



## MASSACHUSETTS

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### Medical Policy

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

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### Policy Number: 524

BCBSA Reference Number: 2.01.61

NCD/LCD: NA

### Related Policies

None

### Policy

#### Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO Blue<sup>SM</sup> and Medicare PPO Blue<sup>SM</sup> Members

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

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

### Prior Authorization Information

#### Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

#### Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	<b>Outpatient</b>
Commercial Managed Care (HMO and POS)	This is <b>not</b> a covered service.
Commercial PPO and Indemnity	This is <b>not</b> a covered service.
Medicare HMO Blue <sup>SM</sup>	This is <b>not</b> a covered service.
Medicare PPO Blue <sup>SM</sup>	This is <b>not</b> a covered service.

## **CPT Codes / HCPCS Codes / ICD Codes**

*Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.*

*Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.*

*The following codes are included below for informational purposes only; this is not an all-inclusive list.*

**The following CPT codes are considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:**

### **CPT Codes**

<b>CPT codes:</b>	<b>Code Description</b>
83987	pH; exhaled breath condensate
95012	Nitric oxide expired gas determination

### **Description**

#### **Asthma**

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

#### **Management**

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 an 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 FeNO. Nitric oxide (NO) is an important endogenous messenger and inflammatory mediator that is widespread in the human body, with functions including the regulation of peripheral blood flow, platelet function, immune reactions, neurotransmission, and the mediation of inflammation. Patients with asthma have been found to have high levels of FeNO, which decreases with treatment with corticosteroids. In biologic tissues, NO is unstable, limiting measurement. However, in the gas phase, NO is fairly stable, permitting its measurement in exhaled air. FeNO is typically measured during single breath exhalations. First, the subject inspires NO-free air via a mouthpiece until total lung capacity is achieved, followed immediately by exhalation through the mouthpiece into the measuring device. Devices measuring FeNO are commercially available in the U. S. According to a joint statement by the American Thoracic Society and European Respiratory Society (2009), there is a consensus that the fractional concentration of FeNO is best measured at an exhaled rate of 50 mL per second maintained within 10% for more than 6 seconds at an oral pressure between 5 and 20 cm H<sub>2</sub>O.<sup>1</sup> Results are expressed as the NO concentration in parts per billion, based on the mean of 2 or 3 values.

#### **Exhaled Breath Condensate**

EBC consists of exhaled air passed through a condensing or cooling apparatus, resulting in an accumulation of fluid. Although EBC is primarily derived from water vapor, it also contains aerosol particles or respiratory fluid droplets, which in turn contain various nonvolatile inflammatory mediators,

such as cytokines, leukotrienes, oxidants, antioxidants, and 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. Eosinophilic asthma is a subtype of asthma associated with sputum and serum eosinophilia, along with later-onset asthma.<sup>2</sup> Until recently, most asthma management strategies did not depend on the recognition or diagnosis of a particular subtype. However, anti-interleukin-5 inhibitors have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of severe asthma with an eosinophilic phenotype. Anti-interleukin-4 and -13 monoclonal antibodies and immunoglobulin E inhibitors are also available to improve uncontrolled asthma.

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

## **Summary**

### **Description**

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

### **Summary of Evidence**

For individuals who have suspected asthma who receive a measurement of FeNO for diagnosis, the evidence includes multiple retrospective and prospective studies of diagnostic accuracy, along with systematic reviews of those studies. Relevant outcomes are test validity, symptoms, change in disease status, morbid events, and functional outcomes. There are multiple reports on the sensitivity and specificity of FeNO in asthma diagnosis; however, most studies are in the setting of patients with asthma symptoms without previous testing (or with unclear previous testing), which is unlikely to be how the test is used in a U.S. setting. The available evidence is limited by variability in FeNO cutoff levels used to diagnose asthma, lack of data on performance characteristics in diagnostic challenging settings, and lack of data on the incremental value of adding FeNO to existing diagnostic algorithms from studies with concurrent controls. Limitations of the published evidence preclude determining the effects of the technology on net health outcome. The evidence is insufficient to determine the effect of the technology on health outcomes.

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

For individuals who have suspected severe asthma who receive a measurement of FeNO to select a targeted biologic therapy, the evidence includes diagnostic accuracy studies and subgroup analyses of RCTs and observational studies. Relevant outcomes are symptoms, change in disease status, morbid

events, and functional outcomes. For the use of FeNO to identify eosinophilic asthma for the purpose of selecting patients for therapy with anti-interleukin (IL)-5 therapy or an anti-IL-4 and -13 monoclonal antibody, subgroup analyses of RCTs are available. The evidence that points toward an interaction between baseline FeNO and treatment for the outcome of response suggests that there may be a quantitative but not necessarily a qualitative interaction between baseline FeNO and anti-IL-4 treatment (dupilumab), ie, it is unclear if baseline FeNO can identify a group for whom there is no benefit from dupilumab. Similarly, a subgroup analysis for mepolizumab suggested a more pronounced effect compared to placebo in those with elevated levels of both blood eosinophils and FeNO. However, outcomes were not reported stratified based on FeNO alone precluding insight into the utility of using FeNO to predict response to treatment. For use of FeNO to predict response to therapy for patients with other severe asthma phenotypes, such as the allergic subtype, where anti-IgE therapy is used, a subgroup analysis of a RCT is available. Subgroup analysis of omalizumab showed an association with more favorable outcomes in patients with high FeNO levels, but as with dupilumab, a qualitative interaction has not been established. Limitations of the published evidence preclude determining the effects of the technology on net health outcome. The evidence is insufficient to determine the effect of the technology on health outcomes.

For individuals who have suspected or confirmed respiratory disorders other than asthma who receive a measurement of FeNO, the evidence includes a crossover trial and observational studies. Relevant outcomes are test validity, symptoms, change in disease status, morbid events, and functional outcomes. The available evidence assessing the use of FeNO for respiratory disorders other than asthma is limited by heterogeneity in the conditions evaluated and uncertainty about how the test fits in defined clinical management pathways. The evidence is insufficient to determine the effect of the technology on health outcomes.

For individuals who have suspected or confirmed respiratory disorders who receive a measurement of EBC, the evidence includes observational studies reporting on the association between various EBC components and disease severity. Relevant outcomes are test validity, symptoms, change in disease status, morbid events, and functional outcomes. There is considerable variability in the particular EBC components measured and criteria for standardized measurements. Also, there is limited evidence on the use of EBC for determining asthma severity, diagnosing other respiratory conditions, or guiding treatment decisions for asthma or other respiratory conditions. The available published evidence does not support conclusions on the utility of EBC for any indication. The evidence is insufficient to determine the effect of the technology on health outcomes.

## Policy History

Date	Action
10/2020	BCBSA National medical policy review. Description, summary, and references updated. Policy statements unchanged.
10/2019	BCBSA National medical policy review. Description, summary, and references updated. Policy statements unchanged.
2/2019	BCBSA National medical policy review. Investigational indications clarified to indicate eosinophilic asthma.
7/2018	New references added from BCBSA National medical policy. Background and summary clarified.
10/2017	New references added from BCBSA National medical policy.
8/2016	BCBSA National medical policy review. Policy statement unchanged. Title changed to "Measurement of Exhaled Nitric Oxide and Exhaled Breath Condensate in the Diagnosis and Management of Respiratory Disorders."
12/2015	Clarified coding information.
3/2015	New references added from BCBSA National medical policy.
7/2014	Updated Coding section with ICD10 procedure and diagnosis codes. Effective 10/2015.
3/2014	New references from BCBSA National medical policy.
2/2013	New references from BCBSA National medical policy.

11/2011-4/2012	Medical policy ICD 10 remediation: Formatting, editing and coding updates. No changes to policy statements.
4/2011	Reviewed - Medical Policy Group – Cardiology and Pulmonology. No changes to policy statements.
3/21/2011	New policy describing ongoing non-coverage.

## Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

[Medical Policy Terms of Use](#)

[Managed Care Guidelines](#)

[Indemnity/PPO Guidelines](#)

[Clinical Exception Process](#)

[Medical Technology Assessment Guidelines](#)

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