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Review

Epigenetic Immunologic Biomarkers in Allergic Rhinitis and CRSwNP: Methylation Signatures and Translational Prospects

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Abstract: Allergic rhinitis (AR) and chronic rhinosinusitis with nasal polyps (CRSwNP) are distinct inflammatory disorders that may share type 2 immune features but differ in tissue pathology, clinical course, and therapeutic decision-making. This narrative review evaluates epigenetic immunologic biomarkers in the two diseases, with emphasis on deoxyribonucleic acid (DNA) methylation while also considering histone regulation and non-coding ribonucleic acid (RNA) networks. A structured literature search was used to organize evidence by disease, specimen, study design, and degree of clinical validation. Human AR studies provide signals in nasal epithelium, peripheral blood, and immune-cell subsets that relate to allergen exposure, symptom burden, immunoglobulin E (IgE)-associated biology, or treatment-associated changes. In CRSwNP, most epigenetic evidence comes from polyp or bulk sinonasal tissue and identifies methylation, chromatin, and microRNA patterns linked to inflammation and remodeling. These findings are biologically informative, but bulk-tissue signals can be strongly influenced by cell composition, and direct comparison across blood, nasal brushings, polyp tissue, and experimental models is not valid without qualification. No methylation- or RNA-based classifier has yet been prospectively validated to screen for future CRSwNP, replace current type 2 inflammatory markers, or select biologic therapy. Epigenetic enzyme inhibition and RNA delivery remain predominantly preclinical and face substantial challenges in target specificity, delivery, durability, and safety. The most credible path toward translation is therefore disease-specific and tissue-aware: standardized nasal sampling, cell-resolved profiling, independent multicenter validation, longitudinal designs, and demonstration of added value over established clinical biomarkers. Early risk prediction should currently be viewed as a research objective rather than a clinical application.

Keywords: Allergic Rhinitis; Chronic Rhinosinusitis with Nasal Polyps; DNA Methylation; Epigenetic Biomarkers; Nasal Epithelium; Non-Coding RNA; Molecular Endotyping; Precision Medicine

1. Introduction

Allergic rhinitis (AR) and chronic rhinosinusitis with nasal polyps (CRSwNP) both involve the upper airway, but they should not be treated as interchangeable manifestations of a single disease process. AR is primarily an allergen-associated inflammatory disorder of the nasal mucosa, often characterized by IgE-dependent responses, episodic or persistent nasal symptoms, and exposure-related variability. CRSwNP is a chronic inflammatory condition of the

sinonasal mucosa in which polyp formation, tissue remodeling, recurrence, olfactory dysfunction, and comorbid asthma or aspirin-exacerbated respiratory disease are clinically important. Type 2 inflammation and epithelial barrier dysfunction can occur in both conditions, yet their tissue context, outcomes, and treatment pathways remain different [1–3].

Epigenetic regulation offers one way to study how environmental exposures, mucosal cells, and immune programs interact without altering the underlying DNA sequence. DNA methylation, histone modifications, and non-coding RNA networks can influence epithelial barrier genes, T-cell polarization, regulatory T-cell function, eosinophilic inflammation, and inflammatory memory [4–8]. However, the biological meaning of an epigenetic signal depends on where and how it was measured. A methylation difference in peripheral blood mononuclear cells (PBMCs), for example, cannot be assumed to represent the nasal epithelium, and a signal detected in a nasal polyp may partly reflect altered proportions of epithelial cells, eosinophils, lymphocytes, fibroblasts, and glandular cells rather than cell-intrinsic reprogramming.

The translational literature is similarly heterogeneous. Some studies show reproducible disease-associated or exposure-responsive epigenetic differences, whereas evidence for prospective disease prediction, clinically deployable endotyping, or treatment selection is much thinner [4,9–11]. For CRSwNP in particular, established clinical decisions about biologic therapy continue to rely on phenotype and type 2 inflammatory markers rather than epigenetic classifiers [3,12]. The present review therefore separates AR-specific evidence, CRSwNP-specific evidence, and indirect evidence from other allergic diseases or experimental systems. It also distinguishes association from validation and treats early screening as a future research possibility rather than a current clinical application. **Figure 1** summarizes the mechanistic domains discussed in this review; its translational elements should be read as investigational rather than as validated clinical pathways.

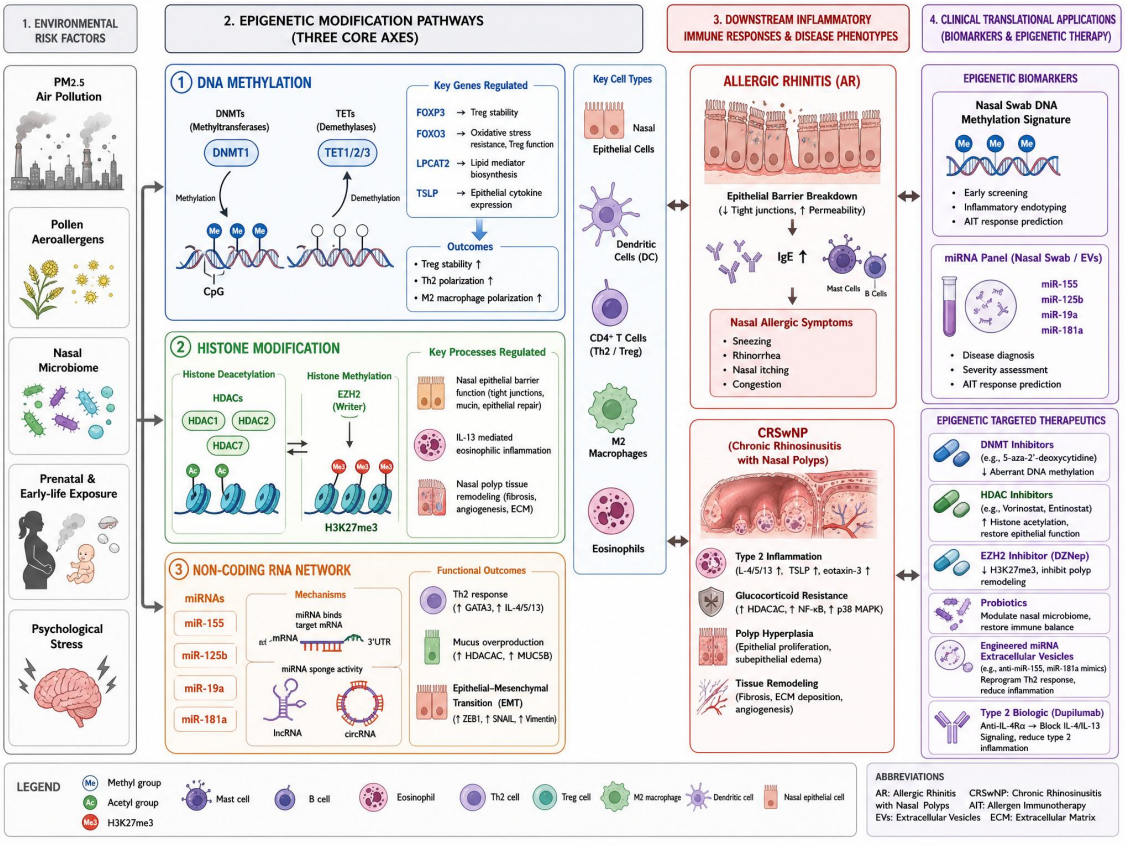

Figure 1. Conceptual overview of environmental exposures, epigenetic regulatory layers, inflammatory pathways, and candidate translational applications in AR and CRSwNP.

Note: The figure is an evidence map rather than a validated clinical workflow: biomarker and therapeutic elements remain investigational unless otherwise stated in the text. Abbreviations: AR, allergic rhinitis; CRSwNP, chronic rhinosinusitis with nasal polyps; DNMT, DNA methyltransferase; HDAC, histone deacetylase; miRNA, microRNA; Treg, regulatory T cell.

2. Literature Search Strategy and Evidence Framework

This article was prepared as a structured narrative review rather than a systematic review or meta-analysis. For the revised manuscript, the reference set was updated through targeted PubMed/MEDLINE searches conducted on 14 September 2026, supplemented by backward reference checking from recent reviews, consensus documents, and the articles specifically suggested during peer review. Search combinations included the disease terms "allergic rhinitis," "chronic rhinosinusitis with nasal polyps," "CRSwNP," and "nasal polyp" together with "epigenetic," "DNA methylation," "methylome," "histone," "HDAC," "EZH2," "microRNA," "miRNA," "lncRNA," "circRNA," "nasal epithelium," "biomarker," "endotype," "immunotherapy," and "environmental exposure." The principal time window was January 2011 through September 2026, with earlier mechanistic concepts considered when needed to interpret later studies.

Eligible publications were peer-reviewed human, translational, or mechanistic studies that directly addressed epigenetic regulation or biomarker development relevant to AR or CRSwNP. Systematic reviews, high-quality narrative reviews, and task-force reports were retained when they provided synthesis or clinical context. Studies in asthma, general atopy, PBMCs, isolated T-cell populations, or animal models were retained only when they addressed a mechanism directly relevant to the review question; these sources are identified in the text as indirect or preclinical evidence and are not presented as disease-specific validation. Duplicate reports, conference abstracts without sufficient methodological detail, and publications that did not allow the disease, tissue, or endpoint to be identified were excluded from the revised evidence set. The retained publications were evaluated for disease population, specimen, study design, epigenetic assay, and clinical endpoint. Because this was a narrative rather than a systematic review, a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-style flow count was not generated; 60 publications were included in the final narrative synthesis.

Evidence was appraised qualitatively. Human studies performed in disease-relevant nasal or sinonasal tissue were weighted more heavily for local biomarker interpretation than blood-only studies; prospective or longitudinal designs were weighted more heavily for prediction than case-control comparisons; and experimental or animal studies were treated as mechanistic support rather than clinical evidence. No formal risk-of-bias score or pooled effect estimate was applied because of substantial heterogeneity in tissues, platforms, endpoints, and study designs. To limit interpretive bias, this revision explicitly labels cross-disease extrapolation, highlights tissue and cell-composition confounding, and identifies claims for which prospective validation is absent.

3. Epigenetic Mechanisms in Nasal Airway Immunity

3.1. DNA Methylation and Demethylation

DNA methylation is the most extensively studied epigenetic layer in allergic airway research. DNA methyltransferases (DNMTs) add methyl groups to cytosine residues, whereas ten-eleven translocation (TET) enzymes participate in active demethylation. The mechanistic evidence is not uniform across tissues or species. In an ovalbumin-induced AR mouse model, DNMT1 inhibition reduced T helper type 2 (Th2) polarization; the proposed pathway involved methylation at the *FOXO3* promoter and downstream changes in NF-kappaB/GATA3 signaling [13]. This is useful mechanistic evidence for AR biology, but it is an animal intervention study and does not establish a human nasal biomarker.

Human AR data provide a different type of evidence. TET1 expression and global 5-hydroxymethylcytosine were reported to be altered in PBMCs and dendritic-cell populations from patients with AR, and ex vivo allergen challenge modified TET1-associated dendritic-cell responses [14]. TET2 has also been linked to macrophage polarization, although the supporting work is predominantly experimental; in an AR mouse model, TET2-dependent RNA demethylation influenced *KLF4* and *ROCK1*-related pathways [15]. These observations support cell-specific epigenetic regulation of allergic immunity, but they should not be merged into a single "nasal methylation" pathway because they arise from different compartments and model systems.

3.2. Histone Regulation and Chromatin Remodeling

Histone acetylation and methylation regulate chromatin accessibility and can alter inflammatory gene expression. Reviews of AR describe changes in HDAC activity and experimental benefit from HDAC inhibition, but much of this evidence is preclinical rather than derived from controlled human therapeutic studies [16]. In CRSwNP, histone-

related observations include altered HDAC expression and more recent evidence that epithelial HDAC7 can act as a negative-feedback regulator of interleukin-13 (IL-13)-driven eosinophilic inflammation. Lower HDAC7 expression in CRSwNP tissue was associated with more intense type 2 inflammation, while HDAC7 silencing in epithelial cells increased CCL26 production [17, 18]. This direct CRSwNP evidence is more informative for local disease biology than extrapolation from asthma or systemic immune cells.

EZH2 requires particular caution. Canonically, EZH2 is the catalytic component of polycomb repressive complex 2 (PRC2) and promotes trimethylation of histone H3 lysine 27 (H3K27me3) [19]. A 2025 CRSwNP study reported higher EZH2 and HMGA2 expression in polyp tissue and, in cultured human nasal epithelial cells, reported that EZH2 knockdown increased H3K27me3 signal while reducing HMGA2, whereas EZH2 overexpression produced the opposite pattern [20]. The direction of the H3K27me3 change is counterintuitive relative to the canonical enzymatic function of EZH2. It should therefore be presented as a study-specific observation, not as an established general mechanism. Possible explanations include assay or normalization limitations, differences between global and locus-specific chromatin marks, non-canonical EZH2 effects, or compensation within PRC2 such as EZH1 activity. Independent replication with quantitative chromatin assays is needed before this finding is used to support therapeutic targeting.

The distinction between disease model and disease-specific evidence is also important for pharmacology. The EZH2 inhibitor 3-deazaneplanocin A (DZNep) reduced inflammation in an ovalbumin-driven allergic airway model [21], but this does not constitute evidence that EZH2 inhibition is effective or safe in patients with CRSwNP. The therapeutic implications are therefore addressed separately in Section 8.

3.3. Non-Coding RNA Networks

Non-coding RNAs (ncRNAs), including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), provide an additional regulatory layer. In AR, reviews and small clinical studies describe altered miRNA patterns involving miR-135a, miR-146a, miR-181a, miR-155, miR-19a, and other candidates, with proposed effects on cytokine signaling, T-cell differentiation, eosinophilic inflammation, and epithelial responses [16,22,23]. A pediatric clinical study found disease- and season-dependent differences in miR-125b, miR-181a, and miR-206, but the cohort was small and included several allergic phenotypes, so these signals are best regarded as candidate biomarkers rather than validated diagnostic tests [24]. Serum miR-4497 was reduced across pediatric allergic diseases including AR, and functional experiments supported an anti-inflammatory role; because the clinical signal was shared with atopic dermatitis and asthma, it is not AR-specific [25].

In CRSwNP, miR-125b, miR-155, miR-21, miR-142-3p, miR-19a, miR-4492, and other miRNAs have been reported in polyp tissue or summarized across small observational studies [17,26,27]. Associations with eosinophilia, remodeling, corticosteroid response, or recurrence are biologically plausible, but heterogeneity in tissue processing, normalization, endotype definitions, and sample size limits direct comparison. LncRNA and circRNA networks are also increasingly described, yet the field currently contains more discovery-level signatures than reproducible single-marker clinical assays [11,22,26]. Treatment-associated epitranscriptomic work in AR has identified *LUCAT1* and other messenger RNA (mRNA)/lncRNA changes during allergen immunotherapy, but such changes do not automatically qualify as baseline predictors of response [28]. Representative candidates and their evidence limitations are summarized in **Table 1**.

Table 1. Representative candidate miRNAs/lncRNAs/circRNAs in AR and CRSwNP and their current evidence status.

Disease/Context	Candidate ncRNA(s)	Specimen/Evidence Source	Reported Signal	Current Interpretation	Ref.
AR	miR-125b; miR-181a	Pediatric seasonal/perennial AR cohort	Expression differed by phenotype/season; ROC signal reported for seasonal AR	Exploratory single-cohort signal; requires larger external validation	Tunçer et al. [24]
AR	miR-206	Pediatric perennial AR/non-atopic asthma cohort	Lower expression in perennial AR; association with total IgE reported	Not AR-specific; small cohort and cross-phenotype comparison	Tunçer et al. [24]

Table 1. *Cont.*

Disease/Context	Candidate ncRNA(s)	Specimen/Evidence Source	Reported Signal	Current Interpretation	Ref.
AR/allergic disease	miR-4497	Serum from children with AR, asthma, or atopic dermatitis; functional experiments	Downregulated across allergic diseases; anti-inflammatory effects in experimental systems	Cross-disease rather than AR-specific biomarker	Yoo et al. [25]
AR during AIT	*LUCAT1* and other N6-methyladenosine (m6A)-associated lncRNA/mRNA signals	Nasal mucosal epithelial cells during allergen immunotherapy	Treatment-associated epitranscriptomic changes correlated with clinical scores	Pharmacodynamic association; baseline predictive value not established	Lai et al. [28]
AR	Broader miRNA/lncRNA/circRNA networks	Reviews of nasal/immune-cell and experimental studies	Multiple candidates linked to Th2/Treg and epithelial pathways	Marked heterogeneity; many candidates lack independent replication	Li et al. [22]; Cheng et al. [23]
CRSwNP	miR-125b; miR-155; miR-21; miR-142-3p; miR-19a; miR-4492	Predominantly nasal polyp tissue and small observational studies	Associations reported with inflammation, eosinophilia, remodeling, steroid response, or recurrence	No prospectively validated clinical classifier	Liu et al. [17]; Gatsounia et al. [26]; Pasupat et al. [27]
CRSwNP	miR-18a; miR-124a; miR-142-3p	Candidate literature summarized in epigenetic reviews	Proposed links to glucocorticoid resistance	Mechanistic/association evidence; clinical prediction unvalidated	Liu et al. [17]
CRSwNP	lncRNA/circRNA signatures (multiple discovery candidates)	Omics and review literature	Potential competing endogenous RNA (ceRNA) and inflammatory regulatory networks	Discovery-level; no single lncRNA/circRNA marker has consistent prospective validation	Brar et al. [11]; Gatsounia et al. [26]

Note: Abbreviations: AIT, allergen-specific immunotherapy; AR, allergic rhinitis; circRNA, circular RNA; CRSwNP, chronic rhinosinusitis with nasal polyps; lncRNA, long non-coding RNA; miRNA, microRNA; ROC, receiver operating characteristic. The table is representative rather than exhaustive. None of the listed candidates is currently a prospectively validated stand-alone clinical screening or biologic-selection test.

3.4. Tissue and Cell-Type Specificity: A Central Interpretive Constraint

Tissue specificity is not a secondary methodological issue; it is central to whether an epigenetic biomarker can be interpreted biologically. Blood is convenient and useful for systemic immune phenotyping, but blood methylation may not track the epigenetic state of nasal epithelial cells. Conversely, nasal brushings enrich for epithelial material but can still vary in cell composition, sampling depth, inflammation, and technical handling. Nasal polyp tissue is directly relevant to CRSwNP pathology, yet bulk tissue contains changing proportions of epithelial cells, eosinophils, mast cells, T and B cells, macrophages, fibroblasts, endothelial cells, and glandular cells [4,9,11].

Accordingly, a differentially methylated position or region in bulk tissue may indicate a true cell-intrinsic change, a shift in cell proportions, or both. Seasonal AR provides a clear example: methylation profiles in CD4+ T cells separated allergic patients from controls, but the investigators also noted that differences in memory T-cell composition could contribute to the signal [29]. Similar concerns apply to Similar concerns apply to bulk chronic rhinosinusitis (CRS) methylome studies [30]. Future biomarker work should therefore report cell composition or deconvolution methods, validate key loci in purified or single-cell populations when feasible, and avoid comparing effect directions across PBMCs, nasal brushings, and polyp tissue as though they were measurements of the same biological compartment. Single-cell and cell-resolved approaches offer a way to distinguish lineage composition from cell-intrinsic regulatory change [31].

4. Environmental Exposures and the Nasal Epigenome: Direct and Indirect Evidence

4.1. Air Pollution and Early-Life Exposure

Air pollution can damage epithelial barriers and alter inflammatory signaling, but the available epigenetic literature spans different diseases and tissues [32–34]. Traffic-related air pollution has been linked to AR and to oxidative pathways capable of modifying immune regulation [35]. In a Danish birth cohort, prenatal exposure to nitrogen dioxide (NO_2), particulate matter ≤2.5 μm (PM2.5), and particulate matter ≤10 μm (PM10) was associated with early-life immune perturbations and later allergic outcomes [36]. That study strengthens the exposure-to-immune-risk connection, but it should not be cited as direct proof that nasal DNA methylation mediates CRSwNP or AR pathogenesis unless the epigenetic endpoint was measured in the relevant tissue.

Evidence for pollution-associated methylation often comes from systemic immune cells. In children exposed to

polycyclic aromatic hydrocarbons, increased methylation at the *FOXP3* locus in T cells was associated with impaired regulatory T-cell function and higher IgE [37]. This finding is mechanistically relevant to allergic inflammation, yet it was not a CRSwNP study and does not establish a nasal epithelial biomarker. Such evidence is therefore most appropriately used to support a general gene-environment mechanism rather than disease-specific clinical prediction.

4.2. Aeroallergen and Pollen Exposure

Controlled allergen exposure provides some of the most direct evidence that epigenetic measurements can change with allergic symptoms. In grass pollen-allergic participants, North and colleagues identified exposure-associated methylation changes in blood and nasal samples, including loci related to *TPSG1*, *SLFN12*, and *MUC4*, and baseline methylation was associated with subsequent symptom intensity during challenge [10]. Importantly, the study included both blood and nasal measurements; these should be reported separately rather than collapsed into a single "nasal" signature. A birch-pollen validation component linked *MUC4* methylation in nasal brushings with nasal airflow and expression changes [10].

Seasonal AR studies in isolated CD4+ T cells likewise show that methylation can distinguish patients from controls both in and outside pollen season [29]. These observations are useful for understanding exposure-responsive immune states. They do not, however, demonstrate that an epigenetic test can predict the initial onset of AR in an asymptomatic population. The relevant clinical endpoint is symptom response in known allergic individuals, not population screening.

4.3. Microbial Exposure and the Upper-Airway Microbiome

Among early-life studies, the relationship between upper-airway microbiota and later AR is especially informative because it includes a disease-relevant mucosal compartment. In the Copenhagen Prospective Studies on Asthma in Childhood cohort, early microbial diversity was associated with subsequent AR, and an upper-airway epithelial methylation signature at age 6 partly linked early microbial exposure with AR at the same age [38]. The finding supports an exposure-epigenome-disease relationship, but because methylation and AR were assessed at the same age, it is not equivalent to a prospectively validated pre-symptomatic screening test.

Broader work on microbial-epithelial-immune interactions provides a biological framework for such findings [7]. By contrast, lncRNA differences described in peripheral blood from Finnish and Russian Karelia adolescents with contrasting allergy risk are geographically and immunologically informative but not direct evidence for the nasal epigenome of AR or CRSwNP [39]. The distinction between local mucosal evidence and systemic or cross-population evidence should therefore be maintained.

4.4. Prenatal Stress, Maternal Allergy, and Transgenerational Claims

Prenatal and early-life periods are plausible windows for durable immune programming, but the strength of evidence varies sharply by design [40,41]. Maternal AR models in mice have linked offspring immune abnormalities with *FOXP3* promoter methylation, and some changes were reversible after removal of allergen exposure [42,43]. These studies are valuable for mechanism, but they remain animal evidence. They should not be presented as proof that the same methylation pattern is inherited across human generations or as a validated predictor of childhood AR.

Human epidemiologic observations also require restrained interpretation. Paternal adverse childhood experiences were associated with offspring atopy-related outcomes in a Finnish cohort [44], but the study does not establish a specific nasal epigenetic transmission pathway. Reviews of prenatal stress and regional environmental influences similarly support developmental susceptibility without demonstrating an AR- or CRSwNP-specific epigenetic biomarker [41,45]. Transgenerational epigenetic inheritance in these disorders therefore remains a hypothesis requiring direct molecular and longitudinal confirmation.

5. Disease-Specific Epigenetic Evidence in Allergic Rhinitis

5.1. DNA Methylation Signatures

The AR methylation literature includes both disease-specific studies and broader allergic-airway studies. A large epigenome-wide association study of total serum IgE identified multiple low-methylation loci related to

eosinophil and inflammatory biology [46]. This is important background for allergic immune regulation, but serum IgE is a cross-disease phenotype and the study should not be treated as an AR diagnostic validation. By contrast, AR challenge studies and cedar-pollinosis cohorts directly connect methylation measurements with nasal symptoms or disease severity [10,47].

In cedar pollen AR, methylation of *IL4* in PBMCs was associated with IgE-related measures, whereas *LPCAT2* methylation in nasal scraping samples showed a trend with clinical severity [47]. The difference between these compartments illustrates why a blood signal and a nasal signal may have different biomarker implications. In children, nasal methylome profiling has identified regions associated with asthma, sensitization, AR, IgE, and fractional exhaled nitric oxide, including loci annotated to *EPX*, *IL4*, *IL13*, *ACOT7*, and *SLC25A25* [9]. The strength of this work is the feasibility of minimally invasive nasal sampling and the breadth of airway phenotypes; the limitation is that the signals are not specific to incident AR and were not developed as a prospective clinical screening assay.

5.2. T-Cell Regulation and Non-Coding RNA in AR

Regulatory T-cell stability and Th2 polarization are frequently linked to epigenetic control in allergic disease. Methylation at the *FOXP3* locus can influence regulatory T-cell phenotype, and reviews of allergic airway disease support an association between altered *FOXP3* methylation and impaired immune tolerance [48,49]. In AR models, DNMT1-dependent methylation of the *FOXO3* promoter has been connected to GATA3-associated Th2 signaling [13]. These pathways are mechanistically coherent, but the evidence includes different species and cell types; they should be discussed as mechanisms rather than as a single validated AR biomarker panel.

The same caution applies to ncRNAs. MiR-125b and miR-181a have shown discriminatory signals in seasonal AR, while miR-206 has been associated with perennial AR in a small pediatric cohort [24]. MiR-4497 was reduced in serum across several pediatric allergic diseases, including AR, and showed functional effects in experimental systems [25]. These observations justify further validation but do not yet establish disease-specific reference ranges, inter-laboratory reproducibility, or prospective predictive performance.

6. Disease-Specific Epigenetic Evidence in CRSwNP

6.1. DNA Methylation in Polyp and Sinonasal Tissue

CRSwNP methylation evidence is largely tissue-based. Reviews and genome-wide studies describe differential methylation in pathways related to inflammation, immune regulation, epithelial function, extracellular matrix remodeling, and eicosanoid metabolism [11,17,30]. Reported promoter changes include hypermethylation of *COL18A1*, *PTGES*, *PLAT*, and *TSLP*, together with hypomethylation of genes such as *PTGDS*, *ALOX5AP*, *LTB4R*, *CXCL8*, and *FZD5* [17]. HUGO Gene Nomenclature Committee (HGNC) symbols are used consistently throughout, including *CXCL8* and *PTGDS* for the corresponding gene loci.

Genome-wide analyses have also identified large numbers of differentially methylated CpGs and regions in CRS tissue [30]. Earlier work in nasal polyps from aspirin-intolerant asthma described methylation differences in immune and arachidonic-acid pathways [50]. These studies show that CRSwNP and related CRS phenotypes have distinguishable epigenetic landscapes, but they also illustrate a major limitation: polyp and bulk CRS samples differ markedly in inflammatory-cell and stromal composition. Without cell-resolved validation, a methylation difference cannot be assumed to represent stable reprogramming within a particular cell type.

6.2. Histone-Related Findings, Eosinophilic Inflammation, and Remodeling

Histone-related findings in CRSwNP include altered HDAC expression and experimental links to steroid responsiveness [17]. HDAC7 is notable because recent work directly examined CRSwNP tissue and nasal epithelial cells, identifying a negative-feedback role in IL-13-driven eosinophilic inflammation [18]. EZH2 and HMGA2 were also reported to be increased in CRSwNP tissue [20], but, as discussed in Section 3.2, the reported inverse relation between EZH2 manipulation and H3K27me3 signal requires independent confirmation before it can be used as a mechanistic foundation for therapy.

Eosinophilic inflammation may itself shape the epigenetic environment. Reactive halogen species generated during eosinophilic inflammation have been proposed to produce modified cytosines that can interfere with normal methylation readouts [51]. CRSwNP remodeling also involves epithelial-mesenchymal transition, mucus pro-

duction, matrix deposition, and metabolic adaptation; miRNAs and chromatin regulators may participate in these processes [26,27,52]. These findings are useful for mechanism discovery but do not yet define a clinically validated prognostic test.

6.3. Non-Coding RNAs and Endotype Classification

MiRNA profiling is attractive for CRSwNP endotyping because RNA patterns can reflect inflammatory and remodeling programs. Reported candidates include miR-125b, miR-155, miR-21, miR-142-3p, miR-19a, and miR-4492, among others [17,26,27]. Some studies or reviews relate these candidates to tissue eosinophilia, corticosteroid response, or recurrence. At present, however, no prospectively validated miRNA classifier has demonstrated sufficient reproducibility and incremental clinical value to replace standard endotyping based on clinical phenotype, blood eosinophils, IgE, comorbid asthma or aspirin-exacerbated respiratory disease, and polyp burden [3,12,53].

This distinction matters when discussing biologics. Epigenetic signatures may eventually refine type 2 versus non-type 2 classification, but currently approved or established biologic selection is not based on methylation or miRNA testing. Claims that an epigenetic signature "guides" biologic therapy should therefore be replaced by the more limited statement that such markers are investigational candidates for future stratification studies.

7. Biomarker Translation: What Is Supported Now and What Requires Validation

7.1. Candidate Markers for Diagnosis, Severity, and Prognosis

The most credible near-term biomarker candidates are those measured in disease-relevant tissue with a practical sampling strategy. For AR, nasal epithelial methylation is attractive because brushings or swabs are minimally invasive and can capture exposure-responsive mucosal biology [9,10]. *LPCAT2* methylation in nasal scraping samples and selected miRNA profiles are examples of signals associated with severity or phenotype [24,47]. Nevertheless, independent cohorts, pre-specified thresholds, technical replication, and comparison against routine clinical assessment are still required before such markers can be described as clinically actionable.

For CRSwNP, polyp-tissue methylation and miRNA findings are disease-relevant but are intrinsically limited as screening tools because tissue is generally obtained after disease is established. A clinically useful assay would need to work in a less invasive specimen, preserve disease specificity, and demonstrate value beyond existing endotype markers. This has not yet been shown. The current literature therefore supports candidate discovery and mechanistic stratification, not a validated clinical epigenetic classifier [11,27,30,53].

7.2. Treatment-Associated Epigenetic Signatures in Allergic Rhinitis

Allergen-specific immunotherapy (AIT) provides an important setting for studying dynamic epigenetic change because treatment can modify immune tolerance. Experimental work has linked AIT-related interventions with *FOXP3* demethylation and regulatory T-cell responses [49,54]. In patients receiving AIT, sputum miRNA screening identified treatment-associated changes involving the prostaglandin E2 (PGE2)-prostaglandin E receptor 3 (PTGER3) axis [55], and recent nasal epithelial profiling described m6A changes in mRNAs and lncRNAs, including *LUCAT1*, together with correlations with symptom scores [28].

These studies show that epigenetic and epitranscriptomic measurements can track biological change during therapy. They do not yet establish a pretreatment test that prospectively predicts which patient will respond. Future AIT studies should distinguish predictive biomarkers measured before treatment from pharmacodynamic markers that change after treatment has begun.

7.3. Early Screening and Risk Prediction: A Future Objective

The phrase "early screening" should be used cautiously. Much of the current evidence is cross-sectional, case-control, or based on short-term allergen exposure. The early-life microbiome study linking mucosal methylation and AR is longitudinal with respect to microbial exposure, but the methylation signature and AR outcome were assessed at the same age [38]. Likewise, challenge studies can predict symptom intensity in already allergic individuals [10], which is different from predicting disease onset in an asymptomatic population.

The evidence gap is even larger for CRSwNP. No study discussed in this review demonstrates that a nasal swab methylation pattern measured before polyp formation can prospectively identify individuals who will later develop

CRSwNP. Accordingly, pre-polyp risk prediction should be framed as a testable research hypothesis. A valid screening program would require a clearly defined at-risk population, prospective sampling before disease onset, a locked assay and threshold, independent external validation, and evidence that earlier identification changes management or outcomes.

8. Epigenetic Therapeutics and Translational Barriers

8.1. Current Evidence for Epigenetic Targeting

The reversibility of epigenetic marks makes DNMTs, HDACs, and histone methyltransferases appealing drug targets, but most AR and CRSwNP data remain preclinical. DNMT1 inhibition reduced Th2 polarization in an AR mouse model [13], and HDAC inhibition has shown anti-inflammatory effects in experimental AR systems [16]. Reviews of CRSwNP discuss DNMT and HDAC pathways as potential targets [17,53], while DZNep reduced allergic airway inflammation in an ovalbumin model [21]. None of these observations establish routine therapeutic efficacy in patients with AR or CRSwNP.

RNA-based interventions are at a similarly early stage. Engineered extracellular vesicles or other carriers could, in principle, deliver miRNA cargo to selected cells, but CRSwNP applications remain proof-of-concept [26]. Probiotic and microbiome-directed strategies may influence immune and epigenetic states, including regulatory T-cell biology, yet clinical effects are strain-, population-, and endpoint-dependent and should not be described as established epigenetic therapy for AR or CRSwNP [56]. Conventional biologics such as dupilumab act on cytokine pathways rather than directly editing the epigenome, even though those pathways are influenced by epigenetic regulation [57,58].

8.2. Barriers to Clinical Translation

Several barriers separate mechanistic reversibility from a safe clinical intervention. First, DNMTs, HDACs, and EZH2 regulate many genes in many tissues; systemic inhibition can therefore produce broad off-target effects, unwanted immunomodulation, and potentially oncogenic or tumor-suppressive consequences. Second, the desired direction of epigenetic change may differ among epithelial cells, lymphocytes, macrophages, fibroblasts, and eosinophils. A drug that is beneficial in one compartment may be harmful in another [16,17,19,53].

Third, local delivery to the sinonasal mucosa must achieve adequate penetration and cell specificity without excessive systemic exposure. Fourth, durability is uncertain: epigenetic marks can be dynamic, so the dose and duration required to produce a useful effect may not match those required for safety. Fifth, candidate therapies need pharmacodynamic assays that can show target engagement in the relevant cell type. Finally, long-term studies are required to evaluate immunosuppression, infection, neoplasia, reproductive effects, and interactions with corticosteroids, AIT, or biologics. These barriers argue for staged preclinical development and tissue-specific delivery strategies rather than direct extrapolation from cell culture or mouse models to clinical use.

9. Priorities for Clinical Validation and Future Research

Future work should begin by narrowing, rather than expanding, candidate lists. For AR, the most practical targets for validation are reproducible nasal epithelial methylation or RNA markers that can be obtained by standardized brushing or swabbing and that add information beyond symptoms, sensitization testing, and IgE. For CRSwNP, promising tissue signals should be translated into minimally invasive specimens only after their cell of origin is established. In both diseases, a candidate should advance only if it reproduces across laboratories, ancestry groups, seasons, treatment states, and sampling protocols.

A second priority is prospective design. Discovery cohorts should be separated from validation cohorts, assay thresholds should be specified before testing, and predictive claims should be evaluated before the relevant clinical outcome occurs. Studies should report discrimination, calibration, repeatability, and incremental value over existing clinical markers. The same translational principles are emphasized in epigenetic biomarker research outside rhinology, where assay standardization, external validation, and demonstration of clinical utility remain prerequisites for implementation [59]. Such cross-field comparisons are useful for methodology, but they should not be treated as evidence for AR or CRSwNP biology.

Third, cell-resolved and multi-omic studies can help distinguish causal regulatory changes from shifts in tis-

sue composition. Integrating methylation, chromatin accessibility, transcriptomics, proteomics, metabolomics, and single-cell data from the same participants may identify coherent pathways rather than isolated markers. Artificial intelligence (AI) and machine-learning methods may assist this integration, particularly for high-dimensional feature selection and nonlinear interactions, but they introduce additional concerns about overfitting, data sparsity, model interpretability, population bias, and external validation [60]. Computational performance should therefore be judged against locked external cohorts and clinically meaningful comparators rather than internal cross-validation alone.

Finally, reporting standards should make evidence boundaries explicit. Each biomarker study should identify disease phenotype, specimen, cell composition, platform, preprocessing, validation method, and whether the endpoint is diagnostic, prognostic, predictive, or pharmacodynamic. This level of detail will reduce inappropriate cross-disease extrapolation and make it easier to determine which candidates are genuinely ready for multicenter validation.

10. Conclusions

Epigenetic studies have added important mechanistic detail to allergic rhinitis and CRSwNP, but the two diseases require separate evidentiary frameworks. In AR, nasal and immune-cell methylation studies provide evidence for exposure-responsive and severity-associated changes, while several miRNAs remain exploratory biomarker candidates. In CRSwNP, methylation, histone, and miRNA findings in polyp or sinonasal tissue illuminate inflammatory and remodeling pathways, but bulk-tissue composition and the absence of prospective classifiers limit clinical interpretation. At present, epigenetic markers should complement mechanistic research rather than replace established diagnostic or type 2 inflammatory markers. Early screening for future CRSwNP and epigenetic-guided biologic selection remain research goals. Progress toward clinical use will depend on disease-specific sampling, cell-resolved validation, standardized assays, independent cohorts, longitudinal study designs, and evidence that a biomarker improves decisions or outcomes beyond current clinical practice.

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Conflicts of Interest

The authors declare no conflict of interest.

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