

# Clinical Policy: Fractional Exhaled Nitric Oxide

Reference Number: CP.MP.103

Last Review Date: 11/20

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## Description

Fractional exhaled nitric oxide (FeNO) measurement is a noninvasive and simple test thought to reflect eosinophilic airway inflammation. While measurement of FeNO is standardized, there are currently no reference guidelines available to aid practitioners in appropriately applying test results in practice.

## Policy/Criteria

It is the policy of health plans affiliated with Centene Corporation® that testing for fractionated exhaled nitric oxide (FeNO) is **investigational** for diagnosing and guiding the treatment of asthma, as well as all other conditions, as there is insufficient evidence proving it more than or as effective as existing standards of care.

## Background

There are multiple methods for diagnosing and assessing control of asthma and, according to the American Thoracic Society (ATS), no single test is an adequate indicator of asthma control.<sup>1</sup> Conventional, objective methods to assess asthma include spirometry/peak flow and degree of airway hyper-responsiveness.<sup>2</sup> These methods are often used as measures of asthma control in addition to patient symptoms, clinical questionnaires, and use of rescue medications.<sup>2,3</sup> Newer methods of diagnosing and assessing control of asthma include the use of biomarkers of airway inflammation such as FeNO and induced sputum analysis.<sup>4</sup>

FeNO describes the levels of exhaled nitric oxide (NO) in the breath and NO is a mediator involved in lung inflammation that is largely formed in the lower airways.<sup>5</sup> Increased levels of FeNO are associated with eosinophilic inflammation, severe asthma, and inhaled glucocorticoid-naïve asthma.<sup>4</sup> Although there are some correlations between FeNO and characteristics related to asthma, there is large variability in FeNO levels between individuals. Other factors that may affect FeNO include atopy, sex, age, and cigarette smoking.<sup>3</sup> However, there are no established guidelines for adjusting FeNO values according to these factors,<sup>3</sup> potentially making the test less accurate for certain populations.

There are currently three types of FeNO tests approved by the FDA<sup>5</sup> and there is a large body of literature on FeNO testing for the diagnosis and management of asthma. Overall, the evidence is mixed for using FeNO as an adjunct to the diagnosis or management of asthma. Multiple studies have shown that FeNO can serve as an indicator of glucocorticoid response.<sup>3,4,6</sup> However, large studies, randomized control trials and a meta-review have found no clinical benefit to the use of FeNO testing over other methods of assessing or managing asthma.<sup>2,4,7-9</sup>

Among the studies that found a benefit to the use of FeNO testing,<sup>6,10-13</sup> there was little agreement regarding FeNO cutoff values which would indicate asthma diagnosis or control.<sup>3,5</sup> Although the ATS has recommended specific FeNO cutoff values to serve as guidelines for the

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diagnosis and treatment of asthma,<sup>14</sup> these standardized values have not been consistently used in the research to date on FeNO testing.<sup>3-5</sup> An additional drawback to FeNO testing for the diagnosis or management of asthma is that it is most indicative of inflammation caused by eosinophils, which characterizes only one subtype of asthma.<sup>4</sup>

A 2016 Cochrane Review evaluating the use of FeNO in guiding treatment for adults with asthma concluded that, while management guided by FeNO levels results in reduced exacerbations, it cannot be advocated universally since it does not affect day-to-day clinical symptoms, end-of-study FeNO levels, or inhaled corticosteroid dose.<sup>15</sup> Furthermore, a systematic review and meta-analysis evaluating the diagnostic accuracy of FeNO in asthmatic children found that FeNO has only moderate diagnostic performance.<sup>16</sup>

A recent meta-analysis of pooled randomized controlled trial (RCT) data by Fielding, et al. concluded that the role of repeated FeNO measurements in predicting asthma outcomes in children is uncertain, as large changes in FeNO were associated with small changes in the risk of asthma exacerbation and indicators of asthma control.<sup>23</sup> A different meta-analysis by Fielding, et al. of the same seven pooled RCTs suggested that asthma treatment guided by FeNO may improve outcomes in non-obese children not treated with leukotriene receptor antagonists.<sup>24</sup> However, the treatment protocols in the included RCTs varied in their management protocols based on FeNO levels, and included only data from trials that found positive results from FeNO management.

Given the equivocal results of research on the accuracy and usefulness of FeNO testing for the diagnosis and management of asthma, the lack of standardized cutoff values, and the need for further study, FeNO testing for the diagnosis and/or management of asthma is considered experimental, investigational, or unproven.

**Coding Implications**

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CPT® Codes	Description
95012	Nitric Oxide expired gas determination

**ICD-10-CM Diagnosis Codes that Support Coverage Criteria**

ICD-10-CM Code	Description
N/A	

Reviews, Revisions, and Approvals	Date	Approval Date
Policy created	12/15	01/16
Changed FeNO to investigational from not medically necessary. References reviewed and updated, along with background information.	12/16	01/17
References reviewed and updated.	12/17	01/18
References reviewed and updated.	12/18	12/18
References reviewed and updated.	11/19	11/19
Added that testing FeNO is investigational for all other conditions, in addition to asthma, with supporting sources.	12/19	12/19
Background updated. Replaced all instances of “member” with “member/enrollee.” References reviewed and updated.	11/20	11/20

**References**

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.* 2009; 180: 602-615. doi: 10.1164/rccm.200801-060ST
2. Petsky HL, Cates CJ, Lasserson TJ, et al. A systematic review and meta-analysis: tailoring asthma treatment on eosinophilic markers (exhaled nitric oxide or sputum eosinophils). *Thorax.* 2012; 67: 199-208. doi:10.1136/thx.2010.135574
3. Dweik RA. Exhaled nitric oxide analysis and applications. UpToDate. Barnes PJ (Ed.). Accessed Nov. 12, 2020.
4. Wadsworth SJ, Sin DD, Dorscheid DR. Clinical update on the use of biomarkers of airway inflammation in the management of asthma. *J Asthma Allergy.* 2011; 4: 77-86. <http://dx.doi.org/10.2147/JAA.S15081>
5. Hayes Medical Technology Directory: Nitric oxide breath analysis for the diagnosis of asthma. Hayes. Published Oct. 6, 2016. Reviewed Jan. 2, 2020.
6. Hayes Medical Technology Directory: Nitric oxide breath analysis for the management of asthma. Hayes. Published September 29, 2016. Reviewed Dec. 23, 2020.
7. Donohue JF, Jain N. Exhaled nitric oxide to predict corticosteroid responsiveness and reduce asthma exacerbation rates. *Respiratory Med.* 2013; 107: 943-952.
8. 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.* 2012; 10; 987-997. doi: 10.1001/2012.jama.10893
9. Szeffler SJ, Mitchell H, Sorkness CA, et al. Adding exhaled nitric oxide to guideline-based asthma treatment in inner-city adolescents and young adults: a randomized controlled trial. *Lancet.* 2008; 372(9643): 1065-1072. doi: 10.1016/S0140-6736(08)61448-8
10. Shaw DE, Berry MA, Thomas M, et al. The use of exhaled nitric oxide to guide asthma management. *Am J Respir Crit Care Med.* 2007; 176(3): 231-237. doi: 10.1164/rccm.200610-1427OC
11. Sippel JM, Holden WE, Tilles SA, et al. Exhaled nitric oxide levels correlate with measures of disease control in asthma. *J Allergy Clin Immunol.* 2000; 106: 645-50. doi:10.1067/mai.2000.109618

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12. Dupont LJ, Demedts MG, Verleden M. Prospective evaluation of the validity of exhaled nitric oxide for the diagnosis of asthma. *Chest*. 2003; 123(3): 751-756. doi:10.1378/chest.123.3.751
13. Smith AD, Cowan JO, Filsell S, et al. Diagnosing asthma comparisons between exhaled nitric oxide measurements and conventional tests. *Am J Respir Crit Care Med*. 2004; 169: 473-478. doi: 10.1164/rccm.200310-1376OC
14. Powell H, Murphy VE, Taylor DR, et al. Management of asthma in pregnancy guided by measurement of fraction of exhaled nitric oxide: a double-blind, randomised controlled trial. *Lancet*. 2011; 378(9795): 983-990. [http://dx.doi.org/10.1016/S0140-6736\(11\)60971-9](http://dx.doi.org/10.1016/S0140-6736(11)60971-9).
15. Dweik RA, Boggs RB, 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*. 2011; 184: 602-615. doi: 10.1164/rccm.912011ST
16. Petsky HL, Kew KM, Turner C, Change AB. Exhaled nitric oxide levels to guide treatment for adults with asthma. *Cochrane Database Syst Rev*. 2016 Sep 1;9: CD011440.
17. Tang S, Xie Y, Yuan C, Sun X, Cui Y. Fractional exhaled nitric oxide for diagnosis of childhood asthma: a systematic review and meta-analysis. *Clin Rev Allergy Immunol*. 2016 Jul 21.
18. Global Initiative for Asthma. 2020 GINA Report, Global Strategy for Asthma Management and Prevention. Accessed 11/12/20.
19. Global Initiative for Chronic Obstructive Lung Disease. 2020 Report, Pocket guide to COPD diagnosis, management and prevention: a guide for health care professionals. Accessed 11/12/20.
20. Qaseem A, et al. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. *Ann Intern Med*. 2011 Aug 2;155(3):179-91.
21. Horváth I, Barnes PJ, Loukides S, et al. A European Respiratory Society technical standard: exhaled biomarkers in lung disease. *Eur Respir J*. 2017;49(4).
22. Barnes PJ, Dweik RA, Gelb AF, et al. Exhaled nitric oxide in pulmonary diseases: a comprehensive review. *Chest*. 2010 Sep;138(3):682-92.
23. Fielding S, Pijnenburg M, de Jongste J, et al. Change in FEV1 and Feno Measurements as Predictors of Future Asthma Outcomes in Children. *Chest* 155(2) p. 331-334. Feb 2019.
24. Fielding S, Pijnenburg M, de Jongste J, et al. Does treatment guided by exhaled nitric oxide fraction improve outcomes in subgroups of children with asthma? *Eur. Resp. J* 55(5). May 2020.

#### **Important reminder**

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or

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