

## Medical Coverage Policy | Measurement of Exhaled Nitric Oxide and Exhaled Breath Condensate in the Diagnosis and Management of Respiratory Disorders



**EFFECTIVE DATE:** 03|03|2015

**POLICY LAST UPDATED:** 10|16|2018

### OVERVIEW

Evaluation of exhaled nitric oxide (NO) and exhaled breath condensate (EBC) are proposed as techniques to diagnose and monitor asthma and other respiratory conditions. 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

Measurement of exhaled nitric oxide and exhaled breath condensate is not covered in the diagnosis and management of asthma and other respiratory disorders including, but not limited to, chronic obstructive pulmonary disease and chronic cough as the evidence is insufficient to determine the effect of the technology on health outcomes.

#### 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 as the evidence is insufficient to determine the effect of the technology on health outcomes.

### COVERAGE

Benefits may vary between groups and contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage or Subscriber Agreement for applicable not medically necessary/not covered benefits/coverage.

### BACKGROUND

#### ASTHMA

Asthma is characterized by airway inflammation that leads to airway obstruction and hyperresponsiveness, 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 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 and Exhaled Breath Condensate***

Two proposed strategies are the measurement of fractional exhaled nitric oxide (FeNO) and the evaluation of exhaled breath condensate (EBC). 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. While the role of NO in asthma pathogenesis is still under investigation, 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. Several devices measuring FeNO are commercially available in the United States. According to a 2009 joint statement by the American Thoracic Society and European Respiratory Society, there is 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<sub>2</sub>O. Results are expressed as the NO concentration in parts per billion, based on the mean of 2 or 3 values.

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 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***

Measurement of FeNO has 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. 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 antibody has also been shown to improve uncontrolled asthma, with the greatest improvement observed in the subgroup of patients with the highest blood eosinophil count.

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.

In 2003, the Nitric Oxide Monitoring System (NIOX®; Aerocrine; acquired by Circassia Pharmaceuticals) was cleared for marketing by FDA through the 510(k) process for 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 2008, the NIOX MINO® was cleared for marketing by FDA through the 510(k) process. The main differences between these 2 devices are that the NIOX MINO® is handheld, portable, and unsuitable for

children younger than seven years old. In 2014, the NIOX VERO®, which differs from predicate devices in terms of its battery and display format, was also cleared for marketing by FDA through the 510(k) process.

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 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 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. The available evidence is limited by variability in FeNO cutoff levels used to diagnose asthma, and lack of data on performance characteristics in diagnostic challenging settings. 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. 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 diagnostic accuracy studies, 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. For the use of FeNO to identify eosinophilic asthma for the purpose of selecting patients for therapy with anti-interleukin-5 therapy, using the criterion standard of sputum eosinophilia, the diagnostic accuracy of FeNO is moderate. 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 how the test fits in defined clinical management pathways. 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**

The following CPT codes are not covered for BlueCHiP for Medicare and not medically necessary for Commercial Products:

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

## RELATED POLICIES

Not applicable

## PUBLISHED

Provider Update, January 2019

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