

SUBJECT: MEASUREMENT OF EXHALED MARKERS OF AIRWAY INFLAMMATION IN PATIENTS WITH ASTHMA

POLICY NUMBER: 2.01.41

CATEGORY: Technology Assessment

EFFECTIVE DATE: 04/15/04

REVISED DATE: 02/17/05, 12/15/05, 02/16/06, 12/21/06, 11/15/07, 11/20/08, 11/19/09, 11/18/10, 01/19/12, 03/21/13, 01/16/14

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- *If the member's subscriber contract excludes coverage for a specific service it is not covered under that contract. In such cases, medical policy criteria are not applied.*
- *Medical policies apply to commercial and Medicaid products only when a contract benefit for the specific service exists.*
- *Medical policies only apply to Medicare products when a contract benefit exists and where there are no National or Local Medicare coverage decisions for the specific service.*

POLICY STATEMENT:

- I. Based upon our criteria and assessment of peer-reviewed literature, measurement of exhaled or nasal nitric oxide, as yet, has not demonstrated a benefit to patient outcomes and is considered **not medically necessary** in the diagnosis and management of asthma.
- II. Based upon our criteria and assessment of peer-reviewed literature, the collection and analysis of exhaled breath condensate as yet, has not demonstrated a benefit to patient outcomes and is considered **not medically necessary** in the diagnosis and management of asthma.

POLICY GUIDELINES:

The Federal Employee Health Benefit Program (FEHBP/FEPE) requires that procedures, devices or laboratory tests approved by the U.S. Food and Drug Administration (FDA) may not be considered investigational and thus these procedures, devices or laboratory tests may be assessed only on the basis of their medical necessity.

DESCRIPTION:

Guidelines for the management of persistent asthma stress the importance of long-term suppression of inflammation using corticosteroids, leukotriene inhibitors or other anti-inflammatory drugs. Existing techniques for monitoring the status of underlying inflammation currently are limited but include bronchoscopy with lavage and biopsy or analysis of induced sputum. Due to the nature of these techniques, ongoing assessment of asthma has traditionally focused less on the status of underlying inflammation and more on assessment of pulmonary function tests such as peak flow rates and FEV1/FVC. Therefore, there has been interest in noninvasive techniques to assess the underlying pathogenic chronic inflammation as reflected by measurements of inflammatory mediators. Two strategies that have been investigated include measuring exhaled nitric oxide and the evaluation of exhaled breath condensate.

Nitric oxide is an important endogenous messenger that is widespread in the human body, functioning for example, to regulate peripheral blood flow, platelet function, immune reactions, neurotransmission and as an inflammatory mediator. In the gas phase, nitric oxide is fairly stable, permitting measurement in exhaled air. Recent studies defining the normal and abnormal values in different age groups have shown that asthma patients have nitric oxide measurements in the range of 25-85 ppb (part per billion) compared to control patients whose exhaled nitric oxide measurement is generally less than 20 ppb.

Exhaled breath condensate (EBC) has been investigated as another technique to assess pathogenic chronic inflammation in asthma. 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. The pH of EBC can also be measured. Various studies have focused on different components of EBC as inflammatory markers in respiratory disease.

The following clinical roles for measurement of nitric oxide and EBC have been investigated in the diagnosis and management of asthma:

- I. Diagnosis of asthma – as an alternative or adjunct to spirometry;

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- II. Response to anti-inflammatory treatment – declining levels suggest declining inflammation;
- III. Monitoring compliance of anti-inflammatory treatment – persistent elevation may suggest poor compliance with long-term therapy;
- IV. Detection of corticosteroid resistance – reflected by persistently high nitric oxide levels despite corticosteroid treatment;
- V. Prediction of exacerbation – increasing levels of nitric oxide may precede onset of clinical symptoms or changes in peak flow values; and
- VI. Dose optimization – to guide dosing of anti-inflammatory medications.

Aside from asthma, the following clinical applications for nitric oxide measurement have been proposed:

- I. Assessment of chronic cough – chronic cough may be related to smoking, postnasal drip, gastroesophageal reflux, COPD or asthma. Elevation of exhaled nitric oxide may point to asthma as the etiology.
- II. Assessment of cystic fibrosis – exhaled nitric oxide appears to be decreased in patients with CF.
- III. Rhinitis – nasal nitric oxide (as opposed to exhaled nitric oxide) may be increased in patients with allergic rhinitis.
- IV. Primary ciliary dyskinesia – nasal nitric oxide may be decreased in patients with this condition.

RATIONALE:

Exhaled Nitric Oxide

In 2003, the FDA approved the Nitric Oxide Monitoring System (NIOX) as a device intended to measure changes in fractional exhaled nitric oxide concentration in human breath to aid in evaluating an asthma patient's response to anti-inflammatory therapy, as an adjunct to established clinical and laboratory assessment of asthma. NIOX cannot be used with infants or by children approximately under the age of four, as measurement requires patient cooperation. NIOX should not be used in critical care, emergency care or in anesthesiology. The Breathmeter is another device used to measure exhaled nitric oxide using laser spectroscopy. The Breathmeter has not yet received FDA approval.

While many studies demonstrate the potential role of measurements of exhaled nitric oxide in the diagnosis and management of asthma, few well-designed, controlled studies that compare the conventional diagnosis and management of asthma to diagnosis and management utilizing measurement of exhaled nitric oxide have been published. Compared to asthma, the data regarding the measurement of exhaled nitric oxide is more limited for other respiratory conditions, including COPD, cystic fibrosis and ciliary dyskinesia.

The 2007, National Asthma Education and Prevention Program of the National Health Lung and Blood Institute expert panel report on guidelines for the diagnosis and management of asthma does not include measurement of nitric oxide among its recommendations.

The National Heart, Lung, and Blood Institute's Global Initiative for Asthma (GINA) updated its Global Strategy for Asthma Management and Prevention in December 2008. The GINA guidelines state that level of exhaled nitric oxide has been suggested as a noninvasive marker of airway inflammation in asthma. Levels of nitric oxide are elevated in people with asthma who are not taking inhaled glucocorticosteroids, compared to people without asthma, yet these findings are not specific for asthma. The guideline further states that nitric oxide has not been evaluated prospectively as an aid in asthma diagnosis, but these measurements are being evaluated for potential use in determining optimal treatment.

In October 2005, a BCBS TEC Assessment on exhaled nitric oxide monitoring as a guide to treatment decisions in chronic asthma made the following conclusions:

- I. The available evidence does not permit the conclusion that use of nitric oxide monitoring to guide treatment decisions in asthma leads to improved outcomes.
- II. The two RCTs included in the assessment, Smith and Pijnenburg, suggest possible benefits for nitric oxide monitoring but are not sufficient to conclude that outcomes are improved. Each study reported different benefits that have not been reproduced. Smith reported that equivalent outcomes were achieved in the nitric oxide group, with a lower overall dose of inhaled corticosteroids. Pijnenburg reported that bronchial hyper-reactivity was

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improved in the nitric oxide group. However, bronchial hyper-reactivity is an intermediate outcome that is not well benchmarked to true health outcomes.

- III. Differences in the control management strategy raise questions about the optimal management strategy to which nitric oxide monitoring should be compared.
- IV. The 7 studies that evaluated the ability of nitric oxide to provide prognostic information that could lead to changes in management had considerable methodologic limitations and variability in study methodology that precluded synthesis of their results and definitive conclusions.

Based on the available evidence, the BCBS Medical Advisory Panel determined that the use of ENO levels for monitoring patients with chronic asthma does not meet TEC criteria.

Exhaled Breath Condensate

The basic technique of collecting EBC consists of a technique to cool exhaled air and collect EBC droplets. One commercially available system, the RTube consists of a disposable polypropylene condensation chamber that is cooled by an overlying aluminum-cooling sleeve. There is 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.

Similar to exhaled nitric oxide, there is intense research interests in the analysis of exhaled breath condensate (EBC) as a biomarker of inflammation. However, it appears from the published literature that EBC is at an earlier stage of development compared to exhaled nitric oxide. For example, several review articles note that before routine clinical use in the diagnosis and management of respiratory disorders can be considered the following issues must be resolved:

- I. Standardization of collection and storage techniques,
- II. Effect of dilution of respiratory droplets by water vapor,
- III. Techniques of measuring concentrations of nonvolatile substances in EBC; in most cases these concentrations are very low, which may be at the lower limits of detection of conventional analytic techniques,
- IV. Variability in EBC assays for certain substances,
- V. Further investigation of levels of compounds in health and disease.

The National Heart, Lung, and Blood Institute's GINA Global Strategy for Asthma Management and Prevention, updated in 2007, makes no mention of measurement of EBC.

Ultimately, controlled trials will be required to determine how evaluated of exhaled breath condensate can be used to direct patient management. The National Institute of Allergy and Infectious Disease is currently recruiting asthmatic children to a clinical trial evaluating the use of pH measurement of EBC in the management of asthma. This trial will evaluate both asthmatic patients and normal controls with EBC pH, expired nitric oxide, pulmonary lung function tests and peak flow meters over a period of a year. Neither exhaled nitric oxide or EBC pH are used in the management of the patient, but the study will determine whether these measures are correlated of known parameters of disease including number of hospitalizations, absenteeism from school, number of asthma exacerbations, lost work days (if applicable), and extent of rescue medication used.

CODES: **Number** **Description**

Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.

CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.

Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.

Code Key: Experimental/Investigational = (E/I), Not medically necessary/ appropriate = (NMN).

CPT: **95012 (NMN)** Nitric Oxide expired gas determination

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83987 (NMN) Exhaled breath condensate pH

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HCPCS: No specific codes

ICD9: Not Medically Necessary for all diagnoses

ICD10: Not Medically Necessary for all diagnoses

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* key article

KEY WORDS:

Exhaled nitric oxide, asthma, NIOX, exhaled breath condensate

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently no National Coverage Determination (NCD) or Local Coverage Determination (LCD) for Measurement of Exhaled Markers of Airway Inflammation in Patients with Asthma.