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	☒ 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:	**2/1/2025**

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.

Cross Reference:
MP 2.380 Diagnosis and Treatment of Post Acute COVID (PASC)

II. PRODUCT VARIATIONS

TOP

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.

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

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

III. DESCRIPTION/BACKGROUND

TOP

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.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 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 asthma[3].

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/ Date	Indications/Comments	510(k)
Nitric Oxide Monitoring System (NIOX®)	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."	De novo DEN 030001 K02113

NIOX MINO ®	Aerocrine; acquired by Circassia 2008	Same as above except used for ages 7 and older. Handheld and portable.	K072816/ KI101034
NIOX VERO®	Aerocrine; acquired by Circassia 2014	Same as MINO®. Differs from predicate devices in terms of its battery display and format	K133898
Fenom Pro™ Nitric Oxide Test	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.	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

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.

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

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

TOP

N/A

VI. BENEFIT VARIATIONS

TOP

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

TOP

Capital Blue Cross' 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 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

TOP

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

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

ICD-10-CM Diagnosis Code	Description
J45.901	Unspecified asthma with (acute) exacerbation
J45.902	Unspecified asthma with status asthmaticus
J45.909	Unspecified asthma, uncomplicated
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

TOP

1. *Reddel HK, Taylor DR, Bateman ED, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med. Jul 01, 2009; 180(1): 59-99. PMID 19535666*
2. *Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. Feb 2014; 43(2): 343-73. PMID 24337046*
3. *National Heart Lung and Blood Institute. Guidelines for the Diagnosis and Management of Asthma (EPR-3) 2007; https://www.nhlbi.nih.gov/health-topics/guidelines-for-diagnosis-management-of-asthma. Accessed July 13, 2022*
4. *Bossuyt PM, Irwig L, Craig J, et al. Comparative accuracy: assessing new tests against existing diagnostic pathways. BMJ. May 06, 2006; 332(7549): 1089-92. PMID 16675820*

5. *National Institute for Health and Care Excellence (NICE). Asthma: diagnosis, monitoring and chronic asthma management [NG80]. 2017*
6. *Harnan SE, Essat M, Gomersall T, et al. Exhaled nitric oxide in the diagnosis of asthma in adults: a systematic review. Clin Exp Allergy. Mar 2017; 47(3): 410-429. PMID 27906490*
7. *Karrasch S, Linde K, Rucker G, et al. Accuracy of FENO for diagnosing asthma: a systematic review. Thorax. Feb 2017; 72(2): 109-116. PMID 27388487*
8. *Wang Z, Pianosi PT, Keogh KA, et al. The Diagnostic Accuracy of Fractional Exhaled Nitric Oxide Testing in Asthma: A Systematic Review and Meta-analyses. Mayo Clin Proc. Feb 2018; 93(2): 191-198. PMID 29275031*
9. *Wang Z, Pianosi P, Keogh K, et al. The Clinical Utility of Fractional Exhaled Nitric Oxide (FeNO) in Asthma Management (Comparative Effectiveness Review No. 197). Rockville, MD: Agency for Healthcare Research and Quality; 2017.*
10. *Tang W, Zhou J, Miao L, et al. Clinical features in patients of cough variant asthma with normal and high level of exhaled fractional nitric oxide. Clin Respir J. Feb 2018; 12(2): 595-600. PMID 27731932*
11. *Engel J, van Kampen V, Lotz A, et al. An increase of fractional exhaled nitric oxide after specific inhalation challenge is highly predictive of occupational asthma. Int Arch Occup Environ Health. Oct 2018; 91(7): 799-809. PMID 29850946*
12. *Kim K, Cho HJ, Yoon JW, et al. Exhaled nitric oxide and mannitol test to predict exercise-induced bronchoconstriction. Pediatr Int. Aug 2018; 60(8): 691-696. PMID 29786927*
13. *Guo Z, Wang Y, Xing G, et al. Diagnostic accuracy of fractional exhaled nitric oxide in asthma: a systematic review and meta-analysis of prospective studies. J Asthma. 2016; 53(4): 404-12. PMID 26796787*
14. *Kessler A, Kragl U, Glass A, et al. Exhaled nitric oxide can't replace the methacholine challenge in suspected pediatric asthma. Respir Med. Oct 2019; 157: 21-25. PMID 31476569*
15. *Busse WW, Morgan WJ, Taggart V, et al. Asthma outcomes workshop: overview. J Allergy Clin Immunol. Mar 2012; 129(3 Suppl): S1-8. PMID 22386504*
16. *Fuhlbrigge A, Peden D, Apter AJ, et al. Asthma outcomes: exacerbations. J Allergy Clin Immunol. Mar 2012; 129(3 Suppl): S34-48. PMID 22386508*
17. *Cloutier MM, Schatz M, Castro M, et al. Asthma outcomes: composite scores of asthma control. J Allergy Clin Immunol. Mar 2012; 129(3 Suppl): S24-33. PMID 22386507*
18. *Juniper EF, Svensson K, Mork AC, et al. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. Respir Med. May 2005; 99(5): 553-8. PMID 15823451*
19. *Schatz M, Zeiger RS, Zhang F, et al. Development and preliminary validation of the Asthma Intensity Manifestations Score (AIMS) derived from Asthma Control Test, FEV(1), fractional exhaled nitric oxide, and step therapy assessments. J Asthma. Mar 2012; 49(2): 172-7. PMID 22304003*

20. *Petsky HL, Kew KM, Turner C, et al. Exhaled nitric oxide levels to guide treatment for adults with asthma. Cochrane Database Syst Rev. Sep 01, 2016; 9: CD011440. PMID 27580628*
21. *Petsky HL, Kew KM, Chang AB. Exhaled nitric oxide levels to guide treatment for children with asthma. Cochrane Database Syst Rev. Nov 09, 2016; 11: CD011439. PMID 27825189*
22. *Petsky HL, Cates CJ, Kew KM, et al. Tailoring asthma treatment on eosinophilic markers (exhaled nitric oxide or sputum eosinophils): a systematic review and meta-analysis. Thorax. Dec 2018; 73(12): 1110-1119. PMID 29858277*
23. *Szefler SJ, Mitchell H, Sorkness CA, et al. Management of asthma based on exhaled nitric oxide in addition to guideline-based treatment for inner-city adolescents and young adults: a randomised controlled trial. Lancet. Sep 20, 2008; 372(9643): 1065-72. PMID 18805335*
24. *Calhoun WJ, Ameredes BT, King TS, et al. Comparison of physician-, biomarker-, and symptom-based strategies for adjustment of inhaled corticosteroid therapy in adults with asthma: the BASALT randomized controlled trial. JAMA. Sep 12, 2012; 308(10): 987-97. PMID 22968888*
25. *Hashimoto S, Brinke AT, Roldaan AC, et al. Internet-based tapering of oral corticosteroids in severe asthma: a pragmatic randomised controlled trial. Thorax. Jun 2011; 66(6): 514-20. PMID 21474498*
26. *Shaw DE, Berry MA, Thomas M, et al. The use of exhaled nitric oxide to guide asthma management: a randomized controlled trial. Am J Respir Crit Care Med. Aug 01, 2007; 176(3): 231-7. PMID 17496226*
27. *Smith AD, Cowan JO, Brassett KP, et al. Use of exhaled nitric oxide measurements to guide treatment in chronic asthma. N Engl J Med. May 26, 2005; 352(21): 2163-73. PMID 15914548*
28. *Peirsman EJ, Carvelli TJ, Hage PY, et al. Exhaled nitric oxide in childhood allergic asthma management: a randomised controlled trial. Pediatr Pulmonol. Jul 2014; 49(7): 624-31. PMID 24039119*
29. *Pike K, Selby A, Price S, et al. Exhaled nitric oxide monitoring does not reduce exacerbation frequency or inhaled corticosteroid dose in paediatric asthma: a randomised controlled trial. Clin Respir J. Apr 2013; 7(2): 204-13. PMID 22747899*
30. *Verini M, Consilvio NP, Di Pillo S, et al. FeNO as a Marker of Airways Inflammation: The Possible Implications in Childhood Asthma Management. J Allergy (Cairo). 2010; 2010. PMID 20948878*
31. *Fritsch M, Uxa S, Horak F, et al. Exhaled nitric oxide in the management of childhood asthma: a prospective 6-months study. Pediatr Pulmonol. Sep 2006; 41(9): 855-62. PMID 16850457*
32. *Szefler SJ, Martin RJ, King TS, et al. Significant variability in response to inhaled corticosteroids for persistent asthma. J Allergy Clin Immunol. Mar 2002; 109(3): 410-8. PMID 11897984*
33. *Smith AD, Cowan JO, Brassett KP, et al. Exhaled nitric oxide: a predictor of steroid response. Am J Respir Crit Care Med. Aug 15, 2005; 172(4): 453-9. PMID 15901605*

34. *Knuffman JE, Sorkness CA, Lemanske RF, et al. Phenotypic predictors of long-term response to inhaled corticosteroid and leukotriene modifier therapies in pediatric asthma. J Allergy Clin Immunol. Feb 2009; 123(2): 411-6. PMID 19121860*
35. *Anderson WJ, Short PM, Williamson PA, et al. Inhaled corticosteroid dose response using domiciliary exhaled nitric oxide in persistent asthma: the FENOtype trial. Chest. Dec 2012; 142(6): 1553-1561. PMID 23364390*
36. *Visitsunthorn N, Prottasan P, Jirapongsananuruk O, et al. Is fractional exhaled nitric oxide (FeNO) associated with asthma control in children? Asian Pac J Allergy Immunol. Sep 2014; 32(3): 218-25. PMID 25268339*
37. *Wilson E, McKeever T, Hargadon B, et al. Exhaled nitric oxide and inhaled corticosteroid dose reduction in asthma: a cohort study. Eur Respir J. Dec 2014; 44(6): 1705-7. PMID 25142486*
38. *Phipatanakul W, Mauger DT, Sorkness RL, et al. Effects of Age and Disease Severity on Systemic Corticosteroid Responses in Asthma. Am J Respir Crit Care Med. Jun 01, 2017; 195(11): 1439-1448. PMID 27967215*
39. *Price DB, Buhl R, Chan A, et al. Fractional exhaled nitric oxide as a predictor of response to inhaled corticosteroids in patients with non-specific respiratory symptoms and insignificant bronchodilator reversibility: a randomised controlled trial. Lancet Respir Med. Jan 2018; 6(1): 29-39. PMID 29108938*
40. *Korevaar DA, Westerhof GA, Wang J, et al. Diagnostic accuracy of minimally invasive markers for detection of airway eosinophilia in asthma: a systematic review and meta-analysis. Lancet Respir Med. Apr 2015; 3(4): 290-300. PMID 25801413*
41. *Gao J, Wu F. Association between fractional exhaled nitric oxide, sputum induction and peripheral blood eosinophil in uncontrolled asthma. Allergy Asthma Clin Immunol. 2018; 14: 21. PMID 29796021*
42. *Kroes JA, Zielhuis SW, van Roon EN, et al. Prediction of response to biological treatment with monoclonal antibodies in severe asthma. Biochem Pharmacol. Sep 2020; 179: 113978. PMID 32305434*
43. *Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet. Aug 18, 2012; 380(9842): 651-9. PMID 22901886*
44. *Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med. Sep 25, 2014; 371(13): 1198-207. PMID 25199059*
45. *Ortega HG, Yancey SW, Mayer B, et al. Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies. Lancet Respir Med. Jul 2016; 4(7): 549-556. PMID 27177493*
46. *Shrimanker R, Keene O, Hynes G, et al. Prognostic and Predictive Value of Blood Eosinophil Count, Fractional Exhaled Nitric Oxide, and Their Combination in Severe Asthma: A Post Hoc Analysis. Am J Respir Crit Care Med. Nov 15, 2019; 200(10): 1308-1312. PMID 31298922*

47. *Castro M, Corren J, Pavord ID, et al. Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. N Engl J Med. Jun 28, 2018; 378(26): 2486-2496. PMID 29782217*
48. *Rabe KF, Nair P, Brusselle G, et al. Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma. N Engl J Med. Jun 28, 2018; 378(26): 2475-2485. PMID 29782224*
49. *Global Strategy for Asthma Management and Prevention (GINA). 2020; .*
50. *Hanania NA, Alpan O, Hamilos DL, et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. Ann Intern Med. May 03, 2011; 154(9): 573-82. PMID 21536936*
51. *Hanania NA, Wenzel S, Rosen K, et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. Am J Respir Crit Care Med. Apr 15, 2013; 187(8): 804-11. PMID 23471469*
52. *Casale TB, Luskin AT, Busse W, et al. Omalizumab Effectiveness by Biomarker Status in Patients with Asthma: Evidence From PROSPERO, A Prospective Real-World Study. J Allergy Clin Immunol Pract. Jan 2019; 7(1): 156-164.e1. PMID 29800752*
53. *Tang B, Huang D, Wang J, et al. Relationship of Blood Eosinophils with Fractional Exhaled Nitric Oxide and Pulmonary Function Parameters in Chronic Obstructive Pulmonary Disease (COPD) Exacerbation. Med Sci Monit. Mar 12, 2020; 26: e921182. PMID 32161254*
54. *Gao J, Zhang M, Zhou L, et al. Correlation between fractional exhaled nitric oxide and sputum eosinophilia in exacerbations of COPD. Int J Chron Obstruct Pulmon Dis. 2017; 12: 1287-1293. PMID 28490872*
55. *Chou KT, Su KC, Huang SF, et al. Exhaled nitric oxide predicts eosinophilic airway inflammation in COPD. Lung. Aug 2014; 192(4): 499-504. PMID 24816967*
56. *Oishi K, Hirano T, Suetake R, et al. Exhaled nitric oxide measurements in patients with acute-onset interstitial lung disease. J Breath Res. Jun 29, 2017; 11(3): 036001. PMID 28660859*
57. *Guilleminault L, Saint-Hilaire A, Favelle O, et al. Can exhaled nitric oxide differentiate causes of pulmonary fibrosis? Respir Med. Nov 2013; 107(11): 1789-96. PMID 24011803*
58. *Boon M, Meyts I, Proesmans M, et al. Diagnostic accuracy of nitric oxide measurements to detect primary ciliary dyskinesia. Eur J Clin Invest. May 2014; 44(5): 477-85. PMID 24597492*
59. *Dummer JF, Epton MJ, Cowan JO, et al. Predicting corticosteroid response in chronic obstructive pulmonary disease using exhaled nitric oxide. Am J Respir Crit Care Med. Nov 01, 2009; 180(9): 846-52. PMID 19661244*
60. *Prieto L, Bruno L, Gutierrez V, et al. Airway responsiveness to adenosine 5'-monophosphate and exhaled nitric oxide measurements: predictive value as markers for reducing the dose of inhaled corticosteroids in asthmatic subjects. Chest. Oct 2003; 124(4): 1325-33. PMID 14555562*
61. *Kunisaki KM, Rice KL, Janoff EN, et al. Exhaled nitric oxide, systemic inflammation, and the spirometric response to inhaled fluticasone propionate in severe chronic obstructive*

pulmonary disease: a prospective study. Ther Adv Respir Dis. Apr 2008; 2(2): 55-64. PMID 19124359

62. *Davis MD, Montpetit A, Hunt J. Exhaled breath condensate: an overview. Immunol Allergy Clin North Am. Aug 2012; 32(3): 363-75. PMID 22877615*
63. *Effros RM, Su J, Casaburi R, et al. Utility of exhaled breath condensates in chronic obstructive pulmonary disease: a critical review. Curr Opin Pulm Med. Mar 2005; 11(2): 135-9. PMID 15699785*
64. *Hunt J. Exhaled breath condensate: an overview. Immunol Allergy Clin North Am. Nov 2007; 27(4): 587-96; v. PMID 17996577*
65. *Kazani S, Israel E. Exhaled breath condensates in asthma: diagnostic and therapeutic implications. J Breath Res. Dec 2010; 4(4): 047001. PMID 21383487*
66. *Liu J, Thomas PS. Exhaled breath condensate as a method of sampling airway nitric oxide and other markers of inflammation. Med Sci Monit. Aug 2005; 11(8): MT53-62. PMID 16049390*
67. *Thomas PS, Lowe AJ, Samarasinghe P, et al. Exhaled breath condensate in pediatric asthma: promising new advance or pouring cold water on a lot of hot air? a systematic review. Pediatr Pulmonol. May 2013; 48(5): 419-42. PMID 23401497*
68. *Aldakheel FM, Thomas PS, Bourke JE, et al. Relationships between adult asthma and oxidative stress markers and pH in exhaled breath condensate: a systematic review. Allergy. Jun 2016; 71(6): 741-57. PMID 26896172*
69. *Liu L, Teague WG, Erzurum S, et al. Determinants of exhaled breath condensate pH in a large population with asthma. Chest. Feb 2011; 139(2): 328-336. PMID 20966042*
70. *Navratil M, Plavec D, Erceg D, et al. Urates in exhaled breath condensate as a biomarker of control in childhood asthma. J Asthma. Jun 2015; 52(5): 437-46. PMID 25387148*
71. *Antus B, Barta I, Kullmann T, et al. Assessment of exhaled breath condensate pH in exacerbations of asthma and chronic obstructive pulmonary disease: A longitudinal study. Am J Respir Crit Care Med. Dec 15, 2010; 182(12): 1492-7. PMID 20656939*
72. *Dweik RA, Boggs PB, Erzurum SC, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. Am J Respir Crit Care Med. Sep 01, 2011; 184(5): 602-15. PMID 21885636*
73. *Committee on Standards for Developing Trustworthy Clinical Practice Guidelines, Board on Health Care Services. Clinical Practice Guidelines We Can Trust. Washington, DC: National Academies Press; 2011.*
74. *Holguin F, Cardet JC, Chung KF, et al. Management of severe asthma: a European Respiratory Society/American Thoracic Society guideline. Eur Respir J. Jan 2020; 55(1). PMID 31558662*
75. *Dinakar C, Chipps BE, Matsui EC, et al. Clinical Tools to Assess Asthma Control in Children. Pediatrics. Jan 2017; 139(1). PMID 28025241*
76. *Fishwick D, Forman S. Health surveillance for occupational asthma. Curr Opin Allergy Clin Immunol. Apr 2018; 18(2): 80-86. PMID 29461276*

77. *Turner S, Cotton SC, Emele CD, et al. Reducing Asthma Attacks in Children using Exhaled Nitric Oxide as a biomarker to inform treatment strategy: a randomised trial (RAACENO). Trials. Oct 04, 2019; 20(1): 573. PMID 31585544*
78. *Khatri SB, Iaccarino JM, Barochia A, et al. Use of Fractional Exhaled Nitric Oxide to Guide the Treatment of Asthma: An Official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med. 2021;204(10):e97-e109. PMID: 34779751*
79. *Riccò M, Zaniboni A, Satta E, Ranzieri S, Marchesi F. Potential Use of Exhaled Breath Condensate for Diagnosis of SARS-CoV-2 Infections: A Systematic Review and Meta-Analysis. Diagnostics (Basel). 2022;12(9):2245. Published 2022 Sep 17. PMID: 36140647*
80. *Połomska J, Bar K, Sozańska B. Exhaled Breath Condensate-A Non-Invasive Approach for Diagnostic Methods in Asthma. J Clin Med. 2021;10(12):2697. Published 2021 Jun 18. PMID: 34207327*
81. *Expert Panel Working Group of the National Heart, Lung, and Blood Institute (NHLBI) administered and coordinated National Asthma Education and Prevention Program Coordinating Committee (NAEPPCC), Cloutier MM, Baptist AP, et al. 2020 Focused Updates to the Asthma Management Guidelines: A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group [published correction appears in J Allergy Clin Immunol. 2021 Apr;147(4):1528-1530. doi: 10.1016/j.jaci.2021.02.010]. J Allergy Clin Immunol. 2020;146(6):1217-1270. PMID: 33280709*
82. *Blue Cross Blue Shield Association Medical Policy Reference Manual. 2.01.61, Measurement of Exhaled Nitric Oxide and Exhaled Breath Condensate in the Diagnosis and Management of Respiratory Disorders. July 2024.*

X. POLICY HISTORY

TOP

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 10/1/2021.
	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.

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

Top