Protocol

Measurement of Exhaled Nitric Oxide and Exhaled Breath Condensate in the Diagnosis and Management of Respiratory Disorders

(20161)

Medical Benefit		**Effective Date**: 07/01/12	**Next Review Date**: 03/19
Preauthorization	No	**Review Dates**: 07/07, 07/08, 05/09, 03/10, 03/11, 03/12, 05/12, 03/13, 03/14, 03/15, 03/16, 03/17, 03/18	

This protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • With suspected asthma	Interventions of interest are: • Measurement of fractional exhaled nitric oxide	Comparators of interest are: • Standard clinical diagnosis	Relevant outcomes include: • Test accuracy • Test validity • Symptoms • Change in disease status • Morbid events • Functional outcomes
Individuals: • With suspected eosinophilic asthma	Interventions of interest are: • Measurement of fractional exhaled nitric oxide	Comparators of interest are: • Sputum eosinophil measurement	Relevant outcomes include: • Test accuracy • Test validity • Symptoms • Change in disease status • Morbid events • Functional outcomes
Individuals: • With asthma	Interventions of interest are: • Medication management directed by fractional exhaled nitric oxide	Comparators of interest are: • Standard clinical management	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Functional outcomes
Individuals: • With suspected or confirmed respiratory disorders other than asthma	Interventions of interest are: • Measurement of fractional exhaled nitric oxide	Comparators of interest are: • Standard clinical diagnosis and management	Relevant outcomes include: • Test accuracy • Test validity • Symptoms • Change in disease status • Morbid events • Functional outcomes

Populations	Interventions	Comparators	Outcomes
Individuals: • With suspected or confirmed respiratory disorders	Interventions of interest are: • Measurement of exhaled breath condensate	Comparators of interest are: • Standard clinical diagnosis and management	Relevant outcomes include: • Test accuracy • Test validity • Symptoms • Change in disease status • Morbid events • Functional outcomes

Description

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.

Summary of Evidence

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 one 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 potential clinical 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.

Policy

Measurement of exhaled 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.

Background

Asthma Overview

Asthma is characterized by airway inflammation that leads to airway obstruction and hyperresponsiveness, which in turn leads 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 one 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 FeNO and the evaluation of EBC. 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 six seconds at an oral pressure between five and

20 cm H2O[1]. Results are expressed as the NO concentration in parts per billion, based on the mean of two or three values.

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 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

Measurements of FeNO have particularly 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.[2] Until recently, most asthma management strategies did not depend on the recognition or diagnosis of a particular subtype. However, two anti-interleukin 5 inhibitors have been approved by the Food and Drug Administration (FDA) for the treatment of severe asthma with an eosinophilic phenotype, mepolizumab[3] and reslizumab.[4] 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.[5]

Measurement of NO and EBC has been investigated in the diagnosis and management of asthma. Potential uses in the 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, pulmonary hypertension, and primary ciliary dyskinesia.

Regulatory Status

In 2003, the Nitric Oxide Monitoring System (NIOX®; Aerocrine, Sweden; acquired by Circassia Pharmaceuticals, Oxford, U.K.) was cleared for marketing by the 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 March 2008, the NIOX MINO® was cleared for marketing by the FDA through the 510(k) process. The main differences between this new device and the NIOX® are that the NIOX MINO® is handheld, portable, and unsuitable for children younger than seven years old. In November 2014, the NIOX VERO®, which differs from predicate devices in terms of its battery and display format, was also cleared for marketing by the FDA through the 510(k) process. FDA product code: MXA.

The RTube™ Exhaled Breath Condensate collection system (Respiratory Research, Austin, TX) and the ECoScreen EBC collection system (CareFusion, Germany) are registered with 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.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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