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

### Professional
- **Original Effective Date:** October 3, 2006
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- **Current Effective Date:** June 30, 2009

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### Populations
- **Individuals:**
  - With suspected asthma

### Interventions
- Interventions of interest are:
  - Measurement of fractional exhaled nitric oxide

### Comparators
- Comparators of interest are:
  - Standard clinical diagnosis

### Outcomes
- Relevant outcomes include:
  - Test accuracy
  - Test validity
  - Symptoms
  - Change in disease status
  - Morbid events
  - Functional outcomes
Evaluation of exhaled nitric oxide (NO) and exhaled breath condensate (EBC) are proposed as techniques to diagnose and monitor asthma and other respiratory conditions. There are commercially available devices for measuring NO in expired breath and various laboratory techniques for evaluating components of EBC.

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

Background

ASTHMA OVERVIEW
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 (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, functioning, for example, to regulate peripheral blood flow, platelet function, immune reactions, and neurotransmission and to mediate 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 (ATS) and European Respiratory Society (ERS), 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$_2$O. Results are expressed as the NO concentration in parts per billion based on the mean of 2 or 3 values.

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**

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
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.\(^5\)

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, cystic fibrosis, allergic rhinitis, pulmonary hypertension, and primary ciliary dyskinesia.

**Regulatory Status**

In 2003, the Nitric Oxide Monitoring System (NIOX\(^\text{®},\) Aerocrine, Sweden acquired by Circassia Pharmaceuticals, Oxford, U.K.) was cleared for marketing by 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 March 2008, the NIOX MINO\(^\text{®}\) was cleared for marketing by FDA through the 510(k) process. The main differences between this new device and the NIOX\(^\text{®}\) are that the NIOX MINO\(^\text{®}\) is handheld, portable, and not suitable for children younger than seven years old. In November 2014, the NIOX VERO\(^\text{®}\), 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. FDA product code: MXA.

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

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

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

RATIONALE
This evidence review has been updated with searches of the MEDLINE database. The most recent literature review was performed 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. Assessment of diagnostic technology typically focuses on 3 categories of evidence: (1) technical reliability (test-retest reliability or interrater reliability); (2) clinical validity (sensitivity, specificity, positive and negative predictive values) in relevant populations of patients; and (3) clinical utility (ie, demonstration that the diagnostic information can be used to improve patient outcomes). The diagnosis of asthma is associated with clear changes in management (clinical utility). 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 utility of FeNO and exhaled breath condensate (EBC) tests (when used in the management of asthma or other respiratory disorders) is supported by 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 Concentration of FeNO Measurements
In 2010, Selby et al published a study from the U.K. that evaluated the reproducibility of FeNO measurements in young people.6 The study included 494 teenagers, ages 16 to 18 years, from an unselected birth cohort and 65 asthma patients between the ages of 6 years and 17 years. Paired readings were obtained from each participant. The mean within-participant difference in concentration of FeNO (reading 2 minus reading 1) 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 2 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 age <12 years and ≥12 years), 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 Diagnosing 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 review. 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

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>N</th>
<th>Population</th>
<th>Criterion Standard</th>
<th>Proposed Cutoff, ppb</th>
<th>Sens, %</th>
<th>Spec, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fortuna et al (2007)</td>
<td>50</td>
<td>Patients with suspected asthma</td>
<td>Lung function testing and MCh</td>
<td>20</td>
<td>77</td>
<td>64</td>
</tr>
<tr>
<td>Smith et al (2004)</td>
<td>47</td>
<td>Patients with symptoms suggestive of asthma referred for pulmonary function testing</td>
<td>Relevant symptom history and either positive bronchial hyperresponsiveness or bronchodilator response</td>
<td>20</td>
<td>88</td>
<td>79</td>
</tr>
<tr>
<td>Schneider et al (2013)</td>
<td>393</td>
<td>Individuals with signs/symptoms of obstructive airway disease</td>
<td>Bronchial provocation or bronchodilator testing</td>
<td>25</td>
<td>49</td>
<td>75</td>
</tr>
<tr>
<td>Cordeiro et al (2011)</td>
<td>114</td>
<td>Patients referred for allergy evaluation</td>
<td>Clinical evaluation and histamine challenge and/or FEV\textsubscript{1} improvement</td>
<td>27</td>
<td>78</td>
<td>92</td>
</tr>
<tr>
<td>Sato et al (2008)</td>
<td>71</td>
<td>Patients with prolonged cough</td>
<td>Lung function and bronchial hyperresponsiveness testing</td>
<td>38.8</td>
<td>79.2</td>
<td>91.3</td>
</tr>
<tr>
<td>Children</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sivan et al (2009)</td>
<td>113</td>
<td>Children with suspected asthma not receiving ICS</td>
<td>Spirometry</td>
<td>19</td>
<td>86</td>
<td>89</td>
</tr>
</tbody>
</table>
FeNO: fractional exhaled nitric oxide; FEV\textsubscript{1}: 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.\textsuperscript{15} 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\textsubscript{50}] within a pathway remain poorly evidenced.”

In a separate study, FeNO levels were found to be influenced by ethnicity,\textsuperscript{16} 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 associated with eosinophilia. Eosinophilic asthma is an asthma phenotype associated with severe asthma, responsiveness to ICS, and later onset time. 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 American Thoracic Society (ATS; see Practice Guidelines and Position Statements section) recommended FeNO cutoff values for predicting the presence of eosinophilic inflammation.\textsuperscript{17} Many 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 (2013) concluded that the ATS thresholds were reasonable for clinical decision making.\textsuperscript{18} 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.\textsuperscript{19} Reviewers 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 the pooled analysis, FeNO was associated with an area under the receiver operating characteristic (ROC) curve of 0.78 (95% CI, 0.74 to 0.82). For detecting sputum...
Measurement of Exhaled Nitric Oxide and Exhaled Breath Condensate

Eosinophilia in adults, FeNO was associated with a sensitivity of 66% (95% CI, 57% to 75%) and a specificity of 76% (95% CI, 65% to 85%).

In a study not included in the Korevaar systematic review, Westerhof et al (2015) reported on the accuracy of FeNO in predicting airway eosinophilia in 336 asthmatic patients enrolled in 3 randomized controlled trials (RCTs). Using a cutoff of 12.2 ppb, FeNO had a sensitivity and specificity of 96% (95% CI, 90% to 99%) and 28% (95% CI, 22% to 34%), respectively; using a cutoff of 64.5 ppb, FeNO had a sensitivity and specificity of 39% (95% CI, 30% to 49%) and 95% (95% CI, 92% to 98%), respectively.

**FeNO for Diagnosing Asthma or Wheezing Subtypes**

FeNO has also been studied as a way to identify particular subtypes of asthma or wheezing phenotypes, or identify more severe asthma. Studies related to this indication are primarily cross-sectional studies; they are summarized in Table 2.

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

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Overview</th>
<th>Population</th>
<th>FeNO Cutoff, ppb</th>
<th>Primary Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oh et al (2013)(^{21})</td>
<td>Characterized FeNO levels in different wheezing phenotypes in young children</td>
<td>372 children 4-6 y with and without a history of wheezing:</td>
<td>NA</td>
<td>Persistent wheezers had significantly higher FeNO than transient wheezers (14.4 ppb vs 11.5 ppb; p&lt;0.005) and nonwheezers (14.4 ppb vs 10.1 ppb; p&lt;0.005) and Persistent wheezers with airway hyperresponsiveness and atopy had significantly higher FeNO than wheezers without atopy (27.0 ppb vs 10.9 ppb; p&lt;0.05) and wheezers without airway hyperresponsiveness (27.0 ppb vs 11.2 ppb; p&lt;0.05)</td>
</tr>
<tr>
<td>Dweik et al (2010)(^{22})</td>
<td>Used FeNO levels to characterize asthma severity</td>
<td>446 adults with degrees of asthma severity:</td>
<td>35</td>
<td>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)</td>
</tr>
</tbody>
</table>
### Section Summary: FeNO for Diagnosing Asthma Eosinophilic 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 Predicting Response to Medication Management for Asthma

#### FeNO and Response to ICS

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 guidelines from ATS recommended the use of FeNO to determine the likelihood of response to steroids in individuals with chronic respiratory symptoms possibly due to...
airway inflammation.\textsuperscript{17} Data from 3 RCTs were cited in the guideline to support this recommendation. In a 2002 open-label trial, Szefler et al randomized 30 asthma patients to 1 of 2 types of ICS.\textsuperscript{26} There was a higher rate of response to ICS (defined as an increase in forced expiratory volume in 1 second \((\text{FEV}_1)\) 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.\textsuperscript{27} Steroid response was defined as an increase in \(\text{FEV}_1\) of at least 12\% or an increase in peak morning flow (over the previous 7 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 a sensitivity of 67\% and a specificity of 78\% for predicting response to steroids, when response was defined as an increase in \(\text{FEV}_1\). When response to steroids was defined as an increase in peak morning flow, there was a sensitivity of 82\% and a specificity of 81\% for predicting response. The third study cited by ATS was published by Knuffman et al (2009).\textsuperscript{28} It 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 fluticasone or montelukast. In a multivariate analysis, a baseline FeNO of at least 25 ppb \((p=0.01)\) and a parental history of asthma \((p=0.02)\) were statistically significant predictors of a better asthma control days response to fluticasone over montelukast. All 3 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.\textsuperscript{29} 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 (2014) conducted a cross-sectional study to assess the relation between FeNO measurements and asthma control in 114 children with atopic asthma.\textsuperscript{30} Enrolled subjects had a diagnosis of asthma based on clinical symptoms and a positive reaction to at least 1 aeroallergen on skin prick test. Most patients had mild persistent asthma (79.8\%) followed by moderate-to-severe persistent asthma (14.9\%) and mild intermittent asthma (5.3\%). The median FeNO levels did not differ statistically significantly among patients with controlled, partially controlled, and uncontrolled asthma based on the Asthma Control Test. In a subgroup analysis of the 20 patients who were steroid-naive, patients with uncontrolled asthma had higher median FeNO levels 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 (2014) investigated whether FeNO could predict loss of symptom control after the reduction of ICS dose in a cohort of 191 well-controlled asthmatic patients. Following 50% reduction in ICS dose, 128 (67%) participants had no loss of asthma control (defined as an ACQ-5 score >0.5) or exacerbation, while 63 (33%) participants 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 vs 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 measurement relate to its use in predicting response to ICS, there has been interest in evaluating the relation between FeNO and other medications that target steps in the T-helper type 2 (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 ages 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 vs 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 Predicting Response to Medication Management for Asthma
Several studies have evaluated the association between FeNO levels and response to ICS or loss of asthma control with a reduction of steroid dose. These studies have been inconsistent in demonstrating a significant association between FeNO levels and ICS response or anti-IgE monoclonal antibody therapy.

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. 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

Contains Public Information
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 2016.35 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, FEV1, 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.36 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 Diagnosing Respiratory Disorders Other Than Asthma

Chronic Obstructive Pulmonary Disease
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 3 times in each patient: 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 on results on the use of FeNO measurements in predicting sputum eosinophilia in patients with COPD.\(^{40}\) 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 IgE, and allergy test results, a FeNO value greater than 23.5 ppb was significantly associated with the presence of sputum eosinophilia (adjusted OR=4.329; 95% CI, 1.306 to 14.356; \(p=0.017\)). The authors hypothesized 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.\(^{41}\) However, sputum eosinophilia levels did not correlate with reversibility of airflow in this small study.

**Interstitial Lung Disease**

Oishi et al (2017) evaluated whether there were differences in FeNO levels in different types of acute-onset interstitial lung disease.\(^{42}\) 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.\(^{43}\) 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 (2014) evaluated the role of nasal NO and FeNO in the diagnosis of primary ciliary dyskinesia (PCD).\(^{44}\) 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 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.\(^{45}\) 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 FEV₁/forced vital capacity of less than 70%, and a FEV₁ 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 6 months were excluded. Treatments, given in random order, were 30 mg/d of prednisone 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 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 3 primary outcomes (6-minute walk distance [6MWD], FEV₁) 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 FeNO did not correlate significantly with change in 6MWD (r=0.10, p=0.45) or SGRQ score (r=0.12, p=0.36), but was significantly related to change in FEV₁ (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 FEV₁. (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 unnecessary prescriptions; only about 20% of patients responded to corticosteroid treatments. Limitations of the study 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.46 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. 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.

Earlier prospective and retrospective studies have reported on the association between FeNO and response to ICS in COPD and other nonasthma 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).47 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 (eg, 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 than 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 across numerous markers. 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:

- 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 airway lining fluid nonvolatile constituents to compare with EBC
- Lack of normative values specific to each potential EBC biomarker.

EBC Markers of Asthma

Similar to FeNO, EBC has been associated with asthma severity. In 2013, Thomas et al conducted a systematic review of studies assessing the association between components of EBC and pediatric asthma. 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, 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 (pH), NO, glutathione and aldehydes, hydrogen peroxide, eicosanoids (including prostaglandins and leukotrienes), and cytokines (including interleukins in the Th2 pathway and interferon gamma). The authors 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, the authors 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 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 (H₂O₂, 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 H₂O₂ 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 (2011), 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
In 2014, Navratil et al evaluated the relation between EBC and asthma control in a cross-sectional study of 103 children (age range, 6-18 years) with asthma. 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 2010 study by Antus et al evaluated EBC in 58 hospitalized patients (20 with asthma, 38 with COPD) and 36 healthy controls (18 smokers, 18 nonsmokers). 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: 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 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 variability in FeNO cutoff levels used to diagnose asthma, and by 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. Also, no studies were identified that evaluated whether the use of FeNO improved the accuracy of asthma diagnosis compared with clinical diagnosis. For the 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 FeNO, the evidence includes a 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 assessing 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 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. 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 evidence is insufficient to determine the effect of the technology on health outcomes.

Practice Guidelines and Position Statements

National Institute for Health and Care Excellence
In 2014, the National Institute for Health and Care Excellence issued guidance on the use of fractional exhaled nitric oxide (FeNO) in the management of asthma, based on the results of a
health technology assessment.\cite{58} The guidance, based on the 2012 British guidelines on asthma management, stated:

1.1 “Fractional exhaled nitric oxide (FeNO) testing is recommended as an option to help diagnose asthma in adults and children:
- who, after initial clinical examination, are considered to have an intermediate probability of having asthma … and
- when FeNO testing is intended to be done in combination with other diagnostic options…

“Further investigation is recommended for people whose FeNO test result is negative because a negative result does not exclude asthma.

1.2 “FeNO measurement is recommended as an option to support asthma management … in people who are symptomatic despite using inhaled corticosteroids.”

**American Thoracic Society**

In 2011, the American Thoracic Society published practice guidelines on interpretation of FeNO levels.\cite{17} The guidelines were critically appraised using criteria developed by the Institute of Medicine, which includes 8 standards.\cite{59} 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: external review.

Table 3 lists American Thoracic Society guidelines recommendations on management of patients with asthma.

**Table 3. Guidelines on Management of Patients With Asthma**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>SOR</th>
<th>QOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>“We recommend the use of FENO in the diagnosis of eosinophilic airway inflammation”</td>
<td>Strong</td>
<td>Moderate</td>
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<tr>
<td>“We recommend the use of FENO in determining the likelihood of steroid responsiveness in individuals with chronic respiratory symptoms possibly due to airway inflammation”</td>
<td>Strong</td>
<td>Low</td>
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<tr>
<td>“We recommend accounting for age as a factor affecting FENO in children younger than 12 years of age”</td>
<td>Strong</td>
<td>High</td>
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<tr>
<td>“We recommend that low FENO less than 25 ppb (&lt; 20 ppb in children) be used to indicate that eosinophilic inflammation and responsiveness to corticosteroids are less likely”</td>
<td>Strong</td>
<td>Moderate</td>
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<tr>
<td>“We recommend that FENO greater than 50 ppb (&gt; 35 ppb in children) be used to indicate that eosinophilic inflammation and, in symptomatic patients, responsiveness to corticosteroids are likely”</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>“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”</td>
<td>Strong</td>
<td>Low</td>
</tr>
<tr>
<td>“We recommend accounting for persistent and/or high allergen exposure as a factor associated with higher levels of FENO”</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>“We recommend the use of FENO in monitoring airway inflammation in patients with asthma”</td>
<td>Strong</td>
<td>Low</td>
</tr>
</tbody>
</table>

FENO: fractional exhaled nitric oxide; QOE: quality of evidence; SOR: strength of recommendation.
**European Respiratory Society and American Thoracic Society**

In 2014, the European Respiratory Society and the American Thoracic Society released joint guidelines on the management of severe asthma, which made the following recommendations about the use of FeNO to manage severe asthma:

- We suggest that clinicians do not use FeNO to guide therapy in adults or children with severe asthma (conditional recommendation, very low quality evidence).

A 2009 statement included the following key points on exhaled nitric oxide:

“...The clinical utility of FeNO-based management strategies has not been explored extensively. Currently available evidence suggests a role in identifying the phenotype in airways disease, particularly in the identification of corticosteroid responsiveness. Due to logistic and cost issues, FeNO is the only biomarker likely to have a role in primary care-based asthma studies, although it is possible that with technological improvements, other techniques including sputum induction could have a role in the medium term.”

**National Heart Lung and Blood Institute**

The National Heart Lung and Blood Institute’s 2007 expert panel guidelines for 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).”

**U.S. Preventive Services Task Force Recommendations**

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

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 4.

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<td>NCT00500253</td>
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<td>NCT00961155</td>
<td>Usefulness of Exhaled Breath Condensate and FENO for Evaluation of Markers of Airway Inflammation in Children With Asthma</td>
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<td>NCT01783132a</td>
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<td>NCT02303600</td>
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<td>NCT02294279a</td>
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<td>360</td>
<td>Aug 2016 (completed)</td>
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</table>

NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.

**CODING**

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

**CPT/HCPCS**

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

- There is a CPT code specific to direct determination of exhaled nitric oxide (eg, using the NIOX system): 95012.
- There is also a CPT code to describe the collection of exhaled breath condensate with measurement of the pH: 83987.
- 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.

**Diagnoses**

Experimental / Investigational for all diagnoses related to this medical policy.
## REVISIONS

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<td>01-01-2010</td>
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<td>• Removed CPT Codes: 0064T, 0140T</td>
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<td>• To be clearer, the policy wording was split from one policy statement reading:</td>
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<td>&quot;Measurement of exhaled or nasal nitric oxide, or collection and analysis of exhaled breath condensate, is considered experimental / investigational in the diagnosis and management of asthma and other respiratory disorders.&quot;</td>
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<tr>
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<td>to two separate policy statements, reading:</td>
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<td>&quot;A. Measurement of exhaled or nasal nitric oxide is considered investigational in the diagnosis and management of asthma and other respiratory disorders including but not limited to chronic obstructive pulmonary disease and chronic cough.</td>
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<td></td>
<td>B. Measurement of exhaled breath condensate is considered investigational in the diagnosis and management of asthma and other respiratory disorders including but not limited to chronic obstructive pulmonary disease and chronic cough.&quot;</td>
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<td>• Added CPT code: 94799</td>
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<td>Revised Title from &quot;Exhaled Nitric Oxide and Exhaled Breath Condensate pH Measurement for Respiratory Disorders&quot; to &quot;Measurement of Exhaled Nitric Oxide and Exhaled Breath Condensate in the Diagnosis and Management of Asthma and Other Respiratory Disorders&quot;</td>
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<td>06-10-2015</td>
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<td>• In Item A removed &quot;or nasal&quot; to read &quot;Measurement of exhaled nitric oxide...&quot;</td>
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<td>This change did not impact the intent of the policy.</td>
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<td>01-18-2017</td>
<td>Title revised to &quot;Measurement of Exhaled Nitric Oxide and Exhaled Breath Condensate in the Diagnosis and Management of Respiratory Disorders&quot; from &quot;Measurement of Exhaled Nitric Oxide and Exhaled Breath Condensate in the Diagnosis and Management of Asthma and Other Respiratory Disorders&quot;</td>
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REFERENCES


38. O'Connor GT, Reibman J. Inhaled corticosteroid dose adjustment in mild persistent asthma [editorial]. JAMA. Sep 12 2012;308(10):1036-1037. PMID 22968893


