2.01.61	Measurement of Exhaled Nitric Oxide and Exhaled Breath Condensate in the Diagnosis and Management of Respiratory Disorders		
Original Policy Date:	March 1, 2006	**Effective Date:**	October 1, 2019
Section:	2.0 Medicine	**Page:**	Page 1 of 51

Policy Statement

Measurement of exhaled nitric oxide is considered **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.

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.

Policy Guidelines

Coding
There is a CPT code specific to direct determination of exhaled nitric oxide (e.g., using the NIOX system):

- **95012**: Nitric oxide expired gas determination

There is also a CPT code to describe the collection of exhaled breath condensate with measurement of the pH:

- **83987**: pH; exhaled breath condensate

Various substances have been analyzed in a collected sample of exhaled breath condensate, including but not limited to leukotrienes, cytokines, and other substances reflecting oxidative stress. The above CPT code would not apply to this expanded analysis of exhaled breath condensate. It is likely that specific CPT codes describing the underlying laboratory technique for analysis would be used.

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 is a commercially available device for measuring NO in expired breath and various laboratory techniques for evaluating components of EBC.

Related Policies

- N/A

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. 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.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these

instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

In 2003, the Nitric Oxide Monitoring System (NIOX®; Aerocrine; acquired by Circassia Pharmaceuticals) was cleared for marketing by the FDA through the 510(k) process for the following indication:

"Measurements of the fractional nitric oxide (NO) concentration in expired breath (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."

In 2008, the NIOX MINO® was cleared for marketing by the FDA through the 510(k) process. The main differences between these 2 devices are that the NIOX MINO® is handheld, portable, and unsuitable for children younger than 7 years old. In 2014, the NIOX VERO®, which differs from predicate devices in terms of its battery and display format, was also cleared for marketing by the FDA through the 510(k) process. FDA product code: MXA.

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.

Rationale

Background

Asthma

Asthma is characterized by airway inflammation that leads to airway obstruction and hyperresponsiveness, which in turn lead to characteristic clinical symptoms including wheezing, shortness of breath, cough, and chest tightness.

Management

Guidelines for the management of persistent asthma stress the importance of long-term suppression of inflammation using steroids, leukotriene inhibitors, or other anti-inflammatory drugs. 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 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. FeNO 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 United States. According to a 2009 joint statement by the American Thoracic Society and European Respiratory Society, there is consensus that the fractional concentration of 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 FeNO and EBC

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-5 inhibitors have been approved by the Food and Drug Administration (FDA) for the treatment of severe asthma with an eosinophilic phenotype. An anti-interleukin-4 and -13 monoclonal antibody has also been shown to improve uncontrolled asthma.[3]

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.

Literature Review

The following is based on a view of the evidence, including, but not limited to, published evidence and solicited clinical expert opinion, via BCBSA's Clinical Input Process.

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.

Feno in Asthma Diagnosis

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 harms 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.

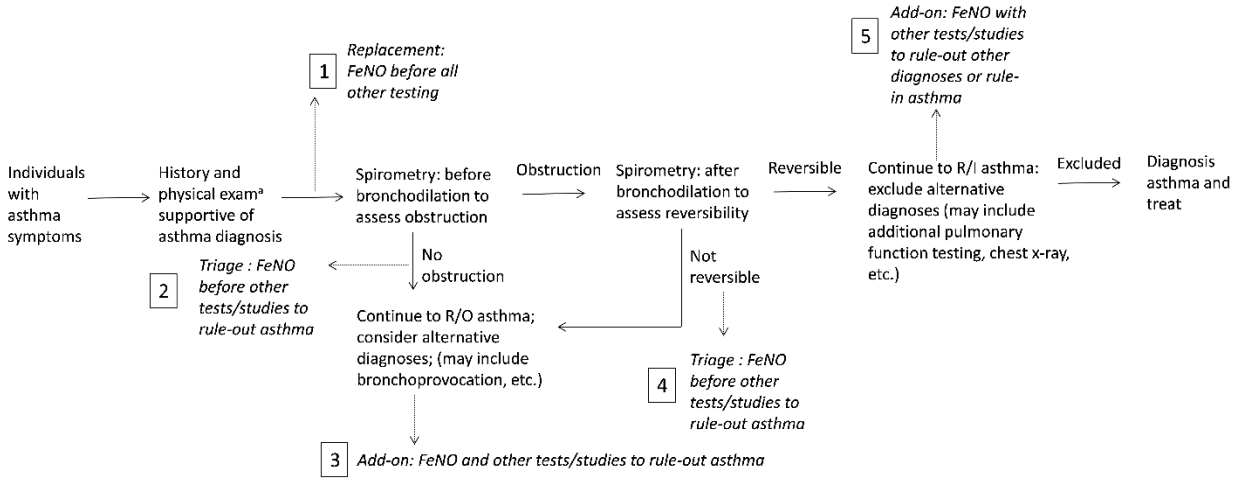
Clinical Context and Test Purpose

The purpose of Feno testing in patients who have symptoms of 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.[4,] Figure 1 shows a simplified asthma diagnostic pathway for adults and children ages five and older. In children younger than five, 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 the 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.[5,] FeNO testing 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 patients with symptoms of asthma but negative spirometry. In position 5, FeNO would be used as an adjunctive test in patients with symptoms of asthma and positive spirometry to rule-in asthma and exclude alternative diagnoses. Using FeNO to diagnosis other conditions is assessed in a separate section of the review.

Given that there is no support in U.S. guidelines for FeNO as a replacement for spirometry as a first-line diagnostic tool for asthma (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 question addressed in this evidence review is: Does measurement of FeNO improve the net health outcome in individuals with suspected asthma?

The following PICOs were used to select literature to inform this review.

Patients
The relevant 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 depending on the position in the diagnostic pathway.

Interventions
The test being considered is FeNO testing. Devices measuring FeNO are commercially available in the U. S.

FeNO measurement 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 three-second plateau can be recorded. Results are expressed as the nitric oxide (NO) concentration in parts per billion (ppb), based on the mean of 2 or 3 values.

Comparators
The appropriate comparator depends on the position of the FeNO 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 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.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires a review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

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).

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 focuses on children was published in 2019. In addition, a review is described in the National Institute for Health and Care Excellence (NICE; 2017)

guidance.[6,] Appendix Table 2 provides a crosswalk of the included primary studies in the systematic reviews. Seventy-two studies were included in the systematic reviews and the NICE guidelines, although there was only moderate overlap in included studies even though selection criteria were similar. 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)[7,] noted high or unclear risk of bias for patient selection, index test (FeNO), reference standard, and patient flow/test timing; Karrasch et al (2017)[8,] noted high or unclear risk of bias particularly for the index test (FeNO) and reference test; Wang et al (2017, 2018)[9,10,] noted high-risk of bias particularly for patient selection. Tang et al (2019) noted a high-risk of bias for patient selection and index test.[11,]

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)[9,10,]	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)[8,]	26	4518 patients with suspected asthma; at least 75% had to be steroid-naive	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	12	14	Conduct or interpretation of the index test; conduct or interpretation of reference test; patient flow
Harnan et al (2017)[7,]	27[b]	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[a]	23[a]	All 4 domains: Patient selection, Index test, Reference standard, Flow and timing
NICE (2017)[6,]	18	Patients with suspected asthma; no more than 50% of participants on corticosteroid treatment	Any design with the specified reference standard; case-control included	Physician dx of asthma based on symptoms plus an objective test[c]	NR	NR	NR	NR

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			
			only if n≥50					
Tang (2019)[11,]	8	Children; symptoms unclear	Any design; reported TP, TN, FP, and FN for asthma dx by FeNO	Any reference standard	0	5	3	Patient selection, index test, reference 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.
[a] Harnan et al (2017) only provided QUADAS-2 risk of bias (4 questions) assessment; it did not include the 3 applicability questions. [b] There appear to be ≥27 studies in the quality assessment table.
[c] Objective test must be one 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 test as indication of a positive test).

Results of the systematic reviews are shown in Table 3. Karrasch et al (2017) and Tang et al (2019) provided a pooled estimates of sensitivity and specificity across various FeNO cutoffs.[8,11,]

The Wang et al (2017) review was conducted for the Agency for Healthcare Research and Quality (AHRQ) and sponsored by NHLBI.[9,] 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.[9,10,] Results were not stratified by the 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 five 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.[7,]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 six studies included patients with chronic cough. In summary, the NICE reviewers (2017) identified 1 study in each of positions 2, 3, and 4. All three studies were rated as having a high or unclear risk of bias for at least two or the four 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 decision tree simulations used for the economic analysis were described in the Appendix of the NICE guidance. The section on "Key assumptions" for the decision tree states that the model assumed the tests are conditionally independent. NICE asked its advisory committee to give its opinion on how strongly it believed the conditional independence assumption between tests. The result of this query is the statement in the Appendix of the NICE guidance that "FeNO does not appear as it was assumed to be conditionally independent with the other 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 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 includes 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)[9,10,]				
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)[8,]	Pooled across cutoffs	28 studies/4518 patients	65 (58 to 72)	82 (76 to 86)
Harnan et al (2017)[7,]				
Asthma symptoms, no previous testing	Range, 20-47	12 studies/1837 patients	Range, 14-88	Range, 60-93
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)[6,]				
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 (2019)[11,]	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.[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, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary 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 diagnosis 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: Feno 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. Limitations of the published evidence preclude determining the effects of the technology on net health outcome. Evidence reported through clinical input suggests a possible adjunctive role when conventional testing may be limited, particularly where diagnosis with standard clinical diagnostic testing (e.g., routine spirometry) may be limited such as in pediatric patients. However, the published evidence does not show whether FeNO testing in such patients would be clinically feasible and clinically valid to be clinically useful. Further details from clinical input included in the Clinical Input section and the Appendices 2 and 3.

Feno in Asthma Management
Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.
To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The RCT is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely

large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

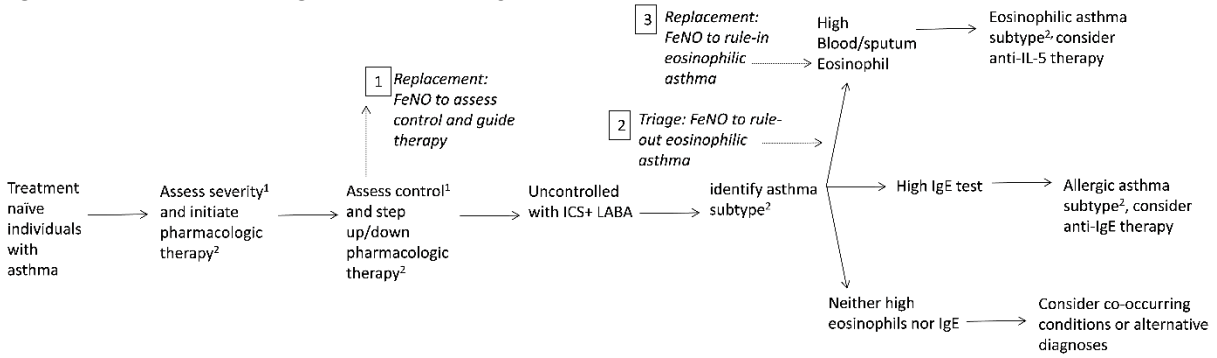
Clinical Context and Test Purpose

The purpose of FeNO testing in patients who have a diagnosis of 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.[4,]

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 anti-interleukin-5 (IL-5) therapies are not approved for children under 12 and anti-immunoglobulin E therapy is only approved for children ages six 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.[5,] FeNO 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 question addressed in this evidence review is: Does measurement of FeNO improve the net health outcome in individuals diagnosed with asthma?
The following PICOs were used to select literature to inform this review.

Patients
The relevant population of interest depends on the position of the FeNO test in the management pathway, as shown in Figure 2.

Interventions
The test being considered is FeNO testing. Several devices measuring FeNO are commercially available in the U. S. Results are expressed as the NO concentration in parts per billion, based on the mean of 2 or 3 values.

Comparators
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. An RCT applying the step-up/step-down management recommendations of guidelines in approximately 1500 patients with all severities of asthma treated and monitored for 1 year found that guidelines-based management resulted in significant improvement in health-related quality of life in most patients, regardless of disease severity.[15,]

In position 2, appropriate comparators are blood and sputum assessment of eosinophils.

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."[16,] There were a series of publications on recommendations for core asthma measures for seven 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 measurement of exacerbations provided a proposed definition of exacerbation and stated that the "preferred" measure for reporting exacerbation outcomes is the overall rate (annual).[17,] It stated that the percentage

with an exacerbation is an "additional" measure. NIH and American Thoracic Society (ATS) recommended definitions for exacerbation in clinical trials are as follows.[1,17,]

- 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 5-11 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 three 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 two 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.[18,] The recommended scales are shown in Table 4.

Table 4. Symptom Control Scales Outcome Measures

Name	Description	Administration	Scoring	MCID
Asthma Control Questionnaire[19,]	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[20,]	Identifying 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).[18,]
$\%FEV_1$: percent forced expiratory volume in 1 second; MCID: minimal clinically important difference.

For evaluation of FeNO in position 2 (selecting patients for treatments targeted for eosinophilic asthma), the ability of FeNO to predict response to therapy compared with blood and/or sputum assessment of eosinophilic asthma is of interest. Trials of anti-IL-5 therapies have generally had inclusion criteria for eosinophilic asthma based on blood eosinophil counts.

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.

Efficacy of FeNO-Guided Medication Management of Asthma
FeNO 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. Appendix Table 3 provides a crosswalk of the trials included in the systematic reviews.

In the Cochrane review by Petsky et al (2016), which assessed on adults, the search included 7 RCTs published up to June 2016.[21] 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.[22] The search identified 9 trials (total n=1426 patients) published up to July 2016. The quality of the evidence was rated moderate for the outcomes of the number of children who had one 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.[23] No additional RCTs were included in the FeNO analyses compared with the 2 earlier Petsky et al (2016) reviews.

Wang et al (2017)[9] reported on a systematic review for AHRQ, which included RCTs, that almost entirely overlapped with the 2 Petsky et al (2016) reviews (see Appendix Table 2). 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)[9]	To Apr 2017	14	Adults or children (ages ≥5 y) diagnosed with asthma	2269	RCT	4-12
Petsky et al (2016)[21]; adults	To Jun 2016	7	Adults diagnosed with who required asthma medications	1700	RCT	4-12
Petsky et al (2016)[22]; 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% CI, 8 to 32) when all studies were included but not when limited to studies with a guidelines-driven control group.[21,] 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. 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.[22,] However, there was no significant difference between groups in exacerbation rates. The number of children requiring oral corticosteroids 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 one person with exacerbation is nine for both adults and children. Results by guidelines-based control vs 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)	Inhaled Corticosteroid Dose at Final Visit	Participants With Exacerbations Requiring Hospitalization, %	Symptoms (Asthma Control Test)
Wang et al (2017)[9,]					
Adults					
Total 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					
Total 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)[21,]; adults					
Overall					
Total N	995	842	482	488	707
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)	-0.08 (-0.18 to 0.01)
I^2 (p)[a]	13% (0.33)	0% (0.64)	82% (<0.001)	NA	0% (0.91)
GRADE QOE	Moderate	Moderate	Very low	NR	NR
Guidelines-driven control					
Total 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% (0.13)	0% (0.76)			
Petsky et al (2016)[22,]; children					

Study	Participants With ≥1 Exacerbations, %	Rate of Exacerbations (per 52 wk)	Inhaled Corticosteroid Dose at Final Visit	Participants With Exacerbations Requiring Hospitalization, %	Symptoms (Asthma Control Test)
Overall					
Total 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% (0.38)	67% (0.03)	40% (0.19)	0% (0.56)	62% (0.11)
GRADE QOE	Moderate	Very low	Moderate	NR	NR
Guidelines-driven control					
Total 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% (0.002)	77% (0.01)			

CI: confidence interval; FeNO: fractional exhaled nitric oxide; 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

FeNO 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 four RCTs (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 five RCTs (Peirsman, Pike, Verini, Szefler, Fritsch) that included guidelines-driven controls. The RCT by Szefler et al (2008) is by far the largest and used a definition of exacerbation most consistent with NIH and ATS guidelines.[24,]

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

Study	Participants	Exacerbation Definition	Duration	Interventions	
Adults				**FeNO Group**	**Control Group**
Calhoun et al (2012)[25,](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 oral corticosteroids, increased ICS, or additional asthma medications	9 mo	• N=115 • <22 decrease • 22-35 maintain • >35 increase	• N=114 • NHLBI guidelines
Hashimoto et al (2011)[26,]	Aged 18-75 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 oral	Decrease in morning FEV_1 >10% vs mean FEV1 from week before, increase in symptoms requiring increased prednisolone >10 mg/d, or course	6 mo	• N=51 • +10 ppb and >10% increase • +10 ppb and ≤0% maintain • minus ≥0 and ≤10 maintain	• N=38 • GINA guidelines

	corticosteroids, high doses of ICS and long-acting bronchodilators	of antibiotics, regardless of hospitalizations		• < -10 ppb decrease	
Shaw et al (2007)[27],	>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 oral steroids or antibiotics	12 mo	• N=58 • <16 once or 16-26 s decrease • >26 increase	• N=60 • BTS guide lines and Asth ma Contr ol Test
Smith et al (2005)[28],	ICSs for 6 mo with no dose change in previous 6 wk	• Minor exacerb ation: global daily asthma score of 2 on ≥2 consecuti ve days • Major exacerb ation: global daily asthma score of 3 on ≥2 consecuti ve days	12 mo	• N=46 • <15 maintain; • ≥15 increase (250 mL/s)	• N=48 • GINA guide lines
Children					
Peirsman et al (2014)[29],	Children with mild-to-severe asthma according to GINA guidelines for >6 mo and allergic sensitization (ie, 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 and controlle d = step down • ≤20 and partially controlle d consider LTRA • >20 = step up	• N=50 • GINA guide lines
Pike et al (2013)[30],	Ages 6-17 y, clinical diagnosis of asthma and treatment with beclomethasone dipropionate/budes onide ≥400 µg/d or fluticasone ≥200 µg/d	• ≥48 h > asthma symptom s or therapy or < PEF (≥25%) • Mild: increase SABA only • Moderat e:	12 mo	• N=44 • ≤15 and well-controlle d = step down • <25 and poorly controlle d = LABA maximize d ≥25 or FeNO	• N=46 • SIGN/ BTS guide lines

		requiring systemic corticosteroids • Severe: requiring hospitalizations ≥8 h		doubled from baseline = step up • If FeNO remained raised after 2 ´steps (SIGN/BTS steps) ICS not increased again unless participant poorly controlled	
Verini et al (2010)[31],	Children admitted for allergic asthma and the diagnosis physician based on ATS/ERS criteria	Episodes of coughing, dyspnea, and wheezing requiring SABA	12 mo	• N=32 At 6-mo visit only: • <12 = step down or no change • >12 = step up	• N=32 • GINA guidelines
Szefler et al (2008)[24],	Ages 12-20 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 and level 1 = no change • 20.1-30 and level 2 = step up • 30.1-40 and level 3 = 2 steps • >40 and level 4 = 3 steps or 2 steps and OCS course	• N=270 • NHLBI guidelines
Fritsch et al (2006)[32],	Ages 6-18 y with asthma diagnosis as based on ATS criteria. Positive SPT or RAST >1	OCS because of asthma symptoms, nonscheduled visit because of asthma symptoms, > symptom score to 2, < FEV_1 (in liters) >10% vs previous visit, or a	6 mo	• N=22 • ≤20 and FEV_1 ≥80%, symptom score 0 or 1 and SABA use <6 = step down	• N=25 • Austrian asthma guidelines

	combination of these	• ≤20 and FEV_1 <80% or symptoms score >1 or SABA use ≥6 = step up Participant on SABA on demand only: • 20 and FEV1 ≥80%, symptom score 0 or 1 and SABA use <6 = step up Participant on ICS: • 20 and FEV_1 ≥80%, symptom score 0 or 1 and SABA use <6 = same step • >20 and FEV_1 <80% or symptoms score >1 or SABA use ≥6 = 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: radio allegro sorbent 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, three RCTs (Calhoun, Shaw, Smith) reported the outcome of the rate of exacerbations over one 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 oral steroids. Two RCTs reported on exacerbations requiring hospitalizations but no qualifying hospitalizations were noted in either group. Two RCTs reported control/symptom scales and two RCTs reported on pulmonary function (percent predicted FEV_1). No study of adults reported a significant difference for any outcomes included here.

In children, three RCTs (Pike, Verini, Szefler) reported the outcome of the rate of exacerbations over one year. Four RCTs (Peirsman, Pike, Verini, Szefler) reported the outcome of percentage with exacerbation over the study period, which was primarily 12 months (46 wk for Szefler). Four RCTs (Peirsman, Pike, Szefler, Fritsch) reported the outcome of exacerbations requiring oral

corticosteroids. 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 vs 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						
Calhoun et al (2012)[25], (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		
Hashimoto et al (2011)[26],						
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)
TE (95% CI)	p=0.95			p=0.37		p=0.73
Shaw et al (2007)[27],						
N	118	158	NR	103	NR	NR
FeNO	0.33	21%		ACQ[c]=1.1		
Control	0.42	32%		ACQ[c]=1.15		
TE (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)[28],						
N	94	94	94	NR	NR	54
FeNO	0.49	30%	28%			86.1%
Control	0.90	23%	31%			82.3%
TE (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						
Peirsman et al (2014)[29],						
N	NR	99	99	NR	86	93
FeNO		24%	2		2%	91.2%
Control		48%	3		2%	93.9%
TE (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)[30],						
N	NR[d]	90	NR	NR	90	77

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		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=0.29		1.84 (0.41 to 8.20)	
Verini et al (2010)[31,]						
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)[24,]						
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)[32,]						
N	NR	NR	47	NR	NR	
FeNO			2			
Control			2			
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; TE: treatment effect.
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).[24,] The Asthma Control Evaluation was a randomized, double-blind, parallel-group trial funded by National Institute of Allergy and Infectious Diseases; it included 546 inner-city participants, ages 12 to 20 years, with persistent asthma (75% ages ≤16). 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 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=0.11). The outcome of patients requiring oral steroids was statistically significant favoring FeNO (32% vs 42%; mean difference [MD], -10%; 95% CI, -18% to -2%; p=0.01).

The purpose of the limitations tables (see 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. Relevance Limitations of RCTs of FeNO-Guided vs Guidelines-Driven Treatment

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Adults					
Calhoun et al (2012)[25],				1. Key exacerbation outcomes not reported	1. Less than 1 y follow-up
Hashimoto et al (2011)[26],		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)[27],				1. Key exacerbation outcomes not reported	
Smith et al (2005)[28],	2. Children >12 y of age included				
Children					
Peirsman et al (2014)[29],				1. Key exacerbation outcomes not reported	
Pike et al (2013)[30],					
Verini et al (2010)[31],				1. Most key outcomes not reported	
Szefler et al (2008)[24],					
Fritsch et al (2006)[32],				1. Most key outcomes not reported	1. Less than 1 follow-up

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitation s assessment.
FeNO: fractional exhaled nitric oxide; RCT: randomized controlled trial.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[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 vs Guidelines-Driven Treatment

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Adults						

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Calhoun et al (2012)[25],	3. Concealment not described	1,2. Blinding unclear				
Hashimoto et al (2011)[26],	3. Concealment not described	1,2. No blinding				
Shaw et al (2007)[27],						
Smith et al (2005)[28],	3. Concealment not described				1-3. Power calculations not reported	
Children						
Peirsman et al (2014)[29],		2. Blinding unclear		6. Unclear if ITT used		
Pike et al (2013)[30],				1. 14% LTFU; 10 participants in FeNO and 3 in control	1-3. Power calculations not reported	
Verini et al (20100[31],	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)[24],						
Fritsch et al (2006)[32],	3. Concealment not described	1,2. Blinding unclear		1. »10% LTFU and 23 missing FeNO measurements due to technical problems 6. Unclear if ITT used	2. Power calculated for FEV_1 difference over 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 limitations 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 FeNO-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, one 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.

FeNO-guided management significantly decreased exacerbations (and exacerbations requiring oral steroids) compared with guidelines-driven controls in children. In the Cochrane meta-analysis, the estimated pooled MD in rate of exacerbations -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). In the Szefler et al (2008) RCT, by far the largest RCT (n=546) and funded by NIH, which used guidelines-driven control and used a definition of exacerbation consistent with NIH and ATS recommendations, the percentage with 1 or more exacerbation was not statistically significant (MD = -6.5%; 95% CI, -14% to 1%; p=0.11) but the percentage requiring oral steroids was statistically significant favoring FeNO (32% vs 42%; MD = -10%; 95% CI, -18% to -2%; p=0.01). FeNO-guided management did not impact day-to-day clinical symptoms, hospitalizations, or pulmonary function measures.

Registered RCTs remain unpublished several years after completion (see in the ongoing trials table in the Supplemental Information section).

Limitations of the published evidence preclude determining the effects of the technology on net health outcome.

Evidence reported through clinical input suggests a possible adjunctive role for FeNO testing particularly for individuals who may have limited awareness of worsening symptoms or when there is suspected nonadherence to medication. However, the published evidence does not examine this subgroup to demonstrate that use of FeNO testing in such patients may be clinically useful to inform treatment decisions by reducing or avoiding unnecessary asthma therapy, or by indicating when step-up therapy is warranted. Further details from clinical input included in the Clinical Input section and Appendices 2 and 3.

FeNO and Response to ICS
Several studies have evaluated the association between FeNO and response to ICS.[33,34,35,36,37,38,39,40,] ICS 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.

FeNO for Selecting Patients for Treatment With Therapies Targeted to Eosinophilic Subtype
Eosinophilic asthma is an asthma phenotype associated with responsiveness to ICS and later onset time. Currently, four drugs approved by the Food and Drug Administration are available to treat asthma with an eosinophilic phenotype: mepolizumab, reslizumab, benralizumab anti-IL-5 therapies, and dupilumab, an anti-IL-4 receptor alpha subunit antibody, 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.

Several observational studies and a systematic review of observational studies have described the association between FeNO and blood or sputum eosinophils.[41,42,]

Randomized Controlled Trials

Subgroup analyses of treatment response stratified by FeNO from pivotal RCTs demonstrating the efficacy of treatments for anti-IL-5 therapies have not been reported. 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.[43,44,] A secondary analysis of the DREAM and MENSA studies stratified by baseline blood eosinophil thresholds was reported by Ortega et al (2016).[45,] The exacerbation rate reductions for mepolizumab vs 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.

The LIBERTY ASTHMA QUEST and 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.[46,47,] 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 11 and 12. In the QUEST trial, the relative risk for severe asthma exacerbations for dupilumab vs 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<0.001). In contrast, while there was a quantitative interaction (p=0.008) between treatment and baseline FeNO, FeNO did not identify a group for whom there appears to be no benefit from dupilumab.

Table 11. Treatment Effect of Dupilumab vs Placebo on Severe Asthma Exacerbations by Blood Eosinophil Count and FeNO (QUEST and VENTURE Trials)

Subgroup	Placebo N	Dupilumab N	RR vs Placebo (95% CI)	Interaction p
Dupilumab 200 mgevery 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)	<0.001
≥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)	0.008
≥25 to <50	91	180	0.39 (0.24 to 0.62)	
<25	149	325	0.75 (0.54 to 1.05)	
Dupilumab 300 mgevery 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)	<0.001
≥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)	<0.001
≥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 weeks (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)	0.14
<300	66	55	0.545 (0.315 to 0.940)	
≥150	69	81	0.418 (0.254 to 0.689)	0.82
<150	38	22	0.396 (0.166 to 0.946)	

Subgroup	Placebo N	Dupilumab N	RR vs Placebo (95% CI)	Interaction p
FeNO, ppb				
≥50	29	24	0.532 (0.228 to 1.239)	0.03
≥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)[46], and Rabe et al (2018)[47], supplemental materials.
CI: confidence interval; FeNO: fractional exhaled nitric oxide; ppb: part per billion; RR relative risk.

Table 12. Treatment Effect of Dupilumab vs Placebo on Percentage Reduction in Oral Glucocorticoid Dose by Blood Eosinophil Count and FeNO (VENTURE Trial)

Subgroup	Placebo N	Dupilumab N	RD (95% CI)	Interaction p
Dupilumab 300 mg every 2 wk for 24 weeks				
Overall	107	103	-28.2 (-40.7 to -15.8)	
Blood eosinophil count, cells/mm³				
≥300	41	48	-36.83 (-54.71 to -18.94)	0.24
<300	66	55	-21.33 (-38.75 to -3.90)	
≥150	69	81	-29.39 (-43.12 to -15.67)	0.71
<150	38	22	-26.89 (-54.52 to 0.73)	
FeNO, ppb				
≥50	29	23	-33.64 (-53.61 to -13.67)	0.34
≥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.[47],
CI: confidence interval; FeNO: fractional exhaled nitric oxide; ppb: part per billion; RD: risk difference.

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.[48], 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 and twenty-two patients had baseline FeNO measurements, of which 44% were >= 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 13.

Table 13. Mean Exacerbation Rate while Treated with Omalizumab (over 12 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	0.40
<25	402	2.8	398	0.7	

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

Subsection Summary: FeNO for Identifying Eosinophilic Asthma

The Food and Drug Administration-approved anti-IL-5 and anti-IL-4 therapies to treat eosinophilic asthma are available. Studies demonstrating the efficacy of anti-IL-5 treatments generally used

blood or sputum eosinophilic measurements to determine eligibility. Subgroup analyses from two trials of dupilumab, one including patients with uncontrolled asthma and one including patients with oral glucocorticoid-treated asthma, reported conflicting results on whether baseline blood eosinophils could be used to identify a group of patient unlikely to benefit from dupilumab with respect to severe exacerbations. However, in both trials, the treatment effect estimate for dupilumab vs placebo for the outcome of severe exacerbations favored dupilumab across the three subgroups of baseline FeNO even when a statistically significant, quantitative interaction was reported. Therefore, it is unclear if baseline FeNO can identify a group for whom there is no benefit from dupilumab. Similarly, a 48-week multicenter prospective observational study with over 700 participants found that asthma exacerbations were reduced with omalizumab over a 12-month treatment period irrespective of baseline FeNO. Limitations of the published evidence preclude determining the effects of the technology on net health outcome.

Evidence reported through clinical input suggests a possible adjunctive role for FeNO testing when it may be particularly difficult to confirm the presence of eosinophils using more invasive methods such as induced sputum or bronchiolar lavage. However, the published evidence does not show whether the adjunctive use of FeNO testing provides significant improvement in net health outcome when conventional testing for the presence of eosinophils is limited or infeasible. Further details from clinical input included in the Clinical Input section and Appendices 2 and 3.

FeNO in Respiratory Conditions Other Than Asthma

Clinical Context and Test Purpose

The purpose of FeNO testing in patients who have symptoms of other respiratory conditions or a diagnosis of 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 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 question addressed in this evidence review is: Does measurement of FeNO improve the net health outcome in individuals with symptoms or diagnosis or other respiratory conditions? The following PICOs were used to select literature to inform this review.

Patients

The relevant populations of interest are patients who have symptoms or a diagnosis of other respiratory conditions. 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 FeNO testing.

Comparators

The appropriate comparator depends on the position of the FeNO in the diagnostic or management pathway.

Outcomes

Outcomes of interest would be diagnostic accuracy, rates of exacerbations, symptoms, hospitalizations, use of medications, and quality of life.

FeNO for Diagnosing Respiratory Disorders Other Than Asthma

Chronic Obstructive Pulmonary Disease

Gao et al (2017) reported on results of a cross-sectional study evaluating the association between FeNO and sputum eosinophilia in 163 patients with chronic obstructive pulmonary disease (COPD)exacerbations.[49,] Sputum eosinophils correlated with both FeNO levels (ρ=0.221,

p<0.01) and blood eosinophilic percentage (ρ=0.399, p<0.001). FeNO 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 results on the use of FeNO measurements in predicting sputum eosinophilia in patients with COPD.[50] 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=0.01). 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 immunoglobulin E , 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=0.017). The authors hypothesized that individuals with COPD with sputum eosinophilia might respond well to inhaled or oral corticosteroids.

Interstitial Lung Disease

Oishi et al (2017) evaluated whether there were differences in FeNO levels in different types of acute-onset interstitial lung disease.[51] 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<0.001). 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.[52] 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, 19-25 ppb; p=0.008). 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 PCD.[53] 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.

FeNO for Predicting Response to Medication Therapy in Respiratory Conditions Other Than Asthma

A double-blind crossover trial by Dummer et al (2009) evaluated the ability of FeNO test results to predict corticosteroid response in COPD.[54] 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 and those taking regular corticosteroids or had used oral corticosteroids for exacerbations more than twice during the past six months were excluded. Treatments, given in random order, were prednisone 30 mg/d 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 zero for the second treatment period. Fifty-five patients completed the study. Two of the three 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=0.45) or St. George's Respiratory Questionnaire score (r=0.12, p=0.36) but was significantly related to change in FEV_1 (r=0.32, p=0.01). 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 oral corticosteroid 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.[55,] 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=0.028).[56,] However, an optimal FeNO cutpoint to discriminate between responders and nonresponders could not be determined.

Section Summary: FeNO 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 identified compared health outcomes in patients with COPD or other respiratory diseases whose treatment was managed with and without FeNO measurement. Limitations of the published evidence preclude determining the effects of the technology on net health outcome. The evidence provided by clinical input was not supportive of the use of FeNO testing for respiratory disorders other than asthma to improve the net health outcome. Further details from clinical input included in the Clinical Input section and Appendices 2 and 3.

Exhaled Breath Condensate

Clinical Context and Test Purpose

The purpose of EBC testing in patients 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 FeNO. A review 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.[57,] 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 must be resolved[57,58,59,60,61,]:

- 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 question addressed in this evidence review is: Does measurement of EBC improve the net health outcome in individuals with symptoms or diagnosis of asthma or other respiratory conditions?

The following PICOs were used to select literature to inform this review.

Patients

The relevant populations of interest are patients who have symptoms or a diagnosis of asthma or other 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 EBC testing.

Comparators

The appropriate comparator depends on the position of the EBC in the diagnostic or management pathway.

Outcomes

Outcomes of interest might be diagnostic accuracy, rates of exacerbations, symptoms, hospitalizations, use of medications, and quality of life.

EBC 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.[62,] 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 reviewed 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 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.[63] 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 seven studies. The association between pH or NO and asthma varied between studies, and in one 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.

EBC 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 National Institutes of Health.[64] This study had the largest sample size (n=572 patients). 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=0.80). 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).

EBC 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, 6-18 years) with asthma.[65] 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<0.001); EBC pH (uncontrolled mean pH, 7.2 vs controlled mean pH, 7.33; p=0.002); and EBC temperature (uncontrolled mean EBT, 34.26°C vs controlled mean EBT, 33.9°C; p=0.014). Also, EBC urate concentration was significantly associated with time from last exacerbation (p<0.001), Asthma Control Test results (p<0.001), and short-acting bronchodilator use (p<0.001) within the entire cohort.

EBC 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 in 58 hospitalized patients (20 with asthma, 38 with COPD) and 36 healthy controls (18 smokers, 18 nonsmokers).[66] EBC pH was significantly lower in patients with asthma exacerbations (all nonsmokers) at hospital admission (6.2) than in nonsmoking controls (6.4; p<0.001). 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.

EBC-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: EBC
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. Limitations of the published evidence preclude determining the effects of the technology on net health outcome. The evidence provided by clinical input was not supportive of the use of EBC as a test to improve the net health outcome. Further details from clinical input included in the Clinical Input section and Appendices 2 and 3.

Clinical Input
Objective
In 2017, 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.

Respondents
Clinical input was provided by the following physician members identified by a specialty society:
- Meagan W. Shepherd, MD; Allergy/Immunology; Identified by American College of Allergy, Asthma & Immunology
- Anonymous, MD; Pediatric Pulmonary/Allergy; Identified by American Academy of Allergy, Asthma & Immunology
- Miles Weinberger, MD; Pediatrics; Allergy & Clinical Immunology; Pediatric Pulmonology; Identified by American Academy of Allergy, Asthma & Immunology

Clinical input provided by the specialty society at an aggregate level is attributed to the specialty society. Clinical input provided by a physician member designated by a specialty society or health system is attributed to the individual physician and is not a statement from the specialty society or health system. Specialty society and physician respondents participating in the Evidence Street® clinical input process provide a review, input, and feedback on topics being evaluated by Evidence Street. However, participation in the clinical input process by a specialty society and/or physician member designated by a specialty society or health system does not imply an endorsement or explicit agreement with the Evidence Opinion published by BCBSA or any Blue Plan.

Clinical Input Responses
Additional Comments
- "Measurement of FeNO in addition to stereotypical symptoms including response to inhaled beta2-agonists and glucocorticoids is very useful, particularly in children, in whom a spirometry-based diagnosis of asthma cannot always be confirmed. FeNO is a clinically helpful tool for diagnosis of suspected asthma and a trial of appropriate treatment." (Dr. Shepherd - identified by ACAAI)
- "I use FeNO to assess inhaled corticosteroid (ICS) response and to see if more ICS needed. I also use FeNO to help give insight if asthma is the diagnosis in difficult cases (i.e., vocal cord dysfunction, eosinophilic bronchitis, interstitial lung disease, chronic obstructive pulmonary disease, etc.). FeNO may be helpful to monitor adherence to therapy." (Anonymous, identified by AAAAI)
- "Rationale: FeNO identifies only eosinophilic inflammation, not specifically asthma which has many phenotypes and endotypes." (Dr. Weinberger - identified by AAAAI)
- "In summation, I find FeNO measurement to be relevant and of clinical value to the diagnosis and management of asthma, including identification of the eosinophilic

asthma phenotype. A review of the literature also reveals utility in areas of medicine in which I do not routinely practice, such as other pulmonary disorders, autoimmune disease, and chronic obstructive pulmonary disease. " (Dr. Shepherd - identified by ACAAI)

- "Nasal FeNO is important for screening for and diagnosing primary ciliary dyskinesia, and all referral pulmonary centers should have the capability." (Dr. Weinberger - identified by AAAAI)

See Appendices 2 and 3 for details.

Summary of Evidence

The following conclusions are based on a view of the evidence, including, but not limited to, published evidence and solicited clinical expert opinion, via BCBSA's Clinical Input Process.

For individuals who have suspected asthma who receive a measurement of FeNO for diagnosis, the evidence includes multiple retrospective and prospective studies of diagnostic accuracy, along with systematic reviews of those studies. The relevant outcomes are test validity, symptoms, change in disease status, morbid events, and functional outcomes. There are multiple reports on the sensitivity and specificity of FeNO in asthma diagnosis; however, most studies are in the setting of patients with asthma symptoms without previous testing (or with unclear previous testing), which is unlikely to be how the test is used in a U.S. setting. The available evidence is limited by variability in FeNO cutoff levels used to diagnose asthma, lack of data on performance characteristics in diagnostic challenging settings, and lack of data on the incremental value of adding FeNO to existing diagnostic algorithms from studies with concurrent controls. Limitations of the published evidence preclude determining the effects of the technology on net health outcome. Evidence reported through clinical input suggests a possible adjunctive role when conventional testing may be limited, particularly where diagnosis with standard clinical diagnostic testing (e.g., routine spirometry) may be limited such as in pediatric patients. However, the published evidence does not show whether FeNO testing in such patients would be clinically feasible and clinically valid to be clinically useful. The evidence is insufficient to determine the effect of the technology on health outcomes.

For individuals who have asthma who receive medication management directed by FeNO, the evidence includes diagnostic accuracy studies, multiple RCTs, and systematic reviews of those trials. The relevant outcomes are symptoms, change in disease status, morbid events, and functional outcomes. The available RCTs evaluating the use of FeNO tests to guide step-up/step-down therapy in patients have not consistently found improvement in health outcomes. Two Cochrane reviews from 2016, one on adults and the other on children, found FeNO-guided asthma management to guide step-up/step-down therapy reduced the number of individuals who had more than 1exacerbation in children but not in adults compared with guidelines-driven therapy but had no impact on day-to-day symptoms or hospitalizations. Limitations of the published evidence preclude determining the effects of the technology on net health outcome. Evidence reported through clinical input suggests a possible adjunctive role for FeNO testing particularly for individuals who may have limited awareness of worsening symptoms or when there is suspected nonadherence to medication. However, the published evidence does not examine this subgroup to demonstrate that use of FeNO testing in such patients may be clinically useful to inform treatment decisions by reducing or avoiding unnecessary asthma therapy, or by indicating when step-up therapy is warranted. The evidence is insufficient to determine the effect of the technology on health outcomes.

For individuals who have suspected eosinophilic asthma who receive a measurement of FeNO to select a therapy, the evidence includes diagnostic accuracy studies and subgroup analyses of RCTsand observational studies. The relevant outcomes are symptoms, change in disease status, morbid events, and functional outcomes. For the use of FeNO to identify eosinophilic asthma for the purpose of selecting patients for therapy with anti-IL-5 therapy or an anti-IL-4 and -13 monoclonal antibody, subgroup analyses of RCTs are available. The evidence that points toward an interaction between baseline FeNO and treatment for the outcome of response

suggests that there may be a quantitative but not necessarily a qualitative interaction between baseline FeNO and anti-IL-4 treatment (dupilumab), i.e., it is unclear if baseline FeNO can identify a group for whom there is no benefit from dupilumab. Similarly, a 48-week multicenter prospective observational study with over 700 participants found that asthma exacerbations were reduced with omalizumab over a 12-month treatment period irrespective of baseline FeNO. Limitations of the published evidence preclude determining the effects of the technology on net health outcome. Evidence reported through clinical input suggests a possible adjunctive role for FeNO testing when it may be particularly difficult to confirm the presence of eosinophils using more invasive methods such as induced sputum or bronchiolar lavage. However, the published evidence does not show whether the adjunctive use of FeNO testing provides significant improvement in net health outcome when conventional testing for the presence of eosinophils is limited or infeasible. The evidence is insufficient to determine the effect of the technology on health outcomes.

For individuals who have suspected or confirmed respiratory disorders other than asthma who receive a measurement of FeNO, the evidence includes a crossover trial and observational studies. The relevant outcomes are test validity, symptoms, change in disease status, morbid events, and functional outcomes. The available evidence assessing the use of FeNO for respiratory disorders other than asthma is limited by heterogeneity in the conditions evaluated and uncertainty about how the test fits in defined clinical management pathways. The evidence provided by clinical input was not supportive of the use of FeNO testing for respiratory disorders other than asthma to improve the net health outcome. The evidence is insufficient to determine the effect of the technology on health outcomes.

For individuals who have suspected or confirmed respiratory disorders who receive a measurement of EBC, the evidence includes observational studies reporting on the association between various EBC components and disease severity. The relevant outcomes are test validity, symptoms, change in disease status, morbid events, and functional outcomes. 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 published evidence does not support conclusions on the utility of EBC for any indication. The evidence provided by clinical input was not supportive of the use of EBC as a test to improve the net health outcome. The evidence is insufficient to determine the effect of the technology on health outcomes.

Supplemental Information

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

In response to requests from Blue Cross Blue Shield Association, in 2017, clinical input on the use of fractional exhaled nitric oxide (FeNO) and exhaled breath condensate in the diagnosis and management of individuals with respiratory disorders was received from 3 physician-level respondents identified through 2 specialty societies including physicians with academic medical center affiliations. Evidence from clinical input is integrated within the Rationale section summaries and the Summary of Evidence.

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

National Institute for Health and Care Excellence

The National Institute for Health and Care Excellence (2017) issued guidance on asthma diagnosis and monitoring.[6,] 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."

American Thoracic Society

The American Thoracic Society (2011) published guidelines on the interpretation of FeNO levels.[67,] The guidelines were critically appraised using criteria developed by the Institute of Medicine, which includes eight standards.[68,] The guidelines were judged not to meet the following standards adequately: Standard 3: guideline development group composition; Standard 4: clinical practice guideline-systematic review intersection; Standard 5: establishing evidence foundation for and rating strength of recommendations; and Standard 7: an external review.

Table 14 lists American Thoracic Society guideline recommendations on the management of patients with asthma.

Table 14. Guidelines on Management of Patients with Asthma

Recommendation	SOR	QOE
"We recommend the use of FENO in the diagnosis of eosinophilic airway inflammation"	Strong	Moderate
"We recommend the use of FENO in determining the likelihood of steroid responsiveness in individuals with chronic respiratory symptoms possibly due to airway inflammation"	Strong	Low
"We recommend accounting for age as a factor affecting FENO in children younger than 12 years of age"	Strong	High
"We recommend that low FENO less than 25 ppb (< 20 ppb in children) be used to indicate that eosinophilic inflammation and responsiveness to corticosteroids are less likely"	Strong	Moderate

Recommendation	SOR	QOE
"We recommend that FENO greater than 50 ppb (> 35 ppb in children) be used to indicate that eosinophilic inflammation and, in symptomatic patients, responsiveness to corticosteroids are likely"	Strong	Moderate
"We recommend that FENO values between 25 ppb and 50 ppb (20-35 ppb in children) should be interpreted cautiously and with reference to the clinical context"	Strong	Low
"We recommend accounting for persistent and/or high allergen exposure as a factor associated with higher levels of FENO"	Strong	Moderate
"We recommend the use of FENO in monitoring airway inflammation in patients with asthma"	Strong	Low

FENO: fractional exhaled nitric oxide; ppb: part per billion; QOE: quality of evidence; SOR: strength of recommendation.

National Heart Lung and Blood Institute

The National Heart Lung and Blood Institute's (2007) 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)."

American Academy of Pediatrics

The American Academy of Pediatrics (2017) issued a report on clinical tools to assess asthma control in children.[69,] 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."

Global Initiative for Asthma

The Global Initiative for Asthma (2018) released its updated global strategy for asthma management and prevention.[70,] The report made the following statements on the use of FeNO for diagnosis:

- "FeNO has not been established as useful for ruling in or ruling out a diagnosis of asthma."
- "In adult steroid-naïve patients with non-specific respiratory symptoms, a finding of FeNO > 50 ppb [parts per billion] was associated with a good short-term response to ICS [inhaled corticosteroid]. However, there are no long-term studies examining the safety (with regard to risk of exacerbations) of withholding ICS in patients with low initial FeNO. Consequently, in patients with a diagnosis or suspected diagnosis of asthma, FeNO cannot be recommended at present for deciding against treatment with ICS."

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

- "At present, neither sputum- nor FeNO-guided treatment is recommended for the general asthma population."
- "FeNO-guided treatment significantly reduces exacerbation rates compared to guideline-based treatment, at least in children (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."

- "...in patients with a diagnosis or suspected diagnosis of asthma, FeNO can support the decision to start ICS, but cannot safely be recommended at present for deciding against treatment with ICS."

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."[71,] 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 mul, 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. 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."

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.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 15.

Table 15. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02717689[a]	A Randomised Pragmatic Trial Of Corticosteroid Optimisation In Severe Asthma Using A Composite Biomarker Algorithm To Adjust Corticosteroid Dose Versus Standard Care	300	Jun 2019 (ongoing)
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)
NCT02303600	Fractional Concentration of Exhaled NO(FENO) to Direct Montelukast Treatment of Sub-acute Cough: A Prospective, Open Label, Randomized and Placebo-Controlled Trial	200	Aug 2015 (unknown)
NCT01783132[a]	Optimization of Inhaled Corticosteroid Treatment in Adult Patients With Asthma Guided by Exhaled NO Measurement at Home	200	Dec 2014 (unknown)

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT00500253	Assessment of Utility of Exhaled Nitric Oxide Measurement for Treatment Monitoring in Children With Asthma	120	Dec 2013 (unknown)

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

Appendix

Appendix 1. Supplemental tables

Appendix Table 1. Comparison of Studies Included in Systematic Reviews of Asthma Diagnosis

Study	Wang et al (2017, 2018)[9, 10]	Karrasch et al (2017)[8]	Harnan et al (2017)[7]	NICE (2017)[6]
Arora et al (2006)	●	●	●	
Avital et al (2001)	●			
Backer et al (2014)	●		●	
Berkman et al (2005)	●			
Berlyne et al (2000)	●			●
Bobolea et al (2012)			●	
Bommarito et al (2007)	●			
Brannan et al (2013)			●	
Cardinale (2005)				●
Chancafe-Morgan et al (2013)			●	
Chatkin (1999)				●
Ciprandi (2013)				●
Cordeiro et al (2011)	●	●	●	●
De La Barra et al (2011)			●	
Deykin et al (2002)	●			●
Dupont et al (2003)	●			
ElHalawani et al (2003)		●	●	
Florentin et al (2014)	●	●		
Fortuna et al (2007)	●	●	●	
Fukuhara et al (2011)	●	●	●	●
Giovannini et al (2014)		●	●	
Grzelewski et al (2014)	●			
Hahn et al (2007)			●	
Heffler et al (2006)	●	●	●	●
Henriksen et al (2000)	●			
Hsu et al (2013)			●	
Ishizuka et al (2011)	●			
Jerzynska et al (2014)	●			
Katsoulis et al (2013)	●	●	●	

Study	Wang et al (2017, 2018)[9. 10.]	Karrasch et al (2017)[8.]	Harnan et al (2017)[7.]	NICE (2017)[6.]
Kostikas et al (2008)	●	●		●
Kowal et al (2009)		●		●
Lemiere et al (2010)	●			
Linkosalo et al (2012)		●		
Louhelainen (2008)				●
Malinovschi et al (2012)	●	●		
Martin et al (2016)	●			
Mathew et al (2011)			●	
Matsunaga et al (2011)	●			
Menzies et al (2007)	●			
Miedinger et al (2007)	●			
Miedinger et al (2009)	●			
Munnik et al (2009)	●			
Nayak et al (2013)	●			
Nickels et al (2014)			●	
Pedrosa et al (2010)	●	●	●	
Perez Tarazona et al (2011)	●			
Pizzimenti et al (2009)	●	●	●	
Prieto et al (2009)			●	
Ramser et al (2008)	●			
Sachs-Olsen et al (2010)	●			
Sastre et al (2013)			●	
Sato et al (2008)	●	●	●	●
Schleich et al (2012)	●	●	●	
Schneider et al (2009)	●		●	
Schneider et al (2013)	●	●	●	
Schneider et al (2014)	●		●	
Shimoda (2013)				●
Shome (2006)				●
Sivan et al (2009)	●	●		●
Smith et al (2004)	●	●	●	
Smith et al (2005)		●	●	
Tilemann et al (2011)		●		
Thomas et al (2005)	●			
Travers et al (2007)	●			
Voutilainen et al (2013)		●		●
Wang et al (2015)		●		
Woo et al (2012)	●	●		●
Yao et al (2011)	●			

Study	Wang et al (2017, 2018)[9, 10]	Karrasch et al (2017)[8]	Harnan et al (2017)[7]	NICE (2017)[6]
Zhang et al (2011)		●	●	
Zietkowski (2006)				●

Appendix Table 2. Comparison of Studies Included in Systematic Reviews of FeNO-Guided Therapy

Study	Wang et al (2018)[10]	Petsky et al (2016[21]); Children	Petsky et al (2016[20]); Adults
Children			
de Jongste et al (2008)	●	●	
Fritsch et al (2006)	●	●	
Peirsman et al (2014)	●	●	
Petsky et al (2015)	●	●	
Pijnenburg et al (2005)	●	●	
Pike et al (2013)	●	●	
Szefler et al (2008)	**	●	
Verini et al (2010)	●	●	
Voorend-van Bergen et al (2015)	●	●	
Adults			
Calhoun et al (2012)	●		●
Hashimoto et al (2011)	●		●
Honkoop et al (2014)	●		●
Powell et al (2011)	●		●
Szefler et al (2008)	● [a]		
Shaw et al (2007)	●		●
Smith et al (2005)	●		●
Syk et al (2013)	●		●

FeNO: fractional exhaled nitric oxide.
[a] Szefler et al (2008) was included in the adult review in Wang et al (2008). At least 75% of the participants were 16 and younger.

Appendix 2. Clinical input Respondents
Appendix Table 3. Respondent Profile

	Physician				
No.	**Name**	**Degree**	**Name of Organization**	**Clinical Specialty**	**Board Certification and Fellowship Training**
Identified by American College of Allergy, Asthma & Immunology					
1	Shepherd, Meagan W.	MD	Marshall University	Allergy/Immunology	American Board of Allergy and Immunology, American Board of Pediatrics, American Board of Internal Medicine, Fellowship training at The Ohio State University and Nationwide Children's Hospital
Identified by American Academy of Allergy, Asthma & Immunology					
2	Anonymous	MD		Pediatric Pulmonology, Allergy	

	Physician				
3	Weinberger, Miles	MD	Emeritus Professor of Pediatrics, University of Iowa Visiting Clinical Professor of Pediatrics, University of California San Diego	Pediatrics, Allergy & Clinical Immunology, Pediatric Pulmonology	Pediatrics, Allergy & Clinical Immunology, Pediatric Pulmonology

Appendix Table 4. Respondent Conflict of Interest Disclosure

No.	1. Research support related to the topic where clinical input is being sought		2. Positions, paid or unpaid, related to the topic where clinical input is being sought		3. Reportable, more than $1000, health care-related assets or sources of income for myself, my spouse, or my dependent children related to the topic where clinical input is being sought		4. Reportable, more than $350, gifts or travel reimbursements for myself, my spouse, or my dependent children related to the topic where clinical input is being sought	
	Yes/No	Explanation	Yes/No	Explanation	Yes/No	Explanation	Yes/No	Explanation
1	No		No		No		No	
2	No		No		No		No	
3	No		No		No		No	

Individual physician respondents answered at individual level. Specialty society respondents provided aggregate information that may be relevant to the group of clinicians who provided input to the Society-level response.

Appendix 3. Clinical Input Responses

Objective

Clinical input is sought to help determine whether measurement of fractional exhaled nitric oxide (FeNO) and exhaled breath condensate (EBC) in the diagnosis and management of individuals with respiratory disorders provides meaningful clinical benefit in net health outcome and whether its use is consistent with generally accepted medical practice.

Responses

Based on the totality of the evidence and your clinical experience, describe the objective indications (i.e., patient selection criteria) and management criteria (i.e., regarding prior trial of standard diagnostic or treatment options) as well as supporting rationale for clinical use of FeNO and EBC in the diagnosis and management of individuals with respiratory disorders. Note that 5 indications are prepopulated below and in questions 2 and 3. You may use the space below to list any additional indications and rationale (include a brief descriptor to add them to the list in questions 2 and 3).

No.	Indications	Response
1	Measurement of FeNO in individuals with suspected asthma	Rationale: Measurement of FeNO in addition to stereotypical symptoms including response to inhaled beta2-agonists and glucocorticoids is very useful, particularly in children, in whom a spirometry-based diagnosis of asthma cannot always be confirmed. FeNO is a

		clinically helpful tool for diagnosis of suspected asthma and a trial of appropriate treatment.
	Measurement of FeNO in individuals with suspected eosinophilic asthma	Rationale: FeNO is a clinically useful biomarker for patients with eosinophilic asthma and is practically much easier and quicker to obtain than induced sputum or bronchiolar lavage fluid to examine for the presence of eosinophils. Early identification of the appropriate asthma phenotype can decrease healthcare utilization and increase the likelihood of appropriate treatment.
	Medication management directed by FeNO in individuals with asthma	Rationale: Measurement of FeNO is often used to help determine current levels of asthma control, especially in patients who are poor perceivers of their symptoms and in patients in whom non-adherence to medical treatment is suspected. A recent study found that FeNO levels correlate with likelihood of viral-induced exacerbations, allowing for greater anticipatory guidance for loss of control of asthma during exacerbations. Additionally, studies indicate that FeNO is a useful biomarker to determine utility and efficacy of dupilumab use in severe asthmatic patients.
	Measurement of FeNO in individuals with suspected or confirmed respiratory disorders other than asthma	Rationale: Although this is not an area of disease that I treat, a search of current literature indicates that measurement of FeNO can be clinically useful for determination of disease activity and/or causation in multiple respiratory and autoimmune disorders including but not limited to interstitial lung disease and systemic lupus erythematosus.
	Measurement of exhaled breath condensate in individuals with suspected or confirmed respiratory disorders	Rationale: In addition to the above statements in the Rational section of number 4, FeNO measurement has been shown to correlate with inhaled beta2-agonist responsiveness in patients with chronic obstructive pulmonary disease.
2	Measurement of FeNO in individuals with suspected asthma	Rationale: May help determine inhaled corticosteroid (ICS) response
	Measurement of FeNO in individuals with suspected eosinophilic asthma	Rationale: May help determine ICS response
	Medication management directed by FeNO in individuals with asthma	Rationale: May help to determine ICS response
	Measurement of FeNO in individuals with suspected or confirmed respiratory disorders other than asthma	Rationale: None except eosinophilic bronchitis
	Measurement of exhaled breath condensate in individuals with suspected or confirmed respiratory disorders	Rationale: None
3	Measurement of FeNO in individuals with suspected asthma	Rationale: FeNO identifies only eosinophilic inflammation, not specifically asthma which has many phenotypes and endotypes.

	Measurement of FeNO in individuals with suspected eosinophilic asthma	Rationale: If eosinophilic asthma is otherwise demonstrated, why measure FeNO.
	Medication management directed by FeNO in individuals with asthma	Rationale: While there may be correlation, evidence for management is unconvincing.
	Measurement of FeNO in individuals with suspected or confirmed respiratory disorders other than asthma	Rationale: Nasal FeNO of value for diagnosing primary ciliary dyskinesia in presence of consistent symptoms and absence of cystic fibrosis.
	Measurement of exhaled breath condensate in individuals with suspected or confirmed respiratory disorders	Rationale: Interesting but data too limited for prime time.

For each indication prepopulated below described in question 1, please fill in the first column of the table below with each indication.

Please respond Yes or No whether this clinical use would be expected to provide meaningful clinical benefit in net health outcome.

Please use the 1 to 5 scale outlined below to indicate your level of confidence that there is adequate evidence that supports your conclusions.

No.	Indications	Yes/No	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
1	Measurement of FeNO in individuals with suspected asthma	Yes					X
	Measurement of FeNO in individuals with suspected eosinophilic asthma	Yes					X
	Medication management directed by FeNO in individuals with asthma	Yes					X
	Measurement of FeNO in individuals with suspected or confirmed respiratory disorders other than asthma	Yes				X	
	Measurement of exhaled breath condensate in individuals with suspected or confirmed respiratory disorders	No			X		

No.	Indications	Yes/No	Low Confidence	Intermediate Confidence	High Confidence
2	Measurement of FeNO in individuals with suspected asthma	Yes			X
	Measurement of FeNO in individuals with suspected eosinophilic asthma	Yes			X
	Medication management directed by FeNO in individuals with asthma	Yes			X
	Measurement of FeNO in individuals with suspected or confirmed respiratory disorders other than asthma	Yes	X		
	Measurement of exhaled breath condensate in individuals with suspected or confirmed respiratory disorders	No			X
3	Measurement of FeNO in individuals with suspected asthma	No		X	
	Measurement of FeNO in individuals with suspected eosinophilic asthma	No		X	
	Medication management directed by FeNO in individuals with asthma	No		X	
	Measurement of FeNO in individuals with suspected or confirmed respiratory disorders other than asthma	No			X

No.	Indications	Yes/No	Low Confidence		Intermediate Confidence		High Confidence
	Measurement of exhaled breath condensate in individuals with suspected or confirmed respiratory disorders	No			X		

For each indication prepopulated below described in question 1, please fill in the first column of the table below for each indication.

Please respond Yes or No whether this clinical use is consistent with generally accepted medical practice.

Please use the 1 to 5 scale outlined below to indicate your level of confidence that this clinical use is consistent with generally accepted medical practice.

No.	Indications	Yes/No	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
1	Measurement of FeNO in individuals with suspected asthma	Yes					X
	Measurement of FeNO in individuals with suspected eosinophilic asthma	Yes					X
	Medication management directed by FeNO in individuals with asthma	Yes					X
	Measurement of FeNO in individuals with suspected or confirmed respiratory disorders other than asthma	Yes				X	
	Measurement of exhaled breath condensate in individuals with suspected or confirmed respiratory disorders	No		X			
2	Measurement of FeNO in individuals with suspected asthma	Yes					X

No.	Indications	Yes/No	Low Confidence	Intermediate Confidence	High Confidence
	Measurement of FeNO in individuals with suspected eosinophilic asthma	Yes			X
	Medication management directed by FeNO in individuals with asthma	Yes		X	
	Measurement of FeNO in individuals with suspected or confirmed respiratory disorders other than asthma	No		X	
	Measurement of exhaled breath condensate in individuals with suspected or confirmed respiratory disorders	No			X
3	Measurement of FeNO in individuals with suspected asthma	No		X	
	Measurement of FeNO in individuals with suspected eosinophilic asthma	No		X	
	Medication management directed by FeNO in individuals with asthma	No			X
	Measurement of FeNO in individuals with suspected or confirmed respiratory disorders other than asthma	No			X
	Measurement of exhaled breath condensate in individuals with suspected or confirmed	No		X	

No.	Indications	Yes/No	Low Confidence	Intermediate Confidence	High Confidence
	respiratory disorders				

4. Additional comments and/or any citations supporting your clinical input on the clinical use on the use of FeNO and EBC in the diagnosis and management of individuals with respiratory disorders.

No.	Additional Comments
1	In summation, I find FeNO measurement to be relevant and of clinical value to the diagnosis and management of asthma, including identification of the eosinophilic asthma phenotype. A review of the literature also reveals utility in areas of medicine in which I do not routinely practice, such as other pulmonary disorders, autoimmune disease, and chronic obstructive pulmonary disease. The below citations were used for rationale as well as the citations listed below in Question 5. Sippel JM, Holden WE, Tilles SA, et al. Exhaled nitric oxide levels correlate with measures of disease control in asthma. J Allergy Clin Immunol. 2000 Oct;106(4):645-50. Papi A, Romagnoli M, Baraldo S, et al. Partial reversibility of airflow limitation and increased exhaled NO and sputum eosinophilia in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2000;162(5):1773.
2	I use FeNO to assess inhaled corticosteroid (ICS) response and to see if more ICS needed. I also use FeNO to help give insight if asthma is the diagnosis in difficult cases (i.e., vocal cord dysfunction, eosinophilic bronchitis, interstitial lung disease, chronic obstructive pulmonary disease, etc.) FeNO may be helpful to monitor adherence to therapy
3	Nasal FeNO is important for screening for and diagnosing primary ciliary dyskinesia, and all referral pulmonary centers should have the capability.

5. Is there any evidence missing from the attached draft review of evidence?

No.	Yes/No	Citations of Missing Evidence
1	Yes	Wenzel S, Castro M, Corren J, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting ß2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. Lancet. 2016; 388(10039):31-44. PMID: 27130691.Chung KF. Dupilumab: a potential new treatment for severe asthma. Lancet. 2016; 388(10039):3-4. PMID: 27130690.Deerojanawong J, Leartphichalak P, Chanakul A, et al. Exhaled nitric oxide, pulmonary function, and disease activity in children with systemic lupus erythematosus. Pediatr Pulmonol. 2017 May 22. Epub ahead of print. PMID: 28544706.Guilleminault L, Saint-Hilaire A, Favelle O, et al. Can exhaled nitric oxide differentiate causes of pulmonary fibrosis? Respir Med. 2013; 107(11):1789-96. PMID: 24011803.Oishi K, Hirano T, Suetake R, et al. Exhaled nitric oxide measurements in patients with acute-onset interstitial lung disease. J Breath Res. 2017; 11(3):036001. PMID: 28660859.Bjerregaard A, Laing IA, Backer V, et al. High fractional exhaled nitric oxide and sputum eosinophils are associated with an increased risk of future virus-induced exacerbations: a prospective cohort study. Clin Exp Allergy. 2017; 47(8):1007-13. PMID: 28390083.
2	No	
3	Yes	Shapiro AJ, Josephson M, Rosenfeld M, et al. Accuracy of nasal nitric oxide measurement as a diagnostic test for primary ciliary dyskinesia. A systematic review and meta-analysis. Ann Am Thorac Soc. 2017; 14(7):1184-96. PMID: 28481653.

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Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

IE
The following services may be considered investigational.

Type	Code	Description
CPT®	83987	pH; exhaled breath condensate
	94799	Unlisted pulmonary service or procedure
	95012	Nitric oxide expired gas determination
HCPCS	None	
ICD-10 Procedure	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action	Reason
03/01/2006	Committee accepted CTAF consent BCBSA TEC February 2006 Vol. 20, No. 17.	Medical Policy Committee
01/15/2010	Coding Update	Administrative Review

Effective Date	Action	Reason
10/01/2010	Policy Revision with title change from Exhaled Nitric Oxide Measurement and Monitoring as Treatment Guide in Chronic Asthma	Medical Policy Committee
09/27/2013	Policy revision without position change	Medical Policy Committee
04/30/2015	Policy title change from Exhaled Nitric Oxide and Exhaled Breath Condensate Measurement for Respiratory Disorders Policy revision without position change	Medical Policy Committee
09/01/2016	Policy title change from Measurement of Exhaled Nitric Oxide and Exhaled Breath Condensate in the Diagnosis and Management of Asthma and Other Respiratory Disorders Policy revision without position change	Medical Policy Committee
11/01/2017	Policy revision without position change	Medical Policy Committee
08/01/2018	Policy revision without position change	Medical Policy Committee
02/01/2019	Policy revision without position change	Medical Policy Committee
10/01/2019	Policy revision without position change	Medical Policy Committee

Definitions of Decision Determinations

Medically Necessary: A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.