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

Effective: February 1, 2017

Next Review: January 2018
Last Review: January 2017

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Exhaled nitric oxide (NO) and exhaled breath condensate measurements are techniques proposed for diagnosing and managing asthma and other respiratory disorders.

MEDICAL POLICY CRITERIA

I. Measurement of exhaled or nasal nitric oxide is considered investigational in the diagnosis and management of respiratory disorders, including but not limited to asthma, chronic obstructive pulmonary disease and chronic cough.

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

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.
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. Guidelines for the management of persistent asthma stress the importance of long-term suppression of inflammation using steroids, leukotriene inhibitors, or other anti-inflammatory drugs. Existing techniques for monitoring the status of underlying inflammation have focused on bronchoscopy, with lavage and biopsy, or analysis by induced sputum. Given the cumbersome nature of these techniques, the ongoing assessment of asthma focuses not on the status of the underlying chronic inflammation, but rather on regular assessments of respiratory parameters such as forced expiratory volume in 1 second and peak flow. Therefore, there has been interest in noninvasive techniques to assess the underlying pathogenic chronic inflammation as reflected by measurements of inflammatory mediators.

FRACTIONAL EXHALED NITRIC OXIDE 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, eg, 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 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 H2O.[1] 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 phenotype, mepolizumab and reslizumab.

A 2015 Cochrane review compared the evidence for mepolizumab and placebo for asthma. The review included 8 studies (total N=1707 patients). One randomized controlled trial (RCT) used FeNO as 1 potential criterion for eosinophilic asthma (Pavord et al, 2012). In another RCT, the criteria for eosinophilic asthma was a prior diagnosis of eosinophilic asthma or evidence of eosinophilic inflammation, but criteria for the diagnosis are not provided (Ortega et al, 2014). Overall, the Cochrane review concluded: “It is not possible to draw firm conclusions from this review with respect to the role of mepolizumab in patients with asthma. Our confidence in the results of this review are limited by the fact that the intravenous route is not currently licensed for mepolizumab, and the evidence for the currently licensed subcutaneous route is limited to a single study in participants with severe eosinophilic asthma.”

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®; Aerocrine, Sweden; acquired by Circassia Pharmaceuticals, Oxford, U.K.) was cleared for marketing by the U.S. Food and Drug Administration (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® 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 not suitable for children younger than age 7 years. 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. FDA product code: MXA.

The RTube™ Exhaled Breath Condensate collection system (Respiratory Research) 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.

**EVIDENCE SUMMARY**

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**

**Reproducibility of 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, 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.
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 review. The sensitivity and specificity of FeNO for the diagnosis of asthma depends on the cutoff point used. 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.

In 2013, See and Christiani published an evaluation of reference ranges for FeNO evaluated with the NIOX MINO for a representative sample of the U.S. population ages 6 to 80 years derived from the National Health and Nutrition Examination Survey (NHANES, 2007-2010).[10] They reported that the range of FeNO values (5th-95th percentile) was 3.5 to 36.5 ppb for children younger than age 12 years and 3.5 to 39 ppb for those 12 to 80 years of age. They concluded that a reasonable upper limit of "normal" values for FeNO, as represented by 95% of the general population is 36 ppb for children younger than age 12 years and 39 ppb for older individuals.

In 2016, Guo et al published a systematic review and meta-analysis of prospective studies reporting on the diagnostic accuracy of FeNO for asthma.[11] The authors identified 25 studies (total N=3983 subjects). In meta-analysis, the pooled sensitivity and specificity were 72% (95% CI, 70% to 74%) and 78% (95% CI, 76% to 80%), respectively, with significant heterogeneity ($I^2=77.9$; $p<0.05$). The pooled diagnostic odds ratio (OR) was 15.92 (95% CI, 10.70 to 23.68), with an area under the receiver operating characteristic (ROC) curve of 0.88.

In 2015, Li et al published a meta-analysis of the diagnostic accuracy of FeNO for asthma, which included 21 studies reported in 19 publications, with a total sample size of 4691 (2269 with asthma).[12] Studies used a wide range of FeNO cutoffs, ranging from 7 to 46 ppb. In a random-effects model, the pooled sensitivity of FeNO for asthma diagnosis was 0.78 (95% CI, 0.76 to 0.80; $I^2=94.7$%) and the pooled specificity was 0.74 (95% CI, 0.72 to 0.76; $I^2=94.7$%). The pooled diagnostic OR for FeNO was 11.37.

A large number of retrospective and prospective studies have reported on the diagnostic accuracy of FeNO for asthma. Some studies reporting the sensitivity and specificity of FeNO in the diagnosis of asthma are summarized in Table 1.

Table 1: Studies Evaluating FeNO in Asthma Diagnosis

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Population</th>
<th>Criterion Standard</th>
<th>Proposed Cutoff</th>
<th>Sens</th>
<th>Spec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maniscalco et al</td>
<td>52</td>
<td>Patients with chronic cough</td>
<td>Lung function testing and MCh</td>
<td>33 ppb</td>
<td>92%</td>
<td>88%</td>
</tr>
<tr>
<td>Arga et al (2015)</td>
<td>116</td>
<td>Patients with diagnosis of asthma on</td>
<td>Hyperresponsiveness to AMP</td>
<td>33.3 ppb</td>
<td>78.4%</td>
<td>74.8%</td>
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<td></td>
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<td>clinical history and evidence of</td>
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<td></td>
<td>reversible airway obstruction on</td>
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<td></td>
<td></td>
<td>spirometry</td>
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<tr>
<td>Buslau et al (2014)</td>
<td>73</td>
<td>Subjects with allergic rhinitis and no</td>
<td>Bronchial allergy provocation testing</td>
<td>18.05 ppb</td>
<td>74.4%</td>
<td>61.1%</td>
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<td></td>
<td></td>
<td>history of asthma</td>
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<tr>
<td>Florentin et al (2014)</td>
<td>178</td>
<td>Adults in bakery or hairdressing</td>
<td>Diagnosis of occupational asthma: clinical evaluation,</td>
<td>25 ppb</td>
<td>42.1%</td>
<td>92.4%</td>
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<tr>
<td></td>
<td></td>
<td>industries</td>
<td>peak-flow monitoring.</td>
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<tr>
<td>Study</td>
<td>N</td>
<td>Population</td>
<td>Criterion Standard</td>
<td>Proposed Cutoff</td>
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<td>Spec</td>
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<td>See above</td>
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<td>See above</td>
<td>spirometry, work-related specific IgE assays</td>
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<tr>
<td>Jerzynska et al (2014)</td>
<td>389</td>
<td>Children with atopy and allergic rhinitis</td>
<td>Physical exam and improved FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>23 ppb</td>
<td>90%</td>
<td>52%</td>
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<tr>
<td>Schneider et al (2014)</td>
<td>302</td>
<td>Subset of above with follow-up to 1 y</td>
<td>Bronchial provocation or bronchodilator testing</td>
<td>26 ppb</td>
<td>47%</td>
<td>73.1%</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 ppb</td>
<td>49%</td>
<td>75%</td>
</tr>
<tr>
<td>109</td>
<td></td>
<td>Subgroup with symptoms but no neutrophilia on induced sputum</td>
<td>See above</td>
<td>23 ppb</td>
<td>67%</td>
<td>77%</td>
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<tr>
<td>Jerzynska et al (2014)</td>
<td>389</td>
<td>Children with atopy and allergic rhinitis</td>
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<td></td>
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<td>See above</td>
<td>23 ppb</td>
<td>67%</td>
<td>77%</td>
</tr>
<tr>
<td>Katsoulis et al (2013)</td>
<td>112</td>
<td>Individuals 25-37 y with asthma-like symptoms (based on 1 positive answer on 12-item questionnaire) and negative bronchodilation testing</td>
<td>Clinical diagnosis by respiratory specialist</td>
<td>17 ppb (current smokers)</td>
<td>56.3%</td>
<td>82.5%</td>
</tr>
<tr>
<td>Malinovschi et al (2012)</td>
<td>282</td>
<td>Ages 14-44 y with signs/ symptoms suggestive of asthma</td>
<td>Mannitol challenge</td>
<td>15 ppb (never smokers)</td>
<td>77.8%</td>
<td>63.5%</td>
</tr>
<tr>
<td>Sverrild et al (2013)</td>
<td>180</td>
<td>Unselected individuals 14-24 y with no history of smoking or ICS use</td>
<td>MCh</td>
<td>25 ppb</td>
<td>86%</td>
<td>84%</td>
</tr>
<tr>
<td>Malinovschi et al (2012)</td>
<td>282</td>
<td>Ages 14-44 y with signs/ symptoms suggestive of asthma</td>
<td>Clinical diagnosis by respiratory specialist</td>
<td>17 ppb (current smokers)</td>
<td>56.3%</td>
<td>82.5%</td>
</tr>
<tr>
<td>Schleich et al (2012)</td>
<td>174</td>
<td>Individuals with suspected asthma referred for MCh</td>
<td>Positive MCh</td>
<td>34 ppb</td>
<td>35.4%</td>
<td>95.4%</td>
</tr>
<tr>
<td>Malinovschi et al (2012)</td>
<td>282</td>
<td>Ages 14-44 y with signs/ symptoms suggestive of asthma</td>
<td>Clinical diagnosis by respiratory specialist</td>
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<td>174</td>
<td>Individuals with suspected asthma referred for MCh</td>
<td>Positive MCh</td>
<td>34 ppb</td>
<td>35.4%</td>
<td>95.4%</td>
</tr>
<tr>
<td>Woo et al (2012)</td>
<td>245</td>
<td>Steroid-naive children with symptoms suggestive of asthma</td>
<td>Clinical evaluation and histamine challenge and/or FEV&lt;sub&gt;1&lt;/sub&gt; improvement</td>
<td>27 ppb</td>
<td>78%</td>
<td>92%</td>
</tr>
<tr>
<td>Cordeiro et al (2011)</td>
<td>114</td>
<td>Patients referred for allergy evaluation</td>
<td>Positive MCh</td>
<td>40 ppb</td>
<td>78.6%</td>
<td>89.5%</td>
</tr>
<tr>
<td>Pedrosa et al (2010)</td>
<td>114</td>
<td>Individuals ≥14 y with symptoms consistent with asthma but normal spirometry and negative bronchodilator challenge</td>
<td>Symptoms and 2 of the following: reversible airflow limitation; airway hyperresponsiveness; sputum eosinophilia</td>
<td>40 ppb</td>
<td>78%</td>
<td>92%</td>
</tr>
<tr>
<td>Malinovschi et al (2012)</td>
<td>282</td>
<td>Ages 14-44 y with signs/ symptoms suggestive of asthma</td>
<td>Clinical diagnosis by respiratory specialist</td>
<td>17 ppb (current smokers)</td>
<td>56.3%</td>
<td>82.5%</td>
</tr>
<tr>
<td>Ciprandi et al (2010)</td>
<td>280</td>
<td>Children with asthma, allergic rhinitis, or both</td>
<td>Positive MCh</td>
<td>40 ppb</td>
<td>74.3%</td>
<td>72.5%</td>
</tr>
<tr>
<td>Schneider et al (2009)</td>
<td>160</td>
<td>Individuals with symptoms suggestive of asthma</td>
<td>Stepwise testing, including spirometry, bronchodilator challenge, and MCh</td>
<td>46 ppb</td>
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<tr>
<td>101</td>
<td></td>
<td>Subgroup with symptoms of asthma but normal spirometry</td>
<td>Positive MCh</td>
<td>46 ppb</td>
<td>35%</td>
<td>90%</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 ppb</td>
<td>86%</td>
<td>89%</td>
</tr>
<tr>
<td>Sato et al (2008)</td>
<td>71</td>
<td>Patients with prolonged cough</td>
<td>Spirometry</td>
<td>19 ppb</td>
<td>86%</td>
<td>89%</td>
</tr>
<tr>
<td>Fortuna et al (2007)</td>
<td>50</td>
<td>Patients with suspected asthma</td>
<td>Spirometry</td>
<td>19 ppb</td>
<td>86%</td>
<td>89%</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 ppb</td>
<td>88%</td>
<td>79%</td>
</tr>
<tr>
<td>Study</td>
<td>N</td>
<td>Population</td>
<td>Criterion Standard</td>
<td>Proposed Cutoff</td>
<td>Sens</td>
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<tr>
<td>Chatkin et al (1999) [34]</td>
<td>105</td>
<td>Adults with chronic cough (n=38), known asthmatics (n=44), healthy controls (n=23)</td>
<td>Clinical evaluation and albuterol response and/or MCh 30 ppb (for chronic cough)</td>
<td>75%</td>
<td>87%</td>
<td></td>
</tr>
</tbody>
</table>

AMP: adenosine 5′-monophosphate; FeNO: fractional exhaled nitric oxide; FEV1: forced expiratory volume in 1 second; ICS: inhaled corticosteroids; IgE: immunoglobulin E; MCh: methacholine challenge; sens: sensitivity; spec: specificity.

In 2013, as part of the development of National Institute for Health and Care Excellence (NICE) guidelines on the use of FeNO in the management of asthma (see Practice Guidelines and Position Statements section), Harnan et al conducted a health technology assessment to assess the clinical and cost-effectiveness of FeNO measurements in people with asthma. [35] They identified 24 studies that met their inclusion criteria for use of FeNO in the diagnosis of asthma. The authors concluded: “Given the wide ranging estimates of sensitivity and specificity, together with heterogeneous cut-off points, it is difficult to draw any firm conclusions as to the diagnostic accuracy of FeNO in any situation and at any given cut-off point.”

**FeNO for the Diagnosis of 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 American Thoracic Society (ATS; see Practice Guidelines and Position Statements section) recommended FeNO cutoff values for predicting the presence of eosinophilic inflammation. [36] 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 for clinical decision making. [10] 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. [37] 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).[38] 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 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</th>
<th>Overview</th>
<th>Population</th>
<th>FeNO Cutoff</th>
<th>Primary Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oh et al (2013)[39]</td>
<td>Characterized FeNO levels in different wheezing phenotypes in young children</td>
<td>372 children 4-6 y with and without history of wheezing: • 67 transient wheezers • 23 persistent wheezers • 282 nonwheezers</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) • 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)[40]</td>
<td>Used FeNO levels to characterize asthma severity</td>
<td>446 adults with various degrees of asthma severity: • 175 with severe asthma • 271 with nonsevere asthma • 49 healthy controls</td>
<td>35 ppb</td>
<td>• Proportion of asthmatics with high FeNO did not differ between severe (40%) and nonsevere asthmatics (40%) • 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>
<tr>
<td>Perez-de-Llano et al (2010)[41]</td>
<td>Used FeNO levels to identify patients who may respond to high-dose ICS or systemic steroids</td>
<td>102 patients with suboptimal asthma control treated with high-dose fluticasone/salmeterol × 1 mo, followed by systemic steroids if ongoing poor control</td>
<td>30 ppb</td>
<td>• 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 95.3%) in predicting those who gained control</td>
</tr>
</tbody>
</table>

ED: emergency department; FeNO: fractional exhaled nitric oxide; ICS: inhaled corticosteroid; ICU: intensive care unit; IgE: immunoglobulin E.

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

Numerous studies have evaluated measurement of FeNO as a tool to 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 wide variability across studies that may be related to different cutoff levels used, different study populations, and different “criterion standards” for asthma diagnosis. ATS has issued consensus guidelines on optimal cutoffs to predict eosinophilic inflammation, but 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 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 guideline 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.[36] 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.[42] There was a higher rate of response to ICS (defined as an increase in forced expiratory volume in 1 second (FEV₁) 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.[43] Steroid response was defined as an increase in FEV₁ 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 FEV₁. 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 in 2009.[44] 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, 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 3 studies found significant associations between baseline FeNO and response to ICS.

Following publication of the ATS clinical practice guideline, several studies addressed the association between FeNO and markers of airway inflammation and response to ICS. Anderson et al conducted a randomized crossover trial in 21 patients with persistent asthma and elevated FeNO levels (>30 ppb) receiving ICS at baseline.[45] 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. 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.

In 2014, Malinovschi et al conducted a retrospective observational study in 153 beclomethasone-treated asthmatic subjects to evaluate whether baseline FeNO measurements are associated with response to therapy.[46] Patients were previously steroid-naive and were treated with ICS according to Global Initiative for Asthma (GINA) guidelines. At follow-up, asthma control (response to therapy) was assessed with the French version of the Asthma Control Questionnaire (ACQ) and spirometry. Asthma inflammation was classified by FeNO based on ATS guidelines into normal (FeNO <25 ppb), intermediate (FeNO ≥25 but <50 ppb), or high (≥50 ppb). Compared with those in the low-inflammation group, a higher proportion of subjects in the groups with intermediate- and high-inflammation achieved an improvement on the ACQ of at least 1 point (p=0.02 for high- vs low-inflammation group, p=0.004 for intermediate- vs low-inflammation group; proportions presented in graphical form but point estimates not provided). In multiple logistic regression analysis, having intermediate (vs low) and high (vs low) FeNO-estimated inflammation were significantly associated with the likelihood of having an ACQ improvement of at least 1 point (adjusted OR [AOR], 7.63 [95% CI, 1.65 to 35.3] for intermediate vs low; AOR=4.10 [95% CI, 1.10 to 15.2] for high vs low).

Visitsunthorn et al conducted a cross-sectional study to assess the relation between FeNO measurements and asthma control in 114 children with atopic asthma.[47] Enrolled subjects had a diagnosis of asthma based on clinical symptoms and a positive reaction to at least 1 aeroallergen on skin prick test (SPT). Most 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 did not differ statistically significantly among 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-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 investigated whether FeNO could predict loss of symptom control after the reduction of ICS dose in a cohort of 191 well-controlled asthmatic patients.[48] Following 50% reduction in ICS dose, 128 participants (67%) had no loss of asthma control (defined as an 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 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 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 levels and response to ICS or loss of asthma control with reduction of steroid dose. These studies have been inconsistent in demonstrating a significant association between FeNO levels 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. The assessment identified 2 RCTs, both published in 2005. Smith et al reported that equivalent outcomes (eg, exacerbations, pulmonary function) were achieved in the group managed using exhaled NO measurements compared with the group managed using conventional guidelines. However, the FeNO group used lower doses of ICS at the end of the study. Pijnenburg et al found similar changes in steroid dose and FEV1 levels in groups managed with and without FeNO measurements. Bronchial hyperreactivity (an intermediate outcome) improved more in the FeNO group. The TEC Assessment concluded that the available evidence did not permit the conclusion that use of NO monitoring to guide treatment decisions in asthma leads to improved outcomes.

In 2012, Petsky et al published a meta-analysis of RCTs evaluating the use of tailoring asthma treatment based on levels of eosinophilic markers (FeNO or sputum eosinophils) or on clinical symptoms (with or without spirometry/peak flow). The study combined 2 Cochrane reviews including a 2009 review on FeNO. Updated literature searches were not performed. As in the 2009 Cochrane review, the 2012 review identified 6 RCTs on FeNO. In addition to the 2 RCTs previously described in the TEC Assessment, the studies were Shaw et al (2007), Fritsch et al (2006), Szefer et al (2008), and de Jongste et al (2009). Four of the studies included children or adolescents, 1 included only adults, and the sixth included both adolescents and adults. Two studies were double-blind and 4 were single-blind. Five studies used hospital-based FeNO measurements, and 1 used a portable at-home NO analyzer. Four studies measured FeNO at a flow rate of 50 milliliters per second. In 2016, Petsky and colleagues published two updated Cochrane reviews focused on medication management in pediatric and asthmatics based on FeNO testing. The reviews included additional RCTs published since the previous Cochrane studies, and concluded that although subgroups within
each population may have reduced exacerbation throughout the study duration, overall daily symptoms or inhaled corticosteroid use was not impacted. Therefore, the authors stated additional well-designed RCTs are needed.

The primary outcome of the meta-analysis was the difference in the number of patients in each group who had asthma exacerbations during follow-up. When findings for the 2 FeNO studies that included adults and/or adolescents were pooled (Shaw et al [2007], Smith et al [2005]), there was no significant difference in the number of patients experiencing an exacerbation (OR=0.85; 95% CI, 0.30 to 2.43). There was also no significant difference in symptom scores (mean difference [MD], -0.10; 95% CI, -0.33 to 0.12). Findings from 3 of the 4 pediatric trials were pooled, Pijnenburg et al (2005), Szefler et al (2008), and de Jongste et al (2009). As with the adult studies, there was no significant difference in the number of patients experiencing an exacerbation (OR=0.75; 95% CI, 0.55 to 1.01). A pooled analysis of 2 of the pediatric studies (Pijnenburg et al [2005], Szefler et al [2008]) did not find a significant difference in symptom scores between patients managed with and without FeNO measurement (MD=0.13; 95% CI, -0.32 to 0.57).

However, there were statistically significant differences between groups in the final dose of ICS, although the direction of this relationship differed in adults and children. In adults, those who had their medication doses adjusted based on FeNO levels had a significantly lower final dose of ICS than those in the control group (pooled analysis of 2 studies: MD = -450 μg budesonide equivalent; 95% CI, -677 to -223 μg). In contrast, children in the FeNO group had a significantly higher dose of ICS compared with the control group (pooled analysis of 3 studies, MD=140 μg; 95% CI, 29 to 251 μg).

In the 2013 Harnan technology assessment that evaluated the clinical and cost-effectiveness of FeNO measurements in people with asthma (previously described), the authors conducted a systematic review of the efficacy of FeNO-guided management of asthma based on RCTs published since the previous systematic reviews. The authors identified 4 studies in adults. In pooled analysis, there was no significant difference between subjects managed with FeNO and control subjects in terms of major/severe exacerbation rates (pooled rate ratio, 0.87 [favored FeNO]; 95% CI, 0.64 to 1.19). However, for the composite outcome of all exacerbations, FeNO-based management was associated with reduced exacerbation rates (pooled rate ratio, 0.58 [favored FeNO]; 95% CI, 0.43 to 0.77). For pooled analysis of ICS use, the authors noted high heterogeneity among studies, but reported no statistically significant differences in mean ICS (standardized mean difference [SMD], -0.24 [favored FeNO]; 95% CI, -0.56 to 0.07). Results were heterogeneous.

The authors identified 5 studies in children. Among the 4 studies that reported on asthma exacerbations or treatment failures, all reported fewer exacerbations or treatment failures in the FeNO-managed groups, although the differences were statistically significant in only 1 study. While most studies provided some information about ICS use, the authors concluded: “The effects on ICS use were heterogeneous, with two studies showing a statistically significant increase in ICS use, one showing no difference, one being difficult to interpret and one further study not reporting this outcome.”
In 2016, Gomersal et al published a systematic review of FeNO in the routine management of childhood asthma, as part of the overall health technology assessment previously described. Seven studies that included children, adolescents, and/or young adults were selected. The authors stated that the quality of the literature varied. Studies differed in outcomes reported. However, most (n=6) reported on all exacerbations or treatment failures; with 2 exceptions, most studies reported fewer exacerbations in the FeNO group, but not always with statistically significant differences. All studies reported on between-group differences in ICS usage, with variability across studies in whether patients increased or decreased ICS use.

In 2015, Lu et al reported on a systematic review and meta-analysis of RCTs comparing a FeNO-based asthma management strategy with a conventional treatment strategy in children with asthma. Six studies were selected, 5 of which were included in the Harnan technology assessment, with a total of 507 patients in the FeNO groups (range, 22-276 patients) and 511 patients in the control groups (range, 25-270 patients). For the 3 studies reporting on change in FeNO from baseline, the SMD between did not differ significantly between groups (-0.10 [favored control]; 95% CI, -0.31 to 0.12; p=0.369). For the 4 studies reporting on the percent change in FEV1 from baseline, the SMD between also did not differ significantly between groups (0.07 [favored FeNO]; 95% CI, -0.07 to 0.20; p=0.323). All 6 studies reported on the percent change in ICS use and the percentage of subjects experiencing at least 1 exacerbation (although the time period over which exacerbation frequencies were measured was not specified). The SMD between groups for ICS was 0.57 (95% CI, -0.67 to 1.8; p=0.369). The event rate for more than 1 exacerbation over the study period was significantly lower for the FeNO group (OR=0.690; 95% CI, 0.532 to 0.895; p=0.005).

Randomized Controlled Trials

Since the Petsky systematic reviews, no additional RCTs evaluating the use of FeNO as part of an asthma management strategy have been identified.

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 numerous 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 group. A 2012 meta-analysis of 6 RCTs did not find significantly improved outcomes (eg, lower rates of asthma exacerbations, lower symptom scores) when medication dose was tailored to FeNO level. In contrast, a subsequent meta-analysis found statistically significant reductions in asthma exacerbations in patients managed with FeNO measurements. RCTs in various populations published since 2012 have had mixed findings. Two RCTs, including a large multicenter NIH-funded trial, found no benefit for a FeNO-based management strategy. Four RCTs, 1 in adults, 2 in children, and 1 in pregnant women, found lower rates of asthma exacerbations in subjects managed with an algorithm that included FeNO measurement compared with an algorithm without FeNO. An additional RCT demonstrated improvements in asthma control with a FeNO-based management approach compared with clinical management targeting “partial control,” although the approach was not compared with clinical management targeting complete control. Most of the RCTs use 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.\(^6\) FeNO was measured 3 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 on the use of FeNO measurements in predicting sputum eosinophilia in patients with COPD.\(^3\) 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 (AOR=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.

Boon et al evaluated the role of FeNO in the diagnosis of primary ciliary dyskinesia (PCD) 226 patients, 38 individuals with PCD, 49 healthy controls, and 139 individuals with other respiratory diseases.\(^5\) A definitive diagnosis of PCD was made by structural and functional evaluation of the cilia on a nasal or bronchial biopsy. Using a FeNO cutoff of 10 ppb, with lower values predictive of PCD, the sensitivity for PCD diagnosis was 89.5%, with a specificity of 58.3%.

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.\(^6\) The study 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 assessed the utility of FeNO measurement for predicting response to ICS in patients with chronic cough.[67] The study included 43 patients with cough of at least 8 weeks in duration who were nonsmokers without a history of other 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).[68] However, an optimal FeNO cutpoint to discriminate between responders and nonresponders could not be determined.

In a 2007 retrospective study in 64 patients with chronic cough who had FeNO measured, Hahn et al reported that the subset of patients (n=41) who had FeNO levels of 35 ppb or greater had reduction in in their chronic cough with ICS therapy (likelihood ratio for positive response, 4.9; 95% CI, 2.2 to 10.9).[69] In contrast, the 23 patients without elevated FeNO levels, 91% had no improvement in chronic cough frequency.

**Efficacy of FeNO-Guided Treatment Decisions in Respiratory Conditions Other Than Asthma**
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 that on 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 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 between components of EBC and pediatric asthma. The authors 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, 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.

Among adults, a number of studies have been published on components of EBC and their relationship with asthma severity. In 2011, Liu et al evaluated the Severe Asthma Research Program, a multicenter study funded by NIH. 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).

In 2012, Piotrowski et al in Poland prospectively studied adult patients with asthma.[77] The study included 27 patients with severe asthma receiving treatment (group 1), 16 newly diagnosed and never-treated asthma patients (group 2), and 11 health controls (group 3). At baseline and at weeks 4 and 8, EBC was collected and patients underwent spirometry and other tests of asthma severity. Patients took all medications needed to control symptoms throughout the study. Levels of 8-isoprostane (8-IP) in breath condensate were analyzed. At baseline, the median level of 8-IP was 4.67 pg/mL, 6.93 pg/mL, and 3.80 pg/mL in groups 1, 2, and 3, respectively. There were no statistically significant differences among groups in 8-IP levels. In addition, 8-IP levels did not correlate significantly with asthma severity measures, including the number of symptom-free days, FEV1 reversibility, and scores on the ACT. In this study, 8-IP levels in EBC were not a useful marker of asthma severity.

In 2014, Keskin et al evaluated the relation between 2 EBC components, cysteinyl leukotrienes (Cys-LTs) and 8-IP, in asthma control among 30 children with asthma.[78] Included patients had a diagnosis of asthma and had been in a stable condition, free from acute exacerbations and respiratory tract infections for the 2 months prior to the EBC evaluation. Asthma control was evaluated with the childhood ACT and by pediatric allergists. Of the entire group, 19 subjects had mild persistent asthma, while 11 had moderate persistent asthma. EBC 8-IP levels were higher in those with moderate persistent asthma (114.0 pg/mL) than in those with mild persistent asthma (52 pg/mL; p=0.05), and higher in those with more than 4 exacerbations per year (114 pg/mL) than in those who had 1 to 4 exacerbations per year (52 pg/mL; p<0.05). Cys-LTs levels were not significantly associated with asthma exacerbation frequency or asthma severity.

Also 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.[79] 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 (uncontrolled mean EBT, 34.26°C vs controlled mean EBT, 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.

Van Vliet et al evaluated whether the combination of FeNO and EBC inflammatory markers (including interleukin [IL] 1α, IL-5, IL-6, IL-8, IL-13, IL-17 and tumor necrosis factor α) predicted asthma exacerbations in a cohort of 102 children ages 6 to 18 years.[80] Ninety-six subjects were included in the analysis. The authors generated 3 predictive models for asthma exacerbations based on EBC components and clinical factors, using a k-nearest neighbor algorithm. The areas under the ROC curves for the 3 models were 0.465, 0.543, and 0.585, respectively.
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, 38 with COPD) and 36 healthy controls (18 smokers, 18 nonsmokers).[81] 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 at discharge. Similarly, pH values in EBC samples from smoking COPD patients (n=21) at admission and discharge did not differ significantly from smoking controls.

Other small studies have reported on the feasibility of using EBC in the diagnosis or recognition of other respiratory conditions, including radiation pneumonitis after stereotactic ablative radiotherapy (N=26).[82]

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. Uncontrolled studies include a 2009 case series investigating whether components of EBC could predict response to steroid treatment in patients with asthma.[83] Eighteen steroid-naive asthma patients were included; EBC collection, spirometry, and methacholine challenge were performed before and 12 weeks after ICS therapy (equivalent daily dose of fluticasone propionate 400 µg). Among the molecules in EBC examined, higher IL-4 and RANTES (regulated on activation normal T cell expressed and secreted) levels and lower 10-IP levels at baseline correlated with an improvement in FEV1. The study had a small sample size, was uncontrolled, and did not address whether EBC measurement could improve patient management or health outcomes.

Section Summary: Exhaled Breath Condensate

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 is insufficient to form conclusions on the utility of EBC for any indication.

PRACTICE GUIDELINE SUMMARY

AMERICAN THORACIC SOCIETY/EUROPEAN RESPIRATORY SOCIETY

The 2009 American Thoracic Society/European Respiratory Society (ERS/ATS) statement on standardizing endpoints for clinical asthma trials and clinical practice includes the following key points on exhaled NO:[84]
“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.”[84]

In 2013, the ERS/ATS published guidelines on the Definition, Evaluation, and Treatment of Severe Asthma, and concluded:[85]

“(C)linicians do not use FeNO to guide therapy in adults or children with severe asthma.” Remarks related to this guideline indicate that, “this recommendation places a higher value on avoiding additional resource expenditure and a lower value on uncertain benefit from monitoring FeNO.” The ERS/ATS also note that the evidence related on the use of FeNO to guide therapy in patients with severe asthma is of low quality.

NATIONAL HEART LUNG AND BLOOD INSTITUTE

The 2007 National Heart Lung and Blood Institute (NHLBI) expert panel guidelines for the diagnosis and management of asthma state:[86]

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

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

AMERICAN THORACIC SOCIETY PRACTICE GUIDELINE: INTERPRETATION OF EXHALED NITRIC OXIDE LEVELS (FENO) FOR CLINICAL APPLICATIONS

Although the 2011 ATS guideline includes some form of evidence review, the recommendations in the guideline appear to be based on consensus rather than evidence.[87] All recommendations included in the guideline are classified as either strong or weak, and levels of evidence in support of the specific recommendations are graded as low, moderate, or high. However, in many instances, the strength of evidence is not reflected in the strength of the recommendation. For example, use of FeNO in the diagnosis of eosinophilic airway inflammation is strongly recommended based on moderate quality evidence. In addition, use of FeNo is strongly recommended in determining the likelihood of steroid responsiveness in
individuals with chronic respiratory symptoms possibly due to airway inflammation; however the level of evidence for this recommendation is categorized as low.

The ATS guideline was identified in a recent report from the Institute of Medicine (IOM) as not adequately meeting several standards that trustworthy guidelines must meet. Specifi
cally, the ATS guideline failed to adequately establish the evidence foundation for and rate the strength of their recommendations. The goal of IOM recommended standards is to enhance the quality and reliability of clinical practice guidelines.

**SUMMARY**

More research is needed to know if or how well measurement of exhaled or nasal nitric oxide impacts patient management decisions or how decisions based on measurement results lead to improved patient outcomes related to respiratory disorders, including but not limited to asthma. This does not mean that it does not work, but more research is needed to know. There is less research on exhaled breath condensate for the diagnosis and management of asthma and other respiratory disorders. No clinical guidelines based on research recommend exhaled or nasal nitric oxide measurement, or exhaled breath condensate measurement for people with respiratory disorders. Therefore, the use of exhaled or nasal nitric oxide, and exhaled breath condensate tests for the diagnosis and management of respiratory disorders, including but not limited to asthma, is considered investigational.

**REFERENCES**


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88. 2011. PMID: 24983061

### CODES

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*Date of Origin: March 2004*