Journal of Inflammation Research

Dovepress
Taylor & Francis Group

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REVIEW

Fractional Exhaled Nitric Oxide (FeNO) as a Biomarker of Lower Airway Eosinophilic Inflammation: Benefits and Limitations

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Abstract: Fractional exhaled nitric oxide (FeNO) has progressively consolidated its role in the assessment of type 2 (T2) airway inflammation, on the strength of standardized methodology, two decades of evidence in asthma and growing data in chronic obstructive pulmonary disease (COPD) and bronchiectasis. The clinical interpretation of the measurement, however, remains uneven, partly because the underlying biology is often condensed into the shorthand of an eosinophilic biomarker. FeNO is generated by the airway epithelium through inducible nitric oxide synthase, whose transcription is driven primarily by interleukin-13 acting through STAT6, with interleukin-4 in a supporting role. The interleukin-5/eosinophil pathway runs in parallel and is not directly captured by FeNO. This single distinction explains the moderate correlation between FeNO and sputum eosinophils, the sensitivity of the measurement to inhaled corticosteroids, smoking, atopy and infection, and the differential magnitude of FeNO suppression observed under biologic therapies that target distinct points of the T2 cascade. Drawing on a non-systematic search of MEDLINE/PubMed up to early 2026, with priority given to society guidelines, position papers and randomized trials with their biomarker analyses, the present narrative review reframes FeNO around its actual biological substrate and traces the implications for diagnosis, phenotyping, prediction of corticosteroid responsiveness, adherence assessment, exacerbation risk and biologic treatment selection across T2-high asthma, severe asthma referred for biologic therapy, eosinophilic COPD, eosinophilic bronchiectasis, chronic cough and the unified airway. Limitations are discussed alongside interpretation, since each constraint maps onto a specific bedside rule. Future directions converge on personalized reference intervals, multiple-flow analysis, breathomics and remote monitoring, and on a shift in the operational unit of decision-making from the isolated cut-off to the longitudinal trajectory interpreted within an integrated biomarker algorithm.

Keywords: fractional exhaled nitric oxide, type 2 airway inflammation, eosinophilic asthma, biologic therapy, pulmonary rehabilitation, disability, outcome

Introduction

Management of asthma and chronic obstructive pulmonary disease (COPD) has progressively shifted from a symptom-based approach to one guided by the inflammatory phenotype of the airway, a transition accelerated by the emergence of targeted biologic therapy.[1,2] Corticosteroid responsiveness, biologic eligibility and exacerbation risk depend on whether the inflammatory substrate is dominated by a type 2 (T2) pathway or not.[1,3] Induced sputum and bronchoscopy provide the most direct assessment of airway cellular infiltrates but are invasive, technically demanding and poorly reproducible outside dedicated centers.[4] Blood eosinophils are accessible and prognostic but only partly reflect the inflammatory state of the bronchial wall, with non-trivial day-to-day and longitudinal variability documented in both asthma and COPD.[5]

https://doi.org/10.2147/JIR.S554147
Received: 10 May 2026
Accepted: 25 June 2026
Published: 10 July 2026

Fractional exhaled nitric oxide (FeNO) has progressively consolidated its role in this setting. It is rapid, non-invasive, reproducible across age groups and has been standardized by two decades of procedural work from the American Thoracic Society (ATS) and the European Respiratory Society (ERS).[6,7] The simplicity of a single numerical output in parts per billion should not obscure the underlying biology. FeNO is generated almost entirely by the airway epithelium through inducible nitric oxide synthase (iNOS), whose transcription is driven by interleukin-13 (IL-13) and, to a lesser extent, by interleukin-4 (IL-4), both acting through signal transducer and activator of transcription 6 (STAT6).[1,4] FeNO therefore reports on the activity of this IL-13/epithelial circuit.[4] It is not a proxy for eosinophil count, for the T2 response in its entirety, or for disease severity.

This distinction shapes the interpretation of every FeNO reading. It accounts for the moderate correlation observed between FeNO and sputum eosinophils even in steroid-naïve T2-high asthma,[7] for the sensitivity of the measurement to any factor that modifies the epithelium independently of inflammation, including inhaled corticosteroid (ICS) exposure, smoking and viral infection,[4,7] and for the differential magnitude of FeNO suppression observed under biologic therapies that target distinct points of the T2 cascade.[8,9] The interpretive framework adopted in the present review follows the Italian position paper on FeNO issued jointly by the Italian Respiratory Society and the Italian Society of Allergy, Asthma and Clinical Immunology (SIP-IRS/SIAAIC), which places FeNO within an integrated biomarker algorithm rather than as a standalone diagnostic tool.[3]

On these premises, the present review is organized around four threads that recur throughout: the epithelial IL-13/iNOS biology that generates the signal, the confounders that modify it independently of inflammation, the position of FeNO relative to the other type 2 biomarkers, and the guideline recommendations that govern its use in practice.

Airway Nitric Oxide Biology and the Meaning of FeNO

Nitric oxide (NO) is a short-lived gaseous mediator synthesized from L-arginine by three isoforms of NO synthase expressed in epithelial, endothelial, neuronal and inflammatory cells, with functions that include bronchodilation, vascular regulation, host defense and signal transduction.[4] In the healthy bronchus the constitutive isoforms contribute a modest baseline output and resting FeNO remains low. The inducible isoform iNOS (also designated NOS2) generates the excess signal that the measurement captures in disease, in a time- and dose-dependent fashion dictated by the local cytokine milieu.[4] The relevant stimulus is the T2 cytokine cocktail reaching the bronchial epithelium during allergic or eosinophilic inflammation. Within this cocktail, IL-13 is the dominant upstream driver of iNOS transcription through STAT6, with IL-4 in a supporting role.[1,4] Interleukin-5 (IL-5), by contrast, acts downstream on eosinophil maturation and tissue recruitment and exerts no direct transcriptional effect on iNOS.[1] Substrate availability adds a further regulatory layer. Arginase, also inducible under T2 stimulation, competes with iNOS for L-arginine and can dampen NO output even when iNOS is fully induced.[4]

This asymmetry carries direct pharmacological implications. Blockade of the IL-4 receptor α chain (IL-4Rα), which abrogates both IL-4 and IL-13 signaling, produces early and marked reductions in FeNO.[10,11] Agents targeting IL-5 or its receptor deplete eosinophils without substantially affecting epithelial NO output, at least over short treatment intervals.[8] Real-world data confirm this prediction. Dupilumab lowers FeNO within days to weeks of treatment initiation,[10,12] whereas anti-IL-5 and anti-IL-5R agents produce a far smaller and more variable effect on the same biomarker.[8,9] Interpreting FeNO as a readout of IL-13 activity, rather than as a surrogate eosinophil count, resolves what would otherwise appear as biomarker discordance.[8,9]

The downstream chemistry of NO further shapes the behavior of the signal in chronic disease. In inflamed tissue NO reacts with reactive oxygen species to generate peroxynitrite and other reactive nitrogen species, which amplify epithelial injury and feed back into the inflammatory cascade.[4] The dual role of NO as mediator and marker implies an intrinsic ceiling on the correlation between FeNO and any single cellular counterpart.[4] In steroid-naïve patients with clearly T2-high asthma, FeNO correlates moderately with sputum eosinophils and is informative as an indirect marker of eosinophilic activity.[7] Discordance between FeNO and sputum eosinophils in individual patients more often reflects differential modulation of the epithelial circuit and of the marrow-to-tissue eosinophil axis by treatment, smoking or infection, rather than biomarker failure.[4] Using FeNO as interchangeable with an eosinophil count is inferentially unsafe

in both directions, producing overestimation of eosinophilic involvement when FeNO is elevated for unrelated reasons and missing it when the IL-13 circuit has been selectively suppressed.[4,8,9]

Measurement Principles, Standardization and Confounders

The standard FeNO maneuver consists of a single slow exhalation at a constant flow of 50 milliliters per second, preceded by inhalation of NO-free air to total lung capacity and performed against an expiratory pressure of 5 to 20 centimeters of water that closes the soft palate and minimizes nasal contamination.[6,13] This velopharyngeal closure is not a technical detail but the conceptual boundary of the measurement: it excludes the nasal and paranasal compartment, where nitric oxide concentrations exceed those of the lower airway by one to two orders of magnitude, so that standardized oral FeNO reflects bronchial epithelial output rather than a composite upper-and-lower airway signal.[6,14] The standardized flow rate has a biological rationale. NO production is concentrated in the bronchial epithelium, and as the exhaled gas traverses progressively narrower airways the local concentration reflects both wall flux and transit time, producing the flow-dependence formalized by the two-compartment model of Tsoukias and George.[15] The same model underlies the multiple-flow approach, which partitions exhaled NO into bronchial flux (J'awNO) and alveolar concentration (CANO) and provides a window on small-airway involvement that the standard 50 mL/s^{-1} measurement cannot resolve. Although multiple-flow FeNO remains largely confined to research settings, it has been associated with peripheral airway dysfunction in severe asthma, atopic disease and a subset of patients with COPD.[13,15]

A valid measurement requires a stable NO plateau and consistency across at least two reproducible maneuvers, as codified in the ATS interpretive statement and subsequent position documents.[3,7,16] Chemiluminescence analyzers remain the reference standard for sensitivity and accuracy, while portable electrochemical devices have enabled routine and outpatient use at the cost of non-negligible inter-device variability documented in direct head-to-head comparisons.[17] In longitudinal monitoring the analyzer should remain constant across visits, and the instrument used should be declared whenever data from different centers or studies are pooled.[17]

Patient preparation deserves equal attention. Smoking, strenuous exercise and nitrate-rich meals should be avoided, atopy and recent allergen exposure documented, and recent viral infections recorded, since each of these modifies FeNO independently of underlying disease activity.[3,7] Forced spirometry should not immediately precede the measurement, because deep inhalation and airflow limitation can transiently reduce FeNO without any change in inflammatory burden.[7] This consideration acquires particular weight in severe asthma, where low FeNO values can underestimate persistent T2 activity under conditions of marked airflow limitation.[8] Atopy and allergen exposure shift FeNO upwards.[3,7] Active and passive smoking reduce it through a combination of NOS downregulation, enhanced NO degradation and reduced cofactor availability.[7] Concomitant rhinosinusitis and nasal polyposis, highly prevalent in T2-dominated disease, can further modulate the measurement through shared epithelial inflammation of the upper airway and are consistent with the unified airway model.[2] In a cohort of patients with stable COPD, intra-individual FeNO variability over short intervals was larger than expected, was not captured by a single isolated measurement and was partly accounted for by body weight, supporting repeated sampling rather than single determinations when FeNO is used for stratification.[5]

Within the ATS framework, adult values below 25 parts per billion (ppb) are considered low, and values above 50 ppb strongly suggest ongoing T2 inflammation with a higher probability of ICS responsiveness, while intermediate values require clinical integration.[7] In children the corresponding ATS thresholds are <20 ppb and >35 ppb[7] and, while the present review focuses on adults, the pediatric framework remains pertinent for transition-of-care settings. Thresholds are not fully harmonized across international documents. The 2021 ATS guideline on treatment decisions, the Global Initiative for Asthma (GINA) strategy, the Italian SIP-IRS/SIAAIC position paper and the British asthma guidelines place FeNO in slightly different hierarchies with respect to blood eosinophils and bronchial provocation testing.[3,16] Within-subject variability is approximately 10% in healthy individuals and can reach 20% in asthma, so a change of at least 20% between consecutive measurements is generally considered clinically meaningful.[7] Although robust and standardized, FeNO is not to be interpreted in isolation, and biological variability, technical quality and clinical phenotype all need to be factored into each reading.[3]

A consolidated summary of the biological, technical and interpretive features of the measurement, distilled from the documents discussed in this section, is provided in Table 1.

Table 1 Biological, Technical and Interpretive Features of Fractional Exhaled Nitric Oxide (FeNO)

Property	Value/Behavior	Reference
Cellular source of the signal	Airway epithelium, via inducible nitric oxide synthase (iNOS, also designated NOS2)	[4]
Upstream molecular driver	IL-13 dominant, IL-4 supporting, both signaling through STAT6	[1,4]
Pathways not directly reflected by FeNO	Eosinophil burden, IL-5 axis, disease severity, systemic inflammation	[4,9]
Standard measurement flow	Constant exhalation at 50 mL/s against 5–20 cm H_2O resistance, after inhalation of NO-free air to total lung capacity	[6,13]
Multiple-flow analysis	Partitions exhaled NO into bronchial flux (J'awNO) and alveolar concentration (CANO); informs on small-airway involvement; research-oriented	[13,15]
ATS low-value cut-off (adults)	<25 parts per billion (ppb)	[7]
ATS high-value cut-off (adults)	>50 ppb	[7]
ATS pediatric cut-offs	Low <20 ppb; high >35 ppb (children)	[7]
Intra-individual variability	Approximately 10% in healthy subjects, up to 20% in asthma; documented also in stable COPD	[5,7]
Minimum clinically meaningful change	≥20% for baseline FeNO >50 ppb, or ≥10 ppb for baseline FeNO ≤50 ppb	[7]
Effect of inhaled corticosteroids	Rapid reduction within days to weeks, dose-dependent	[7,18]
Effect of active and passive smoking	Downregulation of NO synthase, enhanced NO degradation, reduced FeNO	[7]
Effect of atopy and allergen exposure	Upward shift of FeNO values	[3,7]
Effect of viral infection	Variable modulation, with possible iNOS induction through interferon-γ signaling, independently of eosinophilic activity	[4]
Effect of spirometry immediately prior	Transient reduction; test sequencing matters	[7]
Effect of concomitant upper-airway disease	Elevated FeNO possible via shared T2 epithelial activity (unified airway model)	[19,20]
Device categories	Chemiluminescence analyzers (reference standard) and portable electrochemical analyzers, with documented inter-device variability	[17]

Abbreviations: ATS, American Thoracic Society; CANO, alveolar concentration of NO; COPD, chronic obstructive pulmonary disease; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroids; IL, interleukin; iNOS, inducible nitric oxide synthase; J'awNO, bronchial NO flux; NO, nitric oxide; ppb, parts per billion; STAT6, signal transducer and activator of transcription 6; T2, type 2.

FeNO Across T2-Driven Airway Diseases

T2-High Asthma

Asthma is the disease in which FeNO evidence is most consolidated and in which the biological mechanism maps most directly onto clinical behavior. The T2-high endotype, which encompasses allergic, late-onset eosinophilic and many cases of severe asthma, is sustained by T helper 2 (Th2) cells and type 2 innate lymphoid cells (ILC2) that release IL-4, IL-5 and IL-13, driving eosinophilic airway infiltration and progressive remodeling.[1,2,21] In this setting FeNO complements blood eosinophils, sputum eosinophils and serum immunoglobulin E (IgE) by adding a dynamic readout of ongoing epithelial T2 activity that the other biomarkers cannot provide.[3,4] In a symptomatic patient with normal or inconclusive spirometry, an elevated FeNO increases the pre-test probability of T2-high asthma, particularly in steroid-naïve individuals, in children and in cough-variant presentations.[3,7] A persistently low FeNO in a steroid-naïve patient with preserved lung function argues against a T2 mechanism and should influence diagnostic reasoning accordingly, a position made explicit in the ATS guideline and reiterated in the Italian position paper.[3,7]

The clinical relevance of FeNO expanded substantially with the introduction of biologic therapy in routine asthma care. In the LIBERTY ASTHMA QUEST trial, dupilumab reduced severe exacerbations and improved lung function across the study population, with the largest relative effects in patients with higher baseline FeNO, an effect gradient that persisted after adjustment for blood eosinophil count.[10] Subsequent post-hoc analyses showed that baseline FeNO behaves as a prognostic biomarker for future exacerbations in placebo-treated patients with uncontrolled asthma,[22] and as an independent predictor of response to dupilumab beyond the information carried by blood eosinophils.[23] More recent analyses extend this observation to long-term follow-up, showing that an early reduction in FeNO during the first weeks of treatment identifies a subgroup with particularly favorable trajectories, while patients without such early suppression still derive clinical benefit.[12] The correspondence between drug mechanism and biomarker behavior is itself

informative.[8] Anti-IL-4Rα and anti-thymic stromal lymphopoietin (TSLP) strategies produce rapid and marked FeNO suppression, whereas anti-IL-5/IL-5R agents produce a far smaller shift, consistent with the upstream position of IL-13 in the biomarker pathway.[9,10,12,24] Under dupilumab and tezepelumab, FeNO should therefore be interpreted as a pharmacodynamic signal of target engagement rather than as a direct index of residual airway inflammation.[12]

Longitudinal FeNO measurement retains value beyond biologic selection. A decrease after initiation or intensification of controller therapy tracks the suppression of T2 inflammation,[7,16] while persistently high or rising values raise questions of non-adherence, underdosing or continued exposure to a relevant trigger.[7,18] The FeNO suppression test formalizes this observation in difficult asthma, using a defined reduction in FeNO over five to seven days of directly observed ICS therapy as an objective correlate of both adherence and steroid responsiveness.[18] A substantial decrease supports both.[18] The absence of response under supervised inhalation redirects the diagnostic work-up towards non-T2 mechanisms or genuine corticosteroid resistance.[18]

The combination of elevated FeNO and high blood eosinophil count identifies a population at incremental risk of future exacerbations beyond what either biomarker predicts alone,[9,22] and in this clinical context FeNO trajectories, rather than isolated thresholds, become the operational unit of decision-making.[3,16] The interpretive matrix integrating FeNO and blood eosinophil count, which operationalizes this concept at the bedside, is illustrated in Figure 1. FeNO-guided ICS adjustment has shown benefits in selected randomized studies and meta-analyses, particularly for exacerbation prevention, although heterogeneity across trials has tempered unconditional endorsement and the ATS guideline remains conditional on this specific use.[3,16]

In severe asthma referred for biologic therapy, FeNO contributes both to the assessment of T2 activity and to the differential evaluation of patients in whom an apparently low T2 signal could mask either non-T2 disease or pharmacologically suppressed T2 activity. In this context the FeNO suppression test, originally validated to identify non-adherence to inhaled corticosteroids,[18] retains a complementary role in distinguishing genuine corticosteroid resistance from inadequate drug delivery or persistent exposure to a relevant trigger.[3,16,18] Persistently elevated FeNO under directly observed therapy reorients the clinical pathway towards biologic selection, while a marked suppression supports a stepwise approach with optimization of inhaled treatment before escalation.[18]

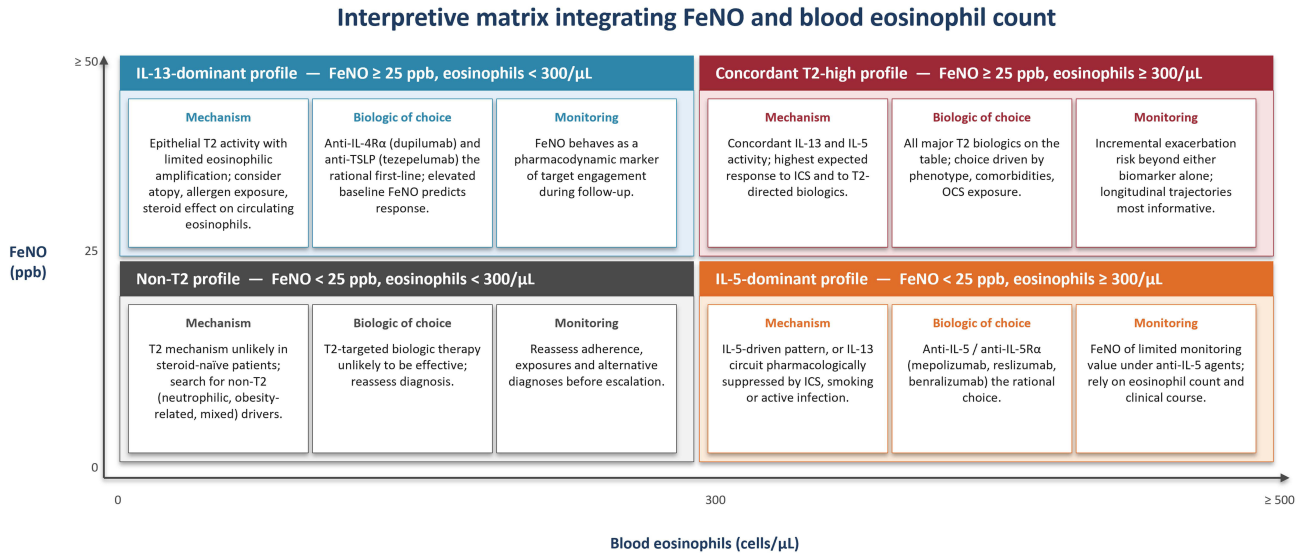

Figure 1 Interpretive matrix combining fractional exhaled nitric oxide (FeNO) and blood eosinophil count for clinical decision-making in T2 airway disease. The four quadrants reflect mechanistically distinct phenotypes rather than a simple severity grading. Cut-offs follow the ATS framework, the 2021 ATS guideline on treatment decisions and the SIP-IRS/SIAAIC position paper, and should be integrated with clinical phenotype, lung function, treatment history and comorbidities. Adapted from.[3,7,9,16,22]

https://doi.org/10.2147/JIR.S554147

Eosinophilic COPD

In COPD, an eosinophilic inflammatory component is present in a substantial minority of patients and has gained recognition as a bona fide treatable trait.[25] The underlying biology differs from that of asthma. Neutrophilic inflammation dominates the average COPD airway, smoking suppresses FeNO independently of disease activity, and structural damage introduces additional sources of signal variance.[7,25] These features place FeNO in a subordinate position with respect to blood eosinophils as the primary biomarker for identifying the endotype,[4,25] and they also make the interpretation of values more context-dependent, although a difference in FeNO values between eosinophilic COPD and asthmatic patients has been reported.[26] Repeated measurements combined with blood eosinophil counts outperform single isolated determinations, and the short-term FeNO variability documented in stable COPD in our own cohort reinforces this approach.[5] During exacerbations FeNO requires particular interpretive caution, because viral infection can induce iNOS expression through interferon-γ signaling independently of eosinophilic activity, as confirmed by a recent meta-analysis of studies on acute exacerbations.[27] Even within this constraint, the rise in FeNO observed in a proportion of exacerbations can identify eosinophil-driven episodes that are more likely to respond to systemic corticosteroids, a distinction of relevance both for antibiotic stewardship and for tailoring rescue treatment.[25,27]

The therapeutic landscape of eosinophilic COPD has been reshaped by two replicate Phase 3 trials. In BOREAS and NOTUS, dupilumab added to optimized triple inhaled therapy reduced moderate-to-severe exacerbations and improved lung function in patients with blood eosinophil counts of at least 300 cells per microliter, with consistent effects across subgroups.[28–30] Although neither trial used FeNO as an inclusion criterion, a subsequent biomarker analysis of BOREAS demonstrated that the magnitude of exacerbation reduction was greater in patients with higher baseline FeNO, with a 28.6% median reduction in FeNO at 52 weeks under dupilumab versus minimal change under placebo, and that elevated baseline FeNO predicted a greater treatment effect independently of blood eosinophil count.[11] This finding, together with the documented short-term FeNO variability in stable COPD[5] and the longitudinal association between FeNO variability and exacerbation etiology in inhaled-corticosteroid-treated patients,[31] moves FeNO from a candidate biomarker to a credible component of integrated stratification algorithms in eosinophilic COPD, even if standalone FeNO-guided decision-making is not yet supported by prospective evidence.[3,25] In this regard, structured care settings such as pulmonary rehabilitation, where patients with COPD undergo systematic clinical reassessment over weeks to months, may offer a natural environment for the longitudinal integration of FeNO into multidimensional disease characterization.[32,33]

Eosinophilic Bronchiectasis

Bronchiectasis has traditionally been conceptualized as an archetypal neutrophilic disease, and the identification of an eosinophilic endotype represents a substantive conceptual shift. The European multi-cohort study by Shoemark et al showed that, after exclusion of asthma and allergic bronchopulmonary aspergillosis, approximately one in five patients has a blood eosinophil count of at least 300 cells per microliter, with a distinct sputum microbiome and, in observational follow-up, a shorter time to exacerbation after adjustment for infection, supporting a pathogenic rather than bystander role.[34] Subsequent cluster analyses have placed eosinophilic bronchiectasis within a broader inflammatory typology in which neutrophil-eosinophil mixed patterns are common and clinical outcomes diverge,[35] while registry data have suggested a U-shaped relationship between blood eosinophil count and disease severity that cautions against a monotonic interpretation.[36] The European multicohort study defined the eosinophilic phenotype on the basis of blood eosinophils alone (≥300 cells per microliter after exclusion of asthma and ABPA),[34] and the incremental value of FeNO over blood eosinophils in bronchiectasis remains to be quantified. Pragmatic integration of FeNO with eosinophil counts is plausible but not formally validated. Identification of the endotype has therapeutic implications. ICS, historically used with caution in bronchiectasis, may be justified in biomarker-defined subgroups,[34,35] and anti-T2 biologic agents are under evaluation with early encouraging signals. On current evidence, FeNO contributes meaningfully when its elevation coincides with a suggestive clinical picture and a high eosinophil count, and its use in isolation remains premature.[34]

Other Eosinophilic Conditions and the Unified Airway

The clinical reach of FeNO extends beyond these three paradigmatic diseases, while the meaning of the measurement remains constant. It reports airway T2 activity and not systemic disease. In eosinophilic granulomatosis with polyangiitis and in idiopathic hypereosinophilic syndrome, elevated FeNO reflects concomitant airway involvement and does not replace blood eosinophil counts or the assessment of extra-pulmonary organ damage.[4] In chronic cough, FeNO functions as a rule-in test for cough-variant asthma and non-asthmatic eosinophilic bronchitis,[37] and helps identify patients likely to respond to a trial of ICS even without wheeze or airflow limitation.[3,4] In the upper airway, elevated FeNO mirrors the inflammatory activity of allergic rhinitis and chronic rhinosinusitis with nasal polyps, consistent with the unified airway model in which a shared IL-13/iNOS axis connects upper and lower compartments.[2] The unified, or united, airway concept holds that rhinitis, chronic rhinosinusitis with nasal polyps and asthma are regional expressions of a single type 2 inflammatory process rather than independent disorders, and it is supported by epidemiological, embryological and immunological evidence converging on shared IL-4, IL-5 and IL-13 signaling.[19,20] It should be emphasized, however, that the standardized oral FeNO maneuver does not physically capture nasal or sinus-derived NO, which is excluded by velopharyngeal closure and is instead quantified separately as nasal NO. Therefore, the correspondence between upper- and lower-airway involvement reflects a shared inflammatory biology rather than a single mixed gas sample.[6] For this reason, when an integrated assessment of the upper compartment is required, separate measurement of nasal NO alongside FeNO, rather than FeNO alone, better characterizes the unified airway, as we have shown for chronic rhinosinusitis,[38] an approach consistent with our earlier work on extended exhaled and nasal NO analysis in chronic cough.[37] In occupational settings, FeNO has been proposed as an adjunct in the diagnosis of occupational asthma and in the monitoring of workers exposed to sensitizing agents, although longitudinal data and disease-specific cut-offs remain limited.[3] In allergic bronchopulmonary aspergillosis and in fungal sensitization in patients with asthma, elevated FeNO supports the presence of active T2 inflammation and may help select candidates for systemic corticosteroids and selected biologic strategies, while specificity remains limited in the context of coexisting severe asthma.[3,4] A synoptic view of the disease-specific role of FeNO across these airway conditions is provided in Table 2.

Limitations as Part of Interpretation

The limitations of FeNO follow directly from what the biomarker measures, and each translates into a specific interpretive rule at the bedside. Specificity and sensitivity for eosinophilic inflammation are imperfect because the IL-13/iNOS axis can be activated by atopy or recent allergen exposure without detectable lower-airway eosinophilia, and can be suppressed by smoking or by specific infections despite active disease.[4,7] Elevated values in a coherent clinical context rule T2 inflammation in with reasonable confidence.[7] Low values rule it out only when persistently low in a steroid-naïve patient with preserved lung function and no evident confounders.[7] A second constraint relates to the rapid and pronounced effect of corticosteroids on FeNO. ICS lower FeNO within days to weeks, and the same absolute value carries different meanings before and after treatment.[7] Rising FeNO during follow-up suggests loss of control, sub-optimal adherence or inadequate drug delivery.[3,18] Stably low values may support maintenance or cautious step-down.[7,16] Under biologic therapy this effect is amplified to the point that FeNO behaves as a pharmacodynamic rather than a disease-activity marker, particularly under dupilumab and tezepelumab.[8]

Imperfect correlation with clinical outcomes constitutes a third constraint. Some patients with high FeNO remain stable, and some with low FeNO deteriorate, because non-T2 mechanisms, airflow limitation or structural damage dominate the clinical picture.[8] FeNO is therefore one component of a multidimensional assessment and not a surrogate for severity.[3,4] A fourth constraint, often underestimated, concerns access. Portable analyzers have narrowed the gap, but device acquisition, consumables, calibration, staff training and quality control remain real barriers in primary care and resource-constrained settings.[3,17] Conversely, dedicated respiratory care environments, including pulmonary rehabilitation programs, provide an organizational scaffold in which FeNO can be embedded into routine multidisciplinary assessment with minimal incremental burden. When embedded within a guideline-based pathway, FeNO-driven management may improve care pathways and has been associated with favorable cost-effectiveness profiles in selected healthcare settings.[3,16] The remaining challenge is largely one of implementation rather than of principle.

https://doi.org/10.2147/JIR.S554147

Table 2 Role of Fractional Exhaled Nitric Oxide (FeNO) Across T2-Driven Airway Disease Settings

Clinical Setting	Diagnostic Role	Prognostic/Predictive Role	Monitoring Role	Setting-Specific Caveats	Reference
T2-high asthma	Rules in T2 endotype when elevated in steroid-naïve patients	Predicts exacerbations and response to anti-IL-4Rα and anti-TSLP, beyond information carried by blood eosinophils	Tracks ICS response and adherence (FeNO suppression test); longitudinal trajectories more informative than isolated cut-offs	Confounded by ICS, smoking, viral infection and acute airflow limitation	[7,10,18,22,23]
Severe asthma referred for biologic therapy	Differentiates genuine non-T2 disease from pharmacologically suppressed T2 activity	Helps select between anti-IL-4Rα, anti-TSLP and anti-IL-5/IL-5Rα strategies	FeNO suppression test under directly observed ICS distinguishes adherence and steroid resistance from non-T2 mechanisms	Persistently elevated FeNO under directly observed therapy reorients towards biologic escalation; marked suppression supports stepwise optimization	[3,16,18]
Eosinophilic COPD	Supportive of endotype; blood eosinophils remain primary	Higher baseline FeNO associated with greater dupilumab benefit on exacerbations and lung function in BOREAS biomarker analysis	Component of integrated stratification algorithms together with blood eosinophil count and exacerbation history	Smoking strongly suppresses FeNO regardless of activity; standalone FeNO-guided decision-making not yet supported by prospective evidence	[5,11,25,28–31]
Acute exacerbation of COPD (AECOPD)	Rise in a subset identifies eosinophil-driven episodes more likely to respond to systemic corticosteroids	May support antibiotic stewardship and tailoring of rescue therapy; prospective validation still limited	Dynamic during the acute event; serial measurements preferable to single readings	Viral infection induces iNOS through interferon-γ signaling independently of eosinophilic activity; cut-offs not standardized	[25,27]
Eosinophilic bronchiectasis	Adjunct to blood eosinophil count, which remains the operational definition	Complementary marker of T2 activity; incremental value over eosinophil count not formally validated	Limited longitudinal data; pragmatic integration with eosinophil counts is plausible but unproven	Endotype historically defined on blood eosinophils ≥300/μL (after exclusion of asthma and ABPA); no consensus FeNO cut-off	[34,35]
Allergic bronchopulmonary aspergillosis and fungal sensitization	Elevated FeNO supports active T2 inflammation in patients with asthma and Aspergillus sensitization	May predict response to systemic corticosteroids and to anti-IL-4Rα in selected refractory cases	Complementary to total IgE and Aspergillus-specific IgE	Specificity limited in coexisting severe asthma; longitudinal evidence still emerging	[3,4]
Chronic cough (cough-variant asthma and non-asthmatic eosinophilic bronchitis)	Rule-in test in absence of wheeze or airflow limitation	Predicts response to a therapeutic ICS trial	Useful for therapeutic trials and longitudinal reassessment	Low specificity when used in isolation	[3,4,37]
Allergic rhinitis and chronic rhinosinusitis with nasal polyps	Mirrors upper-airway T2 activity	Correlates with lower-airway involvement in the unified airway model	Parallel monitoring of upper and lower compartments	Distinction between nasal and bronchial sources requires specific maneuvers	[2,19,20]
Occupational asthma	Adjunct in surveillance of sensitizer-exposed workers	Limited evidence on predictive value	Serial monitoring during exposure and withdrawal	Lack of disease-specific cut-offs	[3]
Eosinophilic granulomatosis with polyangiitis (EGPA) and idiopathic hypereosinophilic syndrome	Indicates airway involvement when present	Does not replace blood eosinophils or organ damage assessment	Limited role	Primarily systemic diseases	[4]

Abbreviations: ABPA, allergic bronchopulmonary aspergillosis; ADCC, antibody-dependent cellular cytotoxicity; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; COPD, chronic obstructive pulmonary disease; EGPA, eosinophilic granulomatosis with polyangiitis; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroids; IgE, immunoglobulin E; IL, interleukin; IL-4Rα, interleukin-4 receptor α chain; IL-5Rα, interleukin-5 receptor α chain; iNOS, inducible nitric oxide synthase; T2, type 2; TSLP, thymic stromal lymphopoietin.

Table 3 Expected Fractional Exhaled Nitric Oxide (FeNO) Response Across Controller and Biologic Therapies in T2 Airway Disease

Agent	Molecular Target	Expected Effect on FeNO	Clinical Interpretation	Reference
Inhaled corticosteroids	Epithelial and immune cells, indirect iNOS downregulation	Reduction within days to weeks, dose-dependent	Adherence and steroid-responsiveness proxy; basis of the FeNO suppression test	[7,18]
Dupilumab	IL-4Rα (blocks IL-4 and IL-13 signaling)	Rapid and marked reduction. In eosinophilic COPD: median percent change –22.2% at week 12 and –28.6% at week 52, versus –3.4% and –6.9% under placebo (BOREAS biomarker analysis)	Pharmacodynamic marker of target engagement; elevated baseline FeNO predicts greater clinical benefit independently of blood eosinophil count, both in moderate-to-severe asthma (QUEST) and in eosinophilic COPD (BOREAS)	[10–12,23]
Tezepelumab	Thymic stromal lymphopoietin (TSLP)	Moderate reduction with slower kinetics than dupilumab. In severe asthma (PATHWAY phase 2b): median percent change –25.2% at week 52, versus 0.0% under placebo	Pharmacodynamic marker; greater FeNO reduction in patients with higher baseline FeNO	[24]
Mepolizumab and Reslizumab	IL-5	Small and variable change; eosinophil depletion uncoupled from FeNO	Limited monitoring value. The discordance between near-complete blood eosinophil depletion and persistent FeNO reflects the upstream position of IL-13 in the biomarker pathway and supports the IL-13/IL-5 dichotomy	[8,9]
Benralizumab	IL-5Rα (eosinophil depletion via ADCC)	Small and variable change	Limited monitoring value; same biological dissociation as for anti-IL-5	[8,9]
Omalizumab	IgE	Modest and inconsistent change, mostly in allergic phenotypes	Useful as adjunct in allergic disease; not a primary monitoring tool	[8]
Itepekimab and other anti-alarmin agents in development (anti-IL-33, anti-ST2)	IL-33/ST2 axis	Reduction reported in T2-defined subgroups in early-phase trials; magnitude smaller than under anti-IL-4Rα	Under investigation; FeNO is a candidate stratifier for trial design and patient selection	[39]

Notes: Median percent changes for dupilumab in eosinophilic COPD are reported from the post-hoc BOREAS biomarker analysis.[11] Median percent change for tezepelumab in severe asthma is reported from the PATHWAY phase 2b biomarker analysis.[24]

Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; IL, interleukin; IL-4Rα, interleukin-4 receptor α chain; IL-5Rα, interleukin-5 receptor α chain; iNOS, inducible nitric oxide synthase; ST2, IL-33 receptor; TSLP, thymic stromal lymphopoietin; T2, type 2.

FeNO Among the Other Biomarkers of T2 Inflammation

No single biomarker of T2 airway inflammation provides a complete representation of the underlying biology, and the informational content of each depends on the concurrent behavior of the others.[3,4] Blood eosinophils are widely available and prognostic for exacerbations and for response to anti-IL-5 therapy in both asthma and COPD, but only loosely reflect the inflammatory state of the bronchial wall and are themselves subject to circadian, seasonal and pharmacological variation.[4,5] Sputum eosinophils capture airway inflammation more directly but remain technically demanding.[4] Periostin, YKL-40 and serum IgE contribute additional information on T2 activity and airway remodeling, but none combines the speed, reproducibility and non-invasiveness of FeNO.[4] The distinctive strength of FeNO in the biologic era lies in its near-real-time readout of the IL-13/epithelial axis, the same axis directly targeted by anti-IL-4Rα and indirectly modulated by anti-TSLP. The expected behavior of FeNO under each major class of controller and biologic therapy, summarized in Table 3, makes this differential mapping operationally usable at the bedside.

Its principal weakness is vulnerability to confounding.[7] Concordance between two biomarkers generally carries more weight than any single measurement. The Italian SIP-IRS/SIAAIC position paper proposes a stepwise diagnostic algorithm in which FeNO is combined with blood eosinophils, clinical phenotype and, when available, sputum analysis, reflecting the differential coverage that each tool provides and converging with international recommendations on biomarker integration.[3,4,9]

Future Directions

The next chapter of FeNO is unlikely to be written through a single innovation. It will probably emerge from the convergence of several research lines, all sharing the same direction of travel: away from fixed thresholds and towards

integrated, individualized and dynamic interpretation. Population-derived cut-offs, largely calibrated on asthma cohorts, are an imperfect transfer to COPD and bronchiectasis, and personalized reference intervals incorporating age, sex, height, smoking history, atopy, environmental exposure and intrinsic variability are a logical evolution that the available data already support.[5] Multiple-flow FeNO, partitioning bronchial flux and alveolar concentration, has remained for two decades a research tool waiting for clinical room, but the increasing interest in small-airway disease in both asthma and COPD makes its broader adoption plausible.[13,15] Breathomics offers a complementary trajectory, in which FeNO is no longer a single number but one channel of a multidimensional molecular signature obtained from exhaled breath condensate, volatile organic compounds and metabolomic profiling, with discriminatory value already documented across asthma, COPD and bronchiectasis.[4,40] Remote and home-based FeNO monitoring, enabled by portable analyzers and digital inhalers, has the potential to convert a clinic-based measurement into a continuous signal that feeds predictive algorithms for impending loss of control, and the FeNO suppression test is likely to evolve in parallel through remotely supervised inhaled-corticosteroid administration.[18] Pulmonary rehabilitation programs, with their inherent longitudinal design and integrated multidisciplinary assessment, may also serve as a testbed for the operational implementation of FeNO monitoring within structured care pathways.[32] Real-world evidence from unselected cohorts and disease-specific registries will be essential to validate disease-specific thresholds, confirm cost-effectiveness and extend the evidence base into COPD, bronchiectasis and the rarer eosinophilic disorders.[25,34]

None of these directions is mutually exclusive, and their cumulative impact is likely to be combinatorial. The common denominator is a shift in the operational unit of decision-making, from the isolated value compared against a cut-off to the longitudinal trajectory interpreted within a biomarker-integrated algorithm.[3,9]

Conclusions

FeNO has earned its place in the management of T2-driven airway disease through a combination of non-invasiveness, reproducibility and a direct mechanistic link to IL-13-driven epithelial activation.[4,16] In routine practice it informs diagnosis, inflammatory phenotyping, prediction of corticosteroid responsiveness, adherence assessment, exacerbation risk estimation and biologic treatment selection with a temporal immediacy that no other T2 biomarker matches.[3,7] The limitations of the measurement are inseparable from its biology: it reports on the activity of the IL-13/epithelial circuit, not on the eosinophil burden, and it is modulated by smoking, infection, atopy, corticosteroid exposure and airflow limitation.[7,9] The clinical value of FeNO is therefore maximized when the reading is integrated with symptoms, lung function, treatment history and the other biomarkers of T2 inflammation, and when interpretation moves from the isolated cut-off to the longitudinal trajectory.[3,9] Refined by multiple-flow analysis, breathomics and remote monitoring, FeNO is well positioned to retain a central role in the precision management of eosinophilic airway disease, with structured care environments such as pulmonary rehabilitation offering a suitable platform for its longitudinal application.[32]

Finally, because the airway behaves as a single inflammatory continuum, FeNO is most informative when the lower-airway reading is interpreted alongside the clinical state of the upper airway, in keeping with the unified airway model and with a management approach shared between pulmonology and rhinology.

Data Sharing Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Author Contributions

Pasquale Ambrosino: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. Salvatore Fuschillo: Investigation, Writing – original draft, Writing – review & editing. Claudio Candia: Investigation, Visualization, Writing – review&editing. Pasquale Di Leo: Investigation, Visualization, Writing – review & editing. Mauro Maniscalco: Conceptualization, Supervision, Writing – original draft, Writing – review & editing. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This research was partially supported by the "Ricerca Corrente" funding scheme of the Italian Ministry of Health.

Disclosure

M.M. reports grants or contracts (with payments to Istituti Clinici Scientifici Maugeri IRCCS) from GlaxoSmithKline and AstraZeneca, and payments or honoraria for lectures, presentations, speaker bureaus, paper writing or educational events from GlaxoSmithKline, AstraZeneca, Damor and Chiesi, outside the submitted work. All other Authors declare no competing financial interests.

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