CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

Subject **Exhaled Nitric Oxide and Exhaled Breath Condensate in the Management of Respiratory Disorders**

Effective Date 2/15/2011
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Hyperlink to Related Coverage Policies

Omalizumab (Xolair®)
Peak Flow Meters

Coverage Policy

CIGNA does not cover the measurement of exhaled nitric oxide or exhaled breath condensate for any indication, including the management of asthma and/or other respiratory disorders, because it is considered experimental, investigational or unproven.

General Background

Asthma is a chronic inflammatory disorder of the airways that may cause recurrent episodes of wheezing, breathlessness, chest tightness and coughing. These episodes are typically associated with widespread but variable airflow obstruction that resolves spontaneously or with treatment. The inflammation of asthma may cause an increase in existing bronchial hyper-responsiveness to a variety of stimuli. Many cells and cellular elements play a role in asthma, including mast cells, eosinophils, T lymphocytes, macrophages, neutrophils and epithelial cells. Fibrosis may occur in some patients with asthma, resulting in persistent abnormalities in lung function.

There is currently no direct measure of inflammation that is widely available clinically. Treatment decisions are therefore made based on indirect measures of inflammation, including symptoms scores, spirometry measures, rescue medication use, and/or other indicators of disease activity. The test used most frequently to assess the risk of future adverse events is spirometry, especially forced expiratory volume in one second (FEV_1), reported as a percent of the predicted value or as a proportion of the forced vital capacity, or FEV_1/FVC. A number of biomarkers have been studied in an effort to find a simple, easily applied test whose deviations from normal may correlate with risk severity. Biomarkers that have been proposed include airway hyperresponsiveness, blood or sputum eosinophils, or eosinophilic cationic protein, serum immunoglobulin E, fractional exhaled nitric oxide concentration, and various metabolites in exhaled breath condensate.

Analysis of exhaled nitric oxide has been proposed as a marker of inflammation that could be useful in monitoring disease activity and directing treatment in patients with asthma and other pulmonary conditions. Nitric oxide affects many organ systems, including the lungs, where it acts as a bronchodilator. Nitric oxide is produced by various lung cells from the amino acid l-arginine by different iso-enzymes of nitric oxide synthase. Exhaled nitric oxide levels have been shown to be elevated in patients with asthma, to be higher during periods of acute exacerbation, and to correlate with other measures of inflammation. Analysis of exhaled breath concentrate (EBC) has also been proposed as a noninvasive method of sampling airway secretions and measuring airway inflammation in patients with asthma and chronic pulmonary diseases. EBC is collected by cooling exhaled air as the patient breathes through a condensing apparatus. Analysis of EBC may detect inflammatory mediators, including cytokines, leukotrienes and prostaglandins. Several studies have suggested that the EBC pH is lower in patients with moderate to severe asthma and normalizes after systemic corticosteroid treatment.

Assessment of these markers by analyzing their relationship to the rate of adverse events or decline in pulmonary function over time has not been performed in studies published to date. In addition, the relationship between normalization of a biomarkers and normalization of risk of adverse events may depend on the treatment provided. Outcomes may vary depending on whether treatment includes an inhaled corticosteroid, leukotriene receptor antagonist, or inhaled long-acting beta$_2$-agonist. Although exhaled nitric oxide and exhaled breath condensate may be accurately measured, the clinical utility of these biomarkers has not been established. Evidence published to date has not demonstrated that the measurement of exhaled nitric oxide and exhaled breath condensate results in meaningful improvement in patient outcomes.

U.S. Food and Drug Administration (FDA)
The NIOX Breath Nitric Oxide Test System® (Aerocrine AB, San Diego, CA) received U.S. Food and Drug Administration (FDA) approval to market as a Class II device through the 510(k) process on April 30, 2003. According to the notification letter, the device is intended to aid in evaluating an asthma patient's response to anti-inflammatory therapy by measuring changes in fractional exhaled nitric oxide concentration as an adjunct to established clinical and laboratory assessments of asthma.

The NIOX MINO® (Aerocrine AB, Washington D.C), a hand-held device designed to measure fractional exhaled nitric oxide in human breath, received U.S. FDA 510(k) approval on March 3, 2008. The device was determined to be substantially equivalent to the predicate device, the NIOX System.

The Apieron INSIGHT™ eNO System received U.S. FDA approval through the 510(k) process on March 14, 2008. The device was considered to be substantially equivalent to the predicate device, Aerocrine NIOX System. The intended use is to quantitatively measure exhaled nitric oxide in expired breath as a maker of inflammation for persons with asthma. The system can be used by trained operators in a physician's office laboratory setting, and should not be used in critical care, emergency care, or in anesthesiology.

Literature Review
Exhaled Nitric Oxide: Lemanske et al. (2010) assessed the frequency of differential responses to three blinded step-up treatments for children with uncontrolled asthma while receiving low-does inhaled corticosteroids. Researchers randomly assigned 182 children age 6 to 17 to receive each of three blinded step-up therapies in random order for 16 weeks: 250 micrograms of fluticasone twice daily (ICS step-up); 100 micrograms of fluticasone plus 50 micrograms of a long-acting beta-agonist twice daily (LABA step-up), or 100 micrograms of fluticasone twice daily plus 5 to 10 milligrams of a leukotriene-receptor antagonist daily (LTRA step-up). A triple crossover design and composite of three outcomes (exacerbations, asthma-control days, and forced expiratory volume in one second) were used to determine whether the frequency of a differential response to the step-up regimens was more than 25%. A clinically significant differential response was seen in nearly all the children, and several characteristics of the children predicted the direction of differential responses, including race or ethnic group and two readily available clinical attributes: asthma control, as indicated by the score on the Asthma Control Test, and the presence or absence of eczema. More expensive and labor-intensive measures of physiological factors and biomarkers (e.g., the fraction of exhaled nitric oxide), did not have predictive value.

A retrospective cohort study by Dweil et al. (2010) assessed alterations of fraction of nitric oxide (FE_{NO}) in patients with severe asthma (n=175) as compared to patients with non-severe asthma (271) and healthy controls (n=49), and the relationship between FE_{NO} and asthma severity. Nitric oxide levels were higher in patients with asthma compared to controls, but there was no significant difference on average between severe and non-severe asthma (FE_{NO} control, 17 ±9; non-severe, 43 ± 42; severe, 43 ± 41; p=0.01). The proportion of patients with high FE_{NO} was the same in severe and non-severe asthma (non-severe, 109 of 271 (40%); severe, 70 of 175 (40%. Compared to patients with asthma and low FE_{NO} scores, patients with asthma and high FE_{NO} levels had the greatest airway reactivity, greatest degree of airflow limitation and most hyperinflation, and high numbers of sputum eosinophils. Emergency room use and intensive care admissions were greatest in this group, although they were less likely to have seen a physician in the prior 12 months. High FE_{NO} also identified a more severe subgroup among the non-severe asthma patients; this group shared more similarities with patients with severe asthma and high FE_{NO}. The authors stated that the availability of a noninvasive marker would greatly simplify and improve severe asthma management, and evaluation of multiple quantitative biologic markers, including FE_{NO}, may provide a cumulative index for definition of asthma severity in the future. The authors acknowledged the fact that the retrospective nature of the study precludes determination of whether FE_{NO} could predict future risk or exacerbations in asthma, but that the correlation with ER visits and hospital admissions suggests the potential for FE_{NO} in identification of patients with the most severe disease. The authors further stated that prospective studies would be helpful in determining whether FE_{NO} could predict future risk of exacerbations in asthma, as suggested by these findings.

De Jongste et al. (2008) conducted a randomized parallel group study to assess daily fraction of nitric oxide (FE_{NO}) monitoring in the management of childhood asthma (n=151). Children with atopic asthma were assigned to two groups: FE_{NO} plus symptom monitoring (n=77) or monitoring of symptoms alone (n=74). Two children in each group were excluded form analysis due to non-compliance, inappropriate inclusion, or unavailability. Patients tracked asthma symptoms in an electronic diary over a 30 week period. Children in the FE_{NO} group performed daily measurements with a NIOX MINO portable monitor, transmitting the data to the coordinating center. Patients were phoned every three weeks, and steroid doses were adjusted based on FE_{NO} and symptoms, or symptoms alone. All patients were seen at randomization and at 3, 12, 21, and 30 weeks. All patients showed an improvement in symptom-free days, improvement in forced expiratory volume in one second (FEV_1) and quality of life, and a reduction in steroid dose. None of the changes from baseline differed between the groups, although there was a trend toward fewer exacerbations in the FE_{NO} group. The difference in symptom-free days over the latest 12 weeks was 0.3% (p=0.95). The authors found no added value of daily FE_{NO} monitoring compared with daily symptom monitoring only.

Petsky et al. (2008) published a Cochrane systematic review on tailored interventions based on ENO vs. clinical symptoms for asthma in children and adults. The review included a single-blind placebo-controlled trial by Smith, et al. (2005); a double-blind, randomized controlled trial by Pijnenburg et al. (2005); and randomized single-blind controlled trials by Fritsch et al. (2006) and Shaw, et al. (2007). The authors stated that tailoring the dose of inhaled corticosteroids based on ENO in comparison to clinical symptoms was carried out in different ways in the four studies, and the results show only modest differences. There was no difference between the two strategies in both adult and pediatric studies in the primary outcome of exacerbation, forced expiratory volume in one second (FEV_1), FE_{NO} levels, or symptom control scores. The only difference found between the two groups was the final daily does of inhaled corticosteroids in adults. This finding was based on post-hoc analysis, however. In children, in whom high inhaled corticosteroid doses are of more concern because of potential adverse events, there was no difference between the two groups, and the data in children actually favored the control group. The authors concluded that the role of utilizing ENO to tailor the dose of inhaled corticosteroids is currently uncertain.

Szefler et al. (2008) conducted a randomized controlled trial to assess whether measurement of exhaled nitric oxide as a biomarker of airway inflammation could increase the effectiveness of asthma treatment for inner-city adolescents and young adults, when used as an adjunct to clinical care based on asthma guidelines. A total of 546 patients aged 12–20 with persistent asthma were randomized to 46 weeks of standard treatment based on guidelines of the National Asthma Education and Prevention Program (n=270) or to treatment modified on the basis of fraction of ENO (n=276). The primary outcome measure, the mean number of days with asthma symptoms, did not differ between the treatment groups (p=0.780). Asthma management that incorporated measurement of fraction of ENO resulted in higher doses of corticosteroids than did management with standard guidelines (p=0.001). This treatment was associated with a small reduction in the need for courses of prednisone, but did not result in an overall improvement in asthma symptoms, lung function or need for health care.

Shaw et al. (2007) conducted a randomized, controlled, single-blind trial to test the hypothesis that the use of fraction of exhaled nitric oxide (FE_{NO}) for titrating corticosteroid dose results in fewer exacerbations and more efficient use of corticosteroid therapy. Patients with a primary care diagnosis of asthma were randomized to corticosteroid therapy based on either FE_{NO} measurement (n=58) or British Thoracic Society guidelines (n=60). Patients were assessed monthly for the first four months, then semimonthly for an additional eight months. The primary outcome was the number of severe asthma exacerbations. The rate of exacerbations in the FE_{NO} group was 0.33 per patient per year compared to 0.42 in the control group (p=0.43). The total amount of inhaled corticosteroid used during the study was 11% greater in the FE_{NO} group than in the control group (p=0.40), although the final daily dose of inhaled corticosteroid was significantly lower in the FE_{NO} group than in the control group (557 vs. 895 micrograms, p=0.028). The authors stated that an asthma treatment strategy based on the measurement of FE_{NO} did not result in a large reduction in asthma exacerbations or in the total amount of inhaled corticosteroid therapy used over 12 months when compared to current asthma guidelines.

The Canadian Coordinating Office of Health Technology (CCOHT) assessment of the NIOX system (Hailey, 2004) states that while this may be an option for clinical assessment of patients' compliance and response to medications, no information was found on the extent to which the use of this device improves patients' compliance with medication use or ensures appropriate prescribing. The CCOHT assessment states that comparative measures to assess such measures of efficacy would be desirable.

Exhaled Breath Condensate (EBC) pH: Leung et al. (2006) evaluated the factors determining EBC pH in 58 asthmatic children and the reproducibility and effects of collection devices on EBC pH in nine healthy adults. EBC was collected once from asthmatic children using EcoScreen and from adults over three consecutive days using both RTubes and EcoScreen. EBC ph was measured immediately by microelectrode pH meter. EBC pH was lower among patients with moderate-to-severe persistent asthma than in those with intermittent asthma. There was poor correlation between pH in EBC collected by RTube and EcoScreen. The authors stated that pH in non-deaerated EBC is influenced by asthma severity in children, and that EBC pH measurement is reproducible but is dependent on the collection device used. The authors concluded that longitudinal monitoring of EBC pH in asthmatic patients is needed to determine the clinical utility of measuring this marker in childhood asthma.

Carpagnano et al. (2005) investigated the usefulness of measuring exhaled markers in 28 patients with mild persistent asthma. The effect of inhaled steroids on these markers was also evaluated. Results were compared to those of 15 healthy patients. EBC was collected using a condenser. The patients breathed through a mouthpiece and a two-way non-rebreathing valve, which also served as a saliva trap. The pH of EBC was lower in asthmatic patients (7.39 ± 0.11) than in controls (7.85 ± 0.14) but trended toward control levels after two months of inhaled steroid treatment.

Carpagnano et al. (2004) conducted a case control study to determine whether there is a change in pH of EBC in children with cystic fibrosis and asthma and to assess whether EBC pH could be used as a marker of airway inflammation. The authors also sought to determine the relationship among EBC pH, severity of disease, and oxidative stress. The study included 20 children with cystic fibrosis, 20 children with asthma, and 15 age-matched healthy children. The pH of EBC was measured using a pH meter. Lower pH values were seen in the EBC of children with CF and asthma compared to control patients (mean pH, 7.23 ± 0.03 and 7.42 ± 0.01 vs. 7.85 ± 0.02, respectively). The authors also reported a relationship between EBC pH, severity of asthma, and the presence of an infective exacerbation of CF.

Effros et al. (2005) reviewed the utility of EBC in chronic obstructive pulmonary disease (COPD) as a noninvasive method of providing direct information about inflammation within the lungs. The authors stated that condensate pH appears to be lower in patients with chronic obstructive lung disease and bronchial asthma, which could reflect airway acidification by inflammatory cells. The authors stated, however, that although EBC is safer and more convenient than bronchoalveolar lavage, interpretation of condensate data is complicated by uncertainty regarding the source of condensate solutes and by variable dilution of respiratory droplets from condensed water vapor, which represents more than 99.9% of condensate volumes. The authors concluded that it is too early to tell how useful condensate studies will be to pulmonary investigators and clinicians and that a thorough understanding of the manner in which these solutions are generated and how they should be analyzed is needed before the potential of this approach can be realized.

National Heart Lung and Blood Institute (NHLBI)
The NHLBI Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma was updated in 2007. The expert panel stated that minimally invasive markers for monitoring asthma control, including spirometry and airway hyper-responsiveness are currently used appropriately and widely in asthma care. The panel further stated that other markers, such as sputum eosinophils and FeNO, are increasingly used in clinical research and will require further evaluation in adults and children before they can be recommended as a clinical tool for routine asthma management. The guideline makes no mention of exhaled breath condensate.

The NHLBI Global Initiative for Asthma (GINA) updated its Global Strategy for Asthma Management and Prevention in 2008. The GINA guidelines state that the 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. 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. The guideline makes no mention of measurement of EBC.

Professional Societies/Organizations
American Thoracic Society (ATS)/European Respiratory Society (ERS)
An ATS/ERS Statement: Asthma Control and Exacerbations, Standardiziing Endpoints for Clinical Asthma Trials And Clinical Practice (Reddel et al., 2009) includes the following statements regarding the use of fractional nitrous oxide in clinical trials :

- FE_{NO} measurements provide easily obtained information on underlying disease activity where it is characterized by eosinophilic airway inflammation, but the positive and negative predictive values for eosinophilia are suboptimal.
- FE_{NO} does not provide information about other types of airway inflammation, and this may be a problem in more severe asthma, where neutrophilic inflammation may be more important.
- The clinical utility of FE_{NO} -based management strategies has not been explored extensively. Currently available evidence suggests a role in identifying the phenotype in airways disease, particularly in the identification of corticosteroid responsiveness.

The ATS/ERS statement includes the following recommendations regarding use of biomarkers in clinical practice:

- Where possible, biomarkers should be employed to provide information about underlying airway inflammation, a domain of the asthma ‘‘syndrome’’ that would not otherwise be available to the clinician
- FE_{NO} measurements may be used as a surrogate marker for eosinophilic airway inflammation. They may be used to evaluate the potential for response to corticosteroid treatment.
- Low values of FE_{NO} (< 25 ppb in adults, < 20 ppb in children) may be of particular value in aiding decisions about reducing corticosteroid dose, or alternatively for determining that ongoing airway symptoms are

The authors acknowledge that more information is required on the utility of FE_{NO} measurement as a tool for monitoring asthma control, and that here is a need for translational research to clarify the relationship between biomarkers and other parameters of asthma control, to establish the optimal frequency of monitoring, and to confirm the clinical and cost effectiveness of biomarker measurements in primary care and other settings.

Regarding exhaled breath condensate, the statement concludes that more work is needed on the validation of the various measures from EBC, and to describe the relationship between these measures and other markers of asthma control. The authors concluded that studies to address whether using EBC results in improved clinical decision-making or better asthma outcomes are required.

Summary
Analysis of exhaled nitric oxide has been proposed as a marker of inflammation that could be useful in monitoring disease activity and directing treatment in patients with asthma. Exhaled nitric oxide levels have been shown to be elevated in patients with asthma, to be higher during periods of acute exacerbation, and to correlate with other measures of inflammation. Although nitric oxide levels may be accurately measured, there is insufficient evidence in the published medical literature to demonstrate the clinical utility or impact on meaningful health outcomes of this procedure. Available evidence does not demonstrate that the addition of exhaled nitric oxide measurement results in improved clinical outcomes for patients with asthma when compared to conventionally managed patients.

Analysis of pH and other markers in exhaled breath concentrate (EBC) has also been proposed as a noninvasive method of sampling airway secretions and measuring airway inflammation in patients with asthma and other chronic pulmonary diseases. Although a noninvasive method of determining inflammation would be useful in monitoring disease activity and directing treatment, well-designed controlled trials are needed in order to establish the clinical utility of this technique.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Experimental/Investigational/Unproven/Not Covered:

CPT* Codes	Description
83987	pH; exhaled breath condensate
94799[†]	Unlisted pulmonary service or procedure
95012	Nitric oxide expired gas determination
0140T	Exhaled breath condensate pH (code deleted 01/01/2010)

[†]**Note: Experimental, investigational or unproven and not covered when used to report measurement of exhaled nitric oxide or exhaled breath condensate**

ICD-9-CM Diagnosis Codes	Description
493.00-493.92	Asthma
	All other codes

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	02/15/2008	0439	Measurement of Exhaled Nitric Oxide and Exhaled Breath Condensate in the Management of Respiratory Disorders