Medical Policy

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Title: Measurement of Exhaled Nitric Oxide and Exhaled Breath Condensate in the Diagnosis and Management of Respiratory Disorders

Professional / Institutional
Original Effective Date: October 3, 2006 / July 30, 2009
Latest Review Date: July 25, 2023
Current Effective Date: March 13, 2019

Populations	Interventions	Comparators	Outcomes
Individuals: • With suspected asthma	Interventions of interest are: • Measurement of fractional exhaled nitric oxide for diagnosis	Comparators of interest are: • Standard clinical diagnosis	Relevant outcomes include: • Test validity • Symptoms • Change in disease status • Morbid events • Functional outcomes
Individuals: • With asthma	Interventions of interest are: • Medication management directed by fractional exhaled nitric oxide	Comparators of interest are: • Standard clinical management	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Functional outcomes

Populations	Interventions	Comparators	Outcomes
Individuals: • With severe asthma	Interventions of interest are: • Measurement of fractional exhaled nitric oxide to select treatment	Comparators of interest are: • Standard clinical management	Relevant outcomes include: • Test validity • Symptoms • Change in disease status • Morbid events • Functional outcomes
Individuals: • With suspected or confirmed respiratory disorders other than asthma	Interventions of interest are: • Measurement of fractional exhaled nitric oxide	Comparators of interest are: • Standard clinical diagnosis and management	Relevant outcomes include: • Test validity • Symptoms • Change in disease status • Morbid events • Functional outcomes
Individuals: • With suspected or confirmed respiratory disorders	Interventions of interest are: • Measurement of exhaled breath condensate	Comparators of interest are: • Standard clinical diagnosis and management	Relevant outcomes include: • Test validity • Symptoms • Change in disease status • Morbid events • Functional outcomes

DESCRIPTION

Evaluation of exhaled nitric oxide (NO) and exhaled breath condensate (EBC) are proposed as techniques to diagnose and monitor asthma and other respiratory conditions. There are commercially available devices for measuring NO in expired breath and various laboratory techniques for evaluating components of EBC.

OBJECTIVE

The objective of this evidence review is to determine whether the measurement of fractional exhaled nitric oxide or exhaled breath condensate improves the net health outcome in individuals with respiratory disorders.

BACKGROUND

Asthma

Asthma is characterized by airway inflammation that leads to airway obstruction and hyper-responsiveness, which in turn lead to characteristic clinical symptoms including wheezing, shortness of breath, cough, and chest tightness. In the United States, the burden of asthma falls disproportionately on Black, Hispanic, and American Indian and Alaska Native populations. Asthma-related emergency department visits are nearly 5 times higher for Black patients when compared to White patients, and Black patients are nearly 3 times as likely to die from asthma when compared to White patients. Differences in life experiences (e.g., family, social, and economic

environment), lifestyle choices (smoking, obesity, leisure-time physical activities), and exposure to adverse indoor and outdoor environment factors (e.g., mold, pollens, house dust mites, cockroaches, rodents, animal allergens, and other air pollutants) may account for some of the racial and ethnic differences in asthma prevalence. A sex difference also exists in asthma prevalence – in children, asthma is more common in males, whereas among adults, females are more likely to have an asthma diagnosis.

Management

Guidelines for the management of persistent asthma stress the importance of long-term suppression of inflammation using inhaled corticosteroids as primary treatment. Existing techniques for monitoring the status of underlying inflammation have focused on bronchoscopy, with lavage and biopsy, or analysis by induced sputum. Given the cumbersome nature of these techniques, the ongoing assessment of asthma focuses not on the status of the underlying chronic inflammation, but rather on regular assessments of respiratory parameters such as forced expiratory volume in 1 second and peak flow. Therefore, there has been an interest in noninvasive techniques to assess the underlying pathogenic chronic inflammation as reflected by measurements of inflammatory mediators.

Fractional Exhaled Nitric Oxide

One proposed strategy is the measurement of fractional exhaled nitric oxide (FeNO). Nitric oxide (NO) is an important endogenous messenger and inflammatory mediator that is widespread in the human body, with functions including the regulation of peripheral blood flow, platelet function, immune reactions, neurotransmission, and the mediation of inflammation. Patients with asthma have been found to have high levels of FeNO, which decreases with treatment with corticosteroids. In biologic tissues, NO is unstable, limiting measurement. However, in the gas phase, NO is fairly stable, permitting its measurement in exhaled air. Fractional exhaled NO is typically measured during single breath exhalations. First, the subject inspires NO-free air via a mouthpiece until total lung capacity is achieved, followed immediately by exhalation through the mouthpiece into the measuring device. Devices measuring FeNO are commercially available in the U.S. According to a joint statement by the American Thoracic Society and European Respiratory Society (2009), there is a consensus that FeNO is best measured at an exhaled rate of 50 mL per second maintained within 10% for more than 6 seconds at an oral pressure between 5 and 20 cm H_2O.[1,] Results are expressed as the NO concentration in parts per billion, based on the mean of 2 or 3 values.

Exhaled Breath Condensate

Exhaled breath condensate (EBC) consists of exhaled air passed through a condensing or cooling apparatus, resulting in an accumulation of fluid. Although EBC is primarily derived from water vapor, it also contains aerosol particles or respiratory fluid droplets, which in turn contain various nonvolatile inflammatory mediators, such as cytokines, leukotrienes, oxidants, antioxidants, and other markers of oxidative stress. There are a variety of laboratory techniques to measure the components of EBC, including such simple techniques as pH measurement and the more sophisticated gas chromatography/mass spectrometry or high-performance liquid chromatography, depending on the component of interest.

Clinical Uses of Fractional Exhaled Nitric Oxide and Exhaled Breath Condensate
Measurement of FeNO has been associated with an eosinophilic asthma phenotype. Eosinophilic asthma is a subtype of asthma associated with sputum and serum eosinophilia, along with later-onset asthma.[2,] Until recently, most asthma management strategies did not depend on the recognition or diagnosis of a particular subtype. However, anti-interleukin (IL)-5 agents have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of severe asthma with an eosinophilic phenotype. Anti-IL-4 receptor/anti-IL-13 monoclonal antibodies, anti-immunoglobulin E monoclonal antibodies, and thymic stromal lymphopoietin blocker monoclonal antibodies are also available to improve uncontrolled asthma that does not necessarily have an eosinophilic phenotype.

Measurement of NO and EBC has been investigated in the diagnosis and management of asthma. Potential management uses include assessing response to anti-inflammatory treatment, monitoring compliance with treatment, and predicting exacerbations. Aside from asthma, they have also been proposed in the management of patients with chronic obstructive pulmonary disease, cystic fibrosis, allergic rhinitis, pulmonary hypertension, and primary ciliary dyskinesia.

REGULATORY STATUS
The devices in Table 1 are cleared by the FDA for measuring FeNO with FDA product code MXA.

Table 1. FeNO Devices Cleared by FDA

Device	Manufacturer	Indication/Comments	Date Cleared	510(k)
Nitric Oxide Monitoring System (NIOX®)	Aerocrine; acquired by Circassia	"[Measurements …FE-NO provide the physician with means of evaluating an asthma patient's response to anti-inflammatory therapy, as an adjunct to established clinical and laboratory assessments in asthma. NIOX should only be used by trained physicians, nurses and laboratory technicians. NIOX cannot be used with infants or by children approximately under the age of 4, as measurement requires patient cooperation. NIOX should not be used in critical care, emergency care or in anesthesiology."	2003	De novo DEN030001 K021133
NIOX MINO®	Aerocrine; acquired by Circassia	Same as above except used for ages 7 and older. Handheld and portable.	2008	K072816/K101034
NIOX VERO®	Aerocrine; acquired by Circassia	Same as MINO. Differs from predicate devices in terms of its battery and display format.	2014	K133898
Fenom Pro™ Nitric Oxide Test	Spirosure	Measurement of FeNO by Fenom Pro is a method to measure the decrease in FeNO concentration in asthma patients that often occurs after treatment with anti-inflammatory pharmacological therapy as an indication of therapeutic effect in patients with elevated FeNO levels. FeNO measurements are to be	2019	K182874

Device	Manufacturer	Indication/Comments	Date Cleared	510(k)
		used as an adjunct to established clinical assessments. Fenom Pro is suitable for children, approximately 7-17 years, and adults 18 years and older. Testing using the Fenom Pro should only be done in a point-of-care healthcare setting under professional supervision. Fenom Pro™ should not be used in critical care, emergency care or in anesthesiology.		
NObreath®	Bedfont Scientific Ltd	Measurement of FeNO by NObreath is a method to measure the decrease in FeNO concentration in asthma patients that often occurs after treatment with anti-inflammatory pharmacological therapy, as an indication of the therapeutic effect in patients with elevated FeNO levels. NObreath is intended for children who are 7-17 years and adults. NObreath 12-second test mode is for ages 7 and up. NObreath 10-second test mode is for ages 7-10, only if successful completion of a 12-second test is not possible. The NObreath cannot be used with infants or by children under the age of 7 as measurement requires patient cooperation. NObreath should not be used in critical care, emergency care, or in anesthesiology.	2021	K203695

FDA: U.S. Food and Drug Administration; FeNO: fractional exhaled nitric oxide.

The RTube™ Exhaled Breath Condensate collection system (Respiratory Research) and the ECoScreen EBC collection system (CareFusion) are registered with the FDA as class I devices that collect expired gas. Respiratory Research has a proprietary gas-standardized pH assay, which, when performed by the company, is considered a laboratory-developed test.

POLICY

A. Measurement of exhaled nitric oxide is considered **experimental / investigational** in the diagnosis and management of asthma, eosinophilic asthma, and other respiratory disorders including but not limited to chronic obstructive pulmonary disease and chronic cough.

B. Measurement of exhaled breath condensate is considered **experimental / investigational** in the diagnosis and management of asthma and other respiratory disorders including but not limited to chronic obstructive pulmonary disease and chronic cough.

Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through April 21, 2023.

Fractional exhaled nitric oxide (FeNO) has been evaluated in various clinical settings, including (but not limited to) the diagnosis of asthma, as a predictor of eosinophilic inflammation, as a predictor of response to inhaled corticosteroids (ICS) and other medications, and as a marker of nonadherence in patients managed with ICS.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harm is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

FRACTIONAL EXHALED NITRIC OXIDE IN ASTHMA DIAGNOSIS

Clinical Context and Test Purpose

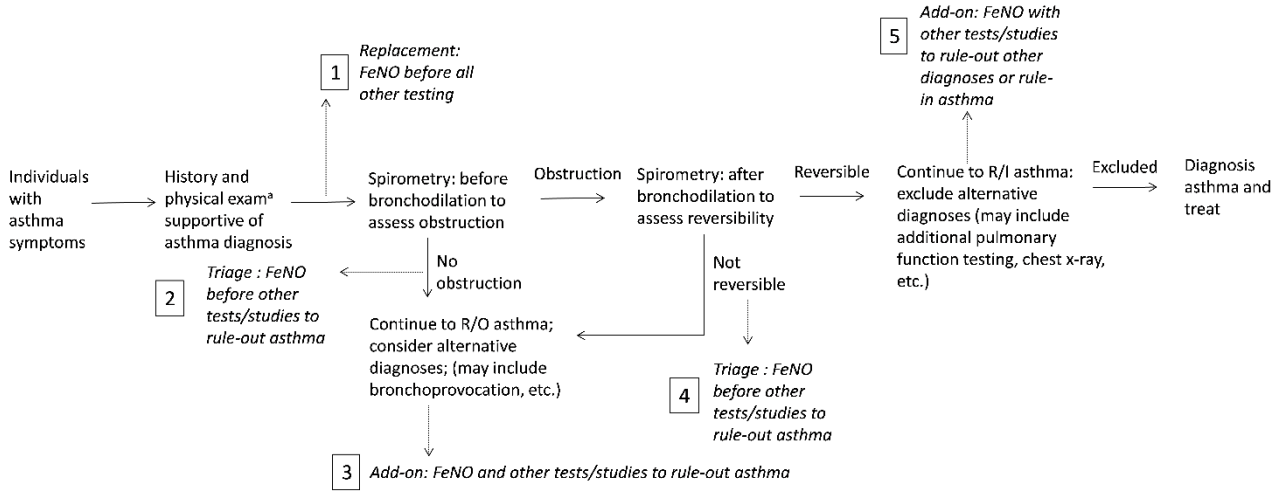
The purpose of FeNO testing in individuals who have suspected asthma is to aid in the diagnosis of asthma.

National Heart, Lung, and Blood Institute (NHLBI) guidelines have suggested clinicians confirm the following to establish the diagnosis of asthma: (1) presence of episodic symptoms of airflow obstruction or hyperresponsiveness; (2) reversibility of airflow obstruction; and (3) exclusion of alternative diagnoses.[3,] Figure 1 shows a simplified asthma diagnostic pathway for adults and children ages 5 and older. In children younger than 5, spirometry often cannot be performed and a trial of asthma medications may help establish the diagnosis.

To evaluate the test performance, the position on the pathway (i.e., the population of interest, what previous testing has been performed) as well as the specification of whether FeNO is meant to be used as a triage, add-on, or replacement test with respect to existing diagnostic tests or procedures are needed.[4,]Testing FeNO could theoretically be used at several positions in the pathway. Five potential positions are shown in Figure 1. In position 1, FeNO would be used as a replacement for initial pulmonary function testing in patients with symptoms of asthma. In positions 2, 3, and 4, FeNO would be used as an adjunctive test to rule out asthma in individuals with symptoms of asthma but negative spirometry. In position 5, FeNO would be used as an adjunctive test in individuals with symptoms of asthma and positive spirometry to rule-in asthma and exclude alternative diagnoses. Using FeNO to diagnose other conditions is assessed in a separate section of the review.

Given that U.S. guidelines do not support FeNO as a replacement for spirometry when spirometry can be performed (position 1), studies reporting on the use of FeNO in positions 2, 3, and 4 in Figure 1 are most relevant for review.

Figure 1. Asthma Diagnostic Pathway



FeNO: fractional exhaled nitric oxide; R/I: rule in; R/O: rule out.
[a] Symptoms likely due to asthma, patterns of symptoms, family history of asthma or allergies; physical exam of upper respiratory tract, chest, and skin.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with suspected asthma. The specific population of interest depends on the position of the FeNO test in the diagnostic pathway as shown in Figure 1; in particular, the patient population will vary depending on the timing and type of the previous testing performed.

Interventions
The test being considered is measurement of FeNO for diagnosis. Devices measuring FeNO are commercially available in the U.S.

The measurement of FeNO may be easier to perform than other tests used for diagnosing asthma, particularly in children. To measure FeNO, the patient exhales directly into the analyzer or container at a constant flow for several seconds so that the mean FeNO value over a 3-second plateau can be recorded. Results are expressed as the NO concentration in parts per billion (ppb), based on the mean of 2 or 3 values.

Comparators
The following practice is currently being used to diagnose asthma: standard clinical diagnosis. The appropriate comparator depends on the position of the FeNO test in the diagnostic pathway. In position 1, an appropriate comparator would be lung function tests (e.g., spirometry) given that FeNO would be a replacement for spirometry. In positions 2, 3, 4, and 5, the appropriate comparators are other tests or procedures used to rule in or rule out asthma after spirometry such as additional pulmonary function testing, bronchoprovocation testing, or tests used to rule-in other respiratory conditions.

There is no definitive reference standard for diagnosing asthma.

Outcomes
The general outcomes of interest are test validity, symptoms, change in disease status, morbid events, and functional outcomes. The performance characteristics of most interest depend on whether the test is used to rule in or rule out asthma. The performance characteristics provide data needed to infer rates of true positives, true negatives, false positives, and false negatives.

Beneficial outcomes that can be a consequence of a true-positive FeNO test result are the avoidance of other diagnostic testing, which could reduce resource utilization and exposure to adverse events of other testing modalities, as well as undergoing correct treatment, which would lead to control of asthma symptoms. The consequence of a true-negative result is avoiding unnecessary or incorrect treatment and other diagnostic testing and limiting exposure to their adverse events.

The harmful outcomes that can be a consequence of a false-positive or -negative FeNO test result are incorrect or unnecessary treatment or unnecessary additional diagnostic testing.

Study Selection Criteria
Because multiple, recent systematic reviews of diagnostic accuracy studies are available, the focus of the following sections is on these systematic reviews. Additional diagnostic accuracy studies published after the systematic review are discussed in detail only if they address limitations identified in the systematic reviews.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

REVIEW OF EVIDENCE

Systematic Reviews

A large number of studies have correlated the presence of asthma with higher FeNO levels; a complete review is beyond this report. Therefore, the primary focus is on systematic reviews of clinical validity studies for diagnosing asthma. Three systematic reviews were published in 2017 and an additional systematic review focusing on children was published in 2019. In addition, a review is described in the National Institute for Health and Care Excellence (NICE; 2017) guidance.[5] Characteristics of the systematic reviews and a summary of the quality of the included studies are shown in Table 2.

All published reviews noted that most included studies had several domains rated as high or unclear risk of bias according to the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) criteria. Harnan et al (2017)[6,] noted a high or unclear risk of bias for patient selection, index test (FeNO), reference standard, and patient flow/test timing; Karrasch et al (2017)[7,] noted a high or unclear risk of bias particularly for the index test (FeNO) and reference test; Wang et al (2017, 2018)[8,9,] noted a high risk of bias, particularly for patient selection. Tang et al (2019) noted a high risk of bias for patient selection and index test.[10,]

Table 2. Characteristics of Systematic Reviews of FeNO for Diagnosing Asthma

Study	No. of Included Studies	Study Population in Included Studies	Design of Included Studies	Reference Standard of Included Studies	QUADAS-2 Quality Assessment for Domains Rated "High" or "Unclear" Risk of Bias or Applicability			
					No. of Studies With No Domains	No. of Studies With 1-2 Domains	No. of Studies With >2 Domains	Domains With ≥33% Studies
Wang et al (2017, 2018)[8,9,]	43	13,747 patients with suspected asthma ages ≥5 y	Any design with a reference standard (i.e., controlled)	Any reference standard	10	13	20	Study included random or consecutive samples
Karrasch et al (2017)[7,]	26	4518 patients with suspected	Any design; reported	Any reference standard	0	12	14	Conduct or interpretation of the

Study	No. of Included Studies	Study Population in Included Studies	Design of Included Studies	Reference Standard of Included Studies	QUADAS-2 Quality Assessment for Domains Rated "High" or "Unclear" Risk of Bias or Applicability			
		asthma; at least 75% had to be steroid-naive	TP, TN, FP, and FN for asthma dx by FeNO vs. reference standard; FeNO measured using 2005 ATS criteria					index test; conduct or interpretation of reference test; patient flow
Harnan et al (2017)[6,]	27[a]	Participants with symptoms of asthma or reported a subgroup of such patients	Any design; reported TP, TN, FP, and FN for asthma dx by FeNO vs reference standard; FeNO measured using 2005 ATS criteria	Any reference standard	0	7[b]	23[b]	All 4 domains: patient selection, index test, reference standard, flow and timing
NICE (2017)[5,]	18	Patients with suspected asthma; no more than 50% of participants on corticosteroid treatment	Any design with the specified reference standard; case-control included only if n≥50	Physician dx of asthma based on symptoms plus an objective test[c]	NR	NR	NR	NR
Tang et al (2019)[10,]	8	Children; symptoms unclear	Any design; reported TP, TN,	Any reference standard	0	5	3	Patient selection, index test, reference

Study	No. of Included Studies	Study Population in Included Studies	Design of Included Studies	Reference Standard of Included Studies	QUADAS-2 Quality Assessment for Domains Rated "High" or "Unclear" Risk of Bias or Applicability			
			FP, and FN for asthma dx by FeNO					standard, flow and timing

ATS: American Thoracic Society; dx: diagnosis; FeNO: fractional exhaled nitric oxide; FN: false negative; FP: false positive; NR: not reported; TN: true negative; TP: true positive; QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies.
a There appear to be ≥27 studies in the quality assessment table.
b Harnan et al (2017) only provided QUADAS-2 risk of bias (4 questions) assessment; it did not include the 3 applicability questions.
c Objective test must be 1 of the following: peak flow variability (cutoff value of >20% variability as indication of a positive test); bronchodilator reversibility (cutoff value of an improvement in forced expiratory volume in 1 second of ≥12%, and an increase in volume of ≥200 mL as indication of a positive test); bronchial hyperresponsiveness (histamine or methacholine challenge test, cutoff value of ≤8 mg/mL on the histamine provocation concentration producing a 20% fall in forced expiratory volume in 1 second as indication of a positive test).

The results of the systematic reviews are shown in Table 3. Karrasch et al (2017) and Tang et al (2019) provided pooled estimates of sensitivity and specificity across various FeNO cutoffs.[7,10,]

The Wang et al (2017) review was conducted for the Agency for Healthcare Research and Quality (AHRQ) and sponsored by NHLBI.[8,] They provided estimates of sensitivity and specificity for different FeNO cutoffs. Sensitivity ranged from 79% at a cutoff of 20 ppb to 41% with a cutoff of 40 ppb, while specificity ranged from 72% with a cutoff of 20 ppb to 94% with a cutoff of 40 ppb.[8,9,] Results were not stratified by previous testing. The strength of evidence was graded using the Evidence-based Practice Center Methods Guide on Comparative Effectiveness Reviews. Reviewers concluded that FeNO had moderate accuracy to diagnose asthma in people ages 5 years and older (strength of evidence: moderate). The AHRQ report did not consider how FeNO fits into the existing diagnostic pathway, provided no comparisons to credible alternative tests, and reported no estimates of the performance characteristics of FeNO in patients who had normal spirometry or diagnostic uncertainty (i.e., it did not address incremental value).

As part of the development of the NICE guidance on the use of FeNO to manage asthma, Harnan et al (2017) conducted a health technology assessment to evaluate the clinical effectiveness of FeNO measurements in people with asthma.[6,] Reviewers presented results according to where studies fell along the diagnostic pathway. Twelve studies were conducted in patients with asthma symptoms but no previous testing, corresponding to position 1 in Figure 1. One study was performed in patients with normal spirometry, corresponding to position 2 in Figure 1. One study reported on patients with a negative methacholine challenge test, corresponding to position 3 in Figure 1. One study was conducted in patients with a negative airway reversibility test, corresponding to position 4 in Figure 1. Three studies were performed in patients referred for airway hyperresponsiveness testing. Although the results of the previous testing were unclear, these patients might correspond to use of the test in positions 2 or 4 in Figure 1. Eight studies were difficult to place in the diagnostic pathway and 6 studies included patients with chronic cough. In summary, the NICE reviewers (2017) identified 1 study in each of positions 2, 3, and 4.

All 3 studies were rated as having a high or unclear risk of bias for at least 2 of the 4 QUADAS-2 domains. Heterogeneity precluded meta-analysis. Results varied even within subgroups of studies located in a similar position on the pathway and with a similar reference standard. Reviewers concluded that "Diagnostic accuracy, optimal cut-off values and best position for FeNO within a pathway remain poorly evidenced."

Although the Harnan et al (2017) review was commissioned by the NICE, the 2017 updated NICE guidance on diagnosing and monitoring asthma did not refer to the review. Instead, another de novo review of the evidence is described in the guidelines and is used as the basis for the conclusions. The summary tables provide ranges of sensitivity and specificity for studies in adults and children sorted by FeNO cutoff; a summary receiver operating characteristic curve (ROC) was created. The review included 3 studies in adults (with FeNO cutoffs of 40, 40, 38.8 ppb), 2 studies in children (with FeNO cutoffs of 25 and 22 ppb), 2 studies in mixed populations of adults and children (with FeNO cutoffs of 27 and 36 ppb), and 1 study with unclear ages (with a FeNO cutoff of 30 ppb). Conclusions were based on an economic analysis in adults that found that "FeNO... was part of the most cost-effective diagnostic pathway used to diagnose asthma in adults aged 16 and over." The section on "Key assumptions" for the decision tree states that the model assumed the tests are conditionally independent. The NICE advisory committee was asked to give its opinion on how strongly it believed the conditional independence assumption between tests. "The guidance stated that for adults the recommendation is to "regard a FeNO level of 40 ppb or more as a positive test." Of note, the NICE summary tables included no studies with a cutoff higher than 40 ppb, 1 study in adults with a FeNO cutoff of 40 ppb, which was rated as a very low-quality study, and 1 study with a cutoff of 38.8 ppb, which was rated as a moderate quality study. The summary table included 2 studies in children with FeNO cutoffs of 22 and 25 ppb. The recommendation for children is to consider FeNO when there is diagnostic uncertainty and "regard a FeNO of 35 ppb or more as a positive test."

Table 3. Results of Systematic Reviews Assessing FeNO for Diagnosing Asthma

Study	FeNO Cutoff	No. of Studies/ No. of Patients	Sensitivity (95% CI), %	Specificity (95% CI), %
Wang et al (2017, 2018)[8,9,]				
Overall	<20 ppb	21 studies/4129 patients	79 (71 to 86)	72 (59 to 81)
	20-30 ppb	22 studies/5189 patients	64 (55 to 72)	81 (74 to 87)
	30-40 ppb	10 studies/1753 patients	53 (37 to 68)	84 (77 to 89)
	>40 ppb	10 studies/1368 patients	41 (27 to 57)	94 (89 to 97)
Karrasch et al (2017)[7,]	Pooled across cutoffs	28 studies/4518 patients	65 (58 to 72)	82 (76 to 86)
Harnan et al (2017)[6,]				
Asthma symptoms, no previous testing	Range, 20-47	12 studies/1837 patients	Range, 14-88	Range, 60-93

Study	FeNO Cutoff	No. of Studies/ No. of Patients	Sensitivity (95% CI), %	Specificity (95% CI), %
Negative airway reversibility test	32	1 study/112 patients	47	85
Referred for hyperresponsiveness testing	Range, 35-47	3 studies/1753 patients	Range, 30-75	Range, 83-96
Normal spirometry	46	1 study/101 patients	35	90
NICE (2017)[5,]				
Adults/mixed	Range, 27-40	6 studies/921 patients	Range, 43-88	Range, 60-92
Children	Range, 22-25	2 studies/358 patients	Range, 57-75	Range, 87-89
Tang et al (2019)[10,]	Pooled across cutoffs	8 studies/2933 patients	79 (64 to 89)	81 (66 to 90)

CI: confidence interval; FeNO: fractional exhaled nitric oxide; ppb: part per billion.

Diagnostic accuracy studies published after the systematic reviews have not addressed the limitations identified.[11,12,13,14,]

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence
Direct evidence of the clinical utility is provided by studies that have compared health outcomes for patients diagnosed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

No direct evidence of clinical utility for using FeNO to diagnose asthma was identified.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Although many studies evaluating the diagnostic accuracy of FeNO have been conducted, study quality has varied, cutoff values were not standardized, and the clinical use of the test in the diagnostic pathway is not clear. Very few studies included patients with difficult diagnostic situations (i.e., when spirometry to assess obstruction or reversibility and/or methacholine challenge testing is negative but suspicion for asthma remains) and diagnostic accuracy in that setting is not well-characterized. Little information on the incremental value of FeNO compared with current diagnostic tests or algorithms from studies with concurrent controls is available. Therefore, a chain of evidence cannot be created for clinical utility.

Section Summary: Fractional Exhaled Nitric Oxide in Asthma Diagnosis
Systematic reviews of diagnostic accuracy of FeNO for asthma have assessed 70 observational studies with varying reference standards, cutoff values, study quality, and positions in the diagnostic pathway. The most useful position for FeNO in the diagnostic pathway is likely in the diagnosis of difficult cases (i.e., when spirometry to assess obstruction or reversibility and/or methacholine challenge testing is negative but suspicion for asthma remains). Very few studies have been conducted in those settings and populations; therefore, diagnostic accuracy is not well-characterized. Data on the incremental value of FeNO compared with spirometry or other tests and algorithms are limited.

FRACTIONAL EXHALED NITRIC OXIDE IN ASTHMA MANAGEMENT

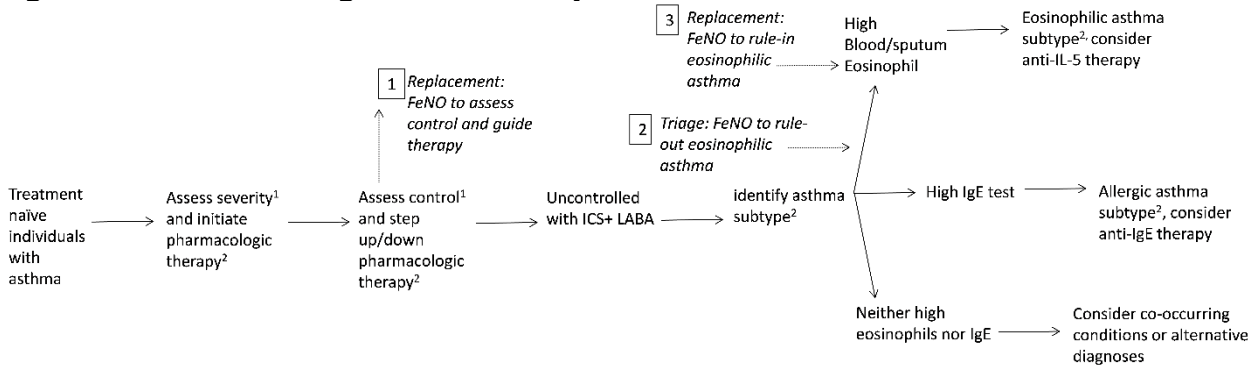
Clinical Context and Test Purpose
The purpose of FeNO testing in individuals who have asthma is to aid in making treatment decisions, including step-up/step-down therapy (see description below) and selection of targeted therapies for eosinophilic asthma.

The NHLBI guidelines have suggested that management of patients with asthma includes routine monitoring of symptoms and lung function, patient education, controlling environmental trigger factors, controlling comorbid conditions, and pharmacologic therapy.[3,]

Although patient education and identification and avoidance of asthma triggers are critical components of successful asthma management, this section focuses on pharmacologic maintenance therapy. In treatment-naive patients, the severity of symptoms is assessed and categorized as intermittent, mild, moderate, or severe based on reported symptoms, lung function, and exacerbations requiring systemic glucocorticoids. Treatment is initially based on asthma severity and then medications are increased or decreased in a stepwise approach ("step-up/step-down") based on the assessment of asthma control. The components of control are also described in guidelines and focus on impairment as determined by patient report or a validated questionnaire, a current forced expiratory volume in 1 second (FEV_1) or peak flow, and estimates of risk.

Figure 2 shows a simplified asthma management pathway for adults and children ages 12 and older. In children younger than 12, the pathway is similar, although pediatric approval for anti-interleukin-5 (IL-5) therapies varies, ranging from no pediatric approval to approval for children ages 6 and older, anti-IL-4 receptor (IL-4R)/anti-IL-13 therapy is approved for children ages 6 and older only when used for asthma management, anti-immunoglobulin E (IgE) therapy is approved for children ages 6 and older, and a thymic stromal lymphopoietin (TSLP) blocker is approved for adolescents ages 12 and older. To evaluate test performance, the position on the pathway (i.e., the population of interest, what previous testing and treatment have been received) as well as the specification of whether FeNO is meant to be used as a triage, add-on, or replacement test with respect to existing diagnostic tests or procedures are needed.[4,] Fractional expired NO testing could theoretically be used at multiple positions in the pathway. Two potential positions are shown in Figure 2. In position 1, FeNO would be used as a replacement for guidelines-driven management to assess control of asthma and to guide therapy. In position 2, FeNO would be used to select patients for treatments targeted to an eosinophilic asthma subtype as a replacement for blood or sputum testing.

Figure 2. Asthma Management Pathway



FeNO: fractional exhaled nitric oxide; ICS: inhaled glucocorticoids; IgE: immunoglobulin E; IL-5: interleukin-5; LABA: long-acting beta-agonist.
[1] Per National Heart, Lung, and Blood Institute guidelines.
[2] Patient education and control of triggers and comorbid conditions are part of all treatment pathways. Acute exacerbation requiring hospitalization requires additional treatment.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with asthma and individuals with severe asthma. The specific population of interest depends on the position of the FeNO test in the management pathway, as shown in Figure 2.

Interventions
The intervention being considered is medication management directed by FeNO testing and measurement of FeNO to select treatment. Several devices measuring FeNO are commercially available in the U.S. Results are expressed as the NO concentration in ppb, based on the mean of 2 or 3 values.

Comparators
The following practice is currently being used to treat asthma and severe asthma: standard clinical management. The appropriate comparator depends on the position of the FeNO in the diagnostic pathway. In position 1, the appropriate comparator would be a guidelines-driven assessment of control and therapy. In position 2, appropriate comparators are blood and sputum assessment of eosinophils.

Once a severe asthma diagnosis is established, consideration of appropriate add-on biologic targeted treatments is required. The appropriate comparator to predict response to therapy would be the guidelines-driven empiric selection of a type 2 inflammation-targeted biologic.

Outcomes
The general outcomes of interest are test validity, symptoms, change in disease status, morbid events, and functional outcomes. For evaluation of FeNO in position 1 (assessing control and guiding therapy), outcomes of interest are exacerbations, symptoms, hospitalizations, use of systemic corticosteroids, and quality of life.

An Asthma Outcomes workshop was convened in 2010 by the National Institutes of Health (NIH) and AHRQ with 2 key objectives "(1) to establish standard definitions and data collection methodologies for validated outcome measures in asthma clinical research with the goal of enabling comparisons across asthma research studies and clinical trials and (2) to identify promising outcome measures for asthma clinical research and comment on their status and further validation needs."[15,] There were a series of publications on recommendations for core asthma measures for 7 domains of asthma clinical research outcome measures: biomarkers, composite scores of asthma control, exacerbations, health care utilization and costs, pulmonary physiology, quality of life, and symptoms. The publication on the measurement of exacerbations provided a proposed definition of exacerbation and stated that the "preferred" measure for reporting exacerbation outcomes is the overall rate (annual).[16,] It stated that the percentage with an exacerbation is an "additional" measure. The NIH and American Thoracic Society (ATS) recommended definitions for exacerbation in clinical trials are as follows.[1,16,]

- NIH suggested that classification of exacerbation outcome measures should include:
    - Systemic corticosteroids for asthma for at least 3 days (any length of use for children 5 to 11 years old)
    - Asthma-specific hospital admissions
    - Asthma-specific emergency department visits (separate urgent care visits when these can be differentiated)
    - Asthma-specific intensive care unit admissions/intubations
    - Death (all-cause and asthma-related)
- ATS definition of severe exacerbation for clinical trials:
    - Use of systemic corticosteroids, or an increase from a stable maintenance dose, for at least 3 days
    - A hospitalization or emergency department visit because of asthma, requiring systemic corticosteroids
- ATS definition of a moderate exacerbation for clinical trials:
    - Deterioration in symptoms, deterioration in lung function, and increased rescue bronchodilator use lasting for 2 days or more
    - Not severe enough to warrant systemic corticosteroid use and/or hospitalization

The NIH publications also described composite scales that measure asthma control.[17,] The recommended scales are shown in Table 4.

Table 4. Symptom Control Scales Outcome Measures

Name	Description	Administration	Scoring	MCID
Asthma Control Questionnaire[18,]	Measures adequacy of asthma control and change in asthma control	• 5 items self-administered on symptoms • 1 item self-administered on rescue medication • 1 item completed by clinic staff on $\%FEV_1$	• 7 items; 1-week recall • 7-point scale (0 [no impairment] to 6 [maximum impairment]) for symptoms and rescue use • 7 categories for $\%FEV_1$ • Scores range between 0 (totally controlled) and 6 (severely uncontrolled)	Change in score of 0.5
Asthma Control Test[19,]	Identifies poorly controlled asthma	Self-administered	• 5 items, with 4-week recall • 5-point scale (for symptoms and activities: 1 [all the time] to 5 [not at all]; for asthma control rating: 1 [not controlled at all] to 5 [completely controlled]) • Scores range from 5 (poor control of asthma) to 25 (complete control of asthma)	3 points between 2 groups or for changes over time

Adapted from Cloutier et al (2012).[17,]
$\%FEV_1$: percent forced expiratory volume in 1 second; MCID: minimal clinically important difference.

For evaluation of FeNO for selecting patients for treatments targeted for severe asthma, the ability of FeNO to predict response to therapy compared with empiric selection of a type 2 inflammation-targeted biologic, or blood and/or sputum assessment for eosinophilic asthma, is of interest. Trials of anti-IL-5 therapies have generally had inclusion criteria for eosinophilic asthma based on blood eosinophil counts. In contrast, trials for dupilumab, an anti-IL-4R/anti-IL-13 therapy, generally did not have minimum requirements of baseline eosinophil counts for inclusion.

Follow-up of patients with asthma depends on asthma severity but ranges from approximately every month to every 6 months. Given that asthma is a chronic condition, outcomes measured at least out to 1 year are preferred.

Study Selection Criteria

A wide variety of factors may affect asthma control and response to therapy. Therefore, assessment of the clinical utility of FeNO-guided treatment cannot be made by a chain of evidence from clinical validity data alone (i.e., it is not sufficient to demonstrate that the test is *associated* with clinical outcomes). Evidence considered must directly demonstrate that FeNO testing *alters* clinical outcomes such as exacerbations, symptoms, and hospitalizations. The following sections focus on RCTs and systematic reviews of RCTs.

REVIEW OF EVIDENCE

FRACTIONAL EXHALED NITRIC OXIDE TO ASSESS CONTROL AND GUIDE STEP-UP/STEP-DOWN THERAPY

Systematic Reviews

Several trials comparing FeNO-guided treatment with usual clinical care have been published, and systematic reviews have summarized the trials for both adults and children. Characteristics of the systematic reviews are shown in Table 5.

In the Cochrane review by Petsky et al (2016), which assessed adults, the search included 7 RCTs published up to June 2016.[20,] A total of 1700 patients were randomized to FeNO or management based on symptoms and clinical guidelines; 1546 patients completed the trials. The RCTs varied in the definition of asthma exacerbations, the FeNO cutoff (15-35 ppb), and the way FeNO was used to adjust the therapy. The GRADE quality assessment of the evidence ranged from moderate for the outcome of exacerbations to very low for the outcome of ICS dose at the final visit.

Petsky et al (2016) also updated a Cochrane review of RCTs in children.[21,] The search identified 9 trials (N=1426) published up to July 2016. The quality of the evidence was rated moderate for the outcomes of the number of children who had 1 or more exacerbations and final ICS dose and rated very low for the outcome of exacerbation rates. The exhaled NO cutoff values used to guide medication change and the definition of exacerbations varied across studies. The length of follow-up ranged from 6 to 12 months.

Petsky et al (2018) also conducted a systematic review tailored to asthma treatment based on FeNO or sputum eosinophils.[22,] No additional RCTs were included in the FeNO analyses compared with the 2 earlier Petsky et al (2016) reviews.

Wang et al (2017)[8,] reported on a systematic review for AHRQ, which included RCTs, that almost entirely overlapped with the 2 Petsky et al (2016) reviews. The strength of evidence was rated as high using GRADE criteria for the outcome of exacerbations for both adults and children and moderate to low for the remaining outcomes.

Table 5. Characteristics of Systematic Reviews of FeNO-Guided Treatment

Study	Dates	Trials	Participants	N	Design	Duration, mo
Wang et al (2017)[8,]	To Apr 2017	14	Adults or children (ages ≥5 y) diagnosed with asthma	2269	RCT	4-12
Petsky et al (2016)[20,]; adults	To Jun 2016	7	Adults diagnosed with asthma who required asthma medications	1700	RCT	4-12
Petsky et al (2016)[21,]; children	To Jul 2016	9	Children diagnosed with asthma	1426	RCT	6-12

FeNO: fractional exhaled nitric oxide; RCT: randomized controlled trial.

Results of the systematic reviews are shown in Table 6. In the Petsky et al (2016) review of adults, the number of people having asthma exacerbations was lower in the FeNO-guided group (odds ratio [OR], 0.60), with a number needed to treat of 12 (95% confidence interval [CI], 8 to 32)

when all studies were included, but not when limited to studies with a guidelines-driven control group.[20,] Patients in the FeNO group also had a lower exacerbation rate than controls (rate ratio, 0.59), but there was no difference between groups for exacerbations requiring hospitalization or rescue oral corticosteroids (OCS). None of the secondary outcomes (FEV_1, FeNO levels, symptoms scores, or ICS doses at final visit) differed significantly between groups.

In the Petsky et al (2016) review of children, the number of children having 1 or more exacerbations was significantly lower in the FeNO groups than in the control group (OR, 0.58) overall and in the studies that included guidelines-driven controls.[21,] However, there was no significant difference between groups in exacerbation rates. The number of children requiring OCS was lower in the FeNO groups than in the control groups (OR, 0.63; 95% CI, 0.48 to 0.83). There were no statistically significant differences between groups for exacerbations requiring hospitalization, FEV_1, FeNO levels, symptom scores, or final ICS dose.

The Wang et al (2017) AHRQ review had similar results, as would be expected given the overlapping studies. Reviewers reported that the number of patients needed to treat using FeNO-based algorithms to prevent 1 person with exacerbation is 9 for both adults and children. Results by guidelines-based control versus other controls were not given. Of note, the AHRQ review pooled the largest existing study of children (Szefler et al [2008]) with adult studies. The Szefler et al (2008) study included participants up to age 20 but 75% of patients were 16 and under.

Table 6. Results of Systematic Reviews of FeNO-Guided Treatment

Study	Participants With ≥1 Exacerbations, %	Rate of Exacerbations (per 52 wk)	ICS Dose at Final Visit	Participants With Exacerbations Requiring Hospitalization, %	Symptoms (Asthma Control Test)
Wang et al (2017)[8,]					
Adults					
N	1536	NR	NR	565	1253
Pooled effect (95% CI)	OR, 0.62 (0.45 to 0.86)			OR, 0.78 (0.14 to 4.29)	MD, -0.08 (-0.21 to 0.06)
I^2 (p)[a]	0% (NR)			0% (NR)	0% (NR)
Children					
N	733	NR	NR	1033	178
Pooled effect (95% CI)	OR, 0.50 (0.31 to 0.82)			OR, 0.70 (0.32 to 1.55)	MD, -0.07 (-0.20 to 0.05)
I^2 (p)[a]	6.8% (NR)			0% (NR)	
Petsky et al (2016)[20,]; adults					
Overall					
Total N	995	842	482	488	707

Study	Participants With ≥1 Exacerbations, %	Rate of Exacerbations (per 52 wk)	ICS Dose at Final Visit	Participants With Exacerbations Requiring Hospitalization, %	Symptoms (Asthma Control Test)
Pooled effect (95% CI)	OR, 0.60 (0.43 to 0.84)	RR, 0.59 (0.45 to 0.77)	MD, -147.15 (-380.85 to 86.56)	OR, 0.14 (0.01 to 2.67)	MD, -0.08 (-0.18 to 0.01)
I^2 (p)[a]	13% (.33)	0% (.64)	82% (<.001)	NA	0% (.91)
GRADE QOE	Moderate	Moderate	Very low	NR	NR
Guidelines-driven control					
N	NR (2 studies)	NR (3 studies)	NR	NR	NR
Pooled effect (95% CI)	OR, 0.87 (0.47 to 1.61)	RR, 0.76 (0.48 to 1.19)			
I^2 (p)[a]	56% (.13)	0% (.76)			
Petsky et al (2016)[21]; children					
Overall					
N	1279	736	317	1110	724
Pooled effect (95% CI)	OR, 0.58 (0.45 to 0.75)	MD, -0.37 (-0.80 to 0.06)	MD, 63.95 (-51.89 to 179.79)	OR, 0.75 (0.41 to 1.36)	MD, 0.14 (-0.18 to 0.47)
I^2 (p)[a]	7% (.38)	67% (.03)	40% (.19)	0% (.56)	62% (.11)
GRADE QOE	Moderate	Very low	Moderate	NR	NR
Guidelines-driven control					
N	799	673	NR	NR	NR
Pooled effect (95% CI)	OR, 0.67 (0.51 to 0.90)	MD, -0.27 (-0.49 to -0.06)			
I^2 (p)[a]	80% (.002)	77% (.01)			

CI: confidence interval; FeNO: fractional exhaled nitric oxide; ICS: inhaled corticosteroid; MD: mean difference; NA: not available: NR: not reported; OR: odds ratio; RR: rate ratio; QOE: quality of evidence rating.
[a] p value for heterogeneity.

Randomized Controlled Trials

Fractional expired NO should be compared with guidelines-directed treatment, which is standard of care. Although the Cochrane systematic reviews in the previous section provided sensitivity analyses for a trial using guidelines-driven controls, this section will further investigate RCTs using guidelines-driven controls. Characteristics of these trials are shown in Table 7. In adults, there are 5 RCTs (Heaney, Calhoun, Hashimoto, Shaw, Smith) that included guidelines-driven controls. None of the RCTs had a definition of exacerbation consistent with NIH or ATS recommendations. In children, there are 6 RCTs (Turner, Peirsman, Pike, Verini, Szefler, Fritsch) that included

guidelines-driven controls. The RCTs by Szefler et al (2008) and Turner (2022) are by far the largest and used a definition of exacerbation most consistent with NIH and ATS guidelines.[23,24,]

Table 7. Characteristics of RCTs of FeNO-Guided versus Guidelines-Driven Treatment

Study	Participants	Exacerbation Definition	Duration	Interventions	
Adults				**FeNO Group**	**Control Group**
Heaney et al (2021)[25,]	Aged 18 to 80 y, diagnosed with severe asthma with FeNO <45 ppb and documented history of reversibility of ≥12% change in FEV_1 within the past 24 months, currently on LABA plus high doses of ICS (≥1000 µg fluticasone propionate daily or equivalent)	Severe asthma exacerbation: new or increased asthma symptoms leading to a doubling of daily OCS dose (for patients on maintenance OCS); the prescription of a course of rescue OCS for ≥3 consecutive days; administration of intravenous or intramuscular corticosteroid for asthma; or hospital visit for asthma	48 wk	• n=240 • Biomarker score of 0 (FeNO <15 ppb, blood eosinophils <150 cells/µL, periostin <45 ng/mL), reduce treatment • Biomarker score of 1 (FeNO 15 to 30 ppb, blood eosinophils 150 to 300 cells/µL, periostin 45 to 55 ng/mL), maintain current treatment • Biomarker score of 2 (FeNO >30 ppb, blood eosinophils >300 cells/µL, periostin	• n=61 • BTS guidelines and Asthma Control Questionnaire

Study	Participants	Exacerbation Definition	Duration	Interventions	
				>55 ng/mL), increase treatment	
Calhoun et al (2012)[26], (guidelines and FeNO arms only)	Physician dx of asthma and either reversible airflow limitation (≥12% improvement in FEV_1 after 360 mg albuterol) or airway hyper-responsiveness (provocative concentration of methacholine <8 mg/mL) causing a 20% drop in FEV_1	Increased asthma symptoms resulting in use of OCS, increased ICS, or additional asthma medications	9 mo	• n=115 • <22 ppb, decrease • 22-35 ppb, maintain • >35 ppb, increase	• n=114 • NHLBI guidelines
Hashimoto et al (2011)[27],	Aged 18 to 75 y, diagnosis of severe refractory asthma as per ATS minor and major criteria; asthma uncontrolled and being assessed by a respiratory physician for 1+ y, currently on OCS, high doses of ICS and long-acting bronchodilators	Decrease in morning FEV_1 >10% vs. mean FEV_1 from week before, increase in symptoms requiring increased prednisolone >10 mg/d, or course of antibiotics, regardless of hospitalizations	6 mo	• n=51 • +10 ppb and >10% change, increase • +10 ppb and ≤10% change, maintain • -10 ppb to +10 ppb change, maintain • < -10 ppb change, decrease	• n=38 • GINA guidelines
Shaw et al (2007)[28],	>18 y, diagnosis of asthma and at least 1 prescription for anti-asthma medication in the past 12 mo	Increasing asthma symptoms requiring course of OCS or antibiotics	12 mo	• n=58 • <16 ppb once or 16-26 ppb twice, decrease • >26 ppb, increase	• n=60 • BTS guidelines and Asthma Control Test

Study	Participants	Exacerbation Definition	Duration	Interventions	
Smith et al (2005)[29],	ICSs for 6 mo with no dose change in previous 6 wk	• Minor exacerbation: global daily asthma score of 2 on ≥2 consecutive days • Major exacerbation: global daily asthma score of 3 on ≥2 consecutive days	12 mo	• n=46 • <15 ppb, maintain • ≥15 ppb, increase (flow rate of 250 mL/s)	• n=48 • GINA guidelines
Children					
Turner et al (2022)[24],	Children 6 to 15 y with a confirmed asthma diagnosis and ICS use who received a course of OCSs for ≥1 asthma exacerbation in the previous year	The initial definition was prescription of ≥1 course of OCSs for 3 to 7 consecutive days in the 12 months after randomization, but 2 recruitment centers started using a single dose of dexamethasone to treat asthma exacerbations. To accommodate this change and capture the primary outcome, the definition was changed to include any number of days of OCSs for an asthma exacerbation.	12 mo	• n=257 • At baseline: reduced FeNo was defined as <20 ppb and elevated FeNO was defined as levels > 35 ppb (children <12 y) or > 50 ppb (children ≥12 y) • When FeNO was elevated (>50% increase from previous	• n=258 • BTS guidelines

Study	Participants	Exacerbation Definition	Duration	Interventions	
				level) or reduced (<50% decrease from previous level), the ICS dose was also elevated or reduced, respectively	
Peirsman et al (2014)[30],	Children with mild-to-severe asthma according to GINA guidelines for >6 mo and allergic sensitization (i.e., positive SPT or specific IgE antibodies against inhalant allergens)	Episode of progressive increased shortness of breath, coughing, wheezing, or chest tightness, or a combination of these symptoms	12 mo	• n=49 • ≤20 ppb and controlled, step down • ≤20 ppb and partially controlled or uncontrolled, consider LTRA • >20 ppb, step up	• n=50 • GINA guidelines
Pike et al (2013)[31],	Ages 6 to 17 y, clinical diagnosis of asthma and treatment with beclomethasone dipropionate/budesonide ≥400 µg/d or fluticasone ≥200 µg/d	• ≥48 h of increased asthma symptoms or therapy or decreased PEF (≥25%) • Mild: increase SABA only • Moderate: requiring systemic	12 mo	• n=44 • ≤15 ppb and well-controlled, step down • <25 ppb and poorly controlled, LABA maximized • ≥25 ppb or FeNO doubled	• n=46 • SIGN/BTS guidelines

Study	Participants	Exacerbation Definition	Duration	Interventions	
		• corticosteroids • Severe: requiring hospitalizations ≥8 h		• from baseline, step up • If FeNO remained raised after increasing by 2 steps (SIGN/BTS steps) ICS not increased again unless participant poorly controlled	
Verini et al (2010)[32,]	Children admitted for allergic asthma and the diagnosis was made by a pediatric respiratory physician based on ATS/ERS criteria	Episodes of coughing, dyspnea, and wheezing requiring SABA	12 mo	• n=32 At 6-mo visit only: • <12 ppb, step down or no change • >12 ppb, step up	• n=32 • GINA guidelines
Szefler et al (2008)[23,]	Ages 12 to 20 y, diagnosed with asthma by their physician, symptoms of persistent asthma or evidence of uncontrolled disease, and residents of urban census tracts in which at least 20% of households had incomes below the federal poverty threshold	Admissions to hospital, unscheduled visits and prednisone use for asthma	46 wk	• n=276 • NHLBI guidelines and FeNO ≤20 ppb and level 1, no change • 20.1 to 30 ppb and level 2, step up • 30.1 to 40 ppb and level	• n=270 • NHLBI guidelines

Study	Participants	Exacerbation Definition	Duration	Interventions	
				3, 2 steps • >40 ppb and level 4, 3 steps or 2 steps and OCS course	
Fritsch et al (2006)[33,]	Ages 6 to 18 y with asthma diagnosis based on ATS criteria; positive SPT or RAST >1	OCS because of asthma symptoms, nonscheduled visit because of asthma symptoms, increase in symptom score to 2, decrease in FEV_1 (in liters) >10% vs. previous visit, or a combination of these	6 mo	• n=22 • ≤20 ppb and FEV_1 ≥80% and symptom score 0 or 1 and SABA use <6 in the last 2 weeks: step down • ≤20 ppb and FEV_1 <80% or symptoms score >1 or SABA use ≥6 in the last 2 weeks: step up Participant on SABA on demand only: • >20 ppb and FEV_1 ≥80% and symptom score 0 or 1 and SABA use <6	• n=25 • Austrian asthma guidelines

Study	Participants	Exacerbation Definition	Duration	Interventions
				in the last 2 weeks: step up Participant on ICS: • >20 ppb and FEV_1 ≥80% and symptom score 0 or 1 and SABA use <6 in the last 2 weeks: same step • >20 ppb and FEV_1 <80% or symptoms score >1 or SABA use ≥6 in the last 2 weeks: step up

ATS: American Thoracic Society; BTS: British Thoracic Society; dx: diagnosis; ERS: European Respiratory Society; FeNO: fractional exhaled nitric oxide; FEV_1: forced expiratory volume in 1 second; GINA: Global Initiative for Asthma; ICS: inhaled corticosteroids; IgE: immunoglobulin E; LABA: long-acting beta-agonist; LTRA: leukotriene receptor antagonist; NHLBI: National Heart, Lung, and Blood Institute; OCS: oral corticosteroids; PEF: peak expiratory flow; ppb: parts per billion; RAST: radioallergosorbent test; RCT: randomized controlled trial; SABA: short-acting beta2 agonist; SIGN: Scottish Intercollegiate Guidelines Network; SPT: skin prick test.

Results of the RCTs that included guidelines-driven controls are shown in Table 8. Reported outcomes varied. In adults, 4 RCTs (Heaney, Calhoun, Shaw, Smith) reported the outcome of the rate of exacerbations over 1 year. Two RCTs (Shaw, Smith) reported the outcome of percentage with exacerbation over the study period (12 months). One RCT (Smith) reported the outcome of percentage with exacerbation requiring OCS. Two RCTs reported on exacerbations requiring hospitalizations but no qualifying hospitalizations were noted in either group. Three RCTs reported control/symptom scales and 3 RCTs reported on pulmonary function (percent predicted FEV_1). No study of adults reported a significant difference for any outcomes included here. Heaney et al (2021) reported a primary outcome of proportion of patients with a reduction in ICS or OCS dose

from baseline to week 48.[25,] In this study, 28.4% of patients in the FeNO/biomarker strategy group were on a lower corticosteroid dose at week 48, compared to 18.5% of patients in the guidelines-driven control group (adjusted OR, 1.71; 95% CI, 0.80 to 3.63; p=.17).

In children, 3 RCTs (Pike, Verini, Szefler) reported the outcome of the rate of exacerbations over 1 year. Four RCTs (Peirsman, Pike, Verini, Szefler) reported the outcome of percentage with exacerbation over the study period, which was primarily 12 months (46 weeks for Szefler). Five RCTs (Turner, Peirsman, Pike, Szefler, Fritsch) reported the outcome of exacerbations requiring OCS. Three RCTs (Peirsman, Pike, Szefler) reported the outcome of exacerbations requiring hospitalization. One RCT (Szefler) reported a control/symptom scale. Three RCTs (Peirsman, Pike, Szefler) reported the percent predicted FEV_1 outcome.

Table 8. Results of RCTs of FeNO-Guided versus Guidelines-Driven Treatment

Study	Rate of Exacerbations per 52 Weeks	No. of Patients With 1+ Exacerbations Over Study Period	No. of Patients Exacerbations Requiring OCS	Symptom Control ACT Score or ACQ Score (95% CI)	No. of Patients With Exacerbations Requiring Hospitalization	Percent Predicted FEV_1
Adults						
Heaney et al (2021)[25,]						
N	262	NR	NR	258	Annual hospitalization rate	258
FeNO	1.36			ACQ, 2.0 (1.8 to 2.1)	0.10	73.2%
Control	1.67			ACQ, 2.2 (1.9 to 2.6)	0.16	72.1%
Adjusted OR (95% CI)	0.84 (0.61 to 1.15)			p=.47	0.77 (0.32 to 1.84)	p=.8
Calhoun et al (2012)[26,] (guidelines and FeNO arms only)						
N	229	NR	NR	229	NR	% Predicted at Visit 4
FeNO	0.21			ACQ[a], 0.79 (SD, 0.54)	0	86.3% (SD, 10.4%)
Control	0.23			ACQ[a], 0.72 (SD, 0.50)	0	87.7% (SD, 12.1%)
RR (95% CI)	0.90 (0.36 to 2.27)			NR		

Study	Rate of Exacerbations per 52 Weeks	No. of Patients With 1+ Exacerbations Over Study Period	No. of Patients Exacerbations Requiring OCS	Symptom Control ACT Score or ACQ Score (95% CI)	No. of Patients With Exacerbations Requiring Hospitalization	Percent Predicted FEV_1
Hashimoto et al (2011)[27,]						
N	89	NR	NR	89	NR	NR
FeNO	1.7 (median)			ACQ[b], 0.26 (0.07 to 0.45)	0	-0.0009 (slope)
Control	1.8 (median)			ACQ[b], 0.12 (0.12 to 0.36)	0	-0.0007 (slope)
p value	.95			.37		.73
Shaw et al (2007)[28,]						
N	118	158	NR	103	NR	NR
FeNO	0.33	21%		ACQ[c], 1.1		
Control	0.42	32%		ACQ[c], 1.15		
Treatment effect (95% CI)	RR , 0.79 (0.44 to 1.43)	OR , 0.56 (0.24 to 1.30)		MD, -0.05 (-0.33 to 0.23)		
Smith et al (2005)[29,]						
N	94	94	94	NR	NR	54
FeNO	0.49	30%	28%			86.1%
Control	0.90	23%	31%			82.3%
Treatment effect (95% CI)	RR, 0.54 (0.19 to 1.55)	OR, 1.47 (0.59 to 3.69)	OR, 0.87 (0.36 to 2.10)			MD, 3.8% (-4.5% to 12.1%)
Children						
Turner et al (2022)[24,]						
N	NR	NR	506	NR	NR	NR
FeNO			48.2%			
Control			51.4%			
Treatment effect (95% CI)			OR, 0.88 (0.61 to 1.27)			
Peirsman et al (2014)[30,]						
N	NR	99	99	NR	86	93

Study	Rate of Exacerbations per 52 Weeks	No. of Patients With 1+ Exacerbations Over Study Period	No. of Patients Exacerbations Requiring OCS	Symptom Control ACT Score or ACQ Score (95% CI)	No. of Patients With Exacerbations Requiring Hospitalization	Percent Predicted FEV_1
FeNO		24%	2		2%	91.2%
Control		48%	3		2%	93.9%
Treatment effect (95% CI)		OR, 0.37 (0.15 to 0.88)	OR, 0.67 (0.11 to 4.17)		OR, 1.00 (0.06 to 16.52)	MD, 2.70% (-2.98% to 8.38%)
Pike et al (2013)[31,]						
N	NR[d]	90	NR	NR	90	NR
FeNO		84%	3 (median no. of exacerbations)		11%	
Control		83%	2 (median no. of exacerbations)		7%	
OR (95% CI)		1.11 (0.37 to 3.38)	p=.29		1.84 (0.41 to 8.20)	
Verini et al (2010)[32,]						
N	64	NR	NR	NR	NR	NR
FeNO	0.83					
Control	1.85					
MD (95% CI)	-1.02 (-1.60 to -0.44)					
Szefler et al (2008)[23,]						
N	546	546	546	546	546	546
FeNO	0.66	37%	32%	ACT, 21.89	3%	96.3%
Control	0.84	44%	42%	ACT, 21.83	4%	95.5%
MD (95% CI)	-0.17 (-0.08 to 0.41)	-6.5% (-14.4% to 1.4%)	-10.3% (-18.5% to -2.2%)	0.06 (-0.28 to 0.40)	-0.8% (-4.0% to 2.3%)	0.80% (-0.51% to 2.07%)
Fritsch et al (2006)[33,]						
N	NR	NR	47	NR	NR	NR
FeNO			2			
Control			2			

Study	Rate of Exacerbations per 52 Weeks	No. of Patients With 1+ Exacerbations Over Study Period	No. of Patients Exacerbations Requiring OCS	Symptom Control ACT Score or ACQ Score (95% CI)	No. of Patients With Exacerbations Requiring Hospitalization	Percent Predicted FEV_1
OR (95% CI)			1.15 (0.15 to 8.93)			

ACT: Asthma Control Test; ACQ: Asthma Control Questionnaire; CI: confidence interval; FeNO: fractional exhaled nitric oxide; FEV_1: forced expiratory volume in 1 second; MD: mean difference; NR: not reported; OCS: oral corticosteroids; OR: odds ratio; RR: relative risk; RCT: randomized controlled trial; SD: standard deviation.
Effect sizes that were not available in the original publication were pulled from the Cochrane review.
[a] ACQ average score at visit 4.
[b] The effect of time on average change in ACQ was modeled nonparametrically and summarized with the change from baseline ACQ averaged over all repeated measurements during follow-up.
[c] ACQ is known as the Juniper Asthma Control Score in the U.K.
[d] Cochrane review reported data for this outcome that could not be located in the original publication.

The largest trial included in the Cochrane review on FeNO-based asthma management of children was a trial by Szefler et al (2008).[23,] The Asthma Control Evaluation was a randomized, double-blind, parallel-group trial funded by the National Institute of Allergy and Infectious Diseases; it included 546 inner-city participants, ages 12 to 20 years, with persistent asthma (75% ages ≤16 years). Participants were randomized to treatment based on NHLBI guidelines alone or guidelines plus FeNO measurements for a 46-week treatment period. The primary outcome was asthma symptom days. The number of asthma symptom days in the last 2 weeks (1.93 [95% CI, 1.74 to 2.11] in FeNO vs. 1.89 [95% CI, 1.71 to 1.74] in control), FEV_1 (difference, 0.8; 95% CI, -0.51 to 2.07), proportion with unscheduled care visits (risk difference, -1.4; 95% CI, -9.3 to -6.7), and proportion with hospitalizations (risk difference, -0.8; 95% CI, -4.0 to 2.3) did not differ between the treatment groups in intention-to-treat analyses. The proportion of patients with at least 1 exacerbation during the study period was 37% in the FeNO group compared with 44% in the control group (risk difference, -6.5; 95% CI, -14.4 to 1.4; p=.11). The outcome of patients requiring OCS was statistically significant favoring FeNO (32% vs. 42%; mean difference [MD], -10%; 95% CI, -18% to -2%; p=.01). Published after the aforementioned Cochrane review is an additional RCT by Turner et al (2022) that was close in size to the trial by Szefler et al (2008) and also used a guidelines-driven control and a definition of exacerbation consistent with NIH and ATS.[24,] This trial similarly found that the addition of FeNO to symptom-guided asthma treatment did not lead to reduced exacerbations among children 6 to 15 years of age; the proportion of children in the FeNO plus standard of care versus standard of care only groups that received OCSs for ≥1 asthma exacerbation during the 12 month treatment period was 48.2% and 51.4%, respectively (OR, 0.88; 95% CI, 0.61 to 1.27; p=.49).

The purpose of the limitations tables (Tables 9 and 10) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of the evidence supporting the position statement.

Table 9. Study Relevance Limitations of RCTs of FeNO-Guided versus Guidelines-Driven Treatment

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Adults					
Heaney et al (2021)[25,]	5. All study sites were in Europe			1. Primary outcome was a reduction in corticosteroid dose; key exacerbation outcomes not reported	1. Less than 1 y follow-up
Calhoun et al (2012)[26,]	4. The majority of enrolled patients (>66%) were White			1. Key exacerbation outcomes not reported	1. Less than 1 y follow-up
Hashimoto et al (2011)[27,]	5. All study sites were in the Netherlands	4. Daily FeNO determination; weekly evaluation; Internet-based		1. All key outcomes not reported	1. Less than 1 y follow-up
Shaw et al (2007)[28,]	5. All study sites were in the UK			1. Key exacerbation outcomes not reported	
Smith et al (2005)[29,]	5. Children >12 y of age included				
Children					
Turner et al (2022)[24,]	5. All study sites were in the UK				
Peirsman et al (2014)[30,]	5. The locations of study sites were not specified			1. Key exacerbation outcomes not reported	
Pike et al (2013)[31,]	5. All study sites were in the UK				
Verini et al (2010)[32,]	5. Single site in Italy			1. Most key outcomes not reported	

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Szefler et al (2008)[23,]					
Fritsch et al (2006)[33,]	5. Single site in Austria			1. Most key outcomes not reported	1. Less than 1 y follow-up

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
FeNO: fractional exhaled nitric oxide; RCT: randomized controlled trial; UK: United Kingdom.

[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 10. Study Design and Conduct Limitations of RCTs of FeNO-Guided versus Guidelines-Driven Treatment

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Adults						
Heaney et al (2021)[25,]		1,2. Single-blind (patients only)		1. High LTFU and many patients did not follow treatment advice		
Calhoun et al (2012)[26,]	3. Concealment not described	1,2. Blinding unclear				
Hashimoto et al (2011)[27,]	3. Concealment not described	1,2. No blinding				
Shaw et al (2007)[28,]						
Smith et al (2005)[29,]	3. Concealment not described				1-3. Power calculations not reported	
Children						

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Turner et al (2022)[24,]		1,2,3. In the FeNO intervention group, participants and clinicians were unblinded; in the standard of care group, patients and clinicians were blinded to FeNO results				
Peirsman et al (2014)[30,]		2. Blinding unclear		6. Unclear if ITT used		
Pike et al (2013)[31,]				1. 14% LTFU; 10 participants in FeNO and 3 in control	1-3. Power calculations not reported	
Verini et al (20100[32,]	3. Concealment not described	1,2. No blinding		1,2. Amount of missing data and method for accounting for missing data unclear 6. Unclear if ITT used	1-3. Power calculations not reported	
Szefler et al (2008)[23,]						
Fritsch et al (2006)[33,]	3. Concealment not described	1,2. Blinding unclear		1. >10% LTFU and 23 missing FeNO measurements due measure groups. Two to technical problems 6. Unclear if ITT used	2. Power calculated for FEV_1 difference over a mean of 5 visits but FEV_1 outcome reported was FEV_1 decline >10%	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
FeNO: fractional exhaled nitric oxide; FEV_1: forced expiratory volume in 1 second; ITT: intention to treat; LTFU: loss to follow-up; RCT: randomized controlled trial.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4.

Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4.Comparative treatment effects not calculated.

Subsection Summary: Efficacy of Fractional Exhaled Nitric Oxide-Guided Medication Management of Asthma

The most direct evidence related to the use of FeNO in the management of asthma comes from RCTs and systematic reviews of these RCTs comparing the management of asthma with and without FeNO. These studies are heterogeneous in terms of patient populations, FeNO cutoff levels, and protocols for managing patients in the control groups.

Two Cochrane reviews from 2016, 1 on adults and a second on children, found that FeNO-guided asthma management reduced the number of individuals who had more than 1 exacerbation but had no impact on day-to-day symptoms or hospitalizations. In adults, the benefit for FeNO on exacerbations was attenuated and no longer statistically significant when only studies using guidelines-driven controls were included.

Fractional exhaled nitric oxide-guided management significantly decreased exacerbations (and exacerbations requiring OCS) compared with guidelines-driven controls in children. In the Cochrane meta-analysis, the estimated pooled MD in the rate of exacerbations was -0.27 (95% CI, -0.49 to -0.06) favoring FeNO and the estimated pooled OR for the percentage of patients with 1 or more exacerbations was 0.67 (95% CI, 0.51 to 0.90). The Szefler et al (2008) RCT, which was by far the largest RCT (N=546) and funded by NIH, used a guidelines-driven control and a definition of exacerbation consistent with NIH and ATS recommendations. The percentage with 1 or more exacerbation in this trial was not statistically significant (MD, -6.5%; 95% CI, -14% to 1%; p=.11) but the percentage requiring OCS was statistically significant favoring FeNO (32% vs. 42%; MD, -10%; 95% CI, -18% to -2%; p=.01). Use of FeNO-guided management did not impact day-to-day clinical symptoms, hospitalizations, or pulmonary function measures. An additional RCT that was close in size and also used a guidelines-driven control and a definition of exacerbation consistent with NIH and ATS recommendations was published by Turner et al (2022).[24,] This trial similarly found that the addition of FeNO to symptom-guided asthma treatment did not lead to reduced exacerbations among children; the proportion of children in the FeNO plus standard of care versus standard of care only groups that received OCSs for ≥1 asthma exacerbation during the 12-month treatment period was 48.2% and 51.4%, respectively (OR, 0.88; 95% CI, 0.61 to 1.27; p=.49). Registered RCTs remain unpublished several years after completion (see the ongoing trials table in the Supplemental Information section).

Fractional Exhaled Nitric Oxide and Response to Inhaled Corticosteroids

Several studies have evaluated the association between FeNO and response to ICS.[34,35,36,37,38,] eosinophils. Several [39,40,41,] Inhaled corticosteroid use is in the guidelines-recommended management pathway for all patients with persistent asthma; however, there are

no RCTs examining the efficacy and safety of withholding ICS in patients with low FeNO. Therefore RCTs are needed to evaluate the utility for FeNO to be used to determine patients who should not receive ICS.

Fractional Exhaled Nitric Oxide for Selecting Patients for Treatment With Type 2-Targeted Biologics for Severe Asthma

Type 2 inflammation is present in about half of patients with severe asthma and is characterized by elevated levels of cytokines, eosinophils, and/or increased FeNO. In patients with elevated type 2 biomarkers despite receipt of high-dose ICS, type 2 phenotypes should be elucidated to determine the best add-on therapy. Eosinophilic asthma is an asthma phenotype associated with responsiveness to ICS and later onset time. Currently, 4 drugs approved by the U.S. Food and Drug Administration (FDA) are available to treat asthma with an eosinophilic phenotype (mepolizumab, reslizumab, and benralizumab, anti-IL-5 therapies, and dupilumab, an anti-IL-4 receptor alpha subunit antibody that also inhibits IL-13 signaling), which makes the identification of eosinophilic asthma of potential clinical importance. Studies demonstrating the efficacy of these treatments generally used blood or sputum eosinophilic measurements to determine eligibility when eligibility was limited to eosinophilic asthma. Of note, dupilumab is also approved as an add-on for moderate-to-severe asthma in patients with oral corticosteroid-dependent asthma (regardless of baseline levels of eosinophils), and tezepelumab, a TSLP blocker, is approved for add-on therapy in severe asthma, also regardless of baseline levels of eosinophils.

Several observational studies and a systematic review of observational studies have described the association between FeNO and blood or sputum eosinophils.[42,43,]

Severe allergic asthma is another asthma phenotype where the underlying inflammation is activated by allergens or other irritants. Currently, there is 1 drug approved by the FDA for moderate-to-severe persistent asthma with a positive skin test or in vitro reactivity to a perennial aeroallergen: omalizumab, an anti-IgE therapy.

Randomized Controlled Trials

For eosinophilic asthma, subgroup analyses of treatment response stratified by FeNO from pivotal RCTs demonstrating efficacy of benralizumab and reslizumab have not been reported.[44,]

The Dose Ranging Efficacy And safety with Mepolizumab in severe asthma (DREAM) and MEpolizumab as adjunctive therapy in patients with Severe Asthma (MENSA) RCTs were both placebo-controlled and included multiple doses of add-on mepolizumab in patients with severe asthma.[45,46,] A secondary analysis of the DREAM and MENSA studies stratified by baseline blood eosinophil thresholds was reported by Ortega et al (2016).[47,] The exacerbation rate reductions for mepolizumab versus placebo increased progressively from 26% (relative risk, 0.74; 95% CI, 0.52 to 1.04) for baseline blood eosinophils of less than 150 cells/μL to 70% (relative risk, 0.30; 95% CI, 0.23 to 0.40) for baseline blood eosinophils of 500 cells/μL or greater. Another post-hoc analysis of the DREAM study reported outcomes by baseline eosinophils and FeNO (Table 11).[48,]Interaction analyses between subgroups were not reported. The beneficial effect of mepolizumab versus placebo was most pronounced in the subgroups with both high levels of baseline eosinophils and FeNO, though it appears that elevated eosinophils contributed more than elevated FeNO to its effect.

Table 11. Treatment Effect of Mepolizumab versus Placebo on Annualized Asthma Exacerbation Rates by Combined Blood Eosinophil Count and FeNO (DREAM Trial)

Subgroup	Placebo N	Mepolizumab N	RR vs Placebo (95% CI)
Mepolizumab every 2 wk for 52 wks (all doses pooled)			
Overall	155	461	not reported for pooled doses
Blood eosinophil count (cells/mm^2, cut point 150), FeNO (ppb)			
≥150, ≥25	72	173	0.38 (0.3 to 0.5)
<150, ≥25	9	51	0.94 (0.4 to 2.4)
≥150, <25	47	168	0.64 (0.4 to 0.99)
<150, <25	23	63	0.86 (0.5 to 1.6)
Blood eosinophil count (cells/mm^2, cut point 300), FeNO (ppb)			
≥300, ≥25	66	140	0.38 (0.27 to 0.53)
<300, ≥25	32	131	0.59 (0.36 to 0.96)
≥300, <25	18	72	0.47 (0.25 to 0.87)
<300, <25	35	112	0.82 (0.48 to 1.41)

Adaptetreatment. Tableer et al (2019)[48,]
CI: confidence interval; DREAM: Dose Ranging Efficacy And safety with Mepolizumab in severe asthma; FeNO: fractional exhaled nitric oxide; ppb: part per billion; RR relative risk.

The Evaluation of Dupilumab in Patients With Persistent Asthma (Liberty Asthma QUEST) and Evaluation of Dupilumab in Patients With Severe Steroid Dependent Asthma (Liberty Asthma VENTURE) trials compared add-on dupilumab with placebo in patients 12 years and older with uncontrolled asthma and oral glucocorticoid-treated asthma, respectively.[49,50,] In these trials, patients were enrolled regardless of baseline blood eosinophil count or other biomarkers of type 2 inflammation. Subgroup analysis of outcomes by baseline blood eosinophils and FeNO were provided and are shown in Tables 12 and 13. In the Liberty Asthma QUEST trial, the relative risk for severe asthma exacerbations for dupilumab versus placebo was largest for patients with eosinophil counts of 300 cells/mm^3 or more and close to null for patients with eosinophil counts less than 150 cells/mm^3 (interaction p<.001). In contrast, while there was a quantitative interaction (p=.008) between treatment and baseline FeNO, FeNO did not identify a group for whom there appears to be no benefit from dupilumab. A post hoc analysis of the LIBERTY ASTHMA QUEST trial reported the annualized severe exacerbation rate during the 52-week treatment period by baseline FeNO.[51,] The analysis found that dupilumab resulted in a 22.7%, 58.3%, and 69.3% reduction in the relative risk of severe asthma attacks for patients with initial FeNO levels below 25 ppb, between 25 and 50 ppb, and over 50 ppb, respectively, suggesting that increased baseline FeNO was associated with greater clinical effects with dupilumab treatment.

Table 12. Treatment Effect of Dupilumab versus Placebo on Severe Asthma Exacerbations by Blood Eosinophil Count and FeNO (Liberty Asthma QUEST and Liberty Asthma VENTURE Trials)

Subgroup	Placebo N	Dupilumab N	RR vs. Placebo (95% CI)	Interaction p
Dupilumab 200 mg every 2 wk for 52 wks (QUEST)				
Overall	317	631	0.52 (0.41 to 0.66)	
Blood eosinophil count, cells/mm^3				
≥300	148	264	0.34 (0.24 to 0.48)	<.001
≥150 to <300	84	173	0.64 (0.41 to 1.02)	
<150	85	193	0.93 (0.58 to 1.47)	
FeNO, ppb				
≥50	71	119	0.31 (0.18 to 0.52)	.008
≥25 to <50	91	180	0.39 (0.24 to 0.62)	
<25	149	325	0.75 (0.54 to 1.05)	
Dupilumab 300 mg every 2 wk for 52 wks (QUEST)				
Overall	321	633	0.54 (0.43 to 0.68)	
Blood eosinophil count, cells/mm^3				
≥300	142	277	0.33 (0.23 to 0.45)	<.001
≥150 to <300	95	175	0.56 (0.35 to 0.89)	
<150	83	181	1.15 (0.75 to 1.77)	
FeNO, ppb				
≥50	75	124	0.31 (0.19 to 0.49)	<.001
≥25 to <50	97	186	0.44 (0.28 to 0.69)	
<25	144	317	0.79 (0.57 to 1.10)	
Dupilumab 300 mg every 2 wk for 24 wks (VENTURE)				
Overall	107	103	0.407 (0.263 to 0.630)	
Blood eosinophil count, cells/mm^3				
≥300	41	48	0.289 (0.139 to 0.601)	.14
<300	66	55	0.545 (0.315 to 0.940)	
≥150	69	81	0.418 (0.254 to 0.689)	.82
<150	38	22	0.396 (0.166 to 0.946)	
FeNO, ppb				

Subgroup	Placebo N	Dupilumab N	RR vs. Placebo (95% CI)	Interaction p
≥50	29	24	0.532 (0.228 to 1.239)	.03
≥25 to <50	28	33	0.195 (0.072 to 0.531)	
<25	46	44	0.704 (0.369 to 1.346)	

Adapted from Castro et al (2018)[49,] and Rabe et al (2018)[50,] supplemental materials.
CI: confidence interval; FeNO: fractional exhaled nitric oxide; Liberty Asthma QUEST: Evaluation of Dupilumab in Patients With Persistent Asthma; Liberty Asthma VENTURE: Evaluation of Dupilumab in Patients With Severe Steroid Dependent Asthma; ppb: part per billion; RR relative risk.

Table 13. Treatment Effect of Dupilumab versus Placebo on Percentage Reduction in Oral Glucocorticoid Dose by Blood Eosinophil Count and FeNO (Liberty Asthma VENTURE Trial)

Subgroup	Placebo N	Dupilumab N	RD (95% CI)	Interaction p
Dupilumab 300 mg every 2 wk for 24 wks				
Overall	107	103	-28.2 (-40.7 to -15.8)	
Blood eosinophil count, cells/mm^3				
billion. Observational			3 (-54.71 to -18.94)	.24
<300	66	55	-21.33 (-38.75 to -3.90)	
≥150	69	81	-29.39 (-43.12 to -15.67)	.71
<150	38	22	-26.89 (-54.52 to 0.73)	
FeNO, ppb				
≥50	29	23	-33.64 (-53.61 to -13.67)	.34
≥25 to <50	28	32	-38.31 (-61.78 to -14.84)	
<25	45	44	-17.27 (38.16 to -3.62)	

Adapted from Rabe et al (2018) supplemental materials.[50,]
CI: confidence interval; FeNO: fractional exhaled nitric oxide; Liberty Asthma VENTURE: Evaluation of Dupilumab in Patients With Severe Steroid Dependent Asthma; ppb: part per billion; RD: risk difference.

For severe allergic asthma, add-on therapy options are limited to anti-IgE therapies.[52,] The Study of Omalizumab (Xolair) in Subjects With Moderate to Severe Persistent Asthma (EXTRA) study evaluated the efficacy of omalizumab versus placebo over 48 weeks in patients with inadequately controlled severe allergic asthma.[53,] A post-hoc analysis further explored the treatment effects based on pre-specified baseline values of type 2 inflammatory biomarkers, including FeNO and blood eosinophil counts, which are summarized in Table 14.[54,] Interaction analyses between subgroups were not reported. Treatment effects were evaluated within each subgroup finding that

omalizumab had a greater effect compared to placebo in the high FeNO subgroup, but quantitative comparisons between high- and low-biomarker subgroups were not conducted.

Table 14. Treatment Effect of Omalizumab versus Placebo on Asthma Exacerbations by Blood Eosinophil Count and FeNO (EXTRA Trial)

	Mean asthma exacerbation rate		
Subgroup (n)	**Placebo**	**Omalizumab**	**Relative Reduction vs. Placebo (95% CI)**
Blood eosinophil count, cells/mm^3			
≥260 (n=414)	1.03	0.70	32 (11 to 48)
<260 (n=383)	0.72	0.65	9 (-24 to 34)
FeNO, ppb			
≥19.5 (n=201)	1.07	0.50	53 (37 to 70)
<19.5 (n=193)	0.71	0.60	16 (-32 to 46)

Adapted from Hanania et al (2013)[54,]
CI: confidence interval; EXTRA: Study of Omalizumab (Xolair) in Subjects With Moderate to Severe Persistent Asthma; FeNO: fractional exhaled nitric oxide; ppb: part per billion.

Observational Studies

Casele et al (2019) reported results of a U.S.-based, prospective, single-arm, 48-week multicenter study called the Prospective Observational Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab (PROSPERO, NCT01922037) study which enrolled 806 patients aged 12 years and older from 2013 to 2015 with allergic asthma who were candidates for omalizumab.[55,] Patients were from a real-world setting where omalizumab was initiated on the basis of physician-assessed need. Median time on omalizumab was 11 months with planned dosing frequency of 2 and 4 weeks in about half of the patients each. Of the 806 enrolled, 622 (77%) completed the 12 months; 91% of patients were adults. Seven-hundred twenty-two patients had baseline FeNO measurements, of which 44% were greater than or equal to 25 ppb. A significant decrease in asthma exacerbations was noted over a 12-month treatment period irrespective of baseline FeNO. Results are shown in Table 15.

Table 15. Mean Exacerbation Rate while Treated with Omaliztreatment. In2 months) by FeNO (PROSPERO study)

Subgroup	**12 months before study**		**Through 12 months on-study**		**Interaction p**
FeNO, ppb	**n**	**Mean Exacerbation Rate**	**n**	**Mean Exacerbation Rate**	
≥25	320	3.3	316	0.8	.40
<25	402	2.8	398	0.7	

FeNO: fractional exhaled nitric oxide; ppb: part per billion; PROSPERO: Prospective Observational Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab.

Subsection Summary: Fractional Exhaled Nitric Oxide for Selecting Treatments for Patients with Severe Asthma

Anti-IL-5 agents are available for the treatment of severe asthma with an eosinophilic phenotype. Anti-IL-4R/anti-IL-13 monoclonal antibodies and TSLP blocker monoclonal antibodies are also available to improve uncontrolled asthma that does not necessarily have an eosinophilic phenotype, and anti-IgE therapies are available to treat severe allergic asthma. To support these uses, studies demonstrating the efficacy of anti-IL-5 treatments generally used blood or sputum eosinophilic measurements to determine eligibility, whereas, trials for anti-IL-4R/anti-IL-13 therapy generally did not have minimum requirements of baseline eosinophil counts for inclusion. Subgroup analyses from 2 trials of dupilumab, 1 including patients with uncontrolled asthma and 1 including patients with oral glucocorticoid-treated asthma, reported conflicting results on whether baseline blood eosinophils could be used to identify a group of patients unlikely to benefit from dupilumab with respect to severe exacerbations. However, in both trials, the treatment effect estimate for dupilumab versus placebo for the outcome of severe exacerbations favored dupilumab across the 3 subgroups of baseline FeNO even when a statistically significant, quantitative interaction was reported. Additionally, one subgroup analysis demonstrated that increased baseline FeNO was associated with greater reductions in severe exacerbations. Therefore, it is unclear if baseline FeNO can identify a group for whom there is no benefit from dupilumab. Evaluation of subgroups in 1 trial of mepolizumab reported annualized rates of exacerbations by baseline eosinophil and FeNO measures showing elevated values for both indices were associated with a more pronounced effect compared to placebo. However, statistical comparisons between subgroups were not performed and outcomes stratified by baseline FeNO only were not reported, precluding insight into the utility of using FeNO alone to predict response to treatment.

In an analysis of the EXTRA trial, omalizumab treatment resulted in numerically similar mean exacerbation rates in patients with high and low baseline FeNO, though the relative reduction was greater in the high FeNO subgroup. Data from the analysis was limited by a large early discontinuation rate (20.8%) in the original trial as well as the absence of statistical comparisons between subgroups. Additionally, a 48-week multicenter prospective observational study with over 700 participants found that asthma exacerbations were reduced with omalizumab studies over a 12-month treatment period irrespective of baseline FeNO.

FRACTIONAL EXHALED NITRIC OXIDE IN RESPIRATORY DISORDERS OTHER THAN ASTHMA

Clinical Context and Test Purpose

The purpose of FeNO testing in individuals with suspected or confirmed respiratory disorders other than asthma is to aid in diagnosis and treatment decisions. To evaluate the test performance, the position on the diagnostic or management pathway as well as the specification of whether FeNO is meant to be used as a triage, add-on, or replacement test with respect to existing diagnostic tests or procedures are needed. Less information is available regarding how FeNO would be used in the diagnosis or management of other respiratory conditions.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with suspected or confirmed respiratory disorders other than asthma. A precise explication of the population of interest depends on the position of the FeNO test in the diagnostic or management pathway.

Interventions
The test being considered is measurement of FeNO.

Comparators
The following practice is currently being used to diagnose and treat respiratory disorders other than asthma: standard clinical diagnosis and management. The appropriate comparator depends on the position of the FeNO in the diagnostic or management pathway.

Outcomes
The general outcomes of interest are test validity, symptoms, change in disease status, morbid events, and functional outcomes. Specific outcomes of interest would be diagnostic accuracy, rates of exacerbations, symptoms, hospitalizations, use of medications, and quality of life.

Study Selection Criteria
Studies were included in this section if they addressed the sensitivity and specificity of FeNO measurements for 1) identifying specific respiratory disorders or respiratory disorder subtypes or 2) predicting patient response to a specific medication therapy. Prospective studies with standard protocols and predefined cutoffs were sought to establish diagnostic accuracy of FeNO. Comparative controlled prospective trials were sought to determine the clinical utility of FeNO in respiratory disorder management; in the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.

REVIEW OF EVIDENCE

FRACTIONAL EXHALED NITRIC OXIDE FOR DIAGNOSING RESPIRATORY DISORDERS OTHER THAN ASTHMA

Chronic Obstructive Pulmonary Disease
Vincken et al (2021) performed a single-center, prospective pilot study to assess the relationship between FeNO and blood eosinophil counts in 136 patients with stable COPD.[56,] In this study, there was a significant correlation between FeNO and blood eosinophils in patients who had experienced at least 2 COPD exacerbations within the previous year (ρ=.48, p=.02). In this population, FeNO was a significant predictor of blood eosinophil counts greater than 300 cells/mcL (area under the curve, 74%, p=.04), with a specificity of 70% and a sensitivity of 71% at a FeNO threshold of 14.7 ppb.

Tang et al (2020) evaluated the association between blood eosinophils and FeNO in a cross-sectional study that evaluated 247 patients with an acute exacerbation of chronic obstructive pulmonary disease (COPD).[57,] Blood eosinophil counts correlated positively with FeNO values (ρ=.383, p=.004). A cutoff value of 22.5 ppb for FeNO was determined to perform best in a ROC analysis to predict blood eosinophilia with a sensitivity of 77.3% and a specificity of 60.0%.

Gao et al (2017) reported on the results of a cross-sectional study evaluating the association between FeNO and sputum eosinophilia in 163 patients with COPD exacerbations.[58,] Sputum eosinophils correlated with both FeNO levels (ρ=0.221, p<.01) and blood eosinophilic percentage (ρ=0.399, p<.001). Fractional expired NO and blood eosinophilic percentage did not correlate significantly. At a cutoff point of 17.5 ppb, the sensitivity and specificity rates of FeNO compared with sputum eosinophilia were 65% and 56%, respectively (precision not reported).

Chou et al (2014) reported on the use of FeNO measurements in predicting sputum eosinophilia in patients with COPD.[59,] The study included 90 subjects with COPD with no known history of asthma or allergic diseases. Compared with patients without sputum eosinophilia, those with sputum eosinophilia had higher FeNO levels (29 ppb vs. 18 ppb; p=.01). In ROC analysis, a FeNO cutoff of 23.5 ppb had the highest sensitivity (62.1%) and specificity (70.5%) for predicting sputum eosinophilia. After adjusting for age, sex, smoking status, serum IgE, and allergy test results, a FeNO value greater than 23.5 ppb was significantly associated with the presence of sputum eosinophilia (adjusted OR, 4.329; 95% CI, 1.306 to 14.356; p=.017). The authors hypothesized that individuals with COPD with sputum eosinophilia might respond well to ICS or OCS.

Interstitial Lung Disease

Oishi et al (2017) evaluated whether there were differences in FeNO levels in different types of acute-onset interstitial lung disease.[60,] The median FeNO level in patients with acute eosinophilic pneumonia (48.1 ppb) was significantly higher than in patients with cryptogenic organizing pneumonia (17.4 ppb), hypersensitivity pneumonia (20.5 ppb), or sarcoidosis (12.0 ppb; p<.001). At a cutoff of 23.4 ppb, the area under the ROC curve was 0.90.

Pulmonary Fibrosis

Guilleminault et al (2013) retrospectively evaluated whether FeNO could differentiate causes of pulmonary fibrosis.[61,] The study included 61 patients divided into 4 groups based on pulmonary fibrosis etiology: idiopathic pulmonary fibrosis, hypersensitivity pneumonitis, connective tissue disease-associated interstitial lung disease, and drug-induced pneumonia. The median FeNO level was higher in patients with hypersensitivity pneumonitis (51 ppb) than in patients in the other groups (median range, 19 to 25 ppb; p=.008). Optimum sensitivity (76.9%) and specificity (85.4%) were established at a cutoff of 41 ppb.

Primary Ciliary Dyskinesia

Boon et al (2014) evaluated the role of nasal NO and FeNO in the diagnosis of primary ciliary dyskinesia (PCD).[62,] The study included 226 individuals; 38 individuals with PCD, 49 healthy controls, and 139 individuals with other respiratory diseases. A definitive diagnosis of PCD was made by structural and functional evaluation of the cilia on a nasal or bronchial biopsy. The highest sensitivity (89.5%) and specificity (87.3%) were obtained with nasal NO measured during plateau against resistance. Using a FeNO cutoff of 10 ppb, with lower values predictive of PCD, the sensitivity for PCD diagnosis was 89.5%, but specificity was low at 58.3%. Diagnostic accuracy would likely be even lower if assessed in the more relevant population of patients with suspected PCD.

Fractional Exhaled Nitric Oxide for Predicting Response to Medication Therapy in Respiratory Conditions Other Than Asthma

Su et al (2021) published the results of an open-label trial completed at a single-center in Taiwan that enrolled treatment-naïve patients with COPD (n=134) and stratified them into high- and low-FeNO groups (cut-off was 23.5 ppb).[63,] Patients in each FeNO group were provided with 12 weeks of treatment with either salmeterol/fluticasone or tiotropium. At the end of the treatment period, patients in the high-FeNO group who received salmeterol/fluticasone had significant reductions in FeNO from baseline ($p<.001$); patients in the high-FeNO group who only received tiotropium did not experience statistically significant reductions in FeNO. In the low-FENO group, neither treatment arm had significant changes in FeNO at 12 weeks. Authors concluded that high baseline FeNO may indicate eosinophilic airway inflammation in COPD, thus identifying patients more likely to have a favorable response to treatment with corticosteroid-based therapies. Limitations of this study include short-term measurement of response and treatment, lack of reporting of specific quantitative results for changes in FeNO, and not basing management decisions on FeNO test results.

A double-blind crossover trial by Dummer et al (2009) evaluated the ability of FeNO test results to predict corticosteroid response in COPD.[64,] The trial included 65 patients with COPD who were 45 years or older, were previous smokers with at least a 10-pack a year history, had persistent symptoms of chronic airflow obstruction, had a postbronchodilator FEV_1/forced vital capacity of less than 70%, and an FEV_1 of 30% to 80% of predicted. Patients with asthma or other comorbidities were excluded, as were those taking regular corticosteroids and those who had used OCS for exacerbations more than twice during the past 6 months. Treatments, given in random order, were prednisone 30 mg/day or placebo for 3 weeks; there was a 4-week washout period before each treatment. Patients who withdrew during the first treatment period were excluded from the analysis. Those who withdrew between treatments or during the second treatment were assigned a net change of 0 for the second treatment period. Fifty-five determined. Section the study. Two of the 3 primary outcomes (6-minute walk distance, FEV_1) increased significantly from baseline with prednisone compared with placebo. There was a nonsignificant decrease in the third primary outcome, score on the St. George's Respiratory Questionnaire. Baseline FeNO did not correlate significantly with change in 6-minute walk distance (r=0.10, p=.45) or St. George's Respiratory Questionnaire score (r=0.12, p=.36) but was significantly related to change in FEV_1 (r=0.32, p=.01). At the optimal FeNO cutoff of 50 ppb, as determined by ROC analysis, there was a 29% sensitivity and 96% specificity for predicting a 0.2-liter increase in FEV_1. (A 0.2-liter change was considered the minimal clinically important difference.) The authors concluded that FeNO is a weak predictor of short-term response to OCS treatment in patients with stable, moderately severe COPD and that a normal test result could help clinicians avoid unnecessary prescriptions; only about 20% of patients responded to corticosteroid treatments. Study limitations included short-term measurement of response to treatment, and not basing management decisions on FeNO test results.

A prospective uncontrolled study by Prieto et al (2003) assessed the utility of FeNO measurement for predicting response to ICS in patients with chronic cough.[65,] The study included 43 patients with cough of at least 8 weeks in duration who were nonsmokers without a history of another lung disease. Patients were evaluated at baseline and 4 weeks after treatment with inhaled fluticasone propionate 100 µg twice daily. Nineteen (44%) patients had a positive response to treatment, defined as at least a 50% reduction in mean daily cough symptom scores. The ROC analysis

showed that using 20 ppb as the FeNO cutoff, the sensitivity was 53% and the specificity was 63%. The authors concluded that FeNO was not an adequate predictor of treatment response.

Other prospective and retrospective studies have reported on the association between FeNO and response to ICS in COPD and other nonasthma respiratory diagnoses. In a prospective study of 60 patients with severe COPD, Kunisaki et al (2008) reported that patients considered responders to ICS had higher FeNO values (46.5 ppb) than nonresponders (25 ppb; p=.028).[66,] However, an optimal FeNO cutpoint to discriminate between responders and nonresponders could not be determined.

Section Summary: Fractional Exhaled Nitric Oxide for Respiratory Disorders Other Than Asthma

Measurement of FeNO is being investigated for various lung disorders other than asthma. These studies are primarily exploratory and establish differences in median FeNO levels for related conditions. Some studies have evaluated the optimum cutoff for sensitivity and specificity. However, the median FeNO level and cutoffs varied by the study of the same condition (e.g., hypersensitivity pneumonia). Prospective studies with standard protocols and predefined cutoffs are needed to determine diagnostic accuracy. Also, evidence of clinical utility is lacking. No controlled studies compared health outcomes in patients with COPD or other respiratory diseases whose treatment was managed with and without FeNO measurement.

EXHALED BREATH CONDENSATE

Clinical Context and Test Purpose

The purpose of exhaled breath condensate (EBC) testing in individuals who have symptoms of asthma or other respiratory conditions or a diagnosis of asthma or other respiratory conditions is to aid in diagnosis and treatment decisions. To evaluate the test performance, the position on the diagnostic or management pathway, as well as the specification of whether EBC is meant to be used as a triage, add-on, or replacement test with respect to existing diagnostic tests or procedures, are needed. For asthma, potential uses of EBC may be similar to those listed for FeNO.

The published literature suggests that EBC is at an earlier stage of development than life. A study by Davis et al (2012) noted that this is due, in part, to the fact that FeNO is a single biomarker and EBC is a matrix that contains so many potential biomarkers that research efforts have thus far been spread across numerous markers.[67,] In addition, several review articles have noted that before routine clinical use in the diagnosis and management of respiratory disorders can be considered, the following issues need to be resolved:[67,68,69,70,71,]:

- Standardization of collection and storage techniques
- Effect of dilution of respiratory droplets by water vapor
- Effect of contamination from oral and retropharyngeal mucosa
- Variability in EBC assays for certain substances, including assay kits for the same biomarker and kit lot numbers from the same manufacturer
- Lack of a criterion standard for determining absolute concentrations of the airway lining fluid nonvolatile constituents to compare with EBC
- Lack of normative values specific to each potential EBC biomarker.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with suspected or confirmed respiratory conditions. A precise explication of the population of interest depends on the position of the EBC test in the diagnostic or management pathway.

Interventions
The test being considered is measurement of EBC.

Comparators
The following practice is currently being used to diagnose and treat respiratory disorders: standard clinical diagnosis and management. The appropriate comparator depends on the position of the EBC in the diagnostic or management pathway.

Outcomes
The general outcomes of interest are test validity, symptoms, change in disease status, morbid events, and functional outcomes. Specific outcomes of interest might be diagnostic accuracy, rates of exacerbations, symptoms, hospitalizations, use of medications, and quality of life.

Study Selection Criteria
Studies were included in this section if they addressed the use of EBC markers for determining asthma severity, diagnosing asthma or other respiratory conditions, or guiding treatment decisions for asthma or other respiratory conditions. Comparative controlled prospective trials were sought to determine the clinical utility of EBC in respiratory disorder management; in the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.

REVIEW OF EVIDENCE

Exhaled Breath Condensate Markers of Asthma
Similar to FeNO, EBC has been associated with asthma severity. Thomas et al (2013) conducted a systematic review of studies assessing the association between components of EBC and pediatric asthma.[72,] Reviewers identified 46 articles that measured at least 1 EBC marker in asthma, allergy, and atopy in children up to age 18 years. Most studies were cross-sectional, and there was wide variation in the definitions used to identify children with asthma and the collection devices and assays for EBC components. Studies in the review evaluated multiple specific EBC components, including hydrogen ions (pH), NO, glutathione and aldehydes, hydrogen peroxide, eicosanoids (including prostaglandins and leukotrienes), and cytokines (including interleukins in the Th2 pathway and interferon-gamma). Reviewers noted that hydrogen ions and markers of oxidative stress, including hydrogen peroxide and oxides of nitrogen, were most consistently associated with asthma severity. Eicosanoids and cytokines demonstrated more variable results but were frequently elevated in the EBC of patients with asthma. Overall, reviewers concluded that while EBC has the potential to aid in the diagnosis of asthma and to evaluate inflammation in pediatric asthma, further studies on EBC collection and interpretation techniques are needed.

In 2016, the same group of reviewers published a qualitative systematic review assessing the relations between adult asthma and oxidative stress markers and pH in EBC.[73,] Sixteen studies met the inclusion criteria and compared 832 patients with asthma and 556 healthy controls. In addition to measuring pH (n=6 studies), studies evaluated nitrite (n=1), nitrate (n=1), total NO (n=3),

hydrogen peroxide (n=8), and 8-isoprostane (n=4). Most studies were cross-sectional (n=11) and the rest were longitudinal (n=5); 1 was double-blinded. A variety of EBC collecting devices were used, with a custom-made condensing device used in 7 studies. The association between pH or NO and asthma varied between studies, and in 1 study, the pH in the same subjects varied by collection device. Concentrations of hydrogen peroxide and 8-isoprostane were significantly higher in patients with asthma in most studies. Reviewers concluded that EBC collection of oxidative stress markers is relatively robust despite variability in techniques, but to become a useful clinical tool, studies were needed to evaluate the ability of EBC biomarkers to predict future asthma exacerbations and tailor asthma treatment.

Exhaled Breath Condensate Markers of Asthma Severity

One study not included in the systematic review of adults with asthma is by Liu et al (2011), who reported on the Severe Asthma Research Program, a multicenter study funded by the NIH.[74,] This study had the largest sample size (N=572). Study participants included 250 patients with severe asthma 291 patients with nonsevere asthma, and 51 healthy controls. Samples of EBC were collected at baseline and analyzed for pH levels. Overall, the median pH of the 2 asthma groups combined (7.94) did not differ significantly from the median pH of controls (7.90; p=.80). However, the median pH of patients with nonsevere asthma (7.90) was significantly lower than that for patients with severe asthma (8.02; p not reported).

Exhaled Breath Condensate Markers of Asthma Control

Navratil et al (2014) evaluated the relation between EBC and asthma control in a cross-sectional study of 103 children (age range, 6 to 18 years) with asthma.[75,] Subjects were enrolled from a single clinic, had an established asthma diagnosis, and were on a stable dosage of their asthma treatment. Patients were considered to have controlled (n=50 [48.5%]) or uncontrolled asthma (n=53 [52.5%]) based on Global Initiative for Asthma guidelines. Controlled and uncontrolled asthmatics differed significantly in EBC urates (uncontrolled median EBC urate, 10 µmol/L vs. controlled median EBC urate, 45 µmol/L; p<.001); EBC pH (uncontrolled mean pH, 7.2 vs. controlled mean pH, 7.33; p=.002); and EBC temperature (uncontrolled mean EBT, 34.26°C vs controlled mean EBT, 33.9°C; p=.014). Also, EBC urate concentration was significantly associated with time from last exacerbation (p<.001), Asthma Control Test results (p<.001), and short-acting bronchodilator use (p<.001) within the entire cohort.

Exhaled Breath Condensate Components as Markers of Respiratory Disorders Other Than Asthma

There is not much published literature on EBC levels in patients with respiratory disorders other than asthma. A study by Antus et al (2010) evaluated EBC 58 hospitalized patients (20 with asthma, 38 with COPD) and 36 healthy controls (18 smokers, 18 nonsmokers).[76,] The EBC pH was significantly lower in patients with asthma exacerbations (all nonsmokers) at hospital admission (6.2) than in nonsmoking controls (6.4; p<.001). The EBC pH in asthma patients increased during the hospital stay and was similar to that of nonsmoking controls at discharge. Contrary to investigators' expectations, EBC pH values in ex-smoking COPD patients (n=17) did not differ significantly from nonsmoking controls, either at hospital admission or discharge. Similarly, pH values in EBC samples from smoking COPD patients (n=21) at admission and discharge did not differ significantly from smoking controls.

Exhaled Breath Condensate-Guided Treatment Decisions for Patients With Asthma or Other Respiratory Disorders

No controlled studies were identified evaluating the role of EBC tests in the management of asthma or other respiratory disorders.

Section Summary: Exhaled Breath Condensate

There is considerable variability in the particular EBC components measured and criteria for standardized measurements. Also, there is limited evidence on the use of EBC for determining asthma severity, diagnosing other respiratory conditions, or guiding treatment decisions for asthma or other respiratory conditions. The available evidence does not support conclusions on the utility of EBC for any indication.

SUPPLEMENTAL INFORMATION

evidence. Remove purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2017 Input

Clinical input was sought to help determine whether measurement of fractional exhaled nitric oxide (FeNO) and exhaled breath condensate in the diagnosis and management of individuals with respiratory disorders would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, clinical input was received from 3 physician-level respondents identified through 2 specialty societies including physicians with academic medical center affiliations. For individuals who have suspected or confirmed respiratory disorders who receive measurement of FeNO or exhaled breath condensate, clinical input does not support a clinically meaningful improvement in net health outcome and does not indicate this use is consistent with generally accepted medical practice. For both FeNO and exhaled breath condensate, limitations of the published evidence preclude determining the effects of the technology on net health outcome.

2012 Input

In response to requests, input was received through 3 physician specialty societies (1 specialty society submitted 2 reviews) and 5 academic medical centers when this policy was under review in 2012. The input was mixed over whether measurement of FeNO is considered investigational in the diagnosis and management of asthma and other respiratory disorders. There was a consensus that the measurement of exhaled breath condensate is considered investigational in the diagnosis and management of asthma and other respiratory disorders. The input was also mixed on whether there is a well-accepted cutoff for FeNO, whether FeNO levels would affect their decision making on prescribing inhaled corticosteroids, whether there is published evidence that using FeNO measurements to guide treatment improves health outcomes and whether recommendations in American Thoracic Society guidelines are supported by evidence.

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Academy of Pediatrics
In 2017, the American Academy of Pediatrics issued a report on clinical tools to assess asthma control in children.[77,] The report stated the following on the use of FeNO: "The value of additional FeNO monitoring in children whose asthma is appropriately managed using guideline-based strategies is unproven."

American Thoracic Society
In 2021, the American Thoracic Society (ATS) published updated guidelines on the use of FeNO to guide the treatment of asthma.[78,] Previous guidelines on this topic were published by the ATS over a decade ago.[79,] The following question was the basis of the updated guideline: "Should patients with asthma in whom treatment is being contemplated undergo FENO testing?" Based on an overall low quality of available evidence, the panel made the following conditional recommendation for FeNO-based care:

"In patients with asthma in whom treatment is being considered, we suggest to use FENO testing in addition to usual care over usual care alone."

The authors go on to note that "..judgment is based on a balance of effects that probably favors the intervention; the moderate costs and availability of resources, which probably favors the intervention; and the perceived acceptability and feasibility of the intervention in daily practice."

European Respiratory Society/American Thoracic Society
In 2020, the European Respiratory Society and American Thoracic Society published a joint guideline on the management of severe asthma.[80,] The guideline addresses whether measurement of a specific biomarker should be used to guide initiation of treatment with an anti-interleukin (IL)-5 therapy or anti-immunoglobulin E (IgE) therapy for adults and children with severe asthma. For anti-IL-5 therapies, the guideline states that most studies focused on blood eosinophils and no data were available for FeNO. For adult and adolescent patients with severe asthma being considered for omalizumab, the guideline suggested "using a FeNO cut-off ≥19.5 ppb to identify adolescents (>12 years) and adults with severe allergic asthma more likely to benefit from anti-IgE treatment (conditional recommendation, low quality of evidence)."

Global Initiative for Asthma
In 2022, the Global Initiative for Asthma released its updated global strategy for asthma management and prevention.[52,]

The report made the following statement on FeNO for asthma diagnosis:
- "FeNO has not been established as useful for ruling in or ruling out a diagnosis of asthma."

The report made the following statement on FeNO for decisions related to initiation of inhaled corticosteroids:

- "In studies mainly limited to non-smoking patients, FeNO >50 ppb [parts per billion] has been associated with a good short-term response to ICS. However, these studies did not examine the longer-term risk of exacerbations. Such evidence therefore does not mean that it is safe with regard to exacerbations to withhold ICS in patients with low initial FeNO. More recently, in two 12-month studies in mild asthma, severe exacerbations were reduced with as-needed ICS-formoterol versus as-needed SABA and versus maintenance ICS, independent of baseline inflammatory characteristics including FeNO."
- "In patients with a diagnosis or suspected diagnosis of asthma, measurement of FeNO can support the decision to start ICS, but cannot be used to decide against treatment with ICS."

The report made the following statements on FeNO for adjusting asthma treatment:

- "In children, FeNO-guided treatment significantly reduces exacerbation rates compared to guideline-based treatment (Evidence A). However, further studies are needed to identify the populations most likely to benefit from sputum-guided or FeNO-guided treatment and the optimal frequency of FeNO monitoring."

Global Initiative for Asthma released a 'pocket guide for health professionals' in Nov 2018 with an update in Apr 2019 entitled "Difficult-to-Treat & Severe Asthma in Adolescent and Adult Patients – Diagnosis and Management." [81,] The guide states the following regarding using FeNO to manage medications:

"The possibility of refractory type 2 inflammation should be considered if any of the following are found while the patient is taking high-dose ICS or daily OCS:

- Blood eosinophils ≥150 µl, and/or
- FeNO ≥20 ppb, and/or
- Sputum eosinophils ≥2%, and/or
- Asthma is clinically allergen-driven."

It continues to state that these criteria are suggested for initial assessment; those for blood eosinophils and FeNO are based on lowest levels associated with response to some biologics. With They are not the criteria for eligibility for type 2-targeted biologic therapy, which may differ. Consider repeating blood eosinophils and FeNO up to 3 times (e.g., when asthma worsens, before giving OCS), before assuming asthma is non-type 2.

The guide also states that if the patient has had a good response to type 2 targeted therapy:

"For oral treatments, consider gradually decreased or stopping OCS first, because of their significant adverse effects. Tapering may be supported by internet-based monitoring of symptoms control and FeNO."

Another update of this guideline is due for release sometime in 2022.

National Heart Lung and Blood Institute

In 2007, the National Heart Lung and Blood Institute's expert panel guidelines on the diagnosis and management of asthma stated:

"Use of minimally invasive markers ('biomarkers') to monitor asthma control and guide treatment decisions for therapy is of increasing interest. Some markers, such as spirometry measures, are currently and widely used in clinical care; others, such as sputum eosinophils and FeNO, may also be useful, but they require further evaluation in both children and adults before they can be recommended as clinical tools for routine asthma management (Evidence D)."

"The Expert Panel recommends some minimally invasive markers for monitoring asthma control, such as spirometry and airway hyper-responsiveness, that are appropriately used, currently and widely, in asthma care (Evidence B). Other markers, such as sputum eosinophils and FeNO, are increasingly used in clinical research and will require further evaluation in adults and children before they can be recommended as a clinical tool for routine asthma management (Evidence D)."[3,]

A focused update to the 2007 guidelines was published in 2020.[82,] The focused update included several updated recommendations on the role of FeNO in asthma diagnosis and management. For asthma diagnosis, the expert panel "conditionally recommends the addition of FeNO measurement as an adjunct to the evaluation process" in individuals 5 years of age or older "for whom the diagnosis of asthma is uncertain using history, clinical findings, clinical course, and spirometry, including bronchodilator responsiveness testing, or in whom spirometry cannot be performed" (conditional recommendation, moderate certainty of evidence). The guidelines mention that FeNO levels greater than 50 parts per billion (ppb) or greater than 35 ppb in children aged 5 to 12 years are consistent with elevated type 2 inflammation and support an asthma diagnosis.

With regard to the role of FeNO testing in asthma management, the expert panel "conditionally recommends the addition of FeNO measurement as part of an ongoing asthma monitoring and management strategy that includes frequent assessments" in "individuals ages 5 years and older with persistent allergic asthma, for whom there is uncertainty in choosing, monitoring, or adjusting anti-inflammatory therapies based on history, clinical findings, and spirometry" (conditional recommendation, low certainty of evidence).[83,82,] Of note, this recommendation does not apply to individuals taking biologic agents, with the exception of omalizumab. The expert panel "recommends against the use of FeNO measurements in isolation to assess asthma control, predict future exacerbations, or assess exacerbation severity" in individuals 5 years of age or older, stating that "FeNO should only be used as part of an ongoing monitoring and management strategy" (strong recommendation, low certainty of evidence). The expert panel also recommended "against FeNO measurement to predict the future development of asthma" in children aged 0 to 4 years with recurrent wheezing (strong recommendation, low certainty of evidence).

National Institute for Health and Care Excellence

National Institute for Health and Care Excellence (2017, last updated March 2021) issued guidance on asthma diagnosis and monitoring.[5,] The guidance recommended the following for diagnosis:

- "Offer a FeNO [fractional exhaled nitric oxide] test to adults (aged 17 and over) if a diagnosis of asthma is being considered...
- Consider a FeNO test in children and young people (aged 5 to 16) if there is diagnostic uncertainty after initial assessment...
- Diagnose asthma in children and young people (aged 5 to 16) if they have symptoms suggestive of asthma and:
    - a FeNO level of 35 ppb or more and positive peak flow variability or
    - obstructive spirometry and positive bronchodilator reversibility.

- Diagnose asthma in adults (aged 17 and over) if they have symptoms suggestive of asthma and:
    - a FeNO level of 40 ppb or more with either positive bronchodilator reversibility or positive peak flow variability or bronchial hyperreactivity, or
    - a FeNO level between 25 and 39 ppb and a positive bronchial challenge test, or
    - positive bronchodilator reversibility and positive peak flow variability irrespective of FeNO level."

The guidance recommended the following for monitoring asthma control:

- "Do not routinely use FeNO to monitor asthma control.
- Consider FeNO measurement as an option to support asthma management in people who are symptomatic despite using inhaled corticosteroids."

U.S. Preventive Services Task Force Recommendations

No U.S. Preventive Services Task Force recommendations for asthma screening or the use of nitric oxide measurements or exhaled breath condensate have been identified.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 16.

Table 16. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Unpublished			
NCT02655562	Fractional Concentration of Exhaled NO (FeNO) to Direct The Treatment of Sub-acute Cough: A Prospective, Open Label, Randomized and Placebo-Controlled Trial	200	Feb 2017 (unknown)
NCT01783132[a]	Optimization of Inhaled Corticosteroid Treatment in Adult Patients With Asthma Guided by Exhaled NO Measurement at Home	200	Terminated Sep 2019 due to device availability

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
83987	pH, exhaled breath condensate
95012	Nitric oxide expired gas determination

REVISIONS	
06-30-2009	Policy added to the bcbsks.com web site. No policy changes were made.
01-01-2010	In Coding Section: ▪ Added CPT Code: 83987 ▪ Removed CPT Codes: 0064T, 0140T
03-07-2011	Description section updated
	In Policy section: ▪ To be clearer, the policy wording was split from one policy statement reading: "Measurement of exhaled or nasal nitric oxide, or collection and analysis of exhaled breath condensate, is considered experimental / investigational in the diagnosis and management of asthma and other respiratory disorders." to two separate policy statements, reading: "A. Measurement of exhaled or nasal nitric oxide is considered investigational in the diagnosis and management of asthma and other respiratory disorders including but not limited to chronic obstructive pulmonary disease and chronic cough. B. Measurement of exhaled breath condensate is considered investigational in the diagnosis and management of asthma and other respiratory disorders including but not limited to chronic obstructive pulmonary disease and chronic cough." The policy intent was not changed.
	In Coding section: ▪ Added CPT code: 94799
	Rationale section updated
	References section updated
03-13-2012	Revised Title from "Exhaled Nitric Oxide and Exhaled Breath Condensate pH Measurement for Respiratory Disorders" to "Measurement of Exhaled Nitric Oxide and Exhaled Breath Condensate in the Diagnosis and Management of Asthma and Other Respiratory Disorders"
	Description section updated
	Rationale section updated
	References section updated
03-19-2013	Description section updated
	In Coding section: ▪ Coding notations updated

REVISIONS	
	Rationale section updated
	References section updated
06-10-2015	Description section updated
	In Policy section: ▪ In Item A removed "or nasal" to read "Measurement of exhaled nitric oxide…" This change did not impact the intent of the policy.
	Rationale section updated
	In Coding section: ▪ Coding notations updated
	References section updated
01-18-2017	Title revised to "Measurement of Exhaled Nitric Oxide and Exhaled Breath Condensate in the Diagnosis and Management of Respiratory Disorders" from "Measurement of Exhaled Nitric Oxide and Exhaled Breath Condensate in the Diagnosis and Management of Asthma and Other Respiratory Disorders"
	Description section updated
	Rationale section updated
	In Coding section: ▪ Coding notations updated
	References updated
11-15-2017	Description section updated
	Rationale section updated
	References updated
08-15-2018	Description section updated
	Rationale section updated
	References updated
03-13-2019	Description section updated
	In Policy section: ▪ In Item A added "eosinophilic asthma" to read "Measurement of exhaled nitric oxide is considered experimental / investigational in the diagnosis and management of asthma, eosinophilic asthma, and other respiratory disorders including but not limited to chronic obstructive pulmonary disease and chronic cough."
	Rationale section updated
	References updated
09-25-2019	Description section updated
	In Coding section: ▪ Removed coding notations
	Rationale section updated
	References updated
04-19-2021	Description section updated
	Rationale section updated
	References updated
08-19-2021	Rationale section updated
	References updated
08-25-2022	Updated Description Section
	Updated Rationale Section
	Updated Coding Section ▪ Removed CPT Code 94799
	Updated References Section
07-25-2023	Updated Description Section
	Updated Rationale Section

REVISIONS	
	Updated Coding Section ▪ Removed ICD- 10 Diagnoses Box
	Updated References Section

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