

## Corporate Medical Policy

### Exhaled Nitric Oxide Measurement

<b>File Name:</b>	exhaled_nitric_oxide_measurement
<b>Origination:</b>	2/2009
<b>Last CAP Review:</b>	3/2012
<b>Next CAP Review:</b>	3/2013
<b>Last Review:</b>	3/2012

#### Description of Procedure or Service

---

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 are proposed. These techniques are also potentially useful in the management of other conditions such as chronic obstructive pulmonary disease (COPD) and chronic cough. There are commercially available devices for measuring nitric oxide in expired breath and various laboratory techniques for evaluating components of exhaled breath condensate.

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 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.

Two proposed strategies are the measurement of exhaled nitric oxide and the evaluation of exhaled breath condensate. Nitric oxide is an important endogenous messenger and inflammatory mediator that is widespread in the human body, functioning, for example, to regulate peripheral blood flow, platelet function, immune reactions, and neurotransmission and to mediate inflammation. In biologic tissues, nitric oxide is unstable, limiting measurement. However, in the gas phase, nitric oxide is fairly stable, permitting its measurement in exhaled air. Exhaled nitric oxide is typically measured during single breath exhalations. First, the subject inspires nitric oxide-free air via a mouthpiece until total lung capacity is achieved, followed immediately by exhalation through the mouthpiece into the measuring device. Several devices measuring exhaled NO are commercially available in the United States. According to a 2009 joint statement by the American Thoracic Society and European Respiratory Society, there is a consensus that the fractional concentration of exhaled nitric oxide (FeNO) is best measured at an exhaled rate of 50 mL per second (FeNO 50 mL/s) maintained within 10% for more than 6 seconds at an oral pressure between 5 and 20 cm H<sub>2</sub>O. (1) Results are expressed as the nitric oxide concentration in parts per billion (ppb), based on the mean of 2 or 3 values.

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 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.

Measurement of nitric oxide and EBC has been investigated in the diagnosis and management of asthma.

# Exhaled Nitric Oxide Measurement

Potential uses in management of asthma 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 and primary ciliary dyskinesia.

## **Regulatory Status**

In 2003, the U.S. Food and Drug Administration (FDA) cleared for marketing the Nitric Oxide Monitoring System (NIOX) (Aerocrine; Sweden) with the following indication: “[Measurements of the fractional nitric oxide (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 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.” 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 hand-held and portable and that it is not suitable for children under age 7 years.

The Breathmeter (Ekipstech) is another device used to measure exhaled nitric oxide using laser spectroscopy. As of November 2010, the Breathmeter is available for research only; it has not yet received FDA approval or clearance.

The RTube Exhaled Breath Condensate collection system (Respiratory Research, Inc) is registered with the FDA as a Class I device that collects expired gas. Respiratory Research has a proprietary gas-standardized pH assay, which, when performed by the company, is considered a laboratory-developed test.

***\*\*\*Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

## **Policy**

---

**Measurement of exhaled or nasal nitric oxide or exhaled breath condensate is considered investigational for the diagnosis and management of asthma and other respiratory disorders. BCBSNC does not provide coverage for investigational services or procedures.**

## **Benefits Application**

---

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

## **When Exhaled Nitric Oxide Measurement is covered**

---

Not applicable.

## **When Exhaled Nitric Oxide Measurement is not covered**

---

Measurement of exhaled or nasal nitric oxide 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.

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.

# Exhaled Nitric Oxide Measurement

## Policy Guidelines

---

Evaluation of exhaled nitric oxide and exhaled breath condensate are proposed as techniques to diagnose and monitor asthma and other respiratory conditions.

Several prospective studies have addressed FeNO measurement; however, there is still no standardized and validated cut-off to use for diagnosing asthma. Multiple randomized controlled studies have evaluated the use of FeNO tests for the management of patients and have not consistently found improvement in health outcomes. Moreover, a 2009 Cochrane review pooling results of studies evaluating FeNO in the management of patients with asthma found a high degree of variability among studies and did not recommend routine use of FeNO in clinical practice. A 2011 RCT with pregnant women who had asthma found better outcomes in the group managed using a FeNO algorithm than standard care. In this study, as in many others, there are concerns that differences in treatment regimens that arise as a result of different algorithms may confound the outcomes, particularly in cases where the control algorithm may lead to undertreatment.

There is less evidence on the utility of FeNO for the diagnosis and management of other respiratory disorders. There are also few studies on exhaled breath condensate evaluation for the diagnosis and treatment of asthma and other conditions. Thus, the evidence is insufficient to determine the effect of exhaled nitric oxide and exhaled breath condensate tests on health outcomes.

American Thoracic Society/European Respiratory Society (ATS):

In 2011, the ATS published a clinical practice guideline on interpretation of FeNO levels. The guideline was critically appraised using criteria developed by the Institute of Medicine (IOM) which includes 8 standards. The guideline was judged to not adequately meet the following standards: Standard 3: guideline development group composition; Standard 4: clinical practice guideline-systematic review intersection; Standard 5: Establishing evidence foundation for and rating strength of recommendations; and Standard 7: external review.

## Billing/Coding/Physician Documentation Information

---

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at [www.bcbsnc.com](http://www.bcbsnc.com). They are listed in the Category Search on the Medical Policy search page.

*Applicable codes: 95012, 83987*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

## Scientific Background and Reference Sources

---

BCBSA TEC Assessment [Electronic Version]. February 2006

Hailey D. Nitric oxide measurement system (NIOX®) for monitoring response to asthma treatment. Canadian Coordinating Office for Health Technology Assessment (CCOHTA). Emerging Technology List No. 22. July 2004. Retrieved 2/2/09 from [http://www.cadth.ca/media/pdf/152\\_No22\\_NIOX\\_etech.pdf](http://www.cadth.ca/media/pdf/152_No22_NIOX_etech.pdf)

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.01.61, 11/13/08

# Exhaled Nitric Oxide Measurement

Reddel HK, Taylor DR, Batement 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(1):59-99. Available at: <http://ajrccm.atsjournals.org/cgi/reprint/180/1/59>

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.01.61, 12/09/10

Specialty Matched Consultant Advisory Panel review meeting 3/30/11

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.01.61, 12/8/11

Specialty Matched Consultant Advisory Panel review 3/2012

## Policy Implementation/Update Information

---

- |         |  |
|---------|--|
| 3/2/09  | New policy issued. Measurement of exhaled or nasal nitric oxide, or collection and analysis of exhaled breath condensate, is considered investigational in the diagnosis and management of asthma and other respiratory disorders. (adn)   |
| 6/22/09 | Specialty Matched Consultant Advisory Panel review meeting 5/13/09. No change in policy statement.   |
| 1/5/10  | CPT Code 0140T deleted and replaced with CPT 83987.  |
| 6/22/10 | Policy Number(s) removed (amw)   |
| 2/15/11 | CPT Code 0064T deleted from Billing/Coding section. (adn)  |
| 4/12/11 | Description and Policy Guidelines sections extensively revised. Not Covered section changed to read: "Measurement of exhaled or nasal nitric oxide is considered <b>investigational</b> in the diagnosis and management of asthma and other respiratory disorders including but not limited to chronic obstructive pulmonary disease and chronic cough. Measurement of exhaled breath condensate is considered <b>investigational</b> in the diagnosis and management of asthma and other respiratory disorders including but not limited to chronic obstructive pulmonary disease and chronic cough." Specialty Matched Consultant Advisory Panel review meeting 3/30/11. |
| 3/30/12 | Specialty Matched Consultant Advisory Panel review 3/2012. Added references and updated policy guidelines. No change to policy statement. (lpr)  |

---

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.