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**: 03/21
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, 03/19, 03/20	

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 for diagnosis	Comparators of interest are: • Standard clinical diagnosis	Relevant outcomes include: • 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 eosinophilic asthma	Interventions of interest are: • Measurement of fractional exhaled nitric oxide to select treatment	Comparators of interest are: • Sputum or blood eosinophil measurement	Relevant outcomes include: • Test validity • 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 validity • Symptoms • Change in disease status • Morbid events • Functional 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 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 is a commercially available device for measuring NO in expired breath and various laboratory techniques for evaluating components of EBC.

SUMMARY OF EVIDENCE

For individuals who have suspected asthma who receive a measurement of fractional exhaled nitric oxide (FeNO) for diagnosis, the evidence includes multiple retrospective and prospective studies of diagnostic accuracy, along with systematic reviews of those studies. Relevant outcomes are test 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 (or with unclear previous testing), which is unlikely to be how the test is used in a U.S. setting. The available evidence is limited by variability in FeNO cutoff levels used to diagnose asthma, lack of data on performance characteristics in diagnostic challenging settings, and lack of data on the incremental value of adding FeNO to existing diagnostic algorithms from studies with concurrent controls. Limitations of the published evidence preclude determining the effects of the technology on net health outcome. Evidence reported through clinical input suggests a possible adjunctive role when conventional testing may be limited, particularly where diagnosis with standard clinical diagnostic testing (e.g., routine spirometry) may be limited such as in pediatric patients. However, the published evidence does not show whether FeNO testing in such patients would be clinically feasible and clinically valid to be clinically useful. 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 (RCTs), and systematic reviews of those trials. Relevant outcomes are symptoms, change in disease status, morbid events, and functional outcomes. The available RCTs evaluating the use of FeNO tests to guide step-up/step-down therapy in 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 to guide step-up/step-down therapy reduced the number of individuals who had more than one exacerbation in children but not in adults compared with guidelines-driven therapy but had no impact on day-to-day symptoms or hospitalizations. Limitations of the published evidence preclude determining the effects of the technology on net health outcome. Evidence reported through clinical input suggests a possible adjunctive role for FeNO testing particularly for individuals who may have limited awareness of worsening symptoms or when there is suspected nonadherence to medication. However, the published evidence does not examine this subgroup to demonstrate that use of FeNO testing in such patients may be clinically useful to inform treatment decisions by reducing or avoiding unnecessary asthma therapy, or by indicating when step-up therapy is warranted. The evidence is insufficient to determine the effect of the technology on health outcomes.

For individuals who have suspected eosinophilic asthma who receive a measurement of FeNO to select a therapy, the evidence includes diagnostic accuracy studies and subgroup analyses of RCTs and observational studies. Relevant outcomes are symptoms, change in disease status, morbid events, and functional outcomes. For the use of FeNO to identify eosinophilic asthma for the purpose of selecting patients for therapy with anti-interleukin (IL)-5 therapy or an anti-IL-4 and -13 monoclonal antibody, subgroup analyses of RCTs are available. The evidence that points toward an interaction between baseline FeNO and treatment for the outcome of response suggests that there may be a quantitative but not necessarily a qualitative interaction between baseline FeNO and anti-IL-4 treatment (dupilumab), i.e., it is unclear if baseline FeNO can identify a group for whom there is no

benefit from dupilumab. Similarly, a 48-week multicenter prospective observational study with over 700 participants found that asthma exacerbations were reduced with omalizumab over a 12-month treatment period irrespective of baseline FeNO. Limitations of the published evidence preclude determining the effects of the technology on net health outcome. Evidence reported through clinical input suggests a possible adjunctive role for FeNO testing when it may be particularly difficult to confirm the presence of eosinophils using more invasive methods such as induced sputum or bronchiolar lavage. However, the published evidence does not show whether the adjunctive use of FeNO testing provides significant improvement in net health outcome when conventional testing for the presence of eosinophils is limited or infeasible. 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 a measurement of FeNO, the evidence includes a crossover trial and observational studies. Relevant outcomes are test 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 provided by clinical input was not supportive of the use of FeNO testing for respiratory disorders other than asthma to improve the net health outcome. 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 a measurement of EBC, the evidence includes observational studies reporting on the association between various EBC components and disease severity. Relevant outcomes are test 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 available published evidence does not support conclusions on the utility of EBC for any indication. The evidence provided by clinical input was not supportive of the use of EBC as a test to improve the net health outcome. 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, eosinophilic 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

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 one second and peak flow. Therefore, there has been an interest in noninvasive techniques to assess the underlying pathogenic chronic inflammation as reflected by measurements of inflammatory mediators.

Fractional Exhaled Nitric Oxide

One proposed strategy is the measurement of FeNO. 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. 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. Devices measuring FeNO are commercially available in the U.S. According to a joint statement by the American Thoracic Society and European Respiratory Society (2009), there is a 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 5 cm 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.

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 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 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, 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 antibodies have also been shown to improve uncontrolled asthma.[3]

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.

REGULATORY STATUS

The devices in Table 1 are cleared by the FDA for measuring FeNO with FDA product code MXA.

Table 1. FeNO Devices Cleared by FDA

Device	Manufacturer	Indication/Comments	Date Cleared	510(k)
Nitric Oxide Monitoring System (NIOX®)	Aerocrine; acquired by Circassia	"[Measurements …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 four, as measurement requires patient cooperation. NIOX should not be used in critical care, emergency care or in anesthesiology."	2003	De novo DEN030001 K021133
NIOX MINO®	Aerocrine; acquired by Circassia	Same as above except used for ages 7 and older. Handheld and portable.	2008	K072816/KI101034
NIOX VERO®	Aerocrine; acquired by Circassia	Same as MINO®. Differs from predicate devices in terms of its battery and display format	2014	K133898
Fenom Pro™ Nitric Oxide Test	Spirosure	Measurement of FeNO by Fenom Pro™ is a method to measure the decrease in FeNO concentration in asthma patients that often occurs after treatment with anti-inflammatory pharmacological therapy as an indication of therapeutic effect in patients with elevated FeNO levels. FeNO measurements are to be used as an adjunct to established clinical assessments. Fenom Pro™ is suitable for children, approximately 7-17 years, and adults 18 years and older. Testing using the Fenom Pro™ should only be done in a point-of-care healthcare setting under professional supervision. Fenom Pro™ should not be used in critical care, emergency care or in anesthesiology.	2019	K182874

FDA: Food and Drug Administration; FeNO: fractional exhaled nitric oxide.

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

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

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

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