MEDICAL POLICY

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

CLINICAL BENEFIT	☒ MINIMIZE SAFETY RISK OR CONCERN. ☒ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☐ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective date:	**7/1/2026**

POLICY

Measurement of exhaled 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. as there is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

PRODUCT VARIATIONS

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

FEP PPO - Refer to FEP medical policy manual. The FEP medical policy manual can be found at: fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies.

DESCRIPTION/BACKGROUND

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 H_2O. 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.

Clinical Uses of FeNO

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, 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 asthma.

Measurement of NO 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/ 501(k)	Manufacturer/ Date	Indications/Comments

Nitric Oxide Monitoring System (NIOX®) De novo DEN 030001 K02113	Aerocrine; acquired by Circassia 2003	"[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."
NIOX MINO ® K072816/ KI101034	Aerocrine; acquired by Circassia 2008	Same as above except used for ages 7 and older. Handheld and portable.
NIOX VERO® K133898	Aerocrine; acquired by Circassia 2014	Same as MINO®. Differs from predicate devices in terms of its battery display and format
Fenom Pro™ Nitric Oxide Test K182874	Spirosure 2019	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.

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.

RATIONALE

TOP

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 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. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

favorable outcomes in patients with high FeNO levels, but as with dupilumab, a qualitative interaction has not been established. 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 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. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

PRACTICE GUIDELINES AND POSITION STATEMENTS

American Academy of Pediatrics

In 2017, the American Academy of Pediatrics issued a report on clinical tools to assess asthma control in children. The report stated the following on the use of FeNO: "The value of additional FeNO monitoring in children whose asthma is appropriately managed using guideline-based strategies is unproven."

American Thoracic Society

In 2021, the American Thoracic Society (ATS) published updated guidelines on the use of FeNO to guide the treatment of asthma. Previous guidelines on this topic were published by the ATS over a decade ago. The following question was the basis of the updated guideline: "Should patients with asthma in whom treatment is being contemplated undergo FENO testing?" Based on an overall low quality of available evidence, the panel made the following conditional recommendation for FeNO-based care:

"In patients with asthma in whom treatment is being considered, we suggest to use FENO testing in addition to usual care over usual care alone."

The authors go on to note that "...judgment is based on a balance of effects that probably favors the intervention; the moderate costs and availability of resources, which probably favors the intervention; and the perceived acceptability and feasibility of the intervention in daily practice."

European Respiratory Society/American Thoracic Society

In 2020, the European Respiratory Society and ATS published a joint guideline on the management of severe asthma. The guideline addresses whether measurement of a specific biomarker should be used to guide initiation of treatment with an anti-interleukin (IL)-5 therapy or anti-immunoglobulin E (IgE) therapy for adults and children with severe asthma. For anti-IL-5 therapies, the guideline states that most studies focused on blood eosinophils and no data were available for FeNO. For adult and adolescent patients with severe asthma being considered for omalizumab, the guideline suggested "using a FeNO cut-off ≥19.5 ppb [parts per billion] to

identify adolescents (>12 years) and adults with severe allergic asthma more likely to benefit from anti-IgE treatment (conditional recommendation, low quality of evidence)."

Global Initiative for Asthma

In 2023, the Global Initiative for Asthma (GINA) released its updated global strategy for asthma management and prevention.

The report made the following statement on FeNO for asthma diagnosis:

- "FeNO has not been established as useful for ruling in or ruling out a diagnosis of asthma."

The report made the following statement on FeNO for decisions realted to initiation of inhaled corticosteroids:

- "In studies mainly limited to non-smoking patients, FeNO >50 ppb [parts per billion] has been associated with a good short-term (weeks) response to ICS [inhaled corticosteroids]. However, these studies did not examine the longer-term risk of exacerbations. In two 12-month studies in mild asthma or taking SABA [short-acting beta$_2$-agonist] alone, severe exacerbations were reduced with as-needed low-dose ICS-formoterol versus as-needed SABA and versus maintenance ICS, independent of baseline inflammatory characteristics including FeNO."
- "In patients with a diagnosis or suspected diagnosis of asthma, measurement of FeNO can support the decision to start ICS but cannot be used to decide against treatment with ICS."

The report made the following statements on FeNO for adjusting asthma treatment:

- "In several studies of FeNO-guided treatment, problems with the design of the intervention and/or control algorithms make comparisons and conclusions difficult. Results of FeNO measurements at a single point in time should be interpreted with caution. In a 2016 meta-analysis, FeNO-guided treatment in children and young adults with asthma was associated with a significant reduction in the number of patients with ≥1 exacerbation and in exacerbation rate compared with guideline-based treatment (Evidence A); similar differences were seen in comparisons between FeNO-guided treatment and non-guidelines-based algoirthms. However, a subsequent good-quality multicenter clinical trial in children with asthma in secondary and primary care centers found that the addition of FeNO to symptom-guided treatment did not reduce severe exacerbations over 12 months... Further studies are needed to identify the populations most likely to benefit from sputum-guided or FeNO-guided adjustment of maintenance ICS-containing treatment, and the optimal frequency of monitoring."

Global Initiative for Asthma released an updated 'short GINA guide for health professionals' in August 2023 entitled "Difficult-to-Treat & Severe Asthma in Adolescent and Adult Patients – Diagnosis and Management." The guide states the following regarding using FeNO to manage medications:

"The possibility of refractory type 2 inflammation should be considered if any of the following are found while the patient is taking high-dose ICS or daily OCS [oral corticosteroids]:

- Blood eosinophils ≥150 µl, and/or
- FeNO ≥20 ppb, and/or
- Sputum eosinophils ≥2%, and/or
- Asthma is clinically allergen driven."

The guide continues to state that these criteria are suggested for initial assessment; those for blood eosinophils and FeNO are based on lowest levels associated with response to some biologics. These above criteria are not the criteria for eligibility for type 2-targeted biologic therapy, which may differ. Consider repeating blood eosinophils and FeNO up to 3 times (e.g., when asthma worsens, before giving OCS, or at least 1 to 2 weeks after a course of OCS, or on the lowest possible OCS dose), before assuming asthma is non-type 2.

The guide also states that if the patient has had a good response to type 2 targeted therapy:

"For oral treatments, consider gradually decreased or stopping OCS first, because of their significant adverse effects. Tapering in severe asthma may be supported by internet-based monitoring of symptom control and FeNO."

DEFINITIONS

N/A

DISCLAIMER

Capital Blue Cross' medical policies are used to determine coverage for specific medical technologies, procedures, equipment, and services. These medical policies do not constitute medical advice and are subject to change as permitted by law or applicable clinical evidence from independent treatment guidelines. Treating providers are solely responsible for medical advice and treatment of members. These policies are not a guarantee of coverage or payment. Payment of claims is subject to a determination regarding the member's benefit program and eligibility on the date of service, and a determination that the services are medically necessary and appropriate. Final processing of a claim is based upon the terms of contract that applies to the members' benefit program, including benefit limitations and exclusions. If a provider or a member has a question concerning this medical policy, please contact Capital Blue Cross' Provider Services or Member Services.

CODING INFORMATION

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.

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POLICY NUMBER	MP 4.038

Investigational; therefore, not covered:

Procedure Codes								
95012								

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POLICY HISTORY

MP 4.038	**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 10/01/2021.
	11/09/2021 Consensus Review. 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.
	09/17/2024 Consensus Review. No change to policy statement. Added cross reference. Updated references.
	02/27/2025 Major Review. Measurement of exhaled nitric oxide is now investigational. Updated background, rationale and references.
	07/10/2025 Administrative Update. Removed Benefit Variations Section and updated Disclaimer.
	03/03/2026 Minor Review. Removed criteria for exhaled breath condensate and associated CPT 83987, delegated to Evicore. Updated background, rationale, references. Updated title.