



Cigna Medical Coverage Policy

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

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[Omalizumab \(Xolair®\)](#)

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Coverage Policy

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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 (FEV₁), reported as a percent of the predicted value or as a proportion of the forced vital capacity, or FEV₁/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 diagnosing and 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 beta₂-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: Peirsman et al. (2013) conducted a randomized controlled trial to investigate the potential yield of incorporating fractional exhaled nitric oxide (FeNO) in childhood allergic asthma measurement (n=99). Five visits (one visit every three months) were organized by physicians from seven Belgian hospitals for children with mild to severe persistent asthma according to GINA guidelines, of at least six months duration, with allergic sensitization (i.e., a positive skin prick test and/or specific IgE antibodies against inhalant allergens). In the clinical group, asthma control and treatment adjustments during each visit were determined by the reporting of symptoms (i.e., limitation of activities, daytime and nocturnal symptoms), need for rescue treatment during the two preceding weeks, and spirometry based on the GINA Guidelines. In the FeNO group FeNO measurements were primarily used to adjust the treatment, with a goal to keep FeNO below 20 parts per billion (ppb). The primary outcome, symptom-free days, was assessed using the first four questions from the Childhood Asthma Control Test, which were completed each day. An exacerbation was defined as an episode of progressive increased shortness of breath, coughing, wheezing, or chest tightness or a combination of these symptoms. There was no difference between groups in the primary outcome, symptom-free days. In terms of secondary outcomes, there were fewer exacerbations in the FeNO group (p=0.02) and fewer unscheduled contacts

($p=0.03$), but no significant differences in hospital or emergency room admissions, missed school, or need for caregivers to take time off to care for the child. More months of leukotriene receptor antagonist use (median [interquartile range]) were seen in the FeNO group: 12 (9-12 months) compared with 9 (3-12 months) ($p=0.019$). Measurement of Inhaled corticosteroid use between visits one and five (median change [interquartile range]) showed a significant increase of +100 micrograms (0, +400) in the FeNO group compared with 0 micrograms (-200, +80) in the clinical group ($p=0.16$). The authors strongly recommend further evaluation of FeNO measurements in double-blind, parallel-group multicenter randomized controlled trials in broad populations in terms of asthma severity, control and level of asthma therapy.

Donahue and Jain (2013) conducted a review of the evidence for use of FeNO, including an updated analysis of data from the Cochrane systematic review, and meta-analysis by Petsky, and included a randomized controlled trial by Powell that was not included in the Cochrane review or Petsky meta-analysis. (All are discussed below.) The author reported that, based on a revised meta-analysis of data from these studies, the rate of exacerbations was significantly reduced in favor of FeNO based asthma management (mean treatment difference, 0.27, 95% CI [-0.42, -0.12] as was the relative rate of asthma exacerbations (relative rate 0.57, 95% CI [0.41, 0.80]).

Syk et al. (2013) conducted a randomized controlled trial to determine whether an FeNO-guided anti-inflammatory treatment algorithm could improve asthma-related quality of life (QOL) and asthma symptom control, and reduce exacerbations in atopic asthmatics within primary care ($n=187$). Nonsmoking asthma patients age 18-64 with perennial allergy and on regular ICS, from 17 primary health care centers, were randomly assigned to the control group ($n=88$) or active treatment group ($n=93$). In the control group, FeNO measurement was blinded to both operator and patient, and anti-inflammatory treatment was adjusted according to usual care. In the active group, treatment was adjusted according to FeNO. The Asthma Control Questionnaire score change over one year improved significantly more in the FeNO-guided group (-0.17 [interquartile range, -0.67 to 0.17] vs. 0 [-0.33 to 0.50], $p=.045$). There was no significant difference between groups in the Mini Asthma QOL Questionnaire. Exacerbations per patient year were reduced by almost 50% in the FeNO-guided group (0.22 [CI, 0.14-0.34] vs. 0.41 [CI, 0.29-0.58], $p=0.024$). Mean overall corticosteroid use was similar in both groups. Limitations of the study include the fact that treatment of the control group consisted of "usual care" vs. structured, guideline-directed care. In addition, all patients treated with combination inhalers (corticosteroid plus long acting beta agonist [LABA]) were required to switch to the corresponding single corticosteroid inhaler and withdraw the LABA component.

Petsky et al. (2012) conducted a systematic review and meta-analysis to evaluate the efficacy of tailoring asthma interventions based on inflammatory markers (sputum analysis and FeNO) in comparison with clinical symptoms (with or without spirometry/peak flow). Randomized controlled comparisons of adjustment of asthma treatment based on sputum analysis or FeNO compared with traditional methods (primarily clinical symptoms and spirometry/peak flow) were reviewed. Six studies (2 adult, 4 child/adolescent) utilizing FeNO and three adult studies utilizing sputum eosinophils were included. There was a degree of heterogeneity, including definition of asthma exacerbations, duration of study and variations in cut-off levels for percentage of sputum eosinophils and FeNO used to alter management. Adults who had treatment adjusted according to sputum eosinophils had a reduced number of exacerbations compared with the control group (52 vs. 77 with at least one exacerbation, $p<0.0006$). There was no significant difference in exacerbations between the FeNO-managed group (26) compared to controls (30), $p=0.763$... The daily dose of inhaled corticosteroids (ICS) was decreased at study end in adults whose treatment was based on FeNO compared to the control group (mean difference -450.03 mcg, 95% CI -676.73—223.34, $p<0.0001$). Children who had treatment adjusted according to FeNO, however, had an increase in their mean daily dose of ICS (mean difference 140.18 mcg, 95% CI -28.94 to 251.42, $p<0.014$). The authors concluded that tailoring of asthma treatment based on sputum eosinophils is effective in decreasing asthma exacerbations. Tailoring of asthma treatment based on FeNO levels, however, has not been shown to be effective in improving asthma outcomes in children and adults. At present there is insufficient justification to advocate the routine use of either sputum analysis (due to technical expertise required) or FeNO in everyday clinical practice.

A prospective case series by Woo et al. (2012) evaluated the diagnostic utility of FeNO measurements as a test for asthma by investigating the sensitivity, specificity, and predictive values of FeNO measurements in consecutive children age 8-16 with a possible diagnosis of asthma ($n=245$). The authors also explored the combined effect of asthma and atopic status on FeNO levels. Children were evaluated using FeNO measurement, questionnaires, skin prick tests, spirometry, and methacholine challenge tests. Asthma was diagnosed in 167 children. The sensitivity, specificity, and positive predictive value (PPV), and negative predictive value (NPV) of

ENO measurements for the diagnosis of asthma at the best cutoff value of 22 ppb were 56.9%, 87.2%, 90.5%, and 48.6%, respectively. The specificity and PPV were both 100% at a cutoff value of 42 ppb, but at the cost of very low sensitivity (23.4%) and NPV (37.9%). Both atopy (i.e., genetic predisposition to hypersensitivity or allergic reaction) and asthma were identified as independent risk factors for high ENO. The association of asthma with high ENO was found only in atopic children; ENO was low in non-atopic children regardless of asthma status. Although the highest ENO was observed in atopic asthmatic patients, 28% of these patients had ENO values lower than 22 ppb. The authors concluded that atopic asthmatic patients with low ENO values and non-atopic asthmatic patients were responsible for false negative cases that might contribute to low sensitivity of ENO measurements in diagnosing asthma. High ENO may help identify patients with atopic asthma among patients with respiratory symptoms.

Calhoun et al., for the Asthma Clinical Research Network of the National Heart, Lung, and Blood Institute (2012), conducted a randomized controlled trial to determine if adjustment of inhaled corticosteroid (ICS) therapy based on exhaled nitric oxide or day-to-day symptoms is superior to guideline-informed physician assessment-based adjustment in preventing treatment failure in adults with mild to moderate asthma (n=342; the BASALT Randomized Controlled Trial, 2012). The BASALT trial was a randomized, parallel, three-group placebo-controlled multiply-blinded trial conducted at ten academic medical centers in the US. Adults with mild to moderate asthma controlled by low-dose ICS therapy were assigned to physician assessment-based adjustment (n=114, 101 completed); biomarker-based adjustment (i.e., ENO) (n=115, 92 completed); or to symptom-based adjustment (n=113, 97 completed). For physician assessment-based adjustment and ENO-based adjustment, ICS were taken with each albuterol rescue use. There were no significant differences in time to treatment failure. The nine-month Kaplan-Meier failure rates were 22% (97.5% CI, 14%–33%, 24 events) for physician-assessment-based adjustment; 20% (97.5% CI 13%–30%; 21 events) for biomarker-based (ENO) adjustment; and 15% (97.5 CI, 9%–25%, 16 events) for symptom-based adjustment. The authors concluded that among participants with mild or moderate persistent asthma, neither symptom-based adjustment nor biomarker (ENO)-based adjustment was superior to the standard physician-assessment-based adjustment of ICS in time to treatment failure.

Powell et al. (2011) conducted a double-blind randomized controlled trial to test the hypothesis that a management algorithm for asthma in pregnancy based on FeNO and symptoms would reduce asthma exacerbations (n=220). Non-smoking pregnant women with asthma were randomly assigned before 22 weeks' gestation to treatment adjustment at monthly visits by an algorithm using clinical symptoms (n=109, 103 completed) or FeNO concentrations (n=111, 100 completed) to titrate inhaled corticosteroid use. Participants and outcome assessors were blinded to group assignment. The primary outcome was total moderate or severe asthma exacerbations. The exacerbation rate was lower in the FeNO group than in the control group (0.288 vs. 0.615 exacerbations per pregnancy (p=0.001).

Lemanske et al. (2010) assessed the frequency of differential responses to three blinded step-up treatments for children with uncontrolled asthma while receiving low-dose 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 (FeNO) 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 FeNO 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 (FeNO control, 17 ± 9 ; non-severe, 43 ± 42 ; severe, 43 ± 41 ; p=0.01). The proportion of patients with high FeNO 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 FeNO scores, patients with asthma and

high FENO 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 FENO also identified a more severe subgroup among the non-severe asthma patients; this group shared more similarities with patients with severe asthma and high FENO. 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 FENO, 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 FENO could predict future risk or exacerbations in asthma, but that the correlation with ER visits and hospital admissions suggests the potential for FENO in identification of patients with the most severe disease. The authors further stated that prospective studies would be helpful in determining whether FENO 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 (FENO) monitoring in the management of childhood asthma (n=151). Children with atopic asthma were assigned to two groups: FENO plus symptom monitoring (n=77) or monitoring of symptoms alone (n=74). Two children in each group were excluded from 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 FENO 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 FENO 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 (FEV₁) 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 FENO 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 FENO monitoring compared with daily symptom monitoring only.

Petsky et al. (2008, updated 2009) published a Cochrane systematic review to evaluate the efficacy of tailored interventions based on FENO in comparison to clinical symptoms (with or without spirometry/peak flow meters) for asthma related outcomes in children and adults. The review included two double-blind parallel groups studies (Pijnenburg, 2005, Szeffler, 2008) and four were single blind, parallel group studies (de Jongste, 2009, Fritsch, 2006, Shaw, 2007, Smith, 2005). The studies differed in a variety of ways, including definition of asthma exacerbations ENO cut-off levels, and the way in which FENO was used to adjust therapy and duration of the studies. In the meta-analysis, there was no significant difference between groups for the primary outcome, asthma exacerbations, or for other outcomes, including clinical symptoms, FENO level and spirometry. Tailoring the dose of inhaled corticosteroids based on ENO (compared to clinical symptoms with or without spirometry/peak flow, was beneficial in reducing the final, but not the overall daily doses of inhaled corticosteroids (ICS) in adults. In children, ICS dose was increased when the ENO guided strategy was used. Therefore, the role of utilizing ENO to tailor the dose of inhaled corticosteroids cannot be routinely recommended for clinical practice at this state and remains uncertain.

Szeffler 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 (FENO) 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 FENO 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 FENO 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 FENO group than in the control group ($p=0.40$), although the final daily dose of inhaled corticosteroid was significantly lower in the FENO 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 FENO 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.

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. 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.

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. 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.

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.

Exhaled Nitric Oxide and Exhaled Breath Condensate: Kostikas et al evaluated ENO and EBC pH in patients with asthma according to the level of control and performance in identifying patients who were not well-controlled. FeNO and EBC were measured in 274 consecutive patients evaluated in two hospital outpatient

asthma clinics and evaluated according to GINA guidelines by two respiratory physicians who were blinded to FeNO and pH measurements. FeNO was higher and EBC was lower in patients who were not well controlled compared to patients who were well controlled. The authors concluded that FeNO and EBC pH levels may be used in identification of patients with not well-controlled asthma. Their performance, however, was inferior to clinical judgment and may be limited to selected subgroups of asthmatic patients. Further longitudinal studies for the prospective evaluation of these biomarkers to guide the management of asthmatic patients are clearly justified.

National Heart Lung and Blood Institute (NHLBI)

The NHLBI Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma (2007) states 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 2012. In a discussion of non-invasive markers of airway inflammation, the GINA guidelines remain unchanged, stating that inflammation associated with asthma may be evaluated by examining spontaneously produced or hypertonic saline-induced sputum for eosinophilic or neutrophilic inflammation. Levels of exhaled nitric oxide and carbon monoxide have also been suggested as non-invasive markers of airway inflammation in asthma. Levels of FeNO are elevated in those with asthma not taking inhaled glucocorticosteroids compared to those without asthma, but these findings are not specific for asthma. Neither sputum eosinophilia nor FENO have been evaluated prospectively as an aid in asthma diagnosis, but are being evaluated for potential use in determining optimal treatment, although it has been shown that the use of FENO as a measure of asthma control does not improve control or enable reduction in dose of inhaled glucocorticosteroids.

Professional Societies/Organizations

American Thoracic Society (ATS)

An ATS Clinical Practice Guideline, Interpretation of Exhaled Nitric Oxide Levels (FENO) for Clinical Applications (Dweik et al., 2011) includes the following recommendations for the use of FENO:

- We recommend the use of FENO in the diagnosis of eosinophilic airway inflammation (strong recommendation, moderate quality of evidence).
- We recommend the use of FENO in determining the likelihood of steroid responsiveness in individuals with chronic respiratory symptoms possibly due to airway inflammation (strong recommendation, low quality of evidence).
- We suggest that FENO may be used to support the diagnosis of asthma in situations in which objective evidence is needed (weak recommendation, moderate quality of evidence).
- We recommend the use of FENO in monitoring airway inflammation in patients with asthma (strong recommendation, low quality of evidence).

For each question, the committee graded the quality of available evidence and made a recommendation for or against. Recommendations were decided by consensus. In discussing the above recommendations, the authors state that given the long established relationship between eosinophilic inflammation and steroid responsiveness in airways disease, the finding the FENO correlates with eosinophilic inflammation suggests its use as an indirect indicator of eosinophilic inflammation, but more importantly, the potential for steroid responsiveness. Since not all patients respond to corticosteroids, the authors state that a reason to use FENO is to help decide who might benefit from steroid treatment and who should try other medications, and to determine whether steroid therapy may be safely withdrawn. Regarding the use of FENO in the diagnosis of asthma, the authors state that increasing FENO provides supportive rather than conclusive evidence for an asthma diagnosis.

American Academy of Allergy, Asthma and Immunology (AAAAI)/American College of Allergy, Asthma and Immunology (ACAAI)

In February 2012 the AAAAI and ACAAI issued a joint statement to formally recognize and support the 2011 ATS Clinical Practice Guideline on the Interpretation of Exhaled Nitric Oxide for Clinical Applications (AAAAI website, 2012).

American Thoracic Society (ATS)/European Respiratory Society (ERS)

An ATS/ERS Statement: Asthma Control and Exacerbations, Standardizing 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 :

- FENO 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.
- FENO 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 FENO -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
- FENO 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 FENO (< 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 FENO 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.

Use Outside the U.S.

National institute for Health and Clinical Excellence (NICE) (United Kingdom): Guidance for the use of exhaled nitric oxide measurement is in development, with published guidance expected in April, 2014. The following provisional recommendations were published in November 2013:

Fractional exhaled nitric oxide (FeNO) testing is recommended as an option to help with diagnosing asthma in adults and children:

- who, after initial clinical examination, are considered to have an intermediate probability of having asthma (as defined in the British guideline on the management of asthma, 2012) and
- when bronchodilator reversibility testing is intended.

Further investigation is recommended for people whose FeNO test result is negative, because a negative result does not exclude asthma.

- FeNO measurement is recommended as an option to support asthma management (in conjunction with the British guideline on the management of asthma, 2012) in people who are symptomatic despite using inhaled corticosteroids.

British Guideline on the Management of Asthma (2012): In a section discussing tests of eosinophilic inflammation in children, the guideline states that a raised FeNO is neither a sensitive nor a specific marker of asthma with overlap with children who do not have asthma. FeNO is closely linked with atopic status, age and

height. In some studies, FeNO correlated better with atopic dermatitis and allergic rhinitis than with asthma. It is not closely linked with underlying lung function. FeNO could not differentiate between groups once atopy was taken into account. The guideline also states that home measurements of FeNO have a highly variable relationship with other measures of disease activity and vary widely from day to day. At present, there is insufficient evidence to support a role for markers of eosinophilic inflammation in the diagnosis of asthma in children. They may have a role in assessing severity of disease or response to treatment.

In a section that addresses diagnosing asthma in adults, the guideline states that there is evidence that markers of eosinophilic airway inflammation are of value in monitoring the response to corticosteroid treatment, but that more experience with these techniques and more information on the long term response to corticosteroid in patients who do not have a raised sputum eosinophil count or FeNO is needed before this approach can be recommended. The authors also state that a raised sputum eosinophil count (>2%) or FeNO (>25 ppb at 50 ml/sec) is seen in 70-80% of patients with untreated asthma, but neither finding is specific to asthma: 30-40% of patients with chronic cough, and a similar proportion of patients with chronic obstructive pulmonary disease have abnormal results.

Canadian Coordinating Office of Health Technology (CCOHT): A CCOHT assessment of the NIOX system (Haley, 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.

Summary

Analysis of exhaled nitric oxide has been proposed as a marker of inflammation that could be useful in diagnosing and 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: 1) This list of codes may not be all-inclusive.

2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

Experimental/Investigational/Unproven/Not Covered:

CPT* Codes	Description
83987	pH; exhaled breath condensate
95012	Nitric oxide expired gas determination

*Current Procedural Terminology (CPT®) © 2013 American Medical Association: Chicago, IL.

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