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Endotyping in Chronic Rhinosinusitis—An EAACI Task Force Report

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ABSTRACT

Chronic rhinosinusitis (CRS) is a clinical syndrome defined by typical sinonasal symptoms persisting for at least 12 weeks. CRS is divided into two distinct phenotypes, CRS with nasal polyps (CRSwNP) and without (CRSsNP). The aim of the review is to provide an update on the current knowledge in CRS endotypes. The prevailing hypothesis regarding the pathogenesis of CRS suggests that dysfunctional interactions between the host and environmental stressors at the mucosal surface drive the diverse inflammatory mechanisms. Genetic and epigenetic variations in the mucosal immune system are believed to play a significant role in the pathomechanisms of CRS. Various environmental agents (such as microbes and irritants) have been implicated in CRS. In a healthy state, the sinonasal mucosa acts as a barrier, modulating environmental stimulation and mounting appropriate immune responses against pathogens with minimal tissue damage. Different endotypes may exist based on the specific mechanistic pathways driving the chronic tissue inflammation of CRS. There is a need to understand endotypes in order to better predict, diagnose, and treat CRS. This literature review provides an update on the role of the endotypes in CRS and the limitations of endotyping CRS in clinical practice. Understanding of the pathogenesis and optimal management of CRS has progressed significantly in the last decades; however, there still are several unmet needs in endotype research.

1 | Introduction

Chronic rhinosinusitis (CRS) is an inflammatory condition of the nose and paranasal sinuses [1]. Its diagnosis requires a combination of symptoms (nasal blockage and/or nasal discharge, combined with facial pain/pressure and/or reduction or loss of smell) and compatible endoscopic findings (nasal polyps, edema, and purulent discharge) with optional radiological findings [1]. Although the disease can occur in the context of systemic conditions (cystic fibrosis, granulomatosis with polyangiitis, etc.) or have a unilateral nature (e.g., fungal ball), CRS is commonly a primary diffuse (bilateral) disease [1]. CRS is also a heterogeneous entity in terms of symptoms, mechanisms, prognosis, and therapy response, where distinct phenotypes and endotypes can be identified [2]. From a historical perspective, international guidelines used to propose a phenotypic classification of the disease based on the presence (CRSwNP) or absence (CRSsNP) of nasal polyps [3]. Recent updates of the CRS classification advocate for an endotypic classification based on the underlying activated immune/inflammatory pathways. This task force report summarizes the knowledge of CRS endotypes and the possibilities and limitations of endotyping CRS in clinical practice.

Single or combined type 1, 2, and 3 immunological response pathways are to eliminate the identified class of pathogen, such as virus, parasite, or bacteria/fungi, correspondingly. Type 1 (T1) canonical cytokines include IFN-gamma (IFN-γ) and IL-12 [4]. Type 2 (T2) cytokines include IL-4, IL-5, and IL-13. Type 3 (T3) cytokines include IL-17A and IL-22. Each immune response pathway is orchestrated by unique innate lymphoid and T helper subsets secreting cytokines. These inflammatory patterns are often mixed, with significant plasticity in the ILC and T-helper cell subsets [4]. In CRS, response is chronic and polyclonal, directed against several, in part unknown environmental factors. T2 cytokines are most commonly associated with CRSwNP, CRS with asthma, and/or N-ERD [4].

CRS pathophysiology involves different factors [5]. On the one hand, there is a dysregulation of the homeostatic mechanism to repair the sinonasal epithelium (the epithelial–mesenchymal transition), leading to a dysfunctional epithelial barrier that is prone to inflammation [3, 6]. The cause of this alteration is unknown, although in some patients' environmental (e.g., smoke from tobacco or heavy industry) or microbial exposures might play a role [3]. Upon this dysfunctional barrier, some patients develop a T2 inflammation leading to mucosal infiltration by Th2 cells, IgE-producing B cells, group 2 innate lymphoid cells (ILC2), M2 macrophages, eosinophils, basophils, mast cells, and IL-4, IL-5, or IL-13 cytokines [2, 7]. Goblet cell and MUC activation increase the viscosity of secretions, whereas M2 macrophages contribute to generating fibrin meshes, which provide a scaffold for the polypoid degeneration of the (ethmoidal) mucosa [8]. T2 inflammatory mediators also interfere with the secretions in the olfactory cleft, promote the infiltration of the olfactory epithelium by mast cells and eosinophils, and stimulate mature olfactory neurons, making them less responsive to aromatic compounds [9, 10]. All these aspects account for an impairment of smell in CRS individuals [3].

Efforts to achieve a better understanding of CRS include the study of environmental and host factors related to endotypes. The aim of the review is to provide an update on the current knowledge in CRS endotypes. A literature search was conducted using Ovid Medline between January 2012 and September 2024, providing 23,835 search results. Titles or abstracts were browsed by one author. Studies ($n \approx 950$) that met the inclusion criteria were selected (Figure 1, Table S1). Due to the high number of search results, a systematic review of all these publications was not undertaken in this review. Instead, 168 publications are presented.

2 | Inflammatory Mechanisms in CRS

Efforts to achieve a better understanding of CRS include the study of environmental and host factors related to endotypes. Figure 2 shows a schematic diagram of the different environmental and immunological entities that affect the endotype of CRS.

2.1 | Environmental Factors

2.1.1 | Viruses

Viruses are divided into RNA and DNA viruses. RNA viruses have high mutation rates, which can contribute to their ability to evade host immune responses and potentially develop

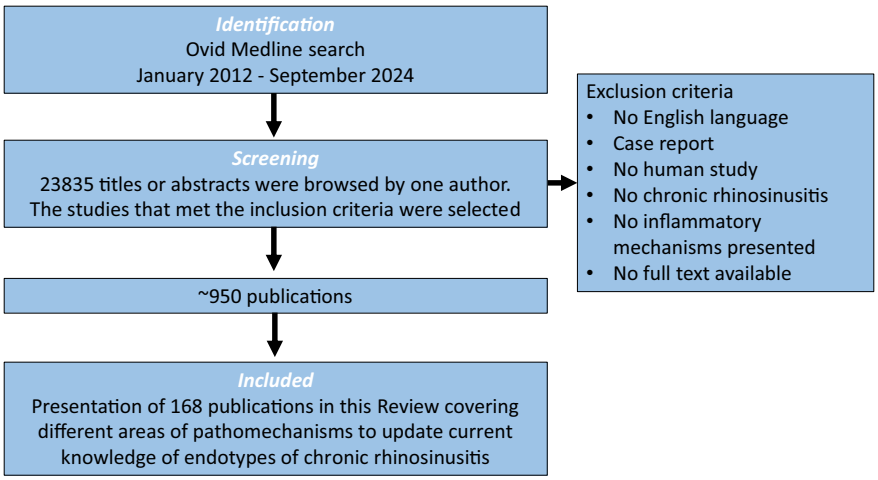

FIGURE 1 | PRISMA flow diagram for primary study selection.

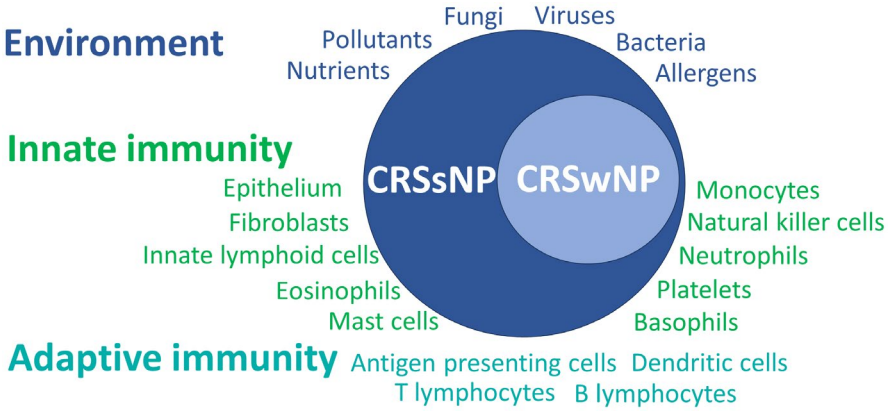

FIGURE 2 | A schematic diagram of the different environmental and immunological entities that affect the endotype of chronic rhinosinusitis (CRS). CRSsNP = CRS without nasal polyps, CRSwNP = CRS with nasal polyps.

resistance to antiviral treatments [11]. Systematic review data has shown that in most studies there is a higher presence of viruses in nasal and serum samples of CRS subjects as compared to controls, yet the exact role of viruses in CRS pathophysiology is unclear [12]. Nasal lavage samples of CRS patients have shown that rhinovirus, parainfluenza virus, influenza virus, and respiratory syncytial virus are associated with CRS, whereas adenovirus or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have shown weak association with CRS [13]. The common cold is the most common viral disease caused by rhinovirus infection, which has been linked with exacerbations of CRS [1, 14]. Cadherin-related family member 3 gene (CDHR3) is a rhinovirus receptor, and its rs6967330 risk allele (A) has been shown to be associated with childhood asthma with severe exacerbations [15] and adult CRS, suggesting a role for aberrant rhinovirus effects in the pathogenesis of both diseases [1, 16]. Similarly, influenza virus infection is a potential contributor of IL-25 in CRSwNP epithelium, which is correlated with T2 inflammatory cytokines [17]. Hence, several acute viral infections might play a role in the initial development as well as subsequent exacerbations of CRS.

2.1.2 | Bacteria

Bacteria can be classified based on their shapes, metabolism, operational taxonomic units (OTUs), or metabolic activity [18]. OTUs involve grouping bacteria based on the DNA sequence similarity of a specific taxonomic marker gene, often using the small subunit 16S ribosomal RNA (16S rRNA) [18]. Metatranscriptomics involves profiling the gene expression of complex microbial communities, providing insights into their functional behavior [18]. The implementation of 16S rRNA gene sequencing technology has provided valuable insights into bacterial dysbiosis [18]. In the context of CRS, there is evidence suggesting that dysbiosis is associated with changes in the sinonasal microbiome of CRS patients. Although it is unclear whether dysbiosis is a primary event or a secondary consequence of CRS, microbial agents are considered significant environmental drivers in the development and progression of CRS [19].

Under normal homeostasis, the sinonasal microbiota is primarily composed of *Staphylococcus aureus*, *Staphylococcus epidermidis*, and Corynebacterium genera [20]. Increased *S. aureus* might perpetuate both Th1- and Th2-high endotypes, leading to CRS exacerbation and polyp formation [20].

Bassiouni et al. used an unsupervised machine learning approach to the International Sinonasal Microbiome Study (ISMS) dataset of 410 sinus swabs and detected three microbiotypes: [1] Corynebacterium-dominated, [2] Staphylococcus-dominated, and [3] dominated by the other core genera (Streptococcus, Haemophilus, Moraxella, and Pseudomonas) [21]. Interestingly, the prevalence of each varied regionally, yet not in controls vs. sinusitis [21]. A Chinese study showed that Actinobacteria and Chlamydia were higher in the control group ($n = 34$) compared to CRSwNP ($n = 77$) and CRSsNP ($n = 36$) groups [22]. Around 20%–30% of the general population are persistently colonized with *S. aureus* on their nasal mucosa, but *S. aureus* and specific IgE formation against its superantigens have been shown to be associated with severe CRSwNP and asthma exhibiting Th2-high inflammation [1].

16S RNA sequencing has shown that microbiota differ between eosinophilic CRSwNP (ECRSwNP) and non-eosinophilic CRSwNP (NECRSwNP), yet there was also regional variation in the results [23]. Feng et al. showed in the Chinese population that microbiota community diversity was significantly lower in NECRSwNP samples compared to controls, and the abundance of Staphylococcus was the lowest in the ECRSwNP versus NECRSwNP or control groups [23]. In the US population, an abundance of Moraxella and Parvimonas was detected in the nasal samples of the ECRSwNP group and dysbiosis in the gut microbiota in both the ECRSwNP and NECRSwNP groups. Korean [24] ECRSwNP patients showed decreased abundance of Anaerococcus and high abundance of Lachnoclostridium compared to controls [25].

A review of 14 studies regarding sinus microbiome in acutely exacerbated CRS patients showed predominance of *Staphylococcus aureus* and *Pseudomonas aeruginosa* [26]. Lu et al. performed 16S rRNA gene sequencing and showed a predominance of anaerobic bacteria in odontogenic vs. non-odontogenic rhinosinusitis [27], and abundance of Haemophilus and absence of Corynebacterium and Fusobacterium in fungal vs. non-fungal rhinosinusitis [28]. *A. flavus* and *Rhizopus oryzae* have been shown to be abundant in fungal rhinosinusitis subtypes [29].

Mahajan et al. performed 16S rRNA gene sequencing of suctioned nasal secretions of US children with rhinosinusitis and showed a predominance of Negativicutes, Bacilli, Mollicutes, and Alphaproteobacteria as compared with controls [30]. Chen et al. performed 16S rDNA gene sequencing of old and young CRS patient groups in China (≥60 years, median age = 66 years, $N = 17$; <60 years, median age = 35.5 years, $N = 14$) and found that the abundance of phylum Actinobacteria and genus Corynebacterium was significantly higher in aged patients, while the abundance of phylum Bacteroidetes, Fusobacteria, and genus Fusobacterium, Peptoniphilus was significantly higher in younger patients [31].

Monoclonal IgE can sensitize and activate resident effector cells upon stimulation of antigens (such as aeroallergens and enterotoxins), thus worsening inflammation [32]. On the other hand, *Staphylococcus aureus* enterotoxins are also active immune players as they display superantigen capacity [3]. Indeed, the majority of mucosal IgE in CRS patients colonized by SA derives from a polyclonal enterotoxin-driven synthesis [33]. Thus, although polyclonal IgE is only partially functional, these antibodies also aggravate inflammation due to their higher relative abundance [34].

Taken together, profiling of bacteria may be used in endotyping and prediction of recurrence of CRS [35]. Yet, the challenge is that the nasal microbiota depends on the population, subtype, age, region, phenotype, exacerbation, and also on the individual's variation [36], on anatomical location, sampling technique [37], operative or conservative therapy [38], and other factors. Hence, further studies on microbiota are needed, and caution would need to be made when interpreting the results of current literature.

High exposure of environmental microplastics has shown to increase the abundance of nasal microbiotas, which were positively associated with respiratory tract diseases, such as Klebsiella and Helicobacter, and to reduce the abundance of those beneficial ones, such as Bacteroides [39].

2.1.3 | Biofilms

A biofilm consists of a bacterial colony embedded within an extracellular matrix of polymeric substances, which makes it resistant to environmental stress, host defenses, and antimicrobial treatment [1]. Pathogens such *as Haemophilus influenzae, Streptococcus pneumoniae, Pseudomonas aeruginosa*, *Moraxella catarrhalis*, *and S. aureus* can all form sinonasal biofilms in CRS patients, some of which have been associated with a worse prognosis [1]. CRS patients with biofilm-forming bacteria have demonstrated clinically significant QOL improvement following ESS, but the degree of improvement has been shown to be decreased over time [40]. Popov et al. performed spinning disk confocal microscopy and qRT-PCR for nasal tissue samples of 85 CRS patients to analyze the biofilm and expression of MUC5AC and MUC5B genes [41]. The results would suggest a possible association between bacterial biofilm formation and the pathology of chronic rhinosinusitis in that patient cohort. A possible connection was also observed between high expression of MUC5B and chronic inflammation of the nasal cavity and sinuses [41]. Shaghayegh G. et al. explored *S. aureus* biofilms and T-cell subsets from ethmoidal samples of 59 subjects with CRSwNP, CRSsNP, and controls. *S. aureus* biofilm properties and severe or relapsing CRS were associated with increased $CD4^+$ T-cell frequencies and reduced frequencies of Th1, Th17, and regulatory T-cell subsets [42]. Rather et al. showed that *L. plantarum* metabolites from camel milk decrease the hydrophobicity of the cell surface, hence influencing the virulence properties and biofilm formation of *S. pyogenes* [43]. In conclusion, the role of biofilms in the pathogenesis of CRS remains unclear. *S. aureus* is the microbe most commonly associated with CRS.

2.1.4 | Fungi

Fungal infections seem to affect only a subset of cases of CRS. Commensal fungi are present in the sinonasal tract. Similar to bacteria, fungi produce biofilms and toxins [1]. The role of fungi in the pathogenesis of CRS is not completely understood [44]. Fungi contribute to the pathogenesis of fungal balls, and putatively also of allergic fungal rhinosinusitis (AFRS). Although the role of fungi in pathogenesis is far from clear, AFRS is associated with a Th2 high-inflammatory pattern, leading to the accumulation of mucus-containing eosinophils and local production of specific IgE against fungal wall polysaccharides [45].

Children with cystic fibrosis and children with nasal polyps had more frequent positive fungal cultures than children without nasal polyps having sinus surgery [46]. Cleland et al. performed 18S rRNA gene sequencing of middle meatal swabs from 23 CRS and 11 control subjects and detected ubiquitous and rich (a total of 207) fungal genera, Malassezia being the most abundant [47]. Mohammadi et al. investigated 100 patients suspected to have AFRS and showed that the proportion of fungal rhinosinusitis was 27% (such as *Aspergillus flavus*, *Penicillium chrysogenum*, and *Candida glabrata* species complex). Of these fungi found, 41% were commensals [1, 48]. Overall, the role of fungi in the pathogenesis of CRS (except AFRS) remains unresolved.

2.1.5 | Other Environmental Factors

Allergic rhinitis (AR) involves a host immune response to allergens and might play a role in molecular mechanisms of CRS endotypes. Kanemitsu et al. evaluated blood, nasal, and sputum samples of 56 CRS patients (20 with comorbid asthma) and 28 healthy controls and showed that sensitization to molds and *Staphylococcus aureus* enterotoxins was associated with Th2-high inflammation pattern [49]. Although there is clearly an overlap between AR and CRS in terms of T2 cytokines, the presence of co-existing allergic rhinitis can contribute to the accentuation of Th2-high inflammatory mechanisms in CRS [1]. Allergens typically possess intrinsic protease activity that can interact with epithelial cells. In Western populations, most CRS cases have a Th2-high inflammation pattern, whereas in Chinese populations, the Th2-high inflammation pattern is more associated with CRSsNP with AR subtype [49]. *Alternaria alternata*, *Dermatophagoides pteronyssinus*, and *Dermatophagoides farinae* have been shown to enhance IL-33 and TSLP production from the cultured nasal epithelial cells through the NF-κB,

AP-1, and MAPK pathways [50], yet the pathobiological events of indoor and outdoor allergens on the sinonasal mucosa of CRS patients have been less studied.

The challenge of evaluating the role of AR in CRS pathogenesis is that the patterns of sensitization to airborne allergens can vary significantly based on factors such as geographical location, genetic predisposition, living conditions, and climate [1].

Exposure to tobacco smoke alters the sinonasal mucosa and is associated with CRS subtypes. Kuhar et al. studied nasal samples of CRS patients (173 never smokers, 85 former smokers, 27 current smokers). Smokers demonstrated increased basement membrane thickening, hyperplastic changes, squamous metaplasia, and fibrosis [51]. Elevated levels of the lipid raft protein raftlin were detected in the nasal epithelium in the smoking versus non-smoking CRSwNP patients, which suggests nasal epithelial remodeling in smokers with CRSwNP [52]. Air pollution (particularly particulate matter) has been shown to be associated with CRS prevalence and disease severity, with evidence of histopathologic changes in CRS tissue samples [53]. Patel et al. detected in 291 CRS patients' nasal samples that higher degree of inflammation was significantly associated with increased ozone exposure. Among the patients with CRSwNP ($n = 131$), the presence of eosinophilic aggregates and Charcot–Leyden crystals was associated with increased ozone exposure [54]. A study showed that fine particulate matter (PM2.5) could be a risk factor for the endotype of ECRSwNP [55]. Occupational airborne exposure to vapors, gases, dusts, fumes, fibers, or mists has been shown to be associated with uncontrolled CRS [56, 57]. Khlifi et al. studied blood concentrations of heavy metals, cadmium, and nickel in 90 CRSwNP and 171 control Tunisian subjects, and higher heavy metal concentrations were associated with CRSwNP, with tobacco consumers and with CRSwNP patients with occupational exposure (presumably to heavy metals) [58]. Increased heavy metal levels have been detected in polyp tissue compared to non-polyp tissue from the same patient [58]. Tas et al. detected an increased number of environmental microplastics in nasal lavage fluid from CRSwNP patients as compared with controls [59].

Vitamin D plays a fundamental role in immunomodulation processes, with consequent anti-inflammatory and antioxidant effects in different immune-mediated pathologies, such as CRS [60]. A meta-analysis detected a significant association between lower serum vitamin D status and CRS, especially in CRSwNP [61]. Chandrakar et al. assessed the levels of 25-hydroxy vitamin D and high-sensitivity C-reactive protein (hs-CRP) in CRSwNP patients and healthy controls and identified their association with CRSwNP and disease severity [62]. Shrestha et al. analyzed blood samples of CRSwNP patients and showed different levels of vitamin D, eosinophils, IL 4, IL 5, and IL 13 as compared to healthy controls [63]. There is very little evidence of other nutritional factors except vitamin D in CRS. Taken together, studies suggest that other environmental factors play some role in the pathogenesis and endotypes of CRS. Yet larger genome–environmental interaction studies and functional approaches are necessary to establish causation and explore the therapeutic potential of these.

Taken together, exposome's interaction with host mucosal immunity is crucial in the pathogenesis of CRS. Increasing evidence has been shown on microbiotas role. Still, there is more limited knowledge on exposure of outdoor or indoor allergens, secondhand smoke, occupational exposures, or dry/humid environments on the sinonasal tissue of CRS patients.

2.2 | Host Mucosal Immunity

2.2.1 | Innate Immunity

Innate immunity removes pathogens, recruits immune cells, activates the complement cascade to detect and remove environmental insults, recognizes foreign substances, and initiates the adaptive immune response through antigen presentation. It includes the epithelial barrier, mucosal cells (e.g., macrophages, dendritic cells), phagocytes (monocytes, neutrophils), innate lymphoid cells, NK cells, and non-cellular elements like the complement system [1].

2.2.1.1 | Epithelial Barrier. The sinonasal tract is lined with various types of epithelium, including ciliated pseudostratified columnar, olfactory, and squamous (in the nostril area). These epithelial cells have crucial functions in humidifying inhaled air, sensing environmental stimuli, and defending against pathogens. They consist of ciliated cells, mucus-secreting goblet cells, and basal cells, which serve as progenitor cells [64]. The epithelial barrier includes also club cells and tuft cells. Olfactory epithelium consists of tuft cells, olfactory cells, and sustentacular cells. Additionally, solitary chemosensory cells have been identified in the sinonasal epithelium, playing a role in T2 immunity [1, 65].

Environmental and mucosal signals influence the maintenance of epithelial stem cells [58]. Ordovas-Montanes et al. performed single cell transcriptomics of polyp/scraping epithelium from 12 CRSwNP and 9 control subjects and detected differences in expression of antimicrobial genes by secretory cells, a loss of glandular cell heterogeneity, and that polyp basal progenitor cells showed a T2 high expression profile [66]. Epithelial basal progenitor cells can transform into various cell types, and epithelial cells may undergo processes like squamous metaplasia or epithelial to mesenchymal transition [67]. Single-cell transcriptomics sequencing studies have shown that the apical and glandular epithelial cells and the ADGRB3+and POSTN+ fibroblasts play a role in the progression of CRSwNP [68].

Epithelial barriers are maintained by tight junctions, which establish cell polarity and control solute and water movement between cells. Factors like allergens, infections, cytokines, hypoxia, or zinc deficiency can affect tight junction molecules and barrier function in CRS [67, 69]. Transcriptomics of nasal epithelial cells of N-ERD patients has shown that mepolizumab enhances ZO-3 and angiomotin expression levels [70]. Blocking IL-4R in inferior turbinate-derived HNECs was able to reverse the decrease in transepithelial electrical resistance induced by IL-4 and IL-13 [71].

Several genes/molecules modulate the physical barrier in CRS, including SPINK5, S100A7, S100A8/9, PCDH1, NDRG1, SPRR, and p63 [69]. Epithelial membrane protein 1 is involved in cell proliferation and shows reduced expression in nasal polyp

epithelium [72]. In vitro studies have shown that mAb anti-IL4ra, dupilumab, restored epithelial integrity by counteracting the effect of IL-4 on the epithelial barrier [73].

Gap junction channels, formed by connexin proteins, facilitate cell communication [74]. Their relevance to CRS pathogenesis is not fully understood. Cilia, hair-like organelles, are crucial for mucociliary clearance (MCC) and maintaining the mechanical barrier in the nose and sinuses. Genetic and acquired defects in MCC are associated with CRS [75, 76–78]. Ma et al. cultured sinonasal epithelial cells and found that cilia loss and decreased expression of WDPCP, a ciliogenesis protein, are associated with CRS compared to controls [67, 79].

Pattern recognition receptors (PRRs) detect foreign patterns and play a role in host defense. Toll-like receptors (TLRs) and NOD family PRRs are expressed in the nasal epithelium and may contribute to CRS pathogenesis [67]. Bitter taste receptors can function as non-classical PRRs, and their activation by bacterial molecules may impact the immune response [80, 81]. Bitter taste receptor agonists can activate cAMP-dependent respiratory epithelial signaling pathways to modulate two-pore potassium currents [82]. Genetic studies suggest associations between taste receptor genetics and CRS [83]. Jeruzal-Świątecka et al. performed qRT-PCR of polyp tissue from 107 CRSwNP patients and inferior turbinate mucosa of 39 controls and showed that the expression of the TAS2R38 receptor is reduced in the sinonasal mucosa in patients with more advanced CRSwNP [84]. Tuft cells are expressed in nasal olfactory epithelium [85]. They have been shown to be induced by bitter taste receptor agonists, coordinate secretion of antimicrobial products, and induce T2 inflammation [86, 87]. Kotas et al. performed nasal epithelial single-cell sequencing and detected different profiles in CRSwNP (increased tuft cell transcripts and decreased ciliated cell transcripts along with an IL-13 activation signature) and in CRSsNP (IL-17 activation signature). IL-13 activation was associated with increased tuft cell, goblet cell, and mast cell scores and decreased ciliated cell scores and PGE2 activation signature [88].

Both mucosal and glandular epithelium secrete host defense molecules (such as surfactant, lactoferrin, and defensin) that can kill or neutralize microorganisms [1]. Studies on polyp and control tissue show that CRSwNP may be related to decreased expression levels of PLUNC, possibly secondary to loss of glands, as well as increased surfactant-B and alpha-defensin expression [80, 89–91].

The apical surface of the olfactory neuroepithelium consists mainly of sustentacular cells, which support neuronal dendritic projections containing the odor-sensing cilia [92]. Chen et al. have detected ACE-2-staining in the apical surface of Krt18+ sustentacular cells and that ACE-2-positive cells are comparable between healthy controls and CRS [92]. Yee et al. have detected histopathological changes of olfactory epithelium in CRS patients as compared to controls, such as intermixing of goblet cells, metaplasia to squamous-like cells, erosion, and a decreased percentage of normal epithelium and olfactory sensory neurons [93].

CC10 is a protein expressed by epithelial secretory club cells, and it has been shown to play a regulatory role in eosinophilic CRS, presumably by attenuating chitinase 3-like expression [94].

A loss-of-function variant in ALOX15 causes alteration in arachidonate 15-lipoxygenase (15-LO) has shown to protect against CRSwNP [95]. Moreover, Li et al. cultured IL-13-stimulated epithelial cells of patients with CRSwNP, with or without 15LO1 enzymatic inhibitors and two ERK inhibitors, and detected increased 15LO1 expression in nasal polyp epithelial cells, contributing to CCL26 expression through ERK activation [96].

Taken together, several nasal barrier molecules and pathways, such as the arachidonic acid metabolic pathway, might be central in CRS pathogenesis.

2.2.1.2 | Epithelial to Mesenchymal Transition and Remodeling. In CRS, remodeling involves abnormal tissue changes (such as fibrosis, basement membrane thickening, goblet cell hyperplasia, and polypogenesis) driven by T2 inflammation and various factors [1]. Genetic, environmental, and microbial factors weaken the epithelial barrier, contributing to these changes [1]. Additionally, remodeling is linked to edema and the coagulation cascade, particularly in nasal polyp formation. Angiogenesis, regulated by growth factors, is another aspect of CRS remodeling. Angiogenesis, regulated by growth factors, is another aspect of CRS remodeling. Eosinophilic CRSwNP features osteitis, often resulting from infection and biofilm production [1]. Neural function, influenced by infection and the immune system, also contributes to CRSwNP pathogenesis, including olfactory loss, with dysfunctional innervation and neuropeptides playing significant roles [97]. Notably, dysfunctional innervation and neuropeptides play roles in CRSwNP. Ex vivo whole-transcriptome microarray and qRT-PCR study of fibroblasts from CRSwNP tissue has shown an activation of pro-inflammatory and pro-fibrotic transcriptional pathways, along with higher mRNA expression levels of cytokines, growth factors, and extracellular matrix components [98]. In conclusion, epithelial-to-mesenchymal transition plays a pivotal role and might be crucial in the development of CRS.

2.2.1.3 | Innate Lymphoid Cells. Innate lymphoid cells (ILCs) are rapid cytokine producers, including natural killer (NK) cells and three main subsets (ILC1, ILC2, ILC3) [99]. ILCs act as early defenders in the airway epithelial barrier and correspond to $CD4^+$ T-cell subsets (Th1, Th2, Th17) [1]. In CRSwNP, ILC2s are potent innate immune cells that contribute to T2 inflammation by producing cytokines such as interleukin (IL)-4, IL-5, and IL-13 and adapting to produce IFN-γ or IL-17 based on local cues [100]. Different ILC precursors (ILCPs) give rise to mature tissue-resident ILCs, with epigenetic environmental influences on differentiation pathways. Although environmental signals influence epigenetically canonical ILC differentiation pathways and generate substantial functional plasticity [101], each ILC group appears to have a distinct physiologic role and cytokine profile described as T1, T2, and T3 inflammation, respectively. Epithelial cytokines such as IL-25, IL-33, thymic stromal lymphopoietin (TSLP), TNFSF15, a member of the TNF superfamily, and a receptor-mediated activator of NF-kappaB can activate ILC2 cells and other cell types [1, 102, 103]. In CRSwNP patients treated with dupilumab, Th2, Treg, and ILC2 cells, which regulate T2 inflammation, are modulated in the peripheral circulation [104].

2.2.1.4 | Neutrophils. Neutrophils are abundant leukocytes that play a role in early phagocytosis and killing of microbes [1]. They are recruited in response to microbial stimulation

or tissue damage, driven by T3 cytokines. Neutrophil infiltration has been shown in the pathophysiology of CRSwNP [105]. Neutrophils often coexist with T2 cytokine-driven eosinophils, potentially reflecting a response to microbiota and corticosteroid resistance in CRS patients [1]. A cathedrin, LL-37, was able to induce neutrophil extracellular traps (involved in inflammatory pathologies) in polyp tissue of CRSwNP patients [106]. Farrell et al. detected that neither the presence of mucosal eosinophilia nor mucosal neutrophilia demonstrated significant associations with SNOT-22 quality-of-life or BSIT olfactory function scores when adjusted by comorbid nasal polyposis [107]. Kim et al. performed machine-learning immunofluorescence analyses and machine learning models and showed that subepithelial neutrophils in polyp tissues predict postoperative outcomes in Asian CRSwNP patients [108]. Jafari et al. have shown a delay in L-selectin shedding in blood neutrophils from patients with CRSwNP and comorbid asthma in response to *Staphylococcus aureus* enterotoxin A-stimulus putatively affecting neutrophil rolling on activated endothelium and its transendothelial migration at the site of inflammation or infection [109].

2.2.1.5 | Monocytes. Monocytes are less abundant than neutrophils but can also ingest microbes and differentiate into macrophages during inflammation [1]. Macrophages have diverse roles in tissue defense, immune response coordination, inflammation, and tissue repair. Macrophages are classically divided into two subtypes, M1 and M2 [1]. M1 macrophages are proinflammatory and respond to T1 cytokines, while M2 macrophages, activated by T2 cytokines, play a role in tissue repair and humoral immunity. In T2 CRSwNP, M2 macrophages may be important, contributing to CCL23-mediated macrophage recruitment and excessive fibrin deposition [110]. In T1 CRSsNP, macrophages are elevated and play a central role in inflammation, recruiting eosinophils and neutrophils to the site of inflammation. ALOX15+ macrophages contribute to the T2 immunity-driven pathogenesis of eosinophilic CRSwNP by secreting chemokines that recruit eosinophils, monocytes, and Th2 cells [111].

2.2.1.6 | Basophils. Basophils are circulating granulocytes that play a role in allergies and parasite immunity. They are associated with T2 responses and may serve as an early source of IL-4, potentially driving T2 T polarization [99]. Increased nasal polyp tissue basophils are associated with CRSwNP without N-ERD [112]. Basophil infiltration in nasal polyp tissue has been shown to be associated with the severity of CRS [113]. The basophil activation test has shown low sensitivity and specificity to detect N-ERD [114].

2.2.1.7 | Mast Cells and IgE. Mast cells are found especially beneath epithelia and near blood vessels. Mast cells can be activated by microbial products, complement components, or antibodies [1]. Their granules contain histamine and other mediators that cause vasodilation, increased capillary permeability, and immune defense. In CRS, mast cells are of interest in nasal polyposis and may induce and maintain eosinophilic inflammation [115]. Local IgE class switching directed against common aeroallergens may mediate mast cell activation and contribute to subsequent eosinophilic inflammation in CRSwNP, but non-IgE-mediated activation mechanisms such as CD30L may also play a role [116]. Mast cells, along with platelets (see below), may be sources of proinflammatory leukotrienes (cysLTs) and prostaglandins (PGD2) in CRSwNP and N-ERD [117, 118]. The eosinophil-mast cell pattern of intraepithelial infiltration has been shown to be a potent marker of severity in CRSwNP [119]. T2 high CRS individuals can experience mucosal synthesis of IgE directed against any antigen present in their sinonasal space, including aeroallergens but also bacterial products like *Staphylococcus aureus* enterotoxins [114]. Strong T2 microenvironment favors the mucosal production of high-affinity IgE through a classical germinal center reaction [115]. Monoclonal IgE can sensitize and activate resident effector cells upon antigen stimulation, thus worsening inflammation [116]. On the other hand, *Staphylococcus auerus* enterotoxins are also active immune players as they display superantigen capacity [3]. Thus, although polyclonal IgE is only partially functional, these antibodies also aggravate inflammation due to their higher relative abundance [118]. Anti-IgE therapy, omalizumab, has shown significant improvements in SNOT-22 scores, smell tests, sense of smell, postnasal drip, and runny nose as compared to placebo [120]. Anti-IL4Ra therapy, dupilumab, has been shown to reduce local and systemic T2 inflammatory biomarkers in patients with CRSwNP, including mast cells in nasal mucosa and cysteinyl leukotrienes in urine [121].

2.2.1.8 | Eosinophils. Eosinophils play a role in tissue repair and immune defense, particularly against helminths and also bacteria [1]. Single-cell RNA sequencing of eosinophils from nasal polyp tissue has shown that tissue eosinophilia appears to exist in several subtypes that may play important pathogenic roles in CRSwNP, in part by controlling inflammation and hyperproliferation of other cells [122]. Eosinophilia correlates with a poor prognosis in CRS, independent of the presence of polyp [1]. Eosinophil recruitment, activation, and survival are driven by epithelial cytokines, proteases, complement proteins, eicosanoids, stem cell factor, and T2 cytokines, produced by ILC2s and Th2 cells [1]. Eosinophils are steroid-responsive, which explains the therapeutic effects of glucocorticoids in CRS [123]. Targeting specific features of activated eosinophils is being explored as a potential treatment approach of anti-IL4Ra, dupilumab, as well as anti-IL5, mepolizumab, and they have shown to reduce polyp size, symptoms, and improve the sense of smell of CRSwNP patients as compared with placebo [124, 125].

2.2.1.9 | Natural Killer Cells. Natural killer (NK) cells are innate immune system components that play a critical role in recognizing and eliminating infected or stressed cells [1]. They do so by releasing cytotoxic granules and the cytokine IFN-γ upon activation, without expressing specific antigen receptors [1]. Impaired NK cell function, reduced degranulation, and decreased cytokine production have been associated with CRSwNP, especially in patients with concomitant asthma and blood eosinophilia [126]. Eosinophil apoptosis, mediated by NK cells, is reduced in CRS patients [126]. While NK cells are important in host defense, other immune cells like CD8+ T cells play a role in CRSsNP [127]. Kingler et al. performed ELISA, Luminex, and gene set enrichment analysis for control and patient nasal samples and showed that T1-high CRSsNP was associated with IFN-gamma signaling and antiviral immunity controlled by Th1 cells, NK cells, and antigen-presenting cells; T2-high CRSsNP was associated with STAT6 signaling and IgE-mediated

activation controlled by eosinophils, mast cells, Th2 cells, ILC2s, and antigen-presenting cells; and T3-high CRSsNP was associated with IL-17 signaling, acute inflammatory response, complement-mediated inflammation, neutrophils, Th17 cells, B cells, and antigen-presenting cells suggesting different endotypes of CRSsNP [128]. Invariant natural killer T (iNKT) cells and mucosal associated invariant T (MAIT) cells exhibit an activated phenotype and produce higher levels of IL-17A in patients with CRSwNP [129]. Studies have shown that in the presence of NK cells, anti-IL5R benralizumab induces potent eosinophil apoptosis and that afucosylation of benralizumab strongly enhances its potency [130].

2.2.1.10 | Platelets. Platelets are small cell fragments primarily involved in blood clotting, but they can also influence inflammation by interacting with other cells and releasing inflammatory substances [1, 131]. In CRSwNP and N-ERD, platelets are a significant source of proinflammatory compounds like leukotrienes and prostaglandins. Epithelial cells and platelets can interact with immune cells in NERD patients [132]. CRS with alcohol hypersensitivity has been shown to be associated with significantly higher platelet levels, and compounds present in alcoholic beverages can directly mediate both their activation and the activation of platelet-adherent basophils [133].

Collectively, cells of innate immunity play a central role in both maintaining normal tissue function and contributing to the pathogenesis of CRS.

2.2.2 | Mechanisms of Adaptive Immunity

The separation between innate and adaptive immune responses, although somewhat artificial, helps explain how our immune system works at mucosal barriers [1]. When mechanical and innate defenses are breached, the adaptive immune system is activated. The communication between epithelial cells, innate lymphocytes, and dendritic cells is crucial in coordinating the appropriate adaptive response [1]. This balance allows us to tolerate potential allergens and commensals while defending against pathogens without causing chronic inflammation. Adaptive immunity consists of T-cell and B-cell responses, which we will discuss in the context of CRS.

2.2.2.1 | Antigen Presentation, Dendritic Cells, and T Cell Activation. T-cell responses are initiated when dendritic cells (DCs) present antigens to naive T cells and include myeloid mDCs and plasmacytoid pDCs [1]. DCs play a crucial role in the transition from innate to adaptive immune responses, influencing both innate and adaptive immunity through antigen capture, presentation to immature T cells, and secretion of inflammatory mediators [1]. The cytokine response from epithelial cells and ILCs shapes T-cell differentiation. Different subsets of DCs can be found in the context of eosinophilic and noneosinophilic CRSwNP, which may prime Th2 and Th1/Th17 cells, respectively [134]. Kawakami et al. analyzed the ratios of mDC1s to DCs and detected that enhanced immune regulation of mDC1, diminished capacity of pDCs, and increased proportion of the T-cell phenotypes in peripheral blood might be factors in eosinophilic CRS pathogenesis [135]. Antigen presentation and T-cell responses involve co-stimulatory molecules, such as programmed cell death-1 (PD-1) and a study showed PD-1highCXCR5-CD4+ T cells to participate in local immunoglobulin production independent of eLTs in CRSwNP [136]. Osteoprotegerin (OPG) plays an important role in the immune response, regulating the interactions between T cells and DCs, and elevated serum OPG has been shown to predict the positive outcome of dupilumab treatment of CRS patients [137].

2.2.2.2 | T Cells. T cells play a vital role in immune defense, with various subsets that have distinct functions [1]. $CD4^+$ Th cells communicate with other immune cells, while CD8+ cytotoxic T cells kill infected and damaged cells [1] and regulatory T cells (Tregs) maintain immune balance [1]. T-cell plasticity allows them to adapt to different situations [1]. In CRS, there is often an excessive and prolonged immune response, with a decrease in Tregs but an increase in other T-cell subsets depending on the type of CRS. Ma et al. evaluated transcriptomes of single Th cells from nasal polyps, detecting distinct clusters such as Tregs, Th2 cells, ILC2s, and 3 subsets of $CD4^+$ CTLs. GATA3 expression was a feature of polyp Tregs, whereas Th2 cells highly expressed TCN1, CD200R, and HPGDS and were enriched for genes involved in lipid metabolism. A portion of polyp Th2 cells expressed the PGD2 receptor CRTH2, whereas a subpopulation of CD109+CRTH2-Th2 cells expressed LAG3 and TIM3 and produced IL-10 [138]. The $CD4^+$ T-cell/B-cell ratio can be used as a potential indicator to differentiate between eosinophilic CRS and noneosinophilic CRS [139].

B cells and immunoglobulins are involved in CRS. Low immunoglobulin levels can lead to recurrent acute exacerbations of CRSsNP [140]. CRSwNP is associated with elevated B cells, plasma cells, and local immunoglobulin production. Elevated BAFF levels drive class switching to IgE and IgA, and autoimmunity can be a factor in CRSwNP, targeting proteins like BP180 [141, 142]. IgE, IgG4, and IgG antibodies also play roles in CRS, with IgE having a significant impact on CRSwNP. The complement system may be activated excessively in CRS, possibly due to antibody-mediated processes [1, 88]. Antibody-secreting cells of polyp tissue from patients with N-ERD have been shown to express higher levels of functional IL-5Rα and markers associated with cell cycling and proliferation than do antibody-secreting cells from patients with aspirin-tolerant CRSwNP [143].

Together, adaptive immune cells play a crucial role in the pathogenesis of CRS. Events associated with T2-high CRS appear relatively analogous to those observed in T2-high asthma pathogenesis. Conversely, the connection between endotypes and underlying mechanisms is less evident for T2-low CRS compared to T2-low asthma, possibly due to greater heterogeneity among these endotypes.

2.2.3 | Special Aspects on the Mechanisms of CRS With Comorbid Asthma or NERD

Comorbid N-ERD is often seen as a sign of T2 inflammation [144]. However, nasal polyps from these patients show mixed inflammatory profiles [145], as is the case in N-ERD-associated asthma [146]. Clinicians should therefore be careful when automatically labelling N-ERD as a T2 endotype. There are ongoing

placebo-controlled trials of the effect of biologics on patients with CRSwNP and N-ERD. Real-world or post hoc studies of CRSwNP or asthma patients have shown that biologics are effective on N-ERD patients [147, 148]. In individuals with N-ERD, the leukotrienes generated by the 5-lypooxygenase pathway cannot be degraded and accumulate, inducing symptoms in the upper and lower airways [149]. N-ERD is mediated by the inability of eosinophils, mast cells, basophils, and platelets to respond to the additional metabolic demands occurring in patients with severe T2 airway inflammation who take strong cyclooxygenase-1 inhibitors. A study group investigated levels of 33 different nasal and serum cytokines and revealed increased activated naive B-cell levels in CRSwNP and N-ERD, while resting naive B cells were higher in CRSsNP [150]. In addition, nasal samples from patients with N-ERD and CRSwNP have shown high levels of T2 associated cytokines IL-5, IL-9, Eotaxin, and CCL17 [151].

3 | Clinical Tools and Markers for Endotyping

There is some literature that has evaluated the association of endotypes with symptoms, findings, or treatment responses. Although the findings still need validation, they suggest that endotypes produce different clinical patterns, which might be useful, such as in the decision of biologic therapy.

3.1 | Patient Symptoms and Endotyping

In a study with 106 Chinese CRSwNP patients and 31 controls, clinical features were linked to markers of either T1 (interferon gamma), T2 (Charcot–Leyden crystal galectin), or T3 (IL-17A) CRS. Associations were found between facial pain and type 1 endotype, olfactory dysfunction with type 2, and purulent rhinorrhea with T3 [152]. Another study divided 298 Chinese CRSwNP patients between eosinophilic CRS and non-eosinophilic CRS based on peripheral blood samples (which roughly correlates to T2 versus non-T2 as used in EPOS2020). In these subjects, nasal congestion was associated with non-eosinophilic CRS and olfactory dysfunction with eosinophilic CRS [153]. In a similar study from the same group, 502 CRSwNP patients were divided between eosinophilic and non-eosinophilic disease based on tissue levels of eosinophils. In this study, they relied on medical history and nasal endoscopy/nasal polyp scores. The presence of asthma, olfactory dysfunction, rhinorrhea, and a high nasal polyp score was able to predict eosinophilic CRSwNP with good reliability [154]. Nasal tissue expression of IgE, IL-5, and IL-13 has been shown to be associated with clinical features of CRswNP [155].

3.2 | Treatment Responsiveness

Clinically, responsiveness to oral corticosteroids (OCS), especially for smell loss, is linked to T2 inflammation and can as such predict olfactory responsiveness to dupilumab [156]. A Chinese study was performed with 26 CRSwNP patients receiving 30 mg of prednisolone daily for 1 week [157]. Clinical improvement was more clearly associated with eosinophilia than with self-reported improvement, which could suggest that lack of patient-reported OCS-responsiveness does not automatically mean that no changes are brought about at a cellular level [157]. A retrospective histopathological analysis of CRSwNP patients who had received different biologics has shown that decreased mucosal eosinophilia and thickened basement were associated with decreased response to biologic therapy [158].

3.3 | Relation of Clinical Characteristics to Inflammatory Endotype

A study has shown that the presence of nasal polyps, asthma comorbidity, smell loss, and allergic mucin are associated with the presence of T2 endotype in all CRS patients [159]. The T1 endotype was significantly more common in females, and the presence of pus was significantly associated with the T3 endotype in all CRS [159]. Smell loss was associated with the T2 endotype and pus with the T3 endotype.

3.4 | Laboratory Tests for Endotyping

Despite a large number of known markers for inflammatory endotypes, readily available tests for clinicians are contrastingly scarce. At this point, a rough distinction can be made between T2 and non-T2 CRS based on serum total IgE or blood eosinophil levels. EPOS2020 suggested a cut-off of 100 kU/L for IgE [1], although there is no supporting literature. Most publications on IgE levels in CRS are based on tissue or nasal fluid samples. Furthermore, other diseases, such as allergic rhinitis, are also linked to an increased serum total IgE. In a study with 300 severe CRSwNP patients indicated for biologics, blood eosinophils proved to be the dominant determinant for T2 disease [156]. However, one should be aware that the level of blood eosinophils can strongly vary over time and is influenced by therapies such as oral corticosteroids and biologicals. In line with the asthma field, an expert panel from EPOS/EUFOREA has suggested to lower the blood eosinophil threshold for T2 inflammation from 0.25 to 0.15×10^9 cells/L [160].

3.5 | Histology and Cytology for Endotyping

EPOS2020 suggests a cut-off of 10 eosinophils per high-powered field as a marker of T2 inflammation [1]. However, in a systematic review including 142 studies, a wide range of 29 different cut-off values was found for the level of tissue eosinophils. Of these studies, 13 reported their own methodology to establish a cut-off, with reference standards again varying widely, for example, polyp recurrence, or presence of comorbidities, or comparison to healthy controls, or cluster analysis [161]. It is safe to say that tissue eosinophils are a marker of T2 inflammation, but without a clear consensus on cut-offs for quantification. Eosinophil peroxidase levels can be measured from nasal mucosal brushing samples by using ELISA and are associated with clinical markers of T2 inflammation and tissue eosinophilia and may provide a valuable diagnostic tool to delineate eosinophilic CRS [162]. A study group detected significant improvement in nasal polyp score, olfaction, and symptom scores, as well as eosinophil and mast cell infiltration in the nasal cytological samples after dupilumab treatment of CRSwNP patients [163]. Thus, nasal cytology is worth further research for its potential effect to evaluate treatment outcomes together with clinical parameters.

3.6 | Nitric Oxide for Endotyping

Fractional exhaled nitric oxide (FeNO) is used as a measure of eosinophilic inflammation of the lower airways, helping in endotyping and guiding therapy of patients with asthma [164]. There is no or limited evidence of the usefulness of measuring FeNO for assessing CRS endotypes [165]. The mucosa of the paranasal sinuses produces vast amounts of nitric oxide compared to the lower airways already in a healthy state [166]. As there is an inflammation-induced increased production of nasal NO (nNO) in CRSwNP patients with an eosinophilic/T2 endotype, measuring nNO seems to be helpful in distinguishing these from non-T2 CRS patients [167]. However, the increased nNO production in CRS patients might be obscured by the blockage of sinus ostia due to polyps and/or edema. As such, nNO is deemed potentially helpful in CRS patients but not strongly recommended [168]. Although promising results exist, further studies are still warranted to evaluate the clinical role of endotypes.

4 | Unmet Needs

In the previous sections we summarized endotyping of CRS, and yet we must admit that in clinical practice, health care practitioners do not have many practical biomarkers available to them. A workable approach for endotyping must resolve several unmet needs: increasing diagnostic precision, reducing heterogeneity, standardizing outcome measurements and clinical tools, broadening the scope away from T2 disease, and increasing research on basic mechanisms in several areas. Problems and possible solutions are summarized in Table 1.

5 | Conclusion

CRS is an umbrella condition that comprises various disease entities and endotypes. Sinonasal mucosa interacts with various inhaled agents from birth, maintaining a barrier that regulates host immune responses. In healthy individuals, brief breaches of this barrier trigger a specific, self-limited immune response targeting pathogens. In contrast, chronic rhinosinusitis (CRS) is characterized by persistent, complex immune responses involving T1, T2, or T3 pathways, along with tissue remodeling. The cause of CRS remains unclear, likely resulting from a combination of genetic susceptibility and environmental stressors. Host genetics, particularly related to the epithelial barrier and immune response, play a role in CRS onset. The antigens triggering CRS are not well understood, with evidence suggesting bacteria and fungi involvement. Environmental factors and gene–environment interactions may contribute to inflammation in CRS.

TABLE 1 | Unmet needs of endotype research of CRS.

Unmet needs	Problem	Potential solution
Lack of diagnostic precision of underlying disease drivers	Lack of standardized definitions of potential causal disease drivers such as N-ERD, EGPA, AFRS, and microbial infection that can determine the endotype	• Increased research focus on these potential disease drivers to obtain more insights • Consensus about definitions and diagnostic criteria of these drivers • Increased multidisciplinary approach since often multiple organ systems are involved
Lack of valuable standardized outcome measurements	The current standardized outcome measurements (NPS, nasal patency measurements, SNOT-22, and CT) have disadvantages and are unfit to determine the endotype Serum eosinophil counts do not correspond well with local responses	The need for a standardized nasal sampling technique to identify the inflammatory cell population at the local level
T2 bias	Research has focused mainly on eosinophilic CRSwNP, and currently most of the biomarkers available are considering type 2 (T2) inflammatory parameters Current absence of biomarkers to • Distinguish among the different non-T2 endotypes • Predict treatment response and remission • Overlap of endotypes • Intra-individual plasticity of ILCs and T cells	Incentivize researchers to focus on non-eosinophilic CRS/CRSsNP to • Better characterize these populations • To study disease mechanisms • To find potential biomarkers for classification, severity, and therapeutic response • To better understand regulation of immunologic events under normal homeostasis, under defense and in the pathogenesis of CRS
Heterogeneity of available studies	Studies are heterogeneous at the level of • CRS populations tested (inclusion and exclusion criteria) • Outcome measurements • Biological sampling methods (tissue vs. secretions, vs. cytology) • Cut-off values (e.g., eosinophil counts)	Large-scale multicenter studies on CRS endotyping, considering well-defined CRS populations that focus on potential biomarkers obtained by simple and cheap sampling methods

T2 high cytokine pattern is associated with most CRS cases, such as CRSwNP, CRS with asthma and/or N-ERD, and eosinophilic CRS. Biologics, such as dupilumab, mepolizumab, and omalizumab, have been shown to be clinically effective in CRSwNP, even despite the presence or absence of tissue eosinophilia. Still, there is a need for new cost-effective, safe, and accurate biomarkers to help, such as in identifying patients who benefit from biologic treatment and achieve remission. Despite progress in endotype research, most biomarkers are not yet available, helping in clinical decision-making, despite eosinophils and neutrophils. Currently, the lack of knowledge in this area is a significant challenge. Still, thanks to active research, novel wetlab methods, and use of artificial intelligence in analyses, novel diagnostic and therapeutic innovations to treat the burden of CRS will be soon available.

Author Contributions

All authors helped shape the research, participated in writing, and provided critical feedback on the manuscript. STS performed screening of the literature.

Conflicts of Interest

STS reports consultancies for ALK-Abelló, AstraZeneca, Clario, ERT, GlaxoSmithKline, Novartis, Sanofi Pharma, OrionPharma, Roche Products, and grants from GlaxoSmithKline and Sanofi. All are outside the submitted work. SR has acted as a consultant and/or advisory board member for GSK, Sanofi/Regeneron, Novartis, and Boehringer Ingelheim. The department of otorhinolaryngology/head–neck surgery had received research grants from GSK, Sanofi/Regeneron, Novartis. All are outside the submitted work. JMS has received honoraria for consultancy, projects, advisory boards, and talks from AstraZeneca, GlaxoSmithKline, MSD, Novartis and Sanofi. VH Has received consultancy fees from ALK-Albelló, GSK, Sanofi, and Astra-Zeneca outside of the submitted work. SG has acted as a consultant and/or advisory board member for Sanofi, GSK, and Novartis, outside of the submitted work. AMC reports consultancy or advisory fees and/or research support and other, all via Technical University of Munich from ALK-Abello, AstraZeneca, Bencard/Allergen Therapeutics, ASIT Biotech, GSK, Hippo Dx, Novartis, LETI, Roche, Sanofi, Regeneron, Zeller, grants from the Federal German Ministry of Education and Research, German Lung Center, and the European Institute of Technology, all outside this submitted work. PG reports personal fees and non-financial support from Stallergenes Greer during the conduct of the study. LK has received research grants from Allergy Therapeutics/Bencard, Great Britain/Germany; ALK-Abelló, Denmark; Allergopharma, Germany; Aimmune, USA; ASIT Biotech, Belgium; AstraZeneca, Sweden; Bionorica, Germany; Biomay, Austria; Boehringer Ingelheim, Germany, Circassia, USA; Chiesi, Italy; Cytos, Switzerland; Curalogic, Denmark; HAL, Netherlands; Lofarma, Italy; Menarini, Italy; Viatris/Mylan, USA; Novartis, Switzerland; Leti, Spain; ROXALL, Germany; GlaxoSmithKline (GSK), Great Britain; Sanofi, France; Stallergenes, France; Thermofisher, USA; and/or has served on the speaker's bureau or was consulting for the above-mentioned pharmaceutical companies. LK is the current President of German Society of Allergology AeDA, Vice-President of the European Academy for Allergy and Clinical Immunology (EAACI), Vice-President of the German Academy for Allergy and Environmental Medicine, and Editor-in-Chief of AllergoJournal and AllergoJournal International. All are outside of the submitted work. All other authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.