Medical Coverage Policy | Measurement of Exhaled Nitric Oxide and Exhaled Breath Condensate

EFFECTIVE DATE: 03|03|2015
POLICY LAST UPDATED: 12|05|2017

OVERVIEW
Current techniques for diagnosing and monitoring asthma and predicting exacerbations are suboptimal. Two new strategies, evaluation of exhaled nitric oxide (NO) and exhaled breath condensate (EBC) are proposed. These techniques are also potentially useful in the management of other conditions such as chronic obstructive pulmonary disease and chronic cough. There are commercially available devices for measuring NO in expired breath and various laboratory techniques for evaluating components of EBC.

MEDICAL CRITERIA
Not applicable

PRIOR AUTHORIZATION
Not applicable

POLICY STATEMENT
BlueCHiP for Medicare and Commercial Products
Measurement of exhaled nitric oxide and exhaled breath condensate is considered not medically necessary in the diagnosis and management of asthma and other respiratory disorders including, but not limited to, chronic obstructive pulmonary disease and chronic cough because the evidence is insufficient to determine the effect of the technology on health outcomes.

COVERAGE
Benefits may vary between groups/contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage or Subscriber Agreement for limitations of benefits/coverage when services are not medically necessary.

BACKGROUND
®), with the indication that measurements of the fractional NO concentration in expired breath (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 cannot be used with infants or children approximately under the age of 4, as measurement requires patient cooperation. In March 2008, the NIOX MINO was cleared for marketing. The main differences between this new device and the NIOX are that the NIOX MINO is handheld and portable and that it is not suitable for children younger than age 7 years.

Measurement of Exhaled Breath Condensate
Exhaled breath condensate 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 various 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, to the more sophisticated gas chromatography/mass spectrometry or high performance liquid chromatography, depending on the component of interest.

The RTube™ Exhaled Breath Condensate collection system (Respiratory Research Inc.) and the ECoScreen EBC collection system (CareFusion, Germany) 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.

For individuals who have suspected asthma or suspected eosinophilic 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. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbid events, and functional outcomes. There is a large volume of reports on the sensitivity and specificity of FeNO in asthma diagnosis. The available evidence is limited by variability in FeNO cutoff levels used to diagnose asthma, and by variability in sensitivity and specificity for asthma diagnosis. The accuracy of the cutoffs recommended by the American Thoracic Society guidelines has not been evaluated in the diagnosis of asthma. Also, no studies were identified that evaluated whether the use of FeNO improved the accuracy of asthma diagnosis compared with clinical diagnosis. For the use of FeNO in the diagnosis of eosinophilic asthma, using the criterion standard of sputum eosinophilia, the diagnostic accuracy is moderate. The evidence is insufficient to determine the effect of the technology on health outcomes.

For individuals who have asthma who receive medication management directed by FeNO, the evidence includes multiple randomized controlled trials and systematic reviews of those trials. Relevant outcomes are symptoms, change in disease status, morbid events, and functional outcomes. The available randomized controlled trials evaluating the use of FeNO tests for the management of 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 reduced the number of individuals who had more than 1 exacerbation, but had no impact on day-to-day symptoms. The evidence is insufficient to determine the effect of the technology on health outcomes.

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. Relevant outcomes are test accuracy and 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 the potentialclinical use. The evidence is insufficient to determine the effect of the technology on 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. 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 evidence is insufficient to determine the effect of the technology on health outcomes.

CODING

BlueCHiP for Medicare and Commercial Products

The following CPT codes are considered not medically necessary:

83987 pH; exhaled breath condensate
95012 Nitric oxide expired gas determination

RELATED POLICIES

Not applicable

PUBLISHED

Provider Update, January 2018
Provider Update, January 2017
Provider Update, May 2015
Provider Update, June 2014
Provider Update, June 2013
Provider Update, May 2012
Provider Update, May 2011
Provider Update, May 2010

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.* Jul 1 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):343-373. PMID 24337046
3. NUCALA: Highlights of Prescribing Information. 2015; https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Nucala/pdf/NUCALA-PI-PIL.PDF. Accessed August 9, 2017.
4. Cinquair: Highlights of Prescribing Information. 2016; http://www.cinqair.com/pdf/PrescribingInformation.pdf. Accessed August 9, 2017.
5. Wenzel S, Castro M, Corren J, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting beta2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. *Lancet.* Jul 02 2016;388(10039):31-44. PMID 27130691
6. Selby A, Clayton B, Grundy J, et al. Are exhaled nitric oxide measurements using the portable NIOX MINO repeatable? *Respir Res.* Apr 23 2010;11:43. PMID 20416092
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. Fortuna AM, Feixas T, Gonzalez M, et al. Diagnostic utility of inflammatory biomarkers in asthma: exhaled nitric oxide and induced sputum eosinophil count. *Respir Med.* Nov 2007;101(11):2416-2421. PMID 17714927
9. 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.* Feb 15 2004;169(4):473-478. PMID 14644933
10. Schneider A, Schwarzbach J, Faderl B, et al. FENO measurement and sputum analysis for diagnosing asthma in clinical practice. *Respir Med.* Feb 2013;107(2):209-216. PMID 23107283
11. Cordeiro D, Rudolphus A, Snoey E, et al. Utility of nitric oxide for the diagnosis of asthma in an allergy clinic population. *Allergy Asthma Proc.* Mar-Apr 2011;32(2):119-126. PMID 21439165
12. Sato S, Saito J, Sato Y, et al. Clinical usefulness of fractional exhaled nitric oxide for diagnosing prolonged cough. *Respir Med.* Oct 2008;102(10):1452-1459. PMID 18614345
13. Sivan Y, Gadish T, Fireman E, et al. The use of exhaled nitric oxide in the diagnosis of asthma in school children. *J Pediatr.* Aug 2009;155(2):211-216. PMID 19394049
14. Woo SI, Lee JH, Kim H, et al. Utility of fractional exhaled nitric oxide (F(E)NO) measurements in diagnosing asthma. *Respir Med.* Aug 2012;106(8):1103-1109. PMID 22534041
15. 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
16. Blake TL, Chang AB, Chatfield MD, et al. Does Ethnicity Influence Fractional Exhaled Nitric Oxide in Healthy Individuals?: A Systematic Review. *Chest.* Jul 2017;152(1):40-50. PMID 28215791
17. 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 1 2011;184(5):602-615. PMID 21885636
18. See KC, Christiani DC. Normal values and thresholds for the clinical interpretation of exhaled nitric oxide levels in the US general population: results from the National Health and Nutrition Examination Survey 2007-2010. *Chest.* Jan 2013;143(1):107-116. PMID 22628492

19. 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
20. Westerhof GA, Korevaar DA, Amelink M, et al. Biomarkers to identify sputum eosinophilia in different adult asthma phenotypes. *Eur Respir J.* Sep 2015;46(3):688-696. PMID 26113672
21. Oh MA, Shim JY, Jung YH, et al. Fraction of exhaled nitric oxide and wheezing phenotypes in preschool children. *Pediatr Pulmonol.* Jun 2013;48(6):563-570. PMID 23129540
22. Dweik RA, Sorkness RL, Wenzel S, et al. Use of exhaled nitric oxide measurement to identify a reactive, at-risk phenotype among patients with asthma. *Am J Respir Crit Care Med.* May 15 2010;181(10):1033-1041. PMID 20133930
23. Perez-de-Llano LA, Carballada F, Castro Anon O, et al. Exhaled nitric oxide predicts control in patients with difficult-to-treat asthma. *Eur Respir J.* Jun 2010;35(6):1221-1227. PMID 19996191
24. Matsunaga K, Hirano T, Oka A, et al. Persistently high exhaled nitric oxide and loss of lung function in controlled asthma. *Allergol Int.* Jul 2016;65(3):266-271. PMID 26822895
25. Bjerregaard A, Laing IA, Backer V, et al. High fractional exhaled nitric oxide and sputum eosinophils are associated with an increased risk of future virus-induced exacerbations: A prospective cohort study. *Clin Exp Allergy.* Aug 2017;47(8):1007-1013. PMID 28390083
26. 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):410-418. PMID 11897984
27. 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):453-459. PMID 15901605
28. Knuffman JE, Sorkness CA, Lemanske RF, Jr., 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):411-416. PMID 19121860
29. 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
30. 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):218-225. PMID 25268339
31. 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):1705-1707. PMID 25142486
32. 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):804-811. PMID 23471469
33. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Exhaled nitric oxide monitoring as a guide to treatment decisions in chronic asthma. *TEC Assessments.* 2005;Volume 20:Tab 17.
34. 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 35. 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
36. Honkoop PJ, Loijmans RJ, Termeer EH, et al. Symptom- and fraction of exhaled nitric oxide-driven strategies for asthma control: A cluster-randomized trial in primary care. *J Allergy Clin Immunol.* Mar 2015;135(3):682-688.e611. PMID 25174865
37. 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):987-997. PMID 22968888
38. O'Connor GT, Reibman J. Inhaled corticosteroid dose adjustment in mild persistent asthma [editorial]. *JAMA.* Sep 12 2012;308(10):1036-1037. PMID 22968893
39. Rouhos A, Kainu A, Piirila P, et al. Repeatability of exhaled nitric oxide measurements in patients with COPD. *Clin Physiol Funct Imaging.* Jan 2011;31(1):26-31. PMID 21143751

40. 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
41. Papi A, Romagnoli M, Baraldo S, et al. Partial reversibility of airflow limitation and increased exhaled NO and sputum eosinophilia in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* Nov 2000;162(5):1773-1777. PMID 11069811
42. 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
43. Guilleminault L, Saint-Hilaire A, Favelle O, et al. Can exhaled nitric oxide differentiate causes of pulmonary fibrosis? *Respir Med.* Nov 2013;107(11):1789-1796. PMID 24011803
44. 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):477-485. PMID 24597492
45. 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 1 2009;180(9):846-852. PMID 19661244
46. 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):1325-1333. PMID 14555562
47. 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
48. Davis MD, Montpetit A, Hunt J. Exhaled breath condensate: an overview. *Immunol Allergy Clin North Am.* Aug 2012;32(3):363-375. PMID 22877615
49. 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):135-139. PMID 15699785
50. Hunt J. Exhaled breath condensate: an overview. *Immunol Allergy Clin North Am.* Nov 2007;27(4):587-596; v. PMID 17996577
51. Kazani S, Israel E. Exhaled breath condensates in asthma: diagnostic and therapeutic implications. *J Breath Res.* Dec 2010;4(4):047001. PMID 21383487
52. 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
53. 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):419-442. PMID 23401497
54. 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):741-757. PMID 26896172
55. 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
56. Navratil M, Plavec D, Bulat Lokas S, et al. Urates in exhaled breath condensate as a biomarker of control in childhood asthma. *J Asthma.* Nov 11 2014:1-37. PMID 25387148
57. 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):1492-1497. PMID 20656939
58. National Institute for Health and Care Excellence (NICE). Measuring fractional exhaled nitric oxide concentration in asthma: NIOX MINO, NIOX VERO, and NObreath. 2014; http://www.nice.org.uk/guidance/dg12/chapter/1-recommendations. Accessed August 9, 2017.
59. 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.
60. National Heart Lung and Blood Institute. National Heart Lung and Blood Institute Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. 2007; https://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines. Accessed August 8, 2017.

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