Effective February 26, 2018
Policy Replaced by LCD L36954

BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

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

Policy #: 181
Category: Medicine

Latest Review Date: October 2017
Policy Grade: C

Background:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

Description of Procedure or Service:

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

Asthma Overview

Asthma is characterized by airway inflammation that leads to airway obstruction and hyper-responsiveness, which in turn lead to characteristic clinical symptoms including wheezing, shortness of breath, cough, and chest tightness. 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 one second (FEV-1) 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 and Exhaled Breath Condensate

Two proposed strategies are the measurement of fractional exhaled nitric oxide (FeNO) and the evaluation of exhaled breath condensate (EBC). 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. While the role of NO in asthma pathogenesis is still under investigation, 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. Several 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. Results are expressed as the NO concentration in parts per billion, based on the mean of 2 or 3 values.

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 various 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, to the more sophisticated gas chromatography/mass spectrometry or high performance liquid chromatography, depending on the component of interest.

Clinical Uses of FeNO and EBC

Measurements of FeNO have particularly been associated with an eosinophilic asthma phenotype. Eosinophilic asthma is a subtype of severe asthma associated with sputum and serum eosinophilia, along with later-onset asthma. Until recently, most asthma management strategies did not depend on the recognition or diagnosis of a particular subtype. However, 2 anti-interleukin 5 inhibitors have been approved by the Food and Drug Administration (FDA) for the treatment of severe asthma with an eosinophilic phenotype, mepolizumab and reslizumab. An anti-interleukin 4 and 13 monoclonal antibody has also been shown to improve uncontrolled asthma, with the greatest improvement observed in the subgroup of patients with the highest blood eosinophil count.

Measurement of NO and EBC has been investigated in the diagnosis and management of asthma. Potential uses in management of asthma 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 (COPD), cystic fibrosis, allergic rhinitis, pulmonary hypertension, and primary ciliary dyskinesia.

Policy:

Effective for dates of service on or after February 26, 2018 refer to LCD L36954

Effective for dates of service on or after January 24, 2014 and prior to February 26, 2018:
Blue Advantage will treat **measurement of exhaled or nasal nitric oxide** as a **non-covered** benefit and as **investigational** for the diagnosis and management of asthma and other respiratory disorders including but not limited to chronic obstructive pulmonary disease and chronic cough.

Blue Advantage will treat **measurement of exhaled breath condensate** as a **non-covered** benefit and as **investigational** for the diagnosis and management of asthma and other respiratory disorders including but not limited to chronic obstructive pulmonary disease and chronic cough.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

This evidence review has been updated regularly with a literature review using the MEDLINE database, most recently through July 21, 2017.

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.

For the assessment of FeNO in the diagnosis of asthma or other asthma subtypes, studies of diagnostic accuracy compared with standard diagnostic techniques are needed. Evaluation of diagnostic tests requires that the test findings are reproducible on test-retest and that the test is reasonably accurate compared with a validated reference standard. The diagnosis of asthma is associated with clear changes in management. For the utility of any diagnostic technique for asthma subtypes to be established, there should be established management changes associated with improved outcomes associated with that subtype.

Assessment of the clinical role of FeNO and exhaled breath condensate (EBC) tests (when used in the management of asthma or other respiratory disorders) requires controlled studies of those managed conventionally compared with those whose management is additionally directed by test measurements. Following is a summary of the key literature to date.

FeNO in Asthma Management

Analytic Validity

Reproducibility of Fractional Concentration of FeNO Measurements

In 2010, Selby et al published a study from the UK that evaluated the reproducibility of FeNO measurements in young people. The study included 494 teenagers, aged 16 to 18 years, from an unselected birth cohort and 65 asthma patients between the ages of 6 and 17 years. Paired readings were obtained from each participant. The mean within-participant difference in fractional concentration of FeNO (second reading minus the first reading) was 1.37 parts per billion (ppb) (95% confidence interval [CI], -7.61 to 10.34 ppb); this difference was statistically significant ($p<0.001$). When participants with high FeNO values (>75 ppb) were excluded, there was a lower mean within-participant difference, 0.90 ppb (95% CI, -4.89 to 6.70 ppb). Among the 71 participants with asthma, the mean within-participant difference in FeNO in the two measurements was 2.37 ppb (95% CI, -11.38 to 16.12 ppb). When FeNO values were categorized as low, normal, intermediate, or high (using different values for participants younger than age 12 years and 12 years or older), the findings were reproducible. That is, there were no statistically significant differences in the categorization using the first and second measurements.

Clinical Validity

FeNO for the Diagnosis of Asthma and Asthma Subtypes

A large number of studies have been conducted that correlate the presence of asthma with higher FeNO levels; a complete review is beyond the scope of this policy. The sensitivity and specificity of FeNO for the diagnosis of asthma is dependent on the cutoff point that is used. To date, the optimal cutoff point remains undefined; studies that report the sensitivity, specificity,

and/or the positive and negative predictive value or positive and negative likelihood ratios for FeNO with various cutoffs in the diagnosis of asthma are outlined here.

A 2017 systematic review by Karrasch et al included 26 studies (total N=4518 patients) published through November 2015 that evaluated the sensitivity and specificity of FeNO to diagnose asthma. The overall sensitivity was 65% (95% CI, 58% to 72%) with a specificity of 82% (95% CI, 76% to 86%). Specificity increased with higher cutoff values (1.46 per 10 ppb increase in cutoff), but there was no association between cutoff values and sensitivity. Nine studies were considered key, being prospective and recruiting consecutive, undiagnosed, and mostly steroid-naive patients who were not restricted to specific patient groups, and had well-defined cutoff values and an adequate reference standard. Results from some of these key studies, in order of the proposed cutoff levels, are described in Table 1.

Table 1. Prospective Studies Evaluating FeNO in Asthma Diagnosis

Study (Year)	N	Population	Criterion Standard	Proposed Cutoff, ppb	Sens, %	Spec, %
Adults						
Fortuna et al (2007)	50	Patients with suspected asthma	Lung function testing and MCh	20	77	64
Smith et al (2004)	47	Patients with symptoms suggestive of asthma referred for pulmonary function testing	Relevant symptom history and either positive bronchial hyperresponsiveness or bronchodilator response	20	88	79
Schneider et al (2013)	393	Individuals with signs/symptoms of obstructive airway disease	Bronchial provocation or bronchodilator testing	25	49	75
Cordeiro et al (2011)	114	Patients referred for allergy evaluation	Clinical evaluation and histamine challenge and/or FEV_1 improvement	27	78	92
Sato et al (2008)	71	Patients with prolonged cough	Lung function and bronchial hyperresponsiveness testing	38.8	79.2	91.3
Children						
Sivan et al (2009)	113	Children with suspected asthma not receiving ICS	Spirometry	19	86	89
Woo et al (2012)	245	Steroid-naive children with symptoms suggestive of asthma	Spirometry	22	56.9	87.2

FeNO: fractional exhaled nitric oxide; FEV1: forced expiratory volume in 1 second; ICS: inhaled corticosteroids; MCh: methacholine challenge; ppb: parts per billion; sens: sensitivity; spec: specificity.

In 2017, as part of the development of National Institute for Health and Care Excellence guidelines on the use of FeNO in the management of asthma, Harnan et al conducted a health technology assessment to assess the clinical effectiveness of FeNO measurements in people with asthma. Twenty-seven studies met their inclusion criteria for the use of FeNO in the diagnosis of asthma. Cutoff values varied from 12 to 55 ppb. Some studies suggested potential use as a rule-in or rule-out strategy. However, reviewers concluded: “Diagnostic accuracy, optimal cut-off values, and best position for [$FeNO_{50}$] within a pathway remain poorly evidenced.”

In a separate study, FeNO levels were found to be influenced by ethnicity, suggesting that different FeNO cutoffs may be needed for different ethnic groups.

FeNO for Diagnosing Eosinophilic Asthma
Although the studies outlined above reported on the diagnostic accuracy of FeNO for asthma, physiologically FeNO has been considered to be associated with eosinophilia. Eosinophilic asthma is an asthma phenotype associated with severe asthma, responsiveness to ICS, and later onset. Currently, 2 FDA-approved drugs are available to treat asthma with an eosinophilic phenotype, mepolizumab and reslizumab, which makes the identification of eosinophilic asthma of potential clinical importance.

A 2011 clinical practice guideline from the American Thoracic Society (ATS) (described in more detail and critically appraised in the section on Practice Guidelines and Position Statements) recommended FeNO cutoff values for predicting the presence of eosinophilic inflammation. Many, but not all, patients with asthma will have eosinophilic inflammation. The guidelines recommended that FeNO less than 25 ppb (<20 ppb in children) be used to indicate that eosinophilic inflammation is less likely and that FeNO greater than 50 ppb (>35 ppb in children) be used to indicate that eosinophilic inflammation is more likely. Based on their assessment of U.S. population-based normal ranges for FeNO, See and Christiani concluded that the ATS thresholds are reasonable to use for clinical decision making. However, the sensitivity and specificity of these recommended cutoffs have not been evaluated in published studies for the diagnosis of eosinophilic asthma.

In 2015, Korevaar et al published a systematic review and meta-analysis of minimally invasive markers for detection of airway eosinophilia in asthma, which included FeNO, blood eosinophils, and total immunoglobulin (Ig) E. The systematic review included 32 studies, 24 in adults and 8 in children, most of which (88% of studies in adults; 50% of studies in children) used only sputum eosinophilia as the reference standard. Other methods for determining the presence of eosinophilia were sputum or bronchoalveolar lavage in conjunction with endobronchial biopsy, or bronchoalveolar lavage alone. FeNO was compared with a criterion standard for eosinophilia in 17 studies (total N=3216 patients). In pooled analysis, FeNO was associated with an area under the ROC curve of 0.78 (95% CI, 0.74 to 0.82). For detecting sputum eosinophilia in adults, FeNO was associated with a sensitivity of 0.66 (95% CI, 0.57 to 0.75) and a specificity 0.76 (95% CI, 0.65 to 0.85).

In a study not included in the Korevaar systematic review, Westerhof et al reported on the accuracy of FeNO in predicting airway eosinophilia in 336 asthmatic patients enrolled in 3 randomized controlled trials (RCTs).37 Using a cutoff of 12.2 ppb, FeNO had a sensitivity and specificity of 0.96 (95% CI, 0.90 to 0.99) and 0.28 (95% CI, 0.22 to 0.34) respectively; using a cutoff of 64.5 ppb, FeNO had a sensitivity and specificity of 0.39 (95% CI, 0.30 to 0.49) and 0.95 (95% CI, 0.92 to 0.98), respectively.

FeNO for the Diagnosis of Asthma Subtypes
FeNO has also been studied as a way to identify particular subtypes of asthma or wheezing phenotypes, or for the identification of more severe asthma. Studies related to this indication are primarily cross-sectional studies, which are summarized in Table 2.

Table 2. Studies of FeNO for the Diagnosis of Asthma and Wheezing Subtypes

Study (Year)	Overview	Population	FeNO Cutoff, ppb	Primary Results
Oh et al (2013)	Characterized FeNO levels in different wheezing phenotypes in young children	372 children 4-6 y with and without a history of wheezing: • 67 transient wheezers • 23 persistent wheezers • 282 nonwheezers	NA	• Persistent wheezers had significantly higher FeNO than transient wheezers (14.4 ppb vs 11.5 ppb; p<0.005) and nonwheezers (14.4 ppb vs 10.1 ppb; p<0.005) • Persistent wheezers with airway hyperresponsiveness and atopy had significantly higher FeNO than wheezers without atopy (27.0 ppb vs 10.9 ppb; p<0.05) and wheezers without airway hyperresponsiveness (27.0 ppb vs 11.2 ppb; p<0.05)
Dweik et al (2010)	Used FeNO levels to characterize asthma severity	446 adults with degrees of asthma severity: • 175 with severe asthma • 271 with nonsevere asthma • 49 healthy controls	35	• Proportion of asthmatics with high FeNO did not differ between severe (40%) and nonsevere (40%) asthmatics • Asthmatics with high FeNO more likely to be atopic based on positive skin prick tests, serum IgE, and blood eosinophils • Asthmatics with high FeNO more likely to have been in ED (73% vs 66%; p=0.05) or admitted to ICU (25% vs 16%; p=0.02)
Perez-de-Llano et al (2010)	Used FeNO levels to identify patients who might respond to high-dose ICS or systemic steroids	102 patients with suboptimal asthma control treated with high-dose fluticasone plus salmeterol × 1 mo, followed by systemic steroids if ongoing poor control	30	• 53 (52%) patients gained asthma control • FeNO ≥30 ppb had sensitivity of 87.5% (95% CI, 73.9% to 94.5%) and specificity of 90.6% (95% CI, 79.7% to 95.9%) in predicting those who gained control
Matsunaga et al (2016)	Used FeNO levels to predict loss of lung function	140 patients with controlled asthma to identify cutoff point followed by 122 patients categorized with high or non-high FeNO	40	• FEV_1 was assessed every 3 mo over 3 y, FeNO >40.3 ppb had 43% sensitivity and 86% specificity for identifying patients with a rapid decline in FEV_1 (>40 mL/y)
Bjerregaard et al (2017)	Used FeNO levels to predict virus-induced exacerbations	81 patients with controlled asthma were assessed at baseline and followed for 18 mo, 18 had FeNO >25 ppb	25	• 22 (27%) experienced an exacerbation during follow-up. FeNO >25 ppb at baseline increased the risk of a virus- positive exacerbation (27% vs 12%, HR=3.4; 95% CI, 1.1 to 10.4; p=0.033)

CI: confidence interval; ED: emergency department; FeNO: fractional exhaled nitric oxide; FEV_1: forced expiratory volume in 1 second, HR: hazard ratio; ICS: inhaled corticosteroid; ICU: intensive care unit; IgE: immunoglobulin E; ppb: parts per billion.

Section Summary: FeNO for the Diagnosis of Asthma and Asthma Subtypes

Numerous studies have evaluated measurement of FeNO as an aid in the diagnosis of asthma or particular asthma subtypes. The optimal cutoff of FeNO for diagnosing asthma has varied among studies. Available studies tend to report low-to-moderate sensitivity and moderate-to-high specificity, but with variability across studies that is related to different cutoff levels used, different study populations, and different "criterion standards" for asthma diagnosis. In general, specificity increases with higher cutoff levels while sensitivity is largely unchanged, suggesting that FeNO might be used to rule-in asthma. Although ATS has issued consensus guidelines on optimal cutoffs to predict eosinophilic inflammation, these cutoffs have not been evaluated in published studies for diagnosing asthma. FeNO has been used to evaluate airway eosinophilia, and appears to have moderate diagnostic accuracy for that purpose.

FeNO for Prediction of Response to Medication Therapy for Asthma

FeNO and Response to Inhaled Corticosteroids

The largest body of evidence related to the use of FeNO in the management of asthma is in identifying eosinophilic airway inflammation and predicting response to ICS.

The 2011 clinical practice guideline from the ATS recommended the use of FeNO to determine the likelihood of response to steroids in individuals with chronic respiratory symptoms that are possibly due to airway inflammation. Data from three randomized controlled trials (RCTs) were cited in the guideline in support of this recommendation. In a 2002 open-label trial, Szefler et al randomized 30 asthma patients to one of two types of ICS. There was a higher rate of response to ICS (defined as an increase in FEV_1 of at least 15%) in individuals with higher baseline FeNO (median, 17.6 ppb) compared with lower baseline FeNO (median, 11.1 ppb). In 2005, Smith et al conducted a single-blind placebo-controlled trial of inhaled fluticasone in 60 patients presenting with undiagnosed respiratory symptoms. Steroid response was defined as an increase in FEV_1 of at least 12% or an increase in peak morning flow (over the previous seven days) of 15% or greater. In the 52 (87%) patients who completed the study, steroid response was significantly higher in patients with the highest FeNO quartile at baseline (>47 ppb) for both of the study end points. A baseline FeNO of over 47 ppb had 67% sensitivity and 78% specificity for predicting response to steroids, when response was defined as an increase in FEV_1. When response to steroids was defined as an increase in peak morning flow, there was 82% sensitivity and 81% specificity for predicting response. The third study cited in the ATS guideline in support of FeNO for predicting response to corticosteroids was published by Knuffman et al in 2009. The study was a planned post hoc analysis of data from an RCT comparing different treatment regimens in children with asthma. The authors evaluated predictors of long-term response to treatment in 191 children who received either fluticasone or montelukast. In a multivariate analysis, statistically significant predictors of a better asthma control days response to fluticasone over montelukast were a baseline FeNO of at least 25 ppb (p=0.01) and a parental history of asthma (p=0.02). All three studies found significant associations between baseline FeNO and response to ICS.

Following the publication of the ATS clinical practice guidelines, several studies addressed the association between FeNO and markers of airway inflammation and response to ICS. Anderson et al (2012) conducted a randomized crossover trial in 21 patients with persistent asthma and elevated FeNO levels (>30 ppb) receiving ICS at baseline. Following an ICS washout period,

subjects were randomized to low- or high-dose inhaled fluticasone, with a 2-week ICS washout period followed by crossover to the other arm. The primary outcome was diurnal household FeNO level measured by the NIOX MINO device. The analysis was performed on a per protocol basis. The authors reported significant improvements in FeNO levels compared with baseline for both morning and evening values, with a dose-dependent effect: morning FeNO decreased from baseline 71 ppb to 34 ppb for those receiving the lower dose ICS and to 27 ppb for those receiving the higher dose ICS; evening FeNO decreased from baseline 67 ppb to 31 ppb for those receiving the lower dose ICS and to 22 ppb for those receiving the higher dose ICS. While this study suggested that ICS dose is associated with FeNO levels, its small size limits conclusions drawn.

Visitsunthorn et al conducted a cross-sectional study to assess the relationship between FeNO measurements and asthma control in 114 children with atopic asthma. Enrolled subjects had a diagnosis of asthma based on clinical symptoms and a positive reaction to at least one aeroallergen on skin prick testing. Most of the patients had mild persistent asthma (79.8%) followed by moderate to severe persistent asthma (14.9%) and mild intermittent asthma (5.3%). Median FeNO levels were not statistically significantly different between patients with controlled, partially controlled, and uncontrolled asthma based on the Asthma Control Test (ACT). In a subgroup analysis of the 20 patients who were steroid-naïve, patients with uncontrolled asthma had higher median FeNO level than those with controlled asthma (92 ppb vs 31.8 ppb; p=0.034) and partially-controlled asthma (92 ppb vs 34.1 ppb; p=0.027), although confidence intervals around the FeNO estimates were wide.

Wilson et al investigated whether FeNO predicted loss of symptom control after the reduction of dose, 128 participants (67%) had no loss of asthma control (defined as an Asthma Control Questionnaire-5 [ACQ-5] score >0.5) or exacerbation, while 63 participants (33%) had either a loss of asthma control (N=32, 17%) or an asthma exacerbation (N=31, 16%). There was no significant difference in baseline FeNO level between those who successfully reduced their ICS dose and those who had loss of control or an exacerbation with a reduced ICD dose: geometric mean FeNO level 18.9 ppb in the stable group compared with 19.7 ppb in the unstable group (p=0.76).

FeNO and Response to Other Medications

While most studies on the predictive value of FeNO measurements relates to its use in predicting response to ICS, there has been some interest in evaluating the relationship between FeNO and other medications that target steps in the Th2-inflammation cascade. In 2013, Hanania et al evaluated the association between FeNO, along with peripheral blood eosinophil count and periostin level, in the prediction of response to omalizumab, and anti-IgE monoclonal antibody, in the management of patients with uncontrolled severe persistent asthma. The study included 850 individuals aged 12 to 75 who were randomized to treatment with omalizumab or control, of whom 394 (46.4%) had available FeNO measurements. The study predefined the median of FeNO levels as the cutoff for determining high and low subgroups: 19.5 ppb or less versus greater than 19.5 ppb. Patients with high FeNO levels (>19.5 ppb) treated with omalizumab demonstrated a 53% reduction (95% CI, 37% to 70%; p=0.001) in exacerbations compared with those treated with placebo, whereas those with low FeNO levels (≤19.5 ppb) treated with omalizumab demonstrated a nonsignificant 16% reduction (95% CI, -32 to 46; p=0.45). Similar

results were obtained in a post hoc analysis that used the ATS-recommended FeNO cutoffs to determine high and low FeNO groups.

Section Summary: FeNO for Prediction of Response to Medication Therapy for Asthma
Several studies have evaluated the association between FeNO level and response to ICS or loss of asthma control with reduction of steroid dose. These studies have been mixed in demonstrating a significant association between FeNO level and ICS response.

Efficacy of FeNO-Guided Treatment Decisions in Asthma
Systematic Reviews
In 2005, a TEC Assessment was published on exhaled NO monitoring for guiding treatment decisions in patients with chronic asthma.33 The assessment identified 2 RCTs, which did not permit conclusions regarding the use of NO monitoring to guide treatment decisions in asthma. Since the TEC Assessment, there have been a number of RCTs and systematic reviews of those RCTs examining the role of FeNO to guide treatment decisions in adults and children.

In 2016, Petsky et al published a Cochrane review on the use of FeNO to guide asthma treatment in adults. The search included 7 RCTs published up to June 2016. 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 number of people having asthma exacerbations was lower in the FeNO-guided group (odds ratio [OR], 0.60; 95% CI, 0.43 to 0.84), with a number needed to treat of 12 (95% CI, 8 to 32). Patients in the FeNO group also had a lower exacerbation rate than controls (RR=0.59; 95% CI, 0.45 to 0.77), but there was no difference between groups for exacerbations requiring hospitalization or rescue oral corticosteroids. None of the secondary outcomes (FEV1, FeNO levels, symptoms scores, or ICS doses at final visit) differed significantly between groups. Reviewers concluded that although the use of FeNO might be useful in adults who have frequent exacerbations, they could not advocate for universal use of FeNO to help guide treatment.

Petsky et al also published an updated Cochrane review of RCTs comparing adjustments of asthma medications based on FeNO levels in children in 2016. 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 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 nitric oxide 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. The number of children having one or more exacerbations was significantly lower in the FeNO groups than in the control group (OR=0.58; 95% CI, 0.45 to 0.75). However, there was no significant difference between groups in exacerbation rates. The number of children requiring oral corticosteroids was lower in the FeNO groups that 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.

Randomized Controlled Trials

The largest trial included in the Cochrane review on FeNO-based asthma management of adults was a 2015 trial by Honkoop et al. This was a cluster-randomized controlled trial comparing a FeNO-based asthma management strategy with 1 of 2 asthma-control strategies based on Asthma Control Questionnaire (ACQ) score: partial control (ACQ score, <1.5) and control (ACQ score, <0.75). The study included 611 asthmatic adults who required ICS and managed in primary care offices; they were randomized based on general practice site to one of the 3 strategies: 219 to the partial control group; 203 to the control group; and 189 to the FeNO-directed group. Subjects were assessed every 3 months for a year, and at each visit classified based on ACQ score as controlled (ACQ score, ≤0.75), partially controlled (ACQ score, >0.75 but ≤1.5), or uncontrolled (ACQ score, >1.5). FeNO-directed subjects were classified based on FeNO level: low/no inflammation for FeNO of 25 ppb or less; intermediate at 26 to 50 ppb; and high/presence of airway inflammation at greater than 50 ppb. Treatment decisions were made based on a prespecified algorithm for ICS dose increase or decrease, which was implemented with an online decision support tool. Asthma control at follow-up was significantly better in the FeNO-directed group than in the partial control group (change in ACQ score, -0.12; 95% CI, -0.23 to -0.02; p=0.02), although no significant differences were found in ACQ change score between the partial control and control strategies or between the FeNO-directed and control strategies. There were no significant differences across the groups in number of severe exacerbations. ICS dose did not significantly differ among the groups at the study's conclusion, although FeNO-directed subjects had a lower montelukast dose than control subjects (mean difference, -0.38; 95% CI, -0.74 to -0.03; p=0.04). Cost analyses were also presented, with significantly lower asthma medication costs for the partial control ($452) and FeNO-directed ($456) strategies compared with the control strategy ($4551; p≤0.04).

Another of the trials included in the Cochrane review of FeNO-guided treatment for adults was a 2012 multicenter study by Calhoun et al funded by the National Institutes of Health; it is known as the Best Adjustment Strategy for Asthma in the Long Term (BASALT) trial. The trial included 342 adults with mild-to-moderate persistent asthma that was well or partially controlled by low-dose ICS. Participants were randomized to 1 of 3 strategies for medication adjustment: (1) adjusted by physicians at clinic visits (every 6 weeks) according to National Institutes of Health clinical guidelines; (2) adjusted according to FeNO levels at clinic visits (every 6 weeks); or (3) adjusted by patients daily based on their symptoms. The third strategy involved patients using an inhaler that contained corticosteroids whenever they used a rescue inhaler. No details were provided on how steroid dose was adjusted by FeNO level. A total of 290 of 342 randomized patients completed the 9-month study; analysis was intention to treat. The primary study outcome was time to first treatment failure according to predefined criteria. The 9-month Kaplan-Meier first treatment failure rate did not differ significantly among the 3 groups. The rates were 22% (97.5% CI, 14% to 33%) in the physician-directed medication adjustment group, 20% (97.5% CI, 13% to 30%) in the FeNO medication adjustment group, and 15% (97.5% CI, 9% to 25%) in the symptom-based medication adjustment group. The failure rates in the physician-based and FeNO-based medication adjustment groups did not differ significantly (hazard ratio, 1.2; 95.5% CI, 0.6 to 2.3). An editorial accompanying publication of the BASALT trial noted that, given the trial findings, it is difficult to recommend routine monitoring of FeNO in adults with mild-to-moderate asthma.

Section Summary: Efficacy of FeNO-Guided Treatment Decisions in 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 management of asthma with and without FeNO. These studies are heterogeneous in terms of patient populations, FeNO cutoff levels, and protocols for management of 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 one exacerbation, but had no impact on day-to-day symptoms. Most of the RCTs included in these meta-analyses used a relatively low cutoff value for FeNO; in these cases, this might be expected to lead to an overall increase in ICS use among patients managed with a FeNO-based algorithm. However, it does not appear that a FeNO-based management strategy (even using relatively low FeNO cutoffs) systematically leads to an increase in ICS doses.

Respiratory Conditions Other Than Asthma

FeNO for the Diagnosis of Respiratory Disorders Other Than Asthma

Rouhos et al in Finland published a study in 2011 on repeatability of FeNO measurements in 20 patients with stable chronic obstructive pulmonary disease (COPD) and 20 healthy controls. FeNO was measured three times in each individual; a baseline measurement and measurements 10 minutes and 24 hours after baseline. In COPD patients, median FeNO values were 15.2 ppb at baseline, 17.4 ppb 10 minutes later, and 14.5 ppb 24 hours later. In healthy controls, corresponding median FeNO values were 15.6 ppb, 19.6 ppb, and 15.7 ppb. Differences between the baseline and 24-hour measurements in both groups were not statistically significant. FeNO values 10 minutes after baseline were significantly higher than the 24-hour measurement in both groups; the authors attributed this difference to the fact that patients did not rinse their mouths with sodium bicarbonate between the baseline and 10-minute measurements.

In 2014, Chou et al reported results of study to evaluate the use of FeNO measurements in predicting sputum eosinophilia in patients with COPD. The study included 90 subjects with COPD but no known history of asthma or allergic diseases. Compared with patients without sputum eosinophilia, those with sputum eosinophilia had higher FeNO levels (29 vs 18 ppb; p=0.01). In ROC analysis, a FeNO cutoff of 23.5 ppb had the highest sum of sensitivity (62.1%) and specificity (70.5%) in predicting sputum eosinophilia. After adjusting for age, sex, smoking status, serum IgE, and allergy test results, a FeNO value greater than 23.5 ppb was significantly associated with the presence of sputum eosinophilia: adjusted odds ratio 4.329 (95% CI, 1.306 to 14.356; p=0.017). The authors hypothesize that individuals with COPD with sputum eosinophilia may be likely to respond well to inhaled or oral corticosteroids.

This hypothesis is supported by an earlier study by Papi et al (2000) that found higher FeNO levels were associated with partial reversibility of airflow limitation with a bronchodilator in 20 patients with COPD. However, sputum eosinophilia levels did not correlate with reversibility of airflow in this small study.

Interstitial Lung Disease

Oishi et al evaluated whether there were differences in FeNO levels in different types of acute-onset interstitial lung disease. 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

In 2013, Guilleminault et al published a retrospective study to determine whether FeNO could differentiate causes of pulmonary fibrosis. 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) compared 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 evaluated the role of nasal NO and FeNO in the diagnosis of primary ciliary dyskinesia (PCD). 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 who are suspected of PCD.

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

A double-blind crossover trial by Dummer et al evaluated the ability of FeNO test results to predict corticosteroid response in COPD. The study included 65 patients with COPD who were 45 years or older, were previous smokers with at least a ten-pack a year history, had persistent symptoms of chronic airflow obstruction, had a post-bronchodilator FEV_1/FVC of less than 70% and a FEV_1 of 30% to 80% 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 30 mg/d of prednisone or placebo for three weeks; there was a four-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, six- minute walk distance (6MWD) and 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 (SGRQ). The correlation between baseline fraction of FeNO was not significantly correlated with change in 6MWD (r=0.10, p=0.45) or SGRQ (r=0.12, p=0.36) but was significantly related to change in FEV_1 (r=0.32, p=0.01). At the optimal fraction of FeNO cutoff of 50 ppb, as determined by ROC analysis, there was 29% sensitivity and 96% specificity for predicting a 0.2-liter increase in FEV_1. (A 0.2-liter change was considered to be 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 decide to avoid prescriptions that may be unnecessary; only about 20% of patients respond to corticosteroid treatments. Limitations of the study include that the response to treatment measured was short term, and this was not a trial of management decisions based on FeNO test results.

A prospective uncontrolled study by Prieto et al assessed the utility of FeNO measurement for predicting response to ICS in patients with chronic cough. The study included 43 patients with cough of at least eight weeks' duration who were nonsmokers and did not have a history of other lung disease. Patients were evaluated at baseline and after four weeks of treatment with inhaled fluticasone propionate 100 μg twice daily. Nineteen patients (44%) had a positive response to the treatment, defined as at least a 50% reduction in mean daily cough symptom scores. 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 is not an adequate predictor of treatment response.

Earlier prospective and retrospective studies have reported on the association between FeNO and response to ICS in COPD and other non-asthma respiratory diagnoses. A 2008 prospective study in 60 patients with severe COPD reported that patients who were considered responders to ICS had higher FeNO values (46.5 ppb) than nonresponders (25 ppb; p=0.028). 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 a variety of 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 vary by 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 were identified that compared health outcomes in patients with COPD or other respiratory diseases whose treatment was managed with and without FeNO measurement.

Exhaled Breath Condensate
It appears from the published literature that EBC is at an earlier stage of development compared with FeNO. A 2012 review by Davis et al 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 among numerous of these markers. In addition, several review articles note that before routine clinical use in the diagnosis and management of respiratory disorders can be considered, the following issues must be resolved:

- 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 criterion standard for determining absolute concentrations of airway lining fluid nonvolatile constituents to compare with EBC.
- Lack of normative values specific to each potential EBC biomarker.

EBC Markers of Asthma Severity or Control

Similar to FeNO, EBC has been associated with asthma severity. In 2013, Thomas et al conducted a systematic review of studies assessing the association components of EBC with pediatric asthma. The authors identified 46 papers that measured at least one EBC marker in asthma, allergy, and atopy in children up to age 18 years. Most studies were cross-sectional, but 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, NO, glutathione and aldehydes, hydrogen peroxide, eicosanoids (including prostaglandins and leukotrienes), and cytokines (including interleukins in the TH2 pathway and interferon gamma). The authors note 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, the authors conclude that while EBC has the potential to aid diagnosis of asthma and evaluate inflammation in pediatric asthma, further studies on EBC collection and interpretation techniques are needed.

In 2016, the same group of investigators published a qualitative systematic review assessing the relations between adult asthma and oxidative stress markers and pH in EBC. Sixteen studies met the inclusion criteria, with EBC compared between 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 (H_2O_2, n=8), and 8-isoprostane (8-isoP, n=4). Most studies were cross-sectional (n=11) and the rest were longitudinal (n=5); one was double-blinded. A variety of EBC collecting devices were used, with a custom-made condensing device used in 7 studies. The association between pH or NO and asthma varied between studies, and in 1 study, the pH in the same subjects varied by collection device. Concentrations of H_2O_2 and 8-isoP 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 are needed to evaluate the ability of EBC biomarkers to predict future asthma exacerbations and tailor asthma treatment.

EBC Markers of Asthma Severity

One study that was not included in the systematic review of adults with asthma was by Liu et al, who reported on the Severe Asthma Research Program, a multicenter study funded by the National Institutes of Health. This study had the largest sample size, with 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

Also in 2014, Navratil et al evaluated the relationship between EBC and asthma control in a cross-sectional study of 103 children (age, 6-18 years) with asthma. Subjects were enrolled from a single clinic, had an established asthma diagnosis, and were on 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 GINA 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 (EBT: uncontrolled mean EBT 34.26°C vs 33.9 °C; p=0.014). In addition, EBC urate concentration was significantly associated with time from last exacerbation (p<0.001), ACT 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 little published literature on EBC levels in patients with respiratory disorders other than asthma. A 2010 study by Antus et al evaluated EBC in 58 hospitalized patients (20 with asthma and 38 with COPD) and 36 healthy controls (18 smokers, 18 nonsmokers). The EBC pH was significantly lower in patients with asthma exacerbations (all nonsmokers) at hospital admission compared with nonsmoking controls (6.2 vs 6.4, respectively, p<0.001). The pH of EBC 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 that evaluated the role of EBC tests in the management of asthma or other respiratory disorders.

Section Summary: Exhaled Breath Condensate

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

Summary of Evidence

For individuals who have suspected asthma or suspected eosinophilic asthma who receive measurement of fractional exhaled nitric oxide (FeNO), the evidence includes multiple retrospective and prospective studies of diagnostic accuracy, along with systematic reviews of those studies. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbid events, and functional outcomes. There is a large volume of reports on the sensitivity and specificity of FeNO in asthma diagnosis. The available evidence is limited by the use of wide variability in FeNO cutoff levels used to diagnose asthma and wide variability in sensitivity and specificity for asthma diagnosis. The accuracy of the cutoffs recommended by the American Thoracic Society guidelines has not been evaluated in the diagnosis of asthma. In

addition, no studies were identified that evaluated whether use of FeNO improved the accuracy of asthma diagnosis compared with clinical diagnosis. For use of FeNO in the diagnosis of eosinophilic asthma, using the criterion standard of sputum eosinophilia, the diagnostic accuracy is moderate. 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 multiple randomized controlled trials and systematic reviews of those trials. Relevant outcomes are symptoms, change in disease status, morbid events, and functional outcomes. The available randomized controlled trials evaluating the use of FeNO tests for the management of 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 reduced the number of individuals who had more than 1 exacerbation, but had no impact on day-to-day symptoms. 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 measurement of measurement of FeNO, the evidence includes 1 crossover trial and observational studies. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbid events, and functional outcomes. The available evidence for the use of FeNO for respiratory disorders other than asthma is limited by heterogeneity in the conditions evaluated and uncertainty about the potential clinical use. 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 measurement of exhaled breath condensate (EBC), the evidence includes observational studies reporting on the association between various EBC components and disease severity. Relevant outcomes are test accuracy and 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. The evidence is insufficient to determine the effect of the technology on health outcomes.

There is less evidence on the utility of FeNO for the diagnosis and management of other respiratory disorders. There are also few studies on exhaled breath condensate (EBC) evaluation for the diagnosis and treatment of asthma and other conditions. Thus, the evidence is insufficient to determine the utility of FeNO for the management of conditions other than asthma. EBC tests for the management of any respiratory condition, and these tests are therefore considered investigational.

Practice Guidelines and Position Statements

American Thoracic Society

In 2011, the American Thoracic Society (ATS) published a clinical practice guideline on interpretation of FeNO levels. The guideline was critically appraised using criteria developed by the Institute of Medicine (IOM) which includes eight standards. The guideline was judged to not adequately meet the following standards: 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: external review.

The ATS guideline included the following strong recommendations (if not otherwise stated, the recommendations apply to asthma patients):

- We recommend the use of FENO in the diagnosis of eosinophilic airway inflammation (strong recommendation, moderate quality of evidence).
- 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 recommendation, low quality of evidence).
- We recommend accounting for age as a factor affecting FENO in children younger than 12 years of age (strong recommendation, high quality of evidence).
- 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 recommendation, moderate quality of evidence).
- 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 recommendation, moderate quality of evidence).
- 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 recommendation, low quality of evidence).
- We recommend accounting for persistent and/or high allergen exposure as a factor associated with higher levels of FENO (strong recommendation, moderate quality of evidence).
- We recommend the use of FENO in monitoring airway inflammation in patients with asthma (strong recommendation, low quality of evidence).

National Heart Lung and Blood Institute (NHLBI):
NHLBI's 2007 expert panel guidelines for the diagnosis and management of asthma state: "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)."

U.S. Preventive Services Task Force Recommendations
No U.S. Preventive Services Task Force recommendations for asthma screening or the use of NO measurements or EBC have been identified.

Key Words:

Asthma, nitric oxide, NIOX, Breathmeter, exhaled breath condensate pH, exhaled breath condensate, EBC, NIOX MINO, FeNO

Approved by Governing Bodies:

In 2003, the U.S. Food and Drug Administration (FDA) cleared for marketing the Nitric Oxide Monitoring System (NIOX®) (Aerocrine; Sweden; acquired by Circassia Pharmaceuticals, Oxford, U.K.) with 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 four, as measurement requires patient cooperation. NIOX should not be used in critical care, emergency care or in anesthesiology."

In March 2008, the NIOX MINO® was cleared for marketing by FDA through the 510(k) process. The main differences between this new device and the NIOX® are that the NIOX MINO® is handheld, portable, and unsuitable for children younger than seven years old. In November 2014, the NIOX VERO®, which differs from predicate devices in terms of its battery and display format, was also cleared for marketing by FDA through the 510(k) process.
The RTube™ Exhaled Breath Condensate collection system (Respiratory Research, Inc) and the ECoScreen EBC collection system (CareFusion, Germany) are registered with the FDA as a Class I device that collects expired gas. Respiratory Research has a proprietary gas-standardized pH assay, which, when performed by the company, is considered a laboratory-developed test.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

Current Coding:

CPT codes:

83987	pH; exhaled breath condensate
94799	Unlisted pulmonary service or procedure
95012	Nitric oxide expired gas determination

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This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.