# Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 3/1/25**
**(See policy history boxes for previous effective dates)**

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

## Description/Background

### ASTHMA

Asthma is characterized by a variety of symptoms that lead to expiratory airflow obstruction. Asthma may be also caused by airway inflammation which contributes to obstruction and hyper-responsiveness in the large and small bronchioles which in turn leads to characteristic clinical symptoms wheezing, shortness of breath, cough, and chest tightness [1]. Routine surveillance of asthma has focused more on respiratory parameters, such as forced expiratory volume over one second ( FEV1 ) and peak flow values, which measure the volume of rapidly exhaled air rather than assess underlying inflammation. A sex difference also exists in asthma prevalence – in children, asthma is more common in males, whereas among adults, females more likely than men to have an asthma diagnosis.

### *Cough Variant*

Individuals with 'cough-variant asthma' usually have persistent cough as their only symptom, associated with airway hyperresponsiveness. It is often more problematic at night. Lung function may be normal, and documentation of variability in lung function is important. Cough-variant asthma must be distinguished from eosinophilic bronchitis in which individuals have cough and sputum eosinophilia but normal spirometry and airway responsiveness.[1]

### *COPD Overlap*

Asthma-COPD Overlap and Asthma + COPD are terms used to collectively describe individuals who have persistent airflow limitation together with clinical features that are consistent with both asthma and COPD.[1]

## Eosinophilic Asthma

Eosinophilic Asthma is a subtype of asthma that often causes severe asthma. It is commonly seen in people who develop asthma in adulthood, but it can be seen in children and young adults. In eosinophilic asthma, the numbers of eosinophils are increased in blood, lung tissue, and mucus coughed up from the respiratory tract (known as sputum)[2]. The whole respiratory tract is involved in airflow obstruction from the sinuses to the small or distal airways.

## MANANGEMENT

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

## Fractional Exhaled Nitric Oxide

One proposed strategy is the measurement of fractional exhaled nitric oxide (FeNO). Nitric oxide (NO) is an important endogenous messenger and inflammatory mediator that is widespread in the human body, with functions including the regulation of peripheral blood flow, platelet function, immune reactions, neurotransmission, and the mediation of inflammation. individuals with asthma have been found to have high levels of FeNO, which decreases with treatment with corticosteroids. In biologic tissues, NO is unstable which limits its measurement. However, in the gas phase, NO is fairly stable, permitting its measurement in exhaled air flow. Fractional exhaled NO is typically measured during single breath exhalations. First, the subject inspires NO-free air via a mouthpiece until total lung capacity is achieved, followed immediately by exhalation through the mouthpiece into the measuring device. Devices measuring FeNO are commercially available in the U.S. According to a joint statement by the American Thoracic Society and European Respiratory Society (2009), there is a consensus that FeNO is best measured at an exhaled rate of 50 mL per second maintained within 10% for more than 6 seconds at an oral pressure between 5 and 20 cm H2O. [3] Results are expressed as the NO concentration in parts per billion.

## Exhaled Breath Condensate

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

## Clinical Uses of Fractional Exhaled Nitric Oxide and Exhaled Breath Condensate

Measurement of FeNO has been associated with an eosinophilic asthma phenotype. Until recently, most asthma management strategies did not depend on the recognition or diagnosis of a particular subtype. However, anti-interleukin 5 agents have been approved by the U.S.

Food and Drug Administration (FDA) for the treatment of severe asthma with an eosinophilic phenotype. Anti-interleukin-4 and -13 monoclonal antibody has also been shown to improve uncontrolled asthma.

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

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## Regulatory Status

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

**Table 1. FeNO Devices Cleared by FDA**

| Device | Manufacturer | Indication/Comments | Date Cleared | 510(k) |
|---|---|---|---|---|
| Nitric Oxide Monitoring System (NIOX®) | Aerocrine; acquired by Circassia | "[Measurements …FE-NO provide the physician with means of evaluating an asthma individual's response to anti- inflammatory therapy, as an adjunct to established clinical and laboratory assessments in asthma. NIOX should only be used by trained physicians, nurses, and laboratory technicians. NIOX cannot be used with infants or by children approximately under the age of 4, as measurement requires patient cooperation. NIOX should not be used in critical care, emergency care or in anesthesiology." | 2003 | De novo DEN030001 K021133 |
| NIOX MINO® | Aerocrine; acquired by Circassia | Same as above except used for ages 7 and older. Handheld and portable. | 2008 | K072816/KI101034 |
| NIOX VERO® | Aerocrine; acquired by Circassia | Same as MINO®. Differs from predicate devices in terms of its battery and display format | 2014 | K133898 |

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|---|---|---|---|---|
| Fenom Pro™ Nitric Oxide Test | Spirosure | Measurement of FeNO by Fenom Pro™ is a method to measure the decrease in FeNO concentration in asthma individuals that often occurs after treatment with anti-inflammatory pharmacological therapy as an indication of therapeutic effect in individuals with elevated FeNO levels. FeNO measurements are to be used as an adjunct to be established clinical assessments. Fenom Pro™ is suitable for children, approximately 7-17 years, and adults 18 years and older. Testing using the Fenom Pro™ should only be done in a point-of-care healthcare setting under professional supervision. Fenom Pro™ should not be used in critical care, emergency care or in anesthesiology. | 2019 | K182874 |
| NObreath® | Bedfont Scientific Ltd | Measurement of FeNO by NObreath is a method to measure the decrease in FeNO concentration in asthma patients that often occurs after treatment with anti-inflammatory pharmacological therapy, as an indication of the therapeutic effect in patients with elevated FeNO levels. NObreath is intended for children who are 7-17 years and adults. NObreath 12-second test mode is for ages 7 and up. NObreath 10-second test mode is for ages 7-10, only if successful completion of a 12-second test is not possible. The NObreath cannot be used with infants or by children under the age of 7 as measurement requires patient cooperation. NObreath should not be used in critical care, emergency care, or in anesthesiology. | 2021 | K203695 |
| Vivatmo pro | Bosch Healthcare Solutions GmbH | "Vivatmo pro nitric oxide test is a portable, non-invasive device to measure FeNO in human breath. FeNO is increased in some airway inflammatory processes, such as asthma, and often decreases in response to anti-inflammatory treatment. Measurement of FeNO by Vivatmo pro is a method to measure the decrease in FeNO concentration in asthma patients that often occurs after treatment with anti-inflammatory pharmacological therapy as an indication of therapeutic effect in patients with elevated FeNO levels. FeNO measurements are to be used as an adjunct to established clinical assessments. Vivatmo pro is suitable for children, approximately 7 to 17 years, and adults 18 years and older. Testing using the Vivatmo pro should only be done in a point-of-care healthcare setting under professional supervision. Vivatmo pro should not be used in critical care, emergency care or in anesthesiology." | 2024 | K233775 |

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

The RTube™ Exhaled Breath Condensate collection system (Respiratory Research) and the ECoScreen EBC collection system (CareFusion) are registered with 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.

## Medical Policy Statement

Measurement of fractional exhaled nitric oxide is considered **established** in the diagnosis of mild, moderate, or severe asthma and the management of asthma when criteria are met.

Measurement of fractional exhaled nitric oxide in the diagnosis and management of other respiratory disorders such as asthma variants (ex: eosinophilic asthma, cough variant asthma and asthma-COPD Overlap syndrome) is considered **established** when criteria are met.

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

The clinical utility of exhaled breath condensate in the diagnosis and management of respiratory disorders including asthma has not been demonstrated. In addition, there is insufficient evidence that the use of this test improves health outcomes.

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## Inclusionary and Exclusionary Guidelines

**Inclusions:**
**Diagnosis of Asthma:**

Measurement of fractional exhaled nitric oxide (ie, FeNO) is considered medically necessary. It is covered when used as an adjunctive test to aid in the diagnosis of asthma using spirometry for individuals with suspected mild, moderate, severe asthma or asthma variants.

**Management of Asthma:**
Measurement of fractional exhaled nitric oxide (ie,FeNO) in individuals with an established diagnosis of mild, moderate, or severe asthma or asthma variants is considered medically necessary and is established when used for any of the following purposes:

- Evaluation of response to anti-inflammatory treatment
- Monitoring compliance with anti-inflammatory treatment
- Aid with identification of underlying inflammatory phenotype or identification of inflammatory phenotypes to guide with the appropriate therapy.

**Exclusions:**

Measurement of fractional exhaled nitric oxide (ie,FeNO) for the diagnosis and management of other respiratory disorders including, but not limited to, chronic obstructive pulmonary disease (COPD) and chronic cough, is considered experimental/investigational. The safety and efficacy of these procedures have not been shown to improve clinical health outcomes.

Measurement of exhaled breath condensate in the diagnosis and management of asthma and other respiratory disorders including but not limited to chronic obstructive pulmonary disease

and chronic cough is considered experimental/investigational. The safety and efficacy of these procedures have not been shown to improve clinical health outcomes.

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## CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

### ***Established codes:***

95012

### ***Other codes (investigational, not medically necessary, etc.):***

83987

*Note: Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.*

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## Rationale

### FRACTIONAL EXHALED NITRIC OXIDE IN ASTHMA DIAGNOSIS

#### Clinical Context and Test Purpose

The purpose of FeNO testing in pediatric and adult individuals who have suspected asthma is to aid in diagnosis and management of asthma.

National Heart, Lung, and Blood Institute (NHLBI) guidelines have suggested clinicians confirm the following to establish the diagnosis of asthma: [4] presence of episodic symptoms of airflow obstruction or hyperresponsiveness; [4] reversibility of airflow obstruction; and [6] exclusion of alternative diagnoses.[5]

Couillard, Laugerud (2022)[6] A major goal of current asthma management is the reduction of asthma attacks. This study derives a risk scale predicting asthma attacks based on the blood eosinophil count and exhaled nitric oxide (FENO). Biomarker-stratified trials level attack rates were pulled from the control arms of the Novel START, CAPTAIN, QUEST, Benralizumab Phase 2b, PATHWAY, STRATOS 1-2 and DREAM trails (n=3021). These results were used to develop rates ratios and the predicted asthma attack rate for different groups of individuals. The risk scale shows a potential to predict asthma attacks which could be prevented by anti-inflammatory treatment. The studies show an importance of biomarkers in strength and are additive to the independent risk seen with more established risk factors as a history of an attack in the previous year and Global Initiative for Asthma (GINA) treatment steps. In four out of the five studies, the predictive value of blood eosinophils and FeNO were additive.

Biomarkers utilizing blood eosinophils and FENO are identified as providing additive prognostic information that is predictable as both biomarkers provide different and helpful information for management of asthma. Each of the five clinical trials features the predicted annual asthma

attack rate for each scenario if there was no change in asthma management. The predicted asthma attack ranges from 0.06 to 2.60 per year, and they are comparable to observed attack rates in the derivation trial control individuals. FeNO reflects airway type 2 inflammatory activity and the chemotactic pull to the airways, This chemotactic pull draws inflammatory cells into the airways which contributes to airflow obstruction. Blood eosinophils reflect the systemic pool of available effector cells and circulating interleukin 5. However, symptom scores don't necessarily correlate with airway inflammation or with airflow obstruction. The hypothesis needs to be tested, and it also important that the scale is refined using individual's data from large and well-characterized populations. The goal is for these biomarkers to predict which persons have severe asthma and for those in this same group, who would benefit from anti-inflammatory therapies using this protype risk scale.

Couillard, Pavord (2022)[7] FeNO and blood eosinophils relate to different components and compartments of type-2 inflammation, with FENO reflecting the chemotactic pull (magnet) to the airways and blood eosinophils reflecting the systemic pool of available eosinophils (bomb). When both occur together, the risk of asthma attacks (bomb detonating) is particularly high". Type 2 airway inflammation is driven by an adaptive and innate immune response caused by episodic alarmin mediated signaling. FeNO reflects airway type activity and is represented by the chemotactic pull into the airways (the magnet), whereas blood eosinophils reflect the systemic pool of available effector cells and circulating IL-5 (the bomb explosion of chemical mediators). The consequence of type-2 inflammation is airflow limitation due to airway mucus plugging, airway wall edema, airway smooth muscle hyperplasia, and the induction of airway hyperresponsiveness.

In the same Couillard, Pavord[7] commentary it continues to emphasize that individuals with a FeNO-predominant biomarker profile with ICS (inhaled corticosteroid) -resistant inflammation where stratified as a magnet predominant profile, might respond best to a biologic that targets relevant airway mucosal processes such as anti-TSLP or anti-IL 4 receptor (dupilumab). In contrast, individuals with a 'bomb' profile and a blood eosinophil-predominant biomarker profile would respond best to biologics targeting IL-5, there is support for this concept. FeNO and blood eosinophils therefore relate to different components and compartments of type-2 inflammation. FeNO reflects airway type-2 inflammation: FeNO reflects airway type-2 activity and the chemotactic pull to the airways (the magnet), whereas blood eosinophils reflect the systemic pool of available effector cells and circulating IL-5 (the bomb). In the randomized clinical trials, raised values of baseline FeNO and blood eosinophils act together to predict asthma attacks in the placebo arm. An excess risk which is entirely removed with the implementation of type-2 targeted anti-inflammatory therapy.

Fricker et al (2017)[8] evaluated current biomarkers in difficult to manage asthma individuals. Measures improving adherence to therapy, optimizing current treatment, guiding the selection of new targeted biomarker therapies are some of the potential uses of these biomarkers in individuals with severe asthma. Multiple markers of type 2 inflammation have been developed, including eosinophils in sputum and blood, exhaled NO, serum IgE and perisostin. Although these all-show promise in guiding the selection of interventions for refractory type 2 inflammation in asthma, and in determining if the desired response is being achieved, it is becoming clear that different biomarkers reflect distinct components of the complex type 2 inflammatory pathways. In summary, elevated FeNO, and serum periostin are present in a subset of asthmatic individuals and correlate with beneficial responses to ICS in mild forms of asthma. However, in severe asthma, these type 2 inflammatory markers, such as peripheral

eosinophils, have individually been associated with more frequent exacerbations, which has been a guiding principle of clinical trial study design for type 2 targeting biologics. Clinical studies, along with results from type 2 targeting biologics, suggest that individual type 2 biomarkers may provide unique information relating to asthma phenotype.

**Asthma: Diagnosis, monitoring, and asthma management.**
Sher et al (2022)[9] Phase 3 trial: Despite the availability of biologics, many individuals with severe asthma still require chronic oral corticosteroids (OCSs) to maintain asthma control. However, chronic OCS use is limited in preventing exacerbations or sustaining lung function improvement and carries known systemic side effects. Therefore, a need exists for asthma therapies that can improve asthma control while also leading to a durable OCS reduction effect. The aim of this analysis was to evaluate the maintenance of OCS reduction and clinical efficacy among individual individuals treated with dupilumab who are OCS-dependent. They completed the VENTURE study and were enrolled in the TRAVERSE study. Many individuals with severe asthma require chronic corticosteroid treatment to maintain asthma control. The LIBERTY ASTHMA TRAVERSE study was a multinational, multicenter, single-arm, open-label extension study in individuals ≥ 12 of age with asthma who participated in previous dupilumab studies. Treatment consisted of dupilumab 300 mg every 2 weeks for up to 96 weeks. In this analysis, the data is presented from individuals who were initially enrolled in the LIBERTY ASTHMA VENTURE study. RESULTS: Ninety individuals treated with dupilumab/dupilumab and 97 individuals treated with placebo/dupilumab in the VENTURE study were enrolled and treated in the TRAVERSE study, with a mean OCS dosage of 11.0 mg/d (dupilumab) and 11.6 mg/d (placebo) at VENTURE study baseline. At TRAVERSE week 0, the mean daily OCS dosage was 3.1 mg/d and 6.4 mg/d (percentage decrease from the VENTURE study baseline, 68.8% and 41.3%) for the dupilumab/ dupilumab group and placebo/dupilumab group, respectively, and decreased to 2.2 mg/d and 4.9 mg/d (78.3% and 53.4%) at week 48 and to 1.2 mg/d and 3.0 mg/d (89.3% and 74.4%) at week 96, respectively. Exacerbation rates were low during the TRAVERSE study. Further improvements from the VENTURE to TRAVERSE studies also were seen in improvements in the FEV1 metric and 5-item Asthma Control Questionnaire scores. Safety findings were consistent with the known dupilumab safety profile. In conclusion, the study demonstrated that in a population with severe asthma and chronic OCS dependence at patient safety baseline (PSBL), long-term exposure to dupilumab supports sustained reduction in OCS dosage and improvement in clinical end points for up to 96 weeks. The dupilumab safety profile during the TRAVERSE study was consistent with that seen during the VENTURE study.

**Section Summary: Asthma**

For individuals with asthma, the studies show an importance of biomarkers in strength. The use of testing FeNO is an independent risk factor of those who have a history of asthma as seen in Global Initiative for Asthma (GINA) Management and Prevention (GINA). The evidence in the GINA treatment strategy is sufficient in identifying individuals the predictive value of blood eosinophils and FeNO for diagnosing and management of asthma. The evidence from type 2 targeting biologics suggests that individuals with type 2 biomarkers may provide unique information relating to identifying asthma phenotype. For example, individuals may respond best to a biologic that targets relevant airway mucosal processes anti-IL 4 receptor (dupilumab) or anti-thymic stromal lymphopoietin (anti-TSLP) as a new biologic therapy for severe asthma.

**Cough Variant Asthma**

Chen (2021)[10] evaluated the diagnostic value of fractional exhaled nitric oxide (FeNO) and maximum mid-expiratory flow (MMEF) for differentiating cough variant asthma (CVA) from chronic cough individuals with or without allergic rhinitis. The 328 individuals with chronic cough who underwent spirometry and FeNO testing were consecutively included in the retrospective analysis. Subjects were divided into the CVA (n=125) or Non-Cough Variant Asthma (NCVA) (n=203) groups according to the diagnostic criteria of CVA. Results: Eleven subjects were tested with bronchodilation tests and 8 of them were positive. Therefore, 125 (38.1%) subjects were diagnosed with CVA, and 203 (61.9%) individuals were diagnosed with (NCVA). A comparison of the clinical characteristics between the CVA and NCVA groups, including smoking history, spirometry and FeNO. FeNO levels were significantly higher in individuals with CVA (P<0.001). "It was noted that FeNO and MMEF might be useful for identifying cough variant asthma in individuals with chronic cough and might have a greater value as a negative predictive parameter in distinguishing CVA. The combination of FeNO and MMEF (or MEF50) provided a significantly better prediction of CVA than did either parameter alone. When FeNO is > 22 ppb and MMEF < 62.6%, the predictive value for the diagnosis of CVA is the highest. Besides, it is worth noting that FeNO > 24.5 ppb is sensitive for the prediction of CVA in chronic individuals with allergic rhinitis, while FeNO >33.5 ppb is specific in individuals without allergic rhinitis".

**Section Summary: Cough Variant Asthma**

In individuals with cough variant asthma, the evidence includes FeNO and (MMEF) Maximum Mid-Expiratory Flow might be useful for identifying cough variant asthma in individuals from those with chronic cough. The evidence is sufficient to determine that the technology results in improved clinical diagnosis outcomes.

**Interstitial Lung Disease**

Oishi et al (2017)[11] evaluated differences in FeNO levels in different types of acute-onset interstitial lung disease. The median FeNO level in individuals with acute eosinophilic pneumonia (48.1 ppb) was significantly higher than in individuals with cryptogenic organizing pneumonia (17.4 ppb), hypersensitivity pneumonia (20.5 ppb), or sarcoidosis (12.0 ppb; p<0.001). At a cutoff of 23.4 ppb, the area under the ROC curve was 0.90.

**Pulmonary Fibrosis**

Guilleminault et al (2013)[12] retrospectively evaluated whether FeNO could differentiate causes of pulmonary fibrosis. The study included 61 individuals 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 individuals with hypersensitivity pneumonitis (51 ppb) than in individuals 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)[13] evaluated the role of nasal NO and FeNO in the diagnosis of primary ciliary dyskinesia (PCD). The study included 226 individuals: 38 individuals with PCD, 49 healthy controls, and 139 individuals with other respiratory diseases. A definitive diagnosis of PCD was made by structural and functional evaluation of the cilia on a nasal or bronchial biopsy. The

highest sensitivity (89.5%) and specificity (87.3%) were obtained with nasal NO measured during plateau against resistance. Using a FeNO cutoff of 10 ppb, with lower values predictive of PCD, the sensitivity for PCD diagnosis was 89.5%, but specificity was low at 58.3%. Diagnostic accuracy would likely be even lower if assessed in the more relevant population of individuals with suspected PCD.

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

Su et al (2021)[14] published the results of a randomized control open-label trial completed at a single-center in Taiwan that enrolled treatment-naïve individuals with COPD (n=134) and stratified them into high-and low-FeNO groups (cut off was 23.5 ppb). Individuals in each FeNO group were provided with 12 weeks of treatment with either salmerol/fluticasone or tioropium. At the end of the treatment period, individuals in the high-FeNO group who received salmerol/fluticasone had significant reductions in FeNO from baseline (p<.001); individuals in the high-FeNO group who only received tiotropium did not experience statistically significant reductions in FeNO. In the low-FeNO group, neither treatment arm had significant changes in FeNO at 12 weeks. Authors concluded that high baseline FeNO may indicate eosinophilic airway inflammation in COPD, thus identifying individuals more likely to have a favorable response to treatment with corticosteroid-based therapies. Limitations of this study included short-term measurement of response and treatment, lack of reporting of specific quantitative results for changes in FeNO, and not basing management decisions on FeNO test results.

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

Measurement of FeNO is being investigated for various lung disorders other than asthma. These studies are primarily exploratory and establish differences in median FeNO levels for respiratory 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 compared health outcomes in individuals with COPD or other respiratory diseases whose treatment was managed with and without FeNO measurement.

## EXHALED BREATH CONDENSATE

### Clinical Context and Test Purpose

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

The published literature suggests that EBC is at an earlier stage of development than FeNO. A review by Davis et al (2012)[15] noted that this is due, in part, to the fact that FeNO is a single biomarker and EBC is a matrix that contains so many potential biomarkers that research

efforts have thus far been spread among numerous of these markers. In addition, several review articles note that before routine clinical use in the diagnosis and management of respiratory disorders can be considered, the following issues must be resolved [16,17,18]

- 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 gold 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.

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

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

***Interventions***
The test being considered is measurement of EBC.

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

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

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

**Review of Evidence**

**Exhaled Breath Condensate Markers of Asthma**
Similar to FeNO, EBC has been associated with asthma severity. Thomas et al (2013)[19] conducted a systematic review of studies assessing the association components of EBC with pediatric asthma. Reviewers identified 46 articles that measured at least one EBC marker in asthma, allergy, and atopy in children up to age 18 years. Most studies were cross-sectional, but there was wide variation in the definitions used to identify children with asthma and the collection devices and assays for EBC components. Studies in the review evaluated multiple

specific EBC components, including hydrogen ions (pH), NO, glutathione and aldehydes, hydrogen peroxide, eicosanoids (including prostaglandins and leukotrienes), and cytokines (including interleukins in the Th2 pathway and interferon gamma). 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 individuals 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[20] Sixteen studies met the inclusion criteria, with EBC compared between 832 individuals with asthma and 556 healthy controls. In addition to measuring pH (n=6 studies), studies evaluated nitrite (n=1), nitrate (n=1), total NO (n=3), hydrogen peroxide (n=8), and 8-isoprostane (n=4). Most studies were cross-sectional (n=11) and the rest were longitudinal (n=5); 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 hydrogen peroxide and 8-isoprostane were significantly higher in individuals 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.

The authors concluded that a high FeNO before starting ICS therapy may aid in identifying chronic-cough individuals responding to treatment, with a better performance of higher cut-off values. Moreover, these researchers stated that further studies are needed to examine the real usefulness of this biomarker to guide cough therapy and optimize strategies in different healthcare settings (community, hospital, and rehabilitation). They stated that these findings further supported the need for large clinical trials with a robust design aimed at defining more refined prediction strategies before ICS initiation, in order to guide decisions and reduce the risk of AEs and cost-ineffective strategies. In this regard, FeNO may have the potential to be used as an additional tool to identify combined prediction strategies allowing for more individualized approaches.

**Exhaled Breath Condensate Markers of Asthma Severity**

One study not included in the systematic review of adults with asthma is by Liu et al (2011)[21], who reported on the Severe Asthma Research Program, a multicenter study funded by the NIH. This study had the largest sample size (N=572 individuals). Study participants included 250 individuals with severe asthma, 291 individuals with non-severe 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 individuals with non-severe asthma (7.90) was significantly lower than that for individuals with severe asthma (8.02; p not reported).

### Exhaled Breath Condensate Markers of Asthma Control

Navratil et al (2014)[22] evaluated the relation between EBC and asthma control in a cross-sectional study of 103 children (age range, 6 to 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. Individuals 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.

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

There is not much published literature on EBC levels in individuals with respiratory disorders other than asthma. A study by Antus et al (2010)[23] evaluated EBC in 58 hospitalized individuals (20 with asthma and 38 with COPD) and 36 healthy controls (18 smokers, 18 nonsmokers) The EBC pH was significantly lower in individuals with asthma exacerbations (all nonsmokers) at hospital admission (6.2) than in nonsmoking controls (6.4; p<0.001). EBC pH in asthma individuals 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 individuals (n=17) did not differ significantly from nonsmoking controls, either at hospital admission or discharge. Similarly, pH values in EBC samples from smoking COPD individuals (n=21) at admission and discharge did not differ significantly from smoking controls.

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

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

### Section Summary: Exhaled Breath Condensate

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

## SUMMARY OF EVIDENCE

For individuals who have suspected asthma who receive measurement of fractional exhaled nitric oxide (FeNO) for diagnosis, the evidence includes multiple retrospective and prospective studies of diagnostic accuracy, along with systematic reviews of those studies. The relevant outcomes are test validity, symptoms, change in disease status, morbid events, and functional outcomes. There are multiple reports on the sensitivity and specificity of FeNO in asthma diagnosis; however, most studies are in the setting of individuals with asthma symptoms without prior testing. The Couillard, Laugerud 2022 studies show an importance of biomarkers

in strength and additive to the independent risk seen with more established risk factors as a history of an attack in the previous year and Global Initiative for Asthma (GINA) treatment step.[6] In four out of the five studies, the predictive value of blood eosinophils and FeNO was additive.

For individuals who have asthma who receive medication management directed by FeNO, the evidence includes diagnostic accuracy studies, multiple randomized controlled trials (RCTs) and systematic reviews of those trials. The relevant outcomes are symptoms, change in disease status, morbid events, and functional outcomes. The available RCTs evaluating the use of FeNO tests to guide step-up/step-down therapy in individuals have consistently found improvement in health outcomes. Two Cochrane reviews from 2016, 1 on adults and the other on children, found FeNO-guided asthma management to guide step-up/step-down therapy reduced the number of individuals who had more than 1 exacerbation in children but not in adults compared with guidelines-driven therapy. However, it had no impact on day-to-day symptoms or hospitalizations. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have severe asthma who receive measurement of FeNO to select treatment, the evidence includes diagnostic accuracy studies and subgroup analyses of RCTs and observational studies. Relevant outcomes are test validity, symptoms, change in disease status, morbid events, and functional outcomes. For the use of FeNO to identify eosinophilic asthma for the purpose of selecting individuals for therapy with anti-interleukin (IL)-5 therapy or an anti-IL-4 receptor (IL-4R/anti-IL-13) monoclonal antibody, subgroup analyses of RCTs are available. The evidence that points toward an interaction between baseline FeNO and treatment for the outcome of response suggests that there may be a quantitative but not necessarily a qualitative interaction between baseline FeNO and anti-IL-4R/antiIL13 treatment (dupilumab). Sher et al (2022)[9] in the phase III clinical trial, showed further improvements from the VENTURE to TRAVERSE studies also were seen in improvements in the FEV1 metric and 5-item Asthma Control Questionnaire scores. Safety findings were consistent with the known dupilumab safety profile. In conclusion, the study demonstrated that in a population with severe asthma and chronic OCS dependence at parent study baseline, long-term exposure to dupilumab supports sustained reduction in OCS dosage and improvement in clinical end points for up to 96 weeks. The dupilumab safety profile during the TRAVERSE study was consistent with that seen during the VENTURE study. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have suspected or confirmed respiratory disorders other than asthma who receive measurement of FeNO, the evidence includes a crossover trial, an open-label trial a pilot study, and observational studies. The relevant outcomes are test accuracy, test validity, symptoms, change in disease status, morbid events, and functional outcomes. The available evidence assessing the use of FeNO for respiratory disorders other than asthma is limited by heterogeneity in the conditions evaluated and uncertainty about how the test fits in defined clinical management pathways. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have suspected or confirmed respiratory disorders who receive measurement of exhaled breath condensate (EBC), the evidence includes observational studies reporting on the association between various EBC components and disease severity. The relevant outcomes are test accuracy, test validity, symptoms, change in disease status,

morbid events, and functional outcomes. There is considerable variability in the particular EBC components measured and criteria for standardized measurements. Also, there is limited evidence on the use of EBC for determining asthma severity, diagnosing other respiratory conditions, or guiding treatment decisions for asthma or other respiratory conditions. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

## SUPPLEMENTAL INFORMATION

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

### Practice Guidelines and Position Statements

### Global Initiative for Asthma (GINA)[1]

In 2024, the Global Initiative for Asthma (GINA) released its updated global strategy for asthma management and prevention.

For management, FeNO is recommended to assess the severe asthma phenotype during high-dose inhaled corticosteroids (ICS) treatment. FeNO is recognized as a predictor of a good response to certain biologic agents for all classifications of asthma; mild, moderate, or severe asthma: Patient with poor symptom control and/or exacerbations with medium or high dose ICS-LABA treatment should be assessed for contributing factors. If problems continue refer to a specialist center for phenotypic assessment and add-on therapy including biologics.

### 2020: National Heart, Lung, and Blood Institute (USA)[5]

For diagnosis: This practice guideline recommends the addition of FeNO measurement for both children (from 5yo*) and adults if the diagnosis of asthma is uncertain after initial assessment or if spirometry cannot be performed.
For management: This practice guideline recommends the addition of FeNO testing for asthma management for both children (from 5yo) and adults if there is uncertainty on choosing and managing ICS after assessment using traditional methods.

### National Heart Lung and Blood Institute[4]

In 2017, the National Heart Lung and Blood Institute's expert panel guidelines on the diagnosis and management of asthma stated:

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

A focused update to the 2007 guidelines was published in 2020.[5] The focused update included several updated recommendations on the role of FeNO in asthma diagnosis and management.

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

With regard to the role of FeNO testing in asthma management, the expert panel "conditionally recommends the addition of FeNO measurement as part of an ongoing asthma monitoring and management strategy that includes frequent assessments" in "individuals ages 5 years and older with persistent allergic asthma, for whom there is uncertainty in choosing, monitoring, or adjusting anti-inflammatory therapies based on history, clinical findings, and spirometry" (Conditional recommendation, low certainty of evidence).[24,5] Of note, this recommendation does not apply to individuals taking biologic agents, with the exception of omalizumab. The expert panel "recommends against the use of FeNO measurements in isolation to assess asthma control, predict future exacerbations, or assess exacerbation severity" in individuals 5 years of age or older, stating that "FeNO should only be used as part of an ongoing monitoring and management strategy" (strong recommendation, low certainty of evidence). The expert panel also recommended "against FeNO measurement to predict the future development of asthma" in children aged 0 to 4 years with recurrent wheezing (strong recommendation, low certainty of evidence).

**National Asthma Education and Prevention Program Coordinating Committee**

National Asthma Education and Prevention Program Coordinating Committee Expert Panel workgroup to help clinician integrate the new recommendations into clinical care.[25] The 2020 full report, which is focused on selected topics fractional exhaled nitric oxide testing. Nitric oxide can be measured in exhaled breathe and can serves as a measure of the level of airway inflammation. In individuals with asthma, fractional exhaled nitric oxide (FeNO) may be a useful indicator of type 2 (T2) inflammation in the airway. FeNO testing in the diagnosis of Asthma. FeNO measurement may support a diagnosis of asthma in individuals for whom the diagnosis is uncertain, even after a complete history, physical examination, and spirometry testing including bronchodilator responsiveness. In children ages 4 years and younger who have recurrent episodes of wheezing, FeNO measurements does not predict the future development of asthma. FeNO Levels greater than 50 ppb (or greater than 35 ppb in children ages 5-12 years) are consistent with elevated T2 inflammation and support a diagnosis of asthma. Allergic rhinitis and atopy, which can be present in individuals with and without asthma, are associated with increased FeNO levels. Taking these factors into consideration is critical for accurately interpreting FeNO test results.

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## Government Regulations National/Local:

There is no national or local coverage determination on this topic.

*(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)*

## Related Policies

- Acoustic Measurement of Wheeze Rate (Retired)
- Bronchial Thermoplasty for the Treatment of Asthma
- Mannitol Dry Powder Inhalation for the Assessment of Bronchial Hyperresponsiveness (Retired)

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*The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 9/25/24, the date the research was completed.*

## Joint BCBSM/BCN Medical Policy History

| Policy Effective Date | BCBSM Signature Date | BCN Signature Date | Comments |
|---|---|---|---|
| 1/19/06 | 1/19/06 | 3/17/06 | Joint policy established |
| 5/1/07 | 3/1/07 | 3/4/07 | Routine maintenance, code updates |
| 9/1/07 | 7/1/07 | 7/1/07 | Code update |
| 3/1/09 | 12/9/08 | 12/21/08 | Routine maintenance |
| 5/1/10 | 2/16/10 | 3/31/10 | Routine maintenance;<br>Code update: 0140T deleted and replaced with 83987;<br>Added “exhaled breath condensate” to policy title. |
| 9/1/11 | 6/21/11 | 6/21/11 | Routine maintenance |
| 9/1/12 | 6/12/12 | 6/19/12 | Routine maintenance |
| 7/1/13 | 4/16/13 | 4/22/13 | Routine maintenance; updated references and rationale; no change to policy position. |
| 7/1/14 | 4/8/14 | 4/16/14 | Routine maintenance |
| 7/1/16 | 4/19/16 | 4/19/16 | References redone, updated rationale section. No change in policy status. |
| 11/1/16 | 8/16/16 | 8/16/16 | Routine maintenance<br>Rationale and references updated<br>Removed “asthma” from the policy title; added “Measurement of” and “diagnosis” to title |
| 11/1/17 | 8/15/17 | 8/15/17 | Routine maintenance |
| 11/1/18 | 8/21/18 | 8/21/18 | Routine maintenance |
| 11/1/19 | 8/20/19 | | Routine maintenance<br>MPS clarified for each condition |
| 11/1/20 | 8/18/20 | | Routine maintenance<br>Added references 11, 48, 71.<br>Title changed from “Measurement of Exhaled Nitric Oxide…” to “Exhaled Nitric Oxide…” |
| 11/1/21 | 8/17/21 | | Routine maintenance |

| | | | |
|---|---|---|---|
| | | | Added Ref 14,24,43,47,50,51,52, 54,55,76,77,78,81 |
| 11/1/22 | 8/16/22 | | Routine maintenance (ls) |
| 3/1/23 | 12/20/22 | | Routine maintenance (jf) Changed policy statement to established for FeNO, added inclusions and exclusions under Exhaled Nitric Oxide testing |
| 3/1/24 | 12/19/23 | | Routine maintenance (jf)<br>Vendor Managed: NA |
| 3/1/25 | 12/17/24 | | Routine maintenance (jf)<br>Vendor Managed: NA |

Next Review Date: 4th Qtr., 2025

**Pre-Consolidation Medical Policy History**

| Original Policy Date | Comments |
|---|---|
| BCN: | Revised: |
| BCBSM: | Revised: |

# BLUE CARE NETWORK BENEFIT COVERAGE
# POLICY: EXHALED NITRIC OXIDE AND EXHALED BREATH CONDENSATE IN THE DIAGNOSIS AND MANAGEMENT OF RESPIRATORY DISORDERS

## I. Coverage Determination:

| | |
|---|---|
| **Commercial HMO (includes Self-Funded groups unless otherwise specified)** | Covered |
| **BCNA (Medicare Advantage)** | See Government Regulations section. |
| **BCN65 (Medicare Complementary)** | Coinsurance covered if primary Medicare covers the service. |

## II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.
- Duplicate (back-up) equipment is not a covered benefit.