic response characterized by sputum eosinophilia and bronchial hyperresponsiveness.

It is not known why individuals with allergic asthma-rhinitis demonstrate positive skin prick tests and elevated sIgE in blood, whereas non-allergic asthmatics and patients with LAR do not although local mucosal IgE synthesis occurs in all those conditions. One possibility is that local mucosal IgE synthesis may not reach sufficient quantities to spill over into peripheral blood. Alternatively, IgE may be sequestered within the bronchial mucosa. Regardless, efficacy of omalizumab has been shown in non-atopic asthma with evidence of local mucosal IgE production. Pillai et al. (Supporting Information: References S5) randomized 18 such subjects and obtained bronchial biopsies from subjects before and after treatment with 12–14 weeks of omalizumab. The patients subsequently underwent supervised dose reduction of their regular asthma therapy. Compared to placebo, omalizumab therapy significantly

reduced total bronchial mucosal IgE⁺ cells. Lung function declined in the placebo-treated group but improved in the omalizumab-treated group. This small but important study serves as proof-of-concept that anti-IgE can target disease associated with local mucosal IgE production.

2.3 | Non-allergic rhinitis with eosinophilia syndrome-non-allergic eosinophilic asthma

Type 2 (eosinophilic) inflammation can occur in UAD without evidence of IgE-mediated hypersensitivity. In the upper airways, this endotype has been termed non-allergic rhinitis with eosinophilia syndrome (NARES) and is characterized by persistent rhinitis and marked eosinophilia of the nasal mucosa in the absence of local or systemic IgE production, suggesting allergen-independent induction of eosinophilic airway inflammation.¹⁸ Almost half of patients with NARES who do not report asthmatic symptoms nevertheless demonstrate bronchial hyperresponsiveness and sputum eosinophilia, supporting a link between NARES and asthma.¹⁹

TABLE 2 Phenoendotypes of global airways disease

Trait	Endotype/pathophysiology	Method of assessment/biomarker	Clinical phenotype		Targeted treatment
			Upper airway	Lower airway	
Inflammation					
Eosinophilic, high type 2/T _H 2-cytokines	IL-4, IL-5, IL-13	Blood periostin, high FeNO, sputum eosinophilia, blood eosinophilia	CRSwNP	Eosinophilic asthma	Corticosteroids (systemic, inhaled, intranasal), anti-IL-5, IL-4, IL-13, anti-TSLP, ?CRTh2 antagonist
Allergic, systemic	CD4+ T _H 2 cells	Blood total IgE, blood specific IgEs, skin prick tests	Allergic rhinitis	Allergic asthma	Allergen avoidance, corticosteroids, antileukotrienes, anti-IgE, immunotherapy
Allergic, local	Local nasal and bronchial mucosa specific IgE production	Blood total IgE not raised, negative blood specific IgEs, negative skin prick tests, local IgE and specific IgE production, nasal allergen provocation test	Local allergic rhinitis	Intrinsic asthma	?Omalizumab, ?immunotherapy
Non-allergic eosinophilic	IL-25, IL-33, TSLP, group 2 innate lymphoid cells	Blood periostin, high FeNO, sputum eosinophilia, blood eosinophilia, non-reactive skin prick tests, absent specific IgE in blood	Non-allergic rhinitis with eosinophilia syndrome (NARES)	Adult onset eosinophilic asthma	Anti-TSLP, anti-IL-4, IL-5, IL-13, ? CRTh2 antagonist
Neutrophilic	T _H 17 cells, IL-17, CXCL1, CXCL8	IL-8, sputum neutrophilia	CRSsNP	COPD, neutrophilic asthma	Smoking cessation, macrolides
Impaired airway mucosal defense					
Cystic fibrosis	Autosomal recessive disorder in CFTR gene leading to improper salt balance and viscous airway surface liquid	Genetic testing, sweat chloride test	CRSwNP (acid mucin)	Bronchiectasis	CFTR modulators
Primary ciliary dyskinesia	Autosomal recessive mutations causing dynein and radial spoke defects	Low nasal nitric oxide, ciliary motion and ultrastructure	CRSsNP	Bronchiectasis	No validated PCD-specific therapies
Primary antibody deficiency	Deficient immunoglobulins or functional antibody response	Quantitative serum immunoglobulin levels, functional antibody responses	CRS	Bronchiectasis	Immunoglobulins, vaccinations
Exogenous cofactors					
Occupational exposures	High molecular weight sensitizers: IgE-mediated type 2 inflammation Low molecular weight sensitizers: haptens Irritant-induced: no immunological reaction	Total IgE, skin prick tests Peak flow monitoring Specific bronchoprovocation challenge	Occupational rhinitis, reactive upper airways dysfunction syndrome	Occupational asthma, reactive airways dysfunction syndrome	Exposure avoidance, respiratory protection devices, ?anti-IgE

(Continues)

TABLE 2 (Continued)

Trait	Endotype/pathophysiology	Method of assessment/biomarker	Clinical phenotype		Targeted treatment
			Upper airway	Lower airway	
Aspirin/non-steroidal anti-inflammatories	Constitutive overexpression of 5-lipoxygenase and leukotriene C4 synthase	Aspirin/NSAID challenge, urinary leukotriene E4	CRSwNP	Severe asthma	Avoidance, desensitization, antileukotrienes
<i>Staphylococcus aureus</i> enterotoxin	Superantigens elicit Th1, Th17 and Th2 cytokines, including IL-4, IL-5, IL-13	<i>Staph aureus</i> enterotoxin IgE's	CRSwNP	Severe asthma	?anti-IgE
<i>Aspergillus</i> /fungal hypersensitivity	Th2 cells, IL-4, IL-5, IL-13, IgE, eosinophilia	<i>Aspergillus</i> skin test positivity, <i>Aspergillus</i> specific IgE, IgE > 1000 IU/mL, Blood eosinophil >500/ μ L, precipitating antibodies to <i>Aspergillus</i>	Allergic fungal rhinosinusitis	Allergic bronchopulmonary aspergillosis (asthma, bronchiectasis)	Steroids, antifungal, ?anti-IgE
Upper respiratory tract infection	Variable depending on microbe and underlying disease	Respiratory cultures and nucleic acid tests	Exacerbation of rhinitis/rhinosinusitis	Exacerbation of asthma, COPD or bronchiectasis	Antivirals, antibiotics, vaccinations

Typical upper and lower airway clinical phenotypes associated with underlying treatable traits are listed. Taxonomy based on clinical phenotypes has significant limitations: each phenotype may represent comprise treatable traits, for example, CRSwNP and asthma may be neutrophilic or eosinophilic inflammation depending on the population studied. Hence, a more precise approach is needed to identify contributory treatable trait(s) in each case, which can aid in selection of targeted treatments. Question mark (?) indicates targeted therapies under investigation. Treatable traits and targeted therapies may be used to complement the current approaches for patient stratification and treatment selection—including non-targeted treatments—shown in Table 1.

The corresponding asthma phenoendotype is non-allergic eosinophilic asthma, in which eosinophilic inflammation and type 2 cytokine production are not driven by allergen-activated Th2 lymphocytes, but is instead postulated to be initiated by type 2 innate lymphoid cells (ILC2).²⁰ ILC2s are a recently discovered population of lymphocytes capable of producing large amounts of type 2 cytokines (IL-5 and IL-13) and orchestrate eosinophilic inflammation in the absence of adaptive immunity, including Th2 cells, B cells, and IgE antibody.²¹ ILC2s are activated by epithelium-derived cytokines IL-25, IL-33, and thymic stromal lymphopoietins (TSLP), which are released by epithelial cells in response to epithelial damage caused by a wide range of stimuli including microbiota and pollutants. ILC2s are increased in peripheral blood in eosinophilic asthmatics compared to non-eosinophilic asthmatics and their numbers in sputum correlate with eosinophil counts.²² Increased ILC2s has also been observed in eosinophilic nasal polyps,²³ but evidence for the involvement of ILC2 cells in NARES and non-allergic eosinophilic asthma is lacking and should be the focus of future studies.

Potential targeted treatments for this pathway include monoclonal antibodies targeting any of the type 2 cytokines, discussed in the section below. TSLP, targeted by the monoclonal antibody tezepelumab, was shown in a recent dose-ranging proof-of-concept study to reduce exacerbations in patients with uncontrolled asthma, including in those with low IgE (<100 IU/mL).²⁴ Antagonists of CRTH2, the receptor for prostaglandin D2 on ILC2 cells, are currently undergoing evaluation to assess clinical efficacy (Supporting Information: References S6, S7).

2.4 | Asthma-chronic rhinosinusitis

Chronic rhinosinusitis (CRS) is broadly defined as an inflammatory disorder of the paranasal sinuses and mucosa of the nasal passages that lasts 12 weeks or longer. The condition is heterogeneous, with 2 broad clinical phenotypes, with nasal polyps (CRSwNP) and without nasal polyps (CRSsNP), as well as diverse endotypes.²⁵

Epidemiologic studies have demonstrated higher prevalence of CRS in asthmatics compared to non-asthmatics across different populations.^{26,27} However, the inflammatory endotype of CRS varies according to the population being studied. In Caucasian subjects, CRSwNP is predominantly eosinophilic and CRSsNP is predominantly neutrophilic, whereas in Chinese subjects CRSwNP is mainly neutrophilic, with fewer Chinese subjects demonstrating eosinophilic nasal polyps.²⁸

Various studies have elucidated the detailed phenoendotypes of either CRS or asthma separately, but there is a paucity of data about phenoendotypes of combined asthma-CRS. Despite this, phenoendotypes of asthma and CRS are remarkably analogous to each other. Based on sputum inflammatory cells, asthma can be eosinophilic, neutrophilic, mixed eosinophilic and neutrophilic, or paucigranulocytic.²⁹ Based on bronchoepithelial cell gene expression profiles, asthma inflammatory signatures can be partitioned into "Th2 high" (associated with elevated IL-4, IL-5, IL-13, sputum, and blood eosinophilia) or "Th2 low".³⁰ CRS endotypes can be similarly

TABLE 3 Methods for assessing airway inflammation in united airways disease

Method	Comments	Strengths	Limitations
Nasal lavage	Luminal proteins, cytokines and cells	Simple and safe Correlates with, but less invasive than induced sputum	Variable fluid recovery and dilution with lavages No sampling of the epithelium
Nasal brush or scraping	Samples the nasal epithelium	Simple and minimally invasive	Does not sample deeper layers of the mucosa or the nasal lumen
Nasal biopsy	Identifies tissue inflammatory cellular subtypes of rhinitis or rhinosinusitis	Samples the total nasal mucosa	Technically difficult No information about nasal lumen
Blood periostin	Marker of Th2, eosinophilic airway inflammation Predicts severity of chronic rhinosinusitis Predicts chronic rhinosinusitis with nasal polyps phenotype	Noninvasive	Not widely available Conflicting evidence on whether periostin is associated with sputum eosinophilia
Sputum induction	Neutrophil count $\geq 65\%$ or $>500 \times 10^4/\text{mL}$ identifies neutrophilic airway inflammation Eosinophil count $\geq 3\%$ identifies eosinophilic airway inflammation	Noninvasive Well-validated	Not widely available Logistically, technically and practically difficult High failure rate Risk of inducing bronchoconstriction
Peripheral blood eosinophils	Eosinophil count $\geq 2\%$ identifies eosinophilic airway inflammation	Noninvasive, minimal risk Widely available, cheap Predicts with important clinical outcomes such as exacerbation risk and response to treatment	Wide diurnal variation of readings (40%) within the same subject May not be applicable when only local mucosal inflammation occurs
Fractional exhaled nitric oxide (FeNO)	FeNO < 25 ppb indicates low likelihood of airway eosinophilia FeNO > 47 ppb suggests eosinophilic airway inflammation and corticosteroid responsiveness	Noninvasive Quick, easy, and safe to perform	Readings may be affected by smoking, respiratory tract infections Sputum eosinophilia and FeNO are not always concordant
Urinary leukotriene E4 (LTE4)	Marker of cysteinyl leukotriene activity Higher levels observed in aspirin-exacerbated respiratory disease	Collection of urine is simple and of no risk	Special equipment and training are required to measure LTE4

classified into “IL-5 high” and “IL-5 low” clusters.³¹ Subjects with IL-5 high CRS have high eosinophilic cationic protein and IgE from nasal specimens, and present clinically with CRSwNP and asthma. Low IL-5 clusters clinically exhibit the CRSsNP phenotype.

“IL-5 high” CRS appears to be the upper airway analog of “Th2-high” asthma. The inflammatory pattern of the upper and lower airways in patients with nasal polyps and comorbid asthma was evaluated in a recent study using nasal polyp biopsies and exhaled nitric oxide.³² Approximately, two-thirds of patients were eosinophilic and one-third was non-eosinophilic, with concordance demonstrated between the upper and lower airways in individual subjects. More studies are needed to clarify concordance between upper and lower airway phenotypes across the spectrum of inflammatory endotypes in asthma and CRS.

Systemic, inhaled, or intranasal corticosteroids are cost-effective treatments for eosinophilic upper and lower airway inflammation. In cases that are refractory to corticosteroids or in patients who are unable to tolerate high doses of corticosteroids, several biologics targeting eosinophilic inflammation can be considered, such as anti-IL-13 (tralokinumab), anti-IL-5 (mepolizumab and reslizumab), antibodies against alpha chain of IL-5 receptor (benralizumab), and alpha subunit of the IL-4 receptor (dupilumab). Mepolizumab is efficacious in both eosinophilic nasal polyposis and severe eosinophilic asthma,^{33,34} reducing polyp burden and need for surgery in the former and reducing exacerbations in the latter. Similarly, dupilumab was demonstrated in small phase 2 trials to reduce polyp burden in patients with chronic sinusitis and nasal polyposis,³⁵ and was found to decrease exacerbations and improve forced expiratory volume in one second (FEV₁) in patients with severe eosinophilic asthma.³⁶ Patients with asthma and nasal polyps show greater improvement in Asthma Control Questionnaire score with reslizumab compared to asthmatics without nasal polyps.³⁷

2.5 | Chronic obstructive pulmonary disease-chronic rhinosinusitis

Chronic obstructive pulmonary disease is a disease characterized by chronic respiratory symptoms and persistent airflow limitation caused by significant exposure to noxious particles or gases, most commonly tobacco smoke. Although COPD has traditionally been thought to be a purely lower airway disease, there is increasing evidence to suggest frequent concomitant involvement of the upper airways.

Multiple epidemiologic studies have shown a high prevalence of nasal symptoms among COPD patients. An early population-based epidemiologic study conducted in the Swedish general population in 1992 found that 40.1% of individuals with self-reported chronic bronchitis or emphysema had symptoms of rhinosinusitis, compared with 32.7% in the total study sample.³⁸ In a follow-up study in 2000, those who reported thick, yellow, nasal discharge and nasal blockage in 1992 had a higher incidence of COPD diagnosis over an 8-year follow-up period.³⁹ Another cross-sectional population-based Canadian study also found an association between CRS and COPD, both self-

reported.⁴⁰ Self-report may lead to misclassification errors of COPD and sinonasal disease but are an inherent limitation of large-scale epidemiologic studies. Medical record diagnoses, which are considered more reliable than self-reported medical history, were used in one study from Taiwan which extracted International Classification of Diseases diagnostic codes from a national insurance database and found an increased risk of CRSsNP among COPD patients.⁴¹

Recent studies have utilized more stringent and objective criteria for classifying COPD and rhinosinusitis. Bergqvist et al.⁴² used spirometry for identifying COPD, defined as FEV₁/forced vital capacity (FVC) ratio <0.7, and found that the 5-year incidence of nasal symptoms without having a cold was higher in subjects who demonstrated obstruction on spirometry compared to subjects without baseline spirometric evidence of airflow limitation. Hansen et al.⁴³ evaluated the prevalence of paranasal sinus opacification at magnetic resonance imaging in COPD and asthma patients compared to a control group. COPD was defined using similar spirometric criteria as the Bergqvist et al study, whereas asthma was self-reported. COPD and asthma patients were, respectively, found to be 6 and 2 times more likely than healthy controls to demonstrate paranasal sinus opacification. These findings support the link between upper and lower airway diseases in both asthma and COPD, but we cannot conclude from this study that the association with sinonasal disease is stronger for COPD than for asthma because misclassification bias may have occurred among asthma patients, who were diagnosed based on self-report instead of objective evidence of variable airflow limitation. Similarly, uncontrolled COPD cohort studies have also found a high prevalence of up to 75% of sinonasal disease, when using spirometry for COPD diagnosis and CT paranasal sinuses for diagnosis of CRS.^{44,45} An important limitation of all the aforementioned studies is the use of prebronchodilator, instead of postbronchodilator, FEV₁/FVC ratio for identifying cases of COPD. Such a definition could result in other obstructive lung diseases (such as asthma or bronchiectasis) being misclassified as COPD. Only one small study thus far has evaluated COPD using postbronchodilator spirometry and found higher nasal symptoms scored on a visual analogue scale compared to healthy age-matched controls.⁴⁶

Although prevalence of sinonasal disease does not increase with declining FEV₁,^{44,45} the presence of sinonasal disease has profound effects on other important COPD-related outcomes such as symptom morbidity and exacerbations, which are known to be relatively independent of FEV₁. Upper airway symptoms worsen over the natural history of COPD,⁴⁷ and are associated with lower airway symptoms⁴⁴ and impaired quality of life.⁴⁸ Sinonasal symptoms also feature prominently during COPD exacerbations, and are associated with frequent exacerbations⁴⁷ as well as treatment failure of acute exacerbation of COPD.⁴⁹

Tobacco smoke forms the common link between COPD and CRS,⁵⁰ likely by inducing neutrophilic inflammation in the nasal and bronchial mucosa. Compared with non-smoking healthy controls, smokers without COPD present with nasal inflammation characterized by increased neutrophils and CD8 T lymphocytes⁵¹ although this has not been consistently demonstrated.⁵² Nasal and bronchial

IL-8 levels, neutrophil counts, and CD8 Th1 cells are even higher in smoking COPD patients than in smoking "healthy" controls matched for pack-year smoking history.^{51,53} Nasal and sputum IL-8 concentrations correlate in COPD patients,⁵³ indicating concordance of neutrophilic inflammation between upper and lower airways in keeping with the UAD hypothesis. Release of neutrophil-derived proteases such as elastase and matrix metalloproteinase-9 causes alveolar wall destruction and mucous hypersecretion characteristic of COPD, and may contribute to tissue destruction and remodeling of the sinonasal mucosa seen in CRS. Neutrophilic inflammation results in airflow limitation in the lower airways in COPD, which is mirrored in the upper airways by reduced nasal patency⁵⁴ and higher nasal resistance.⁵⁵ Severity of lower airway obstruction, as measured by FEV₁, correlates with severity of CRS symptoms.⁴⁵

Smoking cessation alters the progressive clinical course of COPD by reducing lung function decline and mortality, hence remaining a cornerstone of COPD treatment in addition to other medical therapies. Additionally, in CRS, smoking cessation improves symptoms, quality of life and decreases CRS-related antibiotic use.⁵⁶ Neutrophilic airway inflammation per se may potentially be targeted for treatment using macrolides, which exert a repertory of effects that suppress neutrophilic inflammation, including downregulation of IL-8, elastase and matrix metalloproteinase-9, and reduction of neutrophil chemotaxis and survival.⁵⁷ Macrolides have proven efficacy in decreasing the frequency of COPD exacerbations,⁵⁸ and in a small double-blind randomized controlled trial was associated with improvement in symptoms, endoscopic scores, and nasal lavage IL-8 levels specifically in Th1, neutrophilic CRS patients.⁵⁹ Further studies are needed to confirm the efficacy of macrolides. In addition, long-term macrolides should only be used in carefully selected patients after optimization of other standard medical therapies because of potential cardiac and otological adverse effects, as well as risk of inducing antibiotic resistance.

3 | IMPAIRED AIRWAY MUCOSAL DEFENCE

Major components of the airway mucosal defense mechanism include the mucociliary escalator, immunoglobulins, antimicrobial peptides, the epithelial barrier, and cells of the innate and adaptive immune system. Impaired mucosal airway defense has a causal role in several phenoendotypes of UAD. The predominant lower airway phenotype in UAD due to impaired mucosal defense is bronchiectasis, which is characterized by abnormal and irreversible dilatation of the lower airways. Frequent coexistence of bronchiectasis and sinonasal disease has long been recognized.⁶⁰ Patients with bronchiectasis have a high prevalence of CRS when assessed using European Position Paper on Rhinosinusitis and Nasal Polyps criteria, that is, presence of symptoms and positive findings on either nasendoscopy or CT of paranasal sinuses.^{61,62} Conversely, patients with CRS more frequently demonstrate CT evidence of dilated airways compared to individuals without CRS.⁶³

3.1 | Cystic fibrosis: bronchiectasis-chronic rhinosinusitis due to airway surface liquid viscosity

Airway surface liquid (ASL) viscosity is regulated in part by the cystic fibrosis transmembrane regulator (CFTR) protein, which mediates ion transport at the airway epithelial surface. Pathological processes which impair CFTR activity can result in abnormal ion flux at the epithelial surface, increased sodium reabsorption, periciliary liquid depletion, and increased mucous viscosity, thereby impairing mucociliary clearance.⁶⁴ Loss of CFTR-mediated bicarbonate secretion in the airway epithelium also results in acidification of the ASL, which impairs the action of antimicrobial peptides in the ASL, rendering the airway more susceptible to colonization and infection by microbes.⁶⁴

Cystic fibrosis (CF) is due to heterogeneous autosomal recessive mutations in the CFTR gene and affects mucociliary clearance at the sinoepithelial lining, lower airways, gastrointestinal tract, and exocrine organs. Sinonasal disease is ubiquitous in CF and characterized by neutrophilic polyps with acid mucin glands, mucocoeles, or pseudo-mucocoeles.⁶⁵ Lower airway disease is characterized by intense neutrophilic inflammation resulting in bronchiectasis, which occurs in 70%-75% of children by 5 years of age and represents the major cause of morbidity and death in this condition.

Treatment of CF has been transformed by the discovery of novel CFTR modulators aimed at addressing the specific defects causing reduced CFTR activity. The most common gene mutation in CF is F508del which causes a processing defect that severely reduces CFTR levels at the epithelial surface and also disrupts channel opening. The latter gating defect is also seen in other mutations, such as the G551D mutation. Lumacaftor and tezacaftor are both CFTR correctors, which improve trafficking of CFTR to the epithelial cell surface. Ivacaftor is a CFTR potentiator and acts by increasing the probability of the channel remaining open. Randomized controlled trials have proven that treatment with these compounds is associated with improved lung function in CF,⁶⁶⁻⁶⁹ and improvement of CF-associated CRS following treatment with CFTR modulators has been reported anecdotally.^{70,71}

There is emerging evidence that CFTR dysfunction is a trait in other UADs and may be a target for treatment. CF carrier mutations are implicated in CRS patients who do not have CF.⁷² Constituents in tobacco smoke such as cadmium, arsenic, and acrolein can cause CFTR dysfunction,⁷³ either by reducing CFTR expression or by inducing gating defects. CFTR decrements are also seen in COPD, including reduced nasal and lower airway potential difference⁷⁴ and elevated sweat chloride,⁷⁵ and the degree of CFTR impairment correlates with severity of symptoms and airflow limitation.^{74,75} Ivacaftor reverses the acute reduction of CFTR activity after exposure to cigarette smoke in human bronchoepithelial cells,⁷⁶ and has been demonstrated to ameliorate chronic bronchitis symptoms and improve CFTR activity in a preliminary study.⁷⁷ Roflumilast, a phosphodiesterase-4 inhibitor, can stimulate CFTR by increasing cyclic adenosine monophosphate and reverses smoke-induced inhibition of CFTR activity.⁷⁸ Roflumilast is approved for reducing exacerbations in severe COPD associated with chronic bronchitis.

3.2 | Primary ciliary dyskinesia (PCD): bronchiectasis-chronic rhinosinusitis due to ciliary dysfunction

Chronic rhinosinusitis and bronchiectasis are universal in adults with PCD. The underlying pathophysiology is absent or impaired ciliary motility due to heterogeneous recessive mutations affecting the biogenesis of cilia lining the upper and lower airways.⁷⁹ In turn, this leads to impaired mucociliary clearance manifesting in the neonatal period as difficulty feeding due to nasal blockage/rhinitis, neonatal respiratory distress syndrome and later in life as recurrent sinopulmonary infections, and bronchiectasis. Nasal nitric oxide is an excellent screening test for patients with a history suggestive of PCD.⁸⁰ Other tests to assess for ciliary dyskinesia include analysis of ciliary ultrastructure by electron microscopy, assessment of ciliary beat frequency and pattern by high resolution, high-speed video microscopy, and immunofluorescent staining of ciliary proteins.

Ciliary dysfunction occurs in other airway diseases but is usually acquired, for example, due to smoking or infection. In CRS, blunted ciliary response to environmental stimuli has been demonstrated, and this is reversed once the tissue is removed from infected/inflamed environment.⁸¹ In COPD, cigarette smoke is associated with ciliary abnormalities in both bronchial⁸² and nasal mucosae.⁸³ Sputum from atopic and non-atopic asthmatics have ciliary inhibitory effect on human bronchoepithelial cell cultures, which was reversible upon removal of the sputum.⁸⁴ Bronchial biopsies from asthma patients demonstrate reduced ciliary number which recovers after treatment with inhaled corticosteroids.⁸⁵

There are currently no validated effective therapies for primary ciliary dyskinesia and this should be a focus for future research. In acquired cases, removal of the causative factor may reverse ciliary impairment.

3.3 | Primary antibody deficiency

The most common immunodeficiencies associated with CRS and bronchiectasis are primary antibody deficiencies,⁸⁶ of which common variable immunodeficiency (CVID), characterized by reduced serum IgG concentrations, is the most common in adults. One-third and two-thirds of patients with CVID have bronchiectasis and recurrent sinusitis, respectively.⁸⁷ Specific antibody deficiency, which is associated with normal immunoglobulin and IgG subclass levels but impaired antibody response to encapsulated respiratory pathogens such as *Streptococcus pneumoniae* and *Hemophilus influenza*, is also associated with a high prevalence of CRS and bronchiectasis, accounting for as many as 50% of idiopathic bronchiectasis.⁸⁸ Patients with primary antibody deficiency most likely require lifelong immunoglobulin replacement, vaccinations, and prophylactic antibiotics.

There is also some evidence that antibody deficiency may be a treatable underlying contributor in other airway diseases. For example, low circulating IgG levels are associated with higher rate of exacerbations and shorter time to next exacerbation in two COPD cohorts.⁸⁹ Treatment with immunoglobulin replacement is associated

with significant reduction in exacerbations and rescue antibiotic use in a small case series of 14 COPD patients (Supporting Information: References S8), warranting future prospective, randomized clinical trials to assess the efficacy of IVIG in preventing exacerbations in selected COPD patients with antibody deficiency. A potential contributing role of antibody deficiency in asthma has also been suggested by a small case-control study which found that asthma patients are more likely to have a diagnosis of CVID or selective IgA deficiency than non-asthmatic individuals, potentially accounting for the increased risk of bacterial infections in some individuals with asthma.⁹⁰ A preliminary proof-of-concept study found that IVIG significantly reduces the frequency of asthma exacerbations and improved asthma control in adults with IgG subclass deficiency.⁹¹

4 | EXOGENOUS COFACTORS

The respiratory tract is continuously in contact with air from the environment which contains particulates such as microbes, pollutants, and other noxious agents that can cause or aggravate UAD. Aeroallergens such as house dust mites, pollen, and animal dander are the archetypal examples of how specific exposures can cause and worsen allergic asthma-rhinitis. There are several other well-delineated phenoendotypes of UAD in which specific inciting or aggravating cofactors are implicated.

4.1 | Occupational asthma-rhinitis

More than 90% of individuals with occupational asthma (OA) also have occupational rhinitis (OR).⁹² Different occupational exposures can cause OA-OR by different mechanisms. High molecular weight sensitizers, such as proteins and glycopeptides, often cause symptoms after a latency period via IgE-mediated hypersensitivity.⁹³ In contrast, the mechanism by which low molecular weight agents induces OA-OR is poorly understood. Single or multiple exposures to high concentrations of irritants can lead to nonspecific inflammation in both upper and lower airways, clinically recognized as reactive upper airways dysfunction syndrome and reactive airways dysfunction syndrome, respectively. In addition to usual care for asthma and rhinitis, the management of OA-OR is centered around exposure avoidance and use of appropriate respiratory protection equipment. The efficacy of omalizumab for sensitizing agents with IgE-dependent reactions requires future studies.

4.2 | Aspirin-exacerbated respiratory disease

The clinical phenotype of aspirin-exacerbated respiratory disease (AERD) consists of a triad of asthma, CRSwNP, and exacerbation of upper and lower respiratory tract symptoms within 30 minutes to 3 hours after exposure to aspirin and other cyclooxygenase-1-inhibiting drugs. Nasal polyps in AERD can be distinguished from CRSwNP in individuals without AERD by the presence of enhanced eosinophilia, GM-CSF, and decreased tissue plasminogen activator.⁹⁴

The endotype of AERD is not fully understood but current available data suggest an underlying dysregulation of arachidonic acid metabolism, with constitutive overproduction of proinflammatory cysteinyl leukotrienes and decreased levels of anti-inflammatory mediators such as prostaglandin E₂.⁹⁵ This dysregulation is aggravated by cyclooxygenase inhibition following exposure to aspirin and other non-steroidal anti-inflammatory drugs in susceptible individuals.

The gold standard for diagnosing AERD is aspirin challenge, but challenge testing carries the risk of severe bronchospasm. Urinary leukotriene E₄, the end-product of arachidonic acid metabolism, is raised in AERD and may have a role in diagnosing AERD.⁹⁶ Treatment options include avoidance of aspirin and NSAIDs, desensitization, and leukotriene receptor antagonists. Omalizumab and mepolizumab may be helpful in AERD as suggested by small trials involving subsets of patients with AERD (Supporting Information: References S9, S10). Whether the observed clinical efficacy of these biologics can be attributed to target AERD-specific endotype above and beyond their effect on type-2 eosinophilic inflammation is unclear.

4.3 | Asthma-CRS: hypersensitivity to *Staphylococcus aureus* enterotoxins

Staphylococcus aureus is consistently found in nasal tissues of CRS patients, and evidence supports a role for *S. aureus* in the pathogenesis of CRS-asthma. *S. aureus* colonizes nasal polyps and secretes proteins, including enterotoxins and serine protease-like proteins in the nasal mucosa, which have the ability to elicit a polyclonal IgE response resulting in an intense type 2, IL-5 high, eosinophilic inflammation which is likely responsible for chronic severe inflammation of the airways. Presence of sIgE to *S. aureus* enterotoxins in nasal polyp tissue is strongly associated with asthma in patients with CRSwNP,^{31,97} providing an etiological link between asthma-CRS. In a small placebo-controlled, proof-of-concept study, omalizumab was found to ameliorate nasal polyps and airway symptoms in a small cohort of patients with asthma-CRSwNP who demonstrated sIgE toward *S. aureus* enterotoxins.⁹⁸

4.4 | Allergic bronchopulmonary aspergillosis-allergic aspergillus rhinosinusitis: fungal hypersensitivity

IgE-mediated hypersensitivity to *Aspergillus* hyphae is the underlying endotype for allergic bronchopulmonary aspergillosis (ABPA) and allergic aspergillus rhinosinusitis (AARS). Upper airway disease is characterized by pansinusitis, passage of nasal plugs, and recurrent nasal polyposis. Lower airway disease is characterized by mucus inspissation within the bronchi and severe asthma, central bronchiectasis, mucous plugging, and fleeting pulmonary infiltrates. In a case series, 22/95 patients of ABPA had also concomitant AARS. All these patients had positive skin tests, positive precipitins, and raised total and sIgE (Supporting Information: References S11). This

combination of ABPA and AARS has been termed "sinobronchial allergic mycosis" to recognize their shared etiology and association. The optimal treatment of ABPA and AARS is not known but includes the use of steroids, antifungals, or omalizumab.

5 | CONCLUSION

The evidence for UAD is strongest for asthma and AR/CRS. However, close associations between upper airway diseases and other lower respiratory tract disorders can also be appreciated. UAD is complex and heterogeneous but a "treatable traits" paradigm, based on assessment of airway inflammation, mucosal defense dysfunction, and exogenous cofactors can help to identify pathophysiological mechanisms involved in the development of disease and potential targets for intervention in individuals presenting with combined upper and lower airway disease. A given individual with disease can demonstrate multiple traits which may vary over time. We have summarized the various treatable traits in UAD and their proven or notional targeted treatments in Table 2. Appreciation of these treatable traits is necessary toward advancing the precision medicine approach in UAD.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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