Effective November 1, 2023, refer to CMS Manual 100-02, Chapter 16-General Exclusions from Coverage for services included in this policy.

BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

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

Policy #: 181
Latest Review Date: June 2023
Category: Medicine
ARCHIVED EFFECTIVE 11/1/2023

BACKGROUND:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

POLICY:

Blue Advantage will treat **measurement of exhaled or nasal nitric oxide** as a **non-covered benefit** and as **investigational** for the diagnosis and management of asthma and other respiratory disorders including but not limited to chronic obstructive pulmonary disease and chronic cough.

Blue Advantage will treat **measurement of exhaled breath condensate** as a **non-covered benefit** and as **investigational** for the diagnosis and management of asthma and other respiratory disorders including but not limited to chronic obstructive pulmonary disease and chronic cough.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

DESCRIPTION OF PROCEDURE OR SERVICE:

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.

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. In the United States, the burden of asthma falls disproportionately on Black, Hispanic, and American Indian and Alaska Native populations. Asthma-related emergency department visits are nearly 5 times higher for Black patients when compared to White patients, and Black patients are nearly 3 times as likely to die from asthma when compared to White patients. Differences in life experiences (eg, family, social, and economic environment), lifestyle choices (smoking, obesity, leisure-time physical activities), and exposure to adverse indoor and outdoor environment factors (e.g., mold, pollens, house dust mites, cockroaches, rodents, animal allergens, and other air pollutants) may account for some of the racial and ethnic differences in asthma prevalence. A sex difference also exists in asthma prevalence – in children, asthma is more common in males, whereas among adults, females are more likely to have an asthma diagnosis.

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 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. 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. FeNOFractional 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. Results are expressed as the NO concentration in parts per billion, based on the mean of 2 or 3 values.

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 FeNO and EBC

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. Until recently, most asthma management strategies did not depend on the recognition or diagnosis of a particular subtype. However, anti-interleukin (IL)-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-IL-4 receptor/anti-IL-13 monoclonal antibodies, anti-immunoglobulin E monoclonal antibodies, and thymic stromal lymphopoietin blocker monoclonal antibodies are also available to improve uncontrolled asthma that does not necessarily have an eosinophilic phenotype.

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.

KEY POINTS:

This evidence review has been updated regularly with a literature review using the MEDLINE database, most recently through April 21, 2023.

Summary of Evidence

For individuals who have suspected asthma who receive measurement of fractional exhaled nitric oxide (FeNO), the evidence includes multiple retrospective and prospective studies of diagnostic accuracy, along with systematic reviews of those studies. The relevant outcomes are test accuracy and 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 and lack of data on performance characteristics in challenging diagnostic 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.

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 for the management of patients have not consistently found improvement in health outcomes. Two Cochrane reviews from 2016, 1 on adults and the other on children, found that FeNO-guided asthma management 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 insufficient 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 patients 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/anti-IL-13 treatment (dupilumab). Therefore, 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-immunoglobulin E therapy is used, a subgroup analysis of an 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, an open-label trial, a pilot study, 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 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 and 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 that the technology results in an improvement in 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 American Thoracic Society 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 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 2022, the Global Initiative for Asthma 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 response to ICS. However, these studies did not examine the longer-term risk of exacerbations. Such evidence therefore does not mean that it is safe with regard to exacerbations to withhold ICS in patients with low initial FeNO. More recently, in two 12-month studies in mild asthma, severe exacerbations were reduced with as-needed 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 children, FeNO-guided treatment significantly reduces exacerbation rates compared to guideline-based treatment (Evidence A). However, further studies are needed to identify the populations most likely to benefit from sputum-guided or FeNO-guided treatment and the optimal frequency of FeNO monitoring."

Global Initiative for Asthma released a 'pocket guide for health professionals' in Nov 2018 with an update in Apr 2019 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:

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

It 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. They 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), 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 may be supported by internet-based monitoring of symptoms control and FeNO."

Another update of this guideline is due for release sometime in 2022.

National Heart Lung and Blood Institute
In 2007, 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)."

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

A focused update to the 2007 guidelines was published in 2020. 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). 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 Institute for Health and Care Excellence

The National Institute for Health and Care Excellence (2017, last updated March 2021) issued guidance on asthma diagnosis and monitoring. The guidance recommended the following for diagnosis:

- “Offer a FeNO [fractional exhaled nitric oxide] test to adults (aged 17 and over) if a diagnosis of asthma is being considered.
- Consider a FeNO test in children and young people (aged 5 to 16) if there is diagnostic uncertainty after initial assessment
- Diagnose asthma in children and young people (aged 5 to 16) if they have symptoms suggestive of asthma and:
    - a FeNO level of 35 ppb or more and positive peak flow variability or
    - obstructive spirometry and positive bronchodilator reversibility.
- Diagnose asthma in adults (aged 17 and over) if they have symptoms suggestive of asthma and:
    - a FeNO level of 40 ppb or more with either positive bronchodilator reversibility or positive peak flow variability, or bronchial hyperreactivity, or
    - a FeNO level between 25 and 39 ppb and a positive bronchial challenge test, or

- positive bronchodilator reversibility and positive peak flow variability irrespective of FeNO level."

The guidance recommended the following for monitoring asthma control:

- "Do not routinely use FeNO to monitor asthma control.
- Consider FeNO measurement as an option to support asthma management in people who are symptomatic despite using inhaled corticosteroids."

U.S. Preventive Services Task Force Recommendations

No U.S. Preventive Services Task Force recommendations for asthma screening or the use of NO measurements or EBC have been identified.

KEY WORDS:

Asthma, nitric oxide, NIOX, Breathmeter, exhaled breath condensate pH, exhaled breath condensate, EBC, NIOX MINO, FeNO, NIOX VERO®, RTube™, ECoScreen EBC, Fenom Pro™ Nitric Oxide Test, NObreath®

APPROVED BY GOVERNING BODIES:

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 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 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

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 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-ofcare 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

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.

BENEFIT APPLICATION:

Coverage is subject to member's specific benefits. Group-specific policy will supersede this

CURRENT CODING:

CPT codes:

83987	pH; exhaled breath condensate
94799	Unlisted pulmonary service or procedure
95012	Nitric oxide expired gas determination

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POLICY HISTORY:

Adopted for Blue Advantage, March 2005
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Medical Policy Group, June 2006
Available for comment June 21-August 4, 2006
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