

MEDICAL POLICY

POLICY TITLE	MEASUREMENT OF EXHALED NITRIC OXIDE AND EXHALED BREATH CONDENSATE IN THE DIAGNOSIS AND MANAGEMENT OF ASTHMA AND OTHER RESPIRATORY DISORDERS
POLICY NUMBER	MP 4.038

CLINICAL BENEFIT	<input checked="" type="checkbox"/> MINIMIZE SAFETY RISK OR CONCERN. <input checked="" type="checkbox"/> MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. <input type="checkbox"/> ASSURE APPROPRIATE LEVEL OF CARE. <input type="checkbox"/> ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. <input type="checkbox"/> ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. <input type="checkbox"/> ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	2/1/2024

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I. POLICY

Measurement of exhaled nitric oxide may be considered **medically necessary** for the following indications:

- To aid in the diagnosis of asthma or eosinophilic airway inflammation in individuals with asthma; **or**
- To determine the likelihood of steroid responsiveness in individuals with a diagnosis of asthma; **or**
- To monitor airway inflammation in patients with asthma

Measurement of exhaled nitric oxide is considered **investigational** for all other indications as there is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

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. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at: <https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies>

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III. DESCRIPTION/BACKGROUND

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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 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 (FEV1) 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 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 H₂O.¹ Results are expressed as the NO concentration in parts per billion, based on the mean of 2 or 3 values. The American Thoracic Society (2011) recommends the use of cut points rather than reference values when interpreting FeNO levels and accounting for age as a factor affecting FeNO in children younger than 12. They also recommend accounting for persistent and/or high allergen exposure as a factor associated with higher levels of FeNO.

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

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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.² 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 Food and Drug Administration (FDA) for the treatment of severe asthma with an eosinophilic phenotype. An anti-interleukin-4 and -13 monoclonal antibodies have also been shown to improve uncontrolled asthma³.

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.

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 the FDA

Device	Manufacturer	Indications/Comments	Date	510(k)
Nitric Oxide Monitoring System (NIOX®)	Aerocrine; acquired by Circassia	"[Measurements ...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."	2003	De novo DEN 030001 K02113

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NIOX MINO®	Aerocrine; acquired by Circassia	Same as above except used for ages 7 and older. Handheld and portable.	2008	K072816/ K1101034
NIOX VERO®	Aerocrine; acquired by Circassia	Same as MINO®. Differs from predicate devices in terms of its battery display and format	2014	K133898
Fenom Pro™ Nitric Oxide Test	Spirosure	Measurement of FeNO by Fenom 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 establish 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

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 the 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.

IV. RATIONALE

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SUMMARY OF EVIDENCE

For individuals who have suspected asthma who receive measurement of FeNO, 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 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

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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.

Evidence reported through clinical input suggests a possible adjunctive role when conventional testing may be limited, particularly where diagnosis with standard clinical diagnostic testing (e.g., routine spirometry) may be limited such as in pediatric patients. The American Thoracic Society (2011) recommends the use of FeNo in the diagnosis of asthmatic patients with eosinophilic airway inflammation.

For individuals who have asthma who receive medication management directed by FeNO, the evidence includes diagnostic accuracy studies, multiple 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 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 one 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. Evidence reported through clinical input suggests a possible adjunctive role for FeNO testing particularly for individuals who may have limited awareness of worsening symptoms or when there is suspected non-adherence to medication. The American Thoracic Society (2011) recommends the use of FeNO in asthmatic individuals for 1) determining the likelihood of steroid responsiveness in individuals with chronic respiratory symptoms possible due to airway inflammation and 2) for monitoring airway inflammation.

For individuals who have suspected severe asthma who receive a measurement of FeNO to select a therapy, the evidence includes diagnostic accuracy studies and subgroup analyses of RCTs and observational studies. The 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-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), i.e., 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

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favorable outcomes in patients with high FeNO levels, but as with dupilumab, a qualitative interaction has not been established.

For individuals who have suspected or confirmed respiratory disorders other than asthma who receive measurement of FeNO, the evidence includes a crossover trial and observational studies. The 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 provided by clinical input was not supportive of the use of FeNO testing for respiratory disorders other than asthma to improve the net health outcomes.

For individuals who have suspected or confirmed respiratory disorders who receive measurement of EBC, the evidence includes observational studies reporting on the association between various EBC components and disease severity. The 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 provided by clinical input was not supportive of the use of EBC as a test to improve the net health outcome. The evidence is insufficient to determine the effect of the technology on health outcomes.

V. DEFINITIONS

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N/A

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits, and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER

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Capital Blue Cross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical

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policy and a member’s benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member’s plan of benefits, please contact Capital Blue Cross’ Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational; therefore, not covered:

Procedure Codes								
83987								

Covered when medically necessary:

Procedure Codes								
95012								

ICD-10-CM Diagnosis Code	Description
J45.20	Mild intermittent asthma, uncomplicated
J45.21	Mild intermittent asthma with (acute) exacerbation
J45.22	Mild intermittent asthma with status asthmaticus
J45.30	Mild persistent asthma, uncomplicated
J45.31	Mild persistent asthma with (acute) exacerbation
J45.32	Mild persistent asthma with status asthmaticus
J45.40	Moderate persistent asthma, uncomplicated
J45.41	Moderate persistent asthma with (acute) exacerbation
J45.42	Moderate persistent asthma with status asthmaticus
J45.50	Severe persistent asthma, uncomplicated
J45.51	Severe persistent asthma with (acute) exacerbation
J45.52	Severe persistent asthma with status asthmaticus
J45.901	Unspecified asthma with (acute) exacerbation
J45.902	Unspecified asthma with status asthmaticus
J45.909	Unspecified asthma, uncomplicated

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ICD-10-CM Diagnosis Code	Description
J45.990	Exercise induced bronchospasm
J45.991	Cough variant asthma
J45.998	Other asthma
J82.83	Eosinophilic asthma
R05	Cough
R05.1	Acute cough
R05.2	Subacute cough
R05.3	Chronic cough
R05.4	Cough syncope
R05.8	Other specified cough
R05.9	Cough, unspecified
R06.00	Dyspnea, unspecified
R06.01	Orthopnea
R06.02	Shortness of Breath
R06.03	Acute respiratory distress
R06.09	Other forms of dyspnea
R06.2	Wheezing

IX. REFERENCES

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X. POLICY HISTORY

[TOP](#)

MP 4.038	CAC 09/29/2015 New policy. BCBSA adopted. Both measurement of exhaled nitric oxide and exhaled breath condensate are considered investigational in the diagnosis and management of asthma and other respiratory disorders. FEP variation added. Coding added.
	CAC 11/29/2016 Consensus review. Rational and references updated. No change to policy statements. Coding reviewed. Variation reformatting.
	11/17/2017 Consensus review. Appendix added. Description/Background, Rationale, and Reference sections updated.
	07/17/2018 Consensus review. No change to policy statements. Rationale condensed. Appendix deleted. References updated. 10/29/18 Consensus Coding Review. No Changes.
	05/24/2019 Consensus review. Policy statement unchanged. References updated.
	05/15/2020 Consensus review. Language revised under Product Variation, Benefit Variation and Disclaimer sections. References updated.
	11/16/2020 Major review. Revised measurement of exhaled nitric oxide policy statement from investigational to medically necessary with criteria. Updated coding, references and summary of evidence.
	09/07/2021: Administrative update. Addition of new ICD-10 codes. Effective date 10/1/2021.
	11/09/2021 Consensus No criteria changes. Updated references. Reviewed coding.
	07/12/2022 Consensus review. No change to policy statement. References reviewed and updated.
09/18/2023 Consensus review. No change to policy statement. Added ICD10. References updated.	

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