Name of Policy:
Measurement of Exhaled Nitric Oxide and Exhaled Breath Condensate in the Diagnosis and Management of Asthma and Other Respiratory Disorders

Policy #: 181 Latest Review Date: January 2014
Category: Medicine Policy Grade: C

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
Description of Procedure or Service:

Current techniques for diagnosing and monitoring asthma and predicting exacerbations are suboptimal. Two new strategies, evaluation of exhaled nitric oxide and exhaled breath condensate are proposed. These techniques are also potentially useful in the management of other conditions such as chronic obstructive pulmonary disease (COPD) and chronic cough. There are commercially available devices for measuring nitric oxide in expired breath and various laboratory techniques for evaluating components of exhaled breath condensate.

Asthma is characterized by airway inflammation that leads to airway obstruction and hyper-responsiveness, which in turn lead to characteristic clinical symptoms including wheezing, shortness of breath, cough, and chest tightness. 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 (FEV-1) 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.

Two new strategies have been investigated, the measurement of exhaled nitric oxide (NO) and the evaluation of exhaled breath condensate. Nitric oxide is an important endogenous messenger and inflammatory mediator that is widespread in the human body, functioning, for example, to regulate peripheral blood flow, platelet function, immune reactions, and neurotransmission and to mediate inflammation. While the role of NO in asthma pathogenesis is still under investigation, patients with asthma have been found to have high levels of exhaled NO, 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. Exhaled NO is typically measured during single breath exhalations. First, the subject inspires nitric oxide-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 exhaled NO are commercially available in the United States. According to a 2009 joint statement by the American Thoracic Society (ATS) and European Respiratory Society (ERS), there is a consensus that the fractional concentration of exhaled nitric oxide (FeNO) is best measured at an exhaled rate of 50 mL per second (FeNO 50 mL/s) maintained within 10% for more than six seconds at an oral pressure between five and 20 cm H2O. Results are expressed as the NO concentration in parts per billion (ppb), 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 various 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, to the more sophisticated gas chromatography/mass spectrometry or high performance liquid chromatography, depending on the component of interest.

Measurement of NO and EBC has been investigated in the diagnosis and management of asthma. Potential uses in 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 (COPD), cystic fibrosis, allergic rhinitis, pulmonary hypertension, and primary ciliary dyskinesia.

**Policy:**

**Effective for dates of service on or after January 24, 2014:**

Measurement of exhaled or nasal nitric oxide does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered *investigational* for 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 does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered *investigational* for the diagnosis and management of asthma and other respiratory disorders including but not limited to chronic obstructive pulmonary disease and chronic cough.

**Effective for dates of service prior to January 24, 2014:**

Measurement of exhaled or nasal nitric oxide does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered *investigational* for the management of asthma and other respiratory disorders including but not limited to chronic obstructive pulmonary disease and chronic cough.

Measurement of exhaled breath condensate does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered *investigational* for the management of asthma and other respiratory disorders including but not limited to chronic obstructive pulmonary disease and chronic cough.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member’s contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.
**Key Points:**

A literature search performed on the MEDLINE database identifies a large body of published data regarding exhaled nitric oxide in asthma and other respiratory diseases. However, these studies primarily focus on exhaled nitric oxide as a research tool exploring the underlying pathophysiology of asthma, establishment of the technical performance of the test, establishing cut off values for normal and abnormal values in different age groups. For example, studies have shown that asthma patients have nitric oxide measurements in the range of 25–85 ppb (part per billion) compared to control patients whose exhaled nitric oxide measurement is generally less than 20 ppb. Other studies have shown that levels of exhaled nitric oxide correlate with levels of other known inflammatory markers, such as airway hyper-responsiveness and sputum eosinophils. Pulmonary function tests represent the standard method for assessment asthma, but studies have found an inconsistent relationship between results of pulmonary function tests and exhaled nitric oxide, perhaps because changes in pulmonary function may lag behind changes in exhaled nitric oxide. Several studies have confirmed the expected decrease in exhaled nitric oxide levels after administration of both corticosteroids and anti-leukotriene drugs.

While the cited studies demonstrate the potential role of measurements of exhaled nitric oxide in the diagnosis and management of asthma, assessment of the clinical role of this test would require controlled studies of those diagnosed and managed conventionally and those whose diagnosis and management were additionally directed by measurements of exhaled nitric oxide. No such trials were identified. Compared to asthma, the data are more limited regarding other respiratory conditions, including chronic obstructive pulmonary disease (COPD), cystic fibrosis, and primary ciliary dyskinesia.

In 2002, the National Asthma Education and Prevention Program of the National Heart Lung and Blood Institute issued its second expert panel report on guidelines for the diagnosis and management of asthma. Measurements of nitric oxide were not included among its recommendations.

An October 2005 Technology Evaluation Center (TEC) Assessment on Exhaled Nitric Oxide Monitoring as a Guide To Treatment Decisions in Chronic Asthma the following conclusions and determinations were made. The available evidence does not permit the conclusion that use of nitric oxide monitoring to guide treatment decisions in asthma leads to improved outcomes. In the two trials reviewed there was insufficient evidence to conclude that outcomes are improved with nitric oxide monitoring. The results of these trials have not been reproducible. Questions have arisen due to differences in the control management strategy about the optimal management strategy to which nitric oxide monitoring should be compared. Another 7 studies that met criteria for review in the TEC assessment evaluated the ability of nitric oxide to provide prognostic information that could lead to changes in management had considerable methodologic limitations and variability in study methodology that precluded synthesis of the results and definitive conclusions.

Analysis of exhaled breath condensate, similar to nitric oxide, also has intense research interests as a biomarker of inflammation. It appears from the literature that exhaled breath condensate is at an earlier stage of development compared to exhaled nitric oxide. The following issues must be resolved before routine clinical use of EBC in the diagnosis and management of respiratory
disorders can be considered. The standardization of collection and storage techniques; effect of dilution of respiratory droplets by water vapor; techniques of measuring concentrations of nonvolatile substances in EBC; variability in exhaled breath condensate assays for certain substances and further investigation of levels of compounds in health and disease are among these issues.

Controlled trials will be required to determine how evaluation of exhaled breath condensate can be used to direct patient management. Neither exhaled nitric oxide nor exhaled breath condensate pH is used in the management of the patient.

June 2007 Update
No new studies were identified that would alter the coverage statement of this policy.

December 2009 Update
A Cochrane review was published in 2008 that identified studies comparing outcomes in asthma patients managed with and without findings from exhaled nitric oxide test. Four randomized controlled trials were identified, including the two that were previously included in the TEC Assessment (Smith et al 2005; Pijnenburg et al 2005) and two additional studies, Shaw et al 2007 and Fritsch et al 2006. Two of the four studies were conducted with adults, Smith and Shaw, and findings were pooled for selected outcomes; there were a total of 197 patients. Meta-analyses did not find a significant difference in the number of patients experiencing an exacerbation (effect size = 0.85, 95% confidence interval {CI}= 0.30 to 2.45) or the occurrence of any exacerbation (mean difference = 0.14, 95% CI =-0.41 to 0.12). There was also no significant difference in symptom scores (mean difference of -0.10 {95% CI=-0.33 to 0.12}). Both studies did report a significant difference between groups for the outcome of final daily dose of inhaled corticosteroids; however, this was a post-hoc analysis in the Shaw study. The weighted mean difference was -282.42 (95% CI=-421.81 to -143.03). Results of the two pediatric trials, Fritsch and Pijnenburg et al could not be pooled. Both of the pediatric trials included exacerbations as a secondary outcome and stated that there was no difference between the groups. Moreover, both studies reported no significant difference in respiratory symptoms in the exhaled nitric oxide and control groups. The primary outcome in the Fritsch trial was FEV1 which the authors reported was not significant between groups. The primary outcome of the Pijengurg trial was cumulative dose over five visits. The Cochrane reviewers state that the data in the Pijnenburg forest plot of cumulative dos shows no significant difference between groups. The authors of the Cochrane review concluded: “Tailoring the dose of inhaled corticosteroids based on exhaled nitric oxide in comparison to clinical symptoms was carried out in different ways in the four studies that were found, and the results show only modest differences. The role of utilizing exhaled nitric oxide to tailor the dose of inhaled corticosteroids is currently uncertain.”

Another randomized controlled trial (RCT) was identified in the 2008 policy update, for a total of five published RCTs on this topic. Szefler et al randomly assigned 546 eligible participants (inner-city adolescents and young adults) who adhered to treatment during a run-in period to 46 weeks of either standard treatment, based on the guidelines of the National Asthma Education and Prevention Program (NAEPP), or standard treatment modified on the basis of measurements of fraction of exhaled NO. The primary outcome was the number of days with asthma symptoms. During the 46-week treatment period, the mean number of days with asthma
symptoms did not differ between the treatment groups (1.93 in the NO monitoring group vs. 1.89 in the control group; difference 0.04 [-0.22 to 0.29], p=0.78). Other symptoms, pulmonary function, and asthma exacerbations did not differ between groups. Patients in the NO monitoring group received higher doses of inhaled corticosteroids (difference 119 mug per day, p=0.001) than controls. Adverse events did not differ between treatment groups. The authors concluded that conventional asthma management resulted in good control of symptoms in most participants and that the addition of a fraction of exhaled NO as an indicator of control of asthma resulted in higher doses of inhaled corticosteroids without clinically important improvements in symptomatic control.

No new RCTs were identified in the 2009 literature search. There were several review articles including one systematic review of published RCTs by Gibson that evaluated exhaled nitric oxide tests in the management of patients with asthma. The review cited the 5 RCTs previously discussed in the policy; data were not pooled. The authors commented that the studies did not show a significant reduction in asthma exacerbation when patients are managed with exhaled NO tests and that treatment algorithms based on exhaled NO levels are less successful than treatment based on induced sputum eosinophils. Moreover, the review states that the published RCTs may have study design limitations that limit their ability to adequately test the utility of exhaled NO tests. For example, equipment failure has been a substantial issue and future studies should ensure back-up equipment is available. In addition, there is variation within individuals and an imperfect relationship between exhaled NO and eosinophilic inflammation; exhaled NO levels are also influenced by factors such as age, atopy, gender and smoking status. The review authors recommend that studies alter the cut-point for positive tests to reduce false-positive findings, or use composite outcomes such as exhaled NO and FEV.

**Diagnosis**

Two prospective studies on the diagnosis of asthma using exhaled nitric oxide measurements were identified in the 2009 literature search. (Previously, the policy had focused on literature related to asthma management). Sivan et al evaluated the diagnostic yield of exhaled NO test findings in 150 children age 18 years or less compared to sputum eosinophil count, the “gold standard” for assessment of eosinophilic inflammation of the airways. Final assessment of asthma status was done by a pediatric pulmonologist after at least 18 months of follow-up. Receiver operating curves (ROC) were used to determine the optimal cutoff points for the exhaled NO test. A total of 150 children were included. Eligibility criteria included non-specific respiratory symptoms suggestive of asthma for at least three months and absence of other conditions that could affect exhaled NO or sputum eosinophil count. The area under the ROC for exhaled NO versus eosinophil percent was 0.886. The best cutoff was 18 ppb which provided 82% sensitivity and 84% specificity. This was similar to the best cutoff for eosinophil count, 2.7%, which had 85% sensitivity and 89% specificity. The authors concluded that exhaled NO measurement is useful in early diagnosis of pediatric asthma. The study was conducted in Israel and the device used to measure exhaled NO in the study, the CLD88 FeNO analyzer by Eco Medics (Switzerland), does not appear to be cleared by the FDA.

Schneider et al evaluated a new portable NIOX MINO in a prospective study conducted in a primary care setting. They recruited 160 patients with symptoms suspicious of obstructive airway disease from general practices in Germany. All patients underwent measurement of

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exhaled nitric oxide. The reference standard was a step-wise series of tests, beginning with spirometry. Those with FEV1 less than 80% of predicted or FEV1/vital capacity (VC) ratio of 0.70 or less were referred to bronchodilator reversibility testing. Otherwise, patients net received bronchial provocation with methacholine. Patients were classified as having asthma when: 1) Bronchodilation testing found a change in FEV1 was at least 12% compared to baseline, and at least 200 ml and lung volumes returned to predicted normal range; 2) Bronchial provocation found a 20% decrease in FEV1 from the baseline value after inhaling methacholine stepwise until the maximum concentration. Exhaled nitric oxide test findings were compared to the final diagnosis status. According to standard testing, 75 (46.9%) of the patients had asthma. ROC analysis found the highest sum of sensitivity and specificity of exhaled nitric oxide at a cutoff of 46 ppb. Among patients with unsuspicious spirometry findings (n=101), 49 had asthma. The optimal cutoff of exhaled nitric oxide in this subgroup was 46 ppb; sensitivity of exhaled NO was 35% and specificity was 90%.

The two recent prospective studies on asthma diagnosis found different optimal cutoffs for exhaled nitric oxide, 18 ppb in the Sivan study conducted with children and 46 ppb in the Schneider study with adults. The cutoff level of exhaled nitric oxide also varied in earlier studies: Dupont evaluated 240 non-smoking steroid-naïve patients without age limitations and found the optimal cutoff was 16 ppb exhaled nitric oxide. Berkman studied 95 asthmatic and nonasthmatic patients without age limitation and found that a cutoff of exhaled nitric oxide over seven ppb best differentiated between the two groups. The manufacturer of the NIOX and NIOX MINO devices, Aerocrine, does not have a recommendation on their website for the cutoff of exhaled nitric oxide to use when diagnosing asthma. Thus, the studies on diagnosis of asthma using exhaled nitric oxide can be preliminary. Once there is an agreed-upon cutoff of exhaled NO levels for diagnosing asthma, there is a need for prospective validation studies using that cutoff to determine the diagnostic accuracy of exhaled NO measurement.

**Other Respiratory Disorders**

One RCT, a double-blind cross-over study by Dummer et al, evaluated the ability of exhaled nitric oxide test results to predict corticosteroid response in chronic obstructive pulmonary disease (COPD). The study included 65 patients with COPD who were 45 years of older, were previous smokers with at least a ten pack year history, had persistent symptoms of chronic airflow obstruction, had a post-bronchodilator forced expiratory volume in one second/forced vital capacity ratio (FEV1/FVC) of less than 70% and a FEV1 of 30-80% predicted. Patients with asthma or other co-morbidities, and those taking regular corticosteroids or had used oral corticosteroids for exacerbations more than twice during the past six months were excluded. Treatments, given in random order, were 30 mg/day of prednisone or placebo for three weeks; there was a four-week washout period before each treatment. Patients who withdrew during the first treatment period were excluded from the analysis. Those who withdrew between treatments or during the second treatment were assigned a net change of zero for the second treatment period. Fifty-five patients completed the study. Two of the three primary outcomes, six-minute walk distance (6MWD) and FEV1 increased significantly from baseline with prednisone compared to placebo. There was a non-significant decrease in the third primary outcome, score on the St. George’s Respiratory Questionnaire (SGRQ). The correlation between baseline fraction of exhaled nitric oxide was not significantly correlated with change in 6MWD (r=0.10, p=0.45) or SGRQ (r=0.12, p=0.36) but was significantly related to change in FEV1 (r=0.32,
p=0.01). At the optimal fraction exhaled nitric oxide cutoff of 50ppb, as determined by ROC analysis, there was a 29% sensitivity and 96% specificity for predicting a 0.2 liter increase in FEV1. (A 0.2 liter change was considered to be the minimal clinically important difference). The authors concluded that exhaled nitric oxide is a weak predictor of short-term response to oral corticosteroid treatment in patients with stable, moderately severe COPD and that a normal test result could help clinicians decide to avoid prescriptions that may be unnecessary; only about 20% of patients respond to corticosteroid treatments. Limitations of the study include that the response to treatment measured was short-term and this was not a trial of management decisions based on exhaled nitric oxide test results.

No controlled studies were identified that evaluated the role of exhaled nitric oxides tests in the management of respiratory conditions other than asthma and COPD. A prospective uncontrolled study by Prieto et al assessed the utility of exhaled oxide measurement for predicting response to inhaled corticosteroids in patients with chronic cough. The study included 43 patients with cough of at least eight weeks’ duration who were non-smokers and did not have a history of other lung disease. Patients were evaluated at baseline and after four weeks of treatment with inhaled fluticasone propionate 100 ug twice daily. Nineteen patients (44%) had a positive response to the treatment defined as at least a 50% reduction in mean daily cough symptom scores. ROC analysis showed that, using 20 ppb as the exhaled nitric oxide cutoff, the sensitivity was 53% and the specificity was 63%. The authors concluded that exhaled NO was not an adequate predictor of treatment response.

**Exhaled Breath Condensate**

It appears from the published literature that exhaled breath condensate is at an earlier stage of development compared to exhaled nitric oxide. For example, several review articles note that before routine clinical use in the diagnosis and management of respiratory disorders can be considered the following issues must be resolved:

- Standardization of collection and storage techniques
- Effect of dilution of respiratory droplets by water vapor
- Effect of contamination from oral and retropharyngeal mucosa
- Understanding how particles/droplets form and change during exhalation before leaving the body
- Techniques of measuring concentrations of nonvolatile substances in exhaled breath condensate; in most cases these concentrations are very low, which may be at the lower limits of detection of conventional analytic techniques
- Variability in exhaled breath condensate assays for certain substances
- Lack of gold standard for determining absolute concentrations of airway lining fluid non-volatile constituents to compare with EBC.

**Asthma**

No controlled studies were identified that evaluated the role of exhaled breath condensate tests in the management of asthma. A recent case series investigated whether components of EBC could predict respond to steroid treatment in patients with asthma. Eighteen steroid--naive asthma patients were included; EBC collection, spirometry and methacholine challenge were performed before and 12 weeks after inhaled steroid therapy (equivalent dose of 400 ug fluticasone...
propionate/day). Among the molecules in EBC examined, higher IL-4 and RANTES levels and lower IP-10 levels at baseline were correlated with an improvement in FEV1. The study had a small sample size, was uncontrolled and did not address the clinical utility of EBC testing.

Other Respiratory Disorders
Two preliminary empirical studies compared exhaled breath condensate components in patients with cystic fibrosis and healthy controls. The smaller study by Newport et al found a significantly lower EBP pH at the onset of an acute pulmonary exacerbation in 10 CF patients (median pH=6.61) compared to ten controls (median pH=8.14). However, EPC pH did not change consistently in response to treatment. The Robrocks study, which included 48 children with cystic fibrosis and 50 healthy controls, used multivariate logistic regression to identify components in EPC that best predicted the presence of cystic fibrosis. The authors found that the presence of CF was best indicated by 8-isoprostanate, nitrate and IFN-y and the CF exacerbations were best indicated by 8-isoprostanate and nitrate. The Robrocks et al study indicate that the issue of how to use EPC findings has still not been resolved and neither of the two studies evaluate whether assessment of EPC would be useful in clinical practice.

December 2010 Update

Diagnosis
In 2010, Pedrosa et al published data on the optimal FeNO cut off to use the NIOX MINO for diagnosing asthma. The study was conducted in Spain and included 114 individuals at least 14 years old. Eligible patients had symptoms consistent with asthma, with or without rhinitis symptoms, and had normal parameters on spirometry and a negative bronchodilator test. Definitive diagnosis was based on symptom assessment and a positive methacholine bronchial challenge test. Individuals underwent FeNO assessment (flow rate of 50 ml/s) just before the methacholine inhalation challenge test. According to challenge test finding, 35 patients (31%) were diagnosed with asthma. FeNO levels were significantly higher in individuals diagnosed with asthma (mean 58 ppb) than in nonasthmatics (mean ppb 30ppb); p<0.001. Using ROC analysis, the cut-off point with maximum sensitivity (74.3%) and specificity (72.5%) for diagnosing asthma was a FeNO value of 40 ppb.

Another study was conducted in Israel and evaluated a devie (CLD88 FENO analyzer; EcoMedics, Switzerland) that does not appear to be available in the United States.

There remains no standard cut-off to indicate a positive FeNO or a diagnosis of asthma. The manufacturer of the NIOX and NIOX MINO devices, Aerocrine, does not have a recommended cut-off on its Website. Moreover, the 2009 joint statement of the American Thoracic Society and European Respiratory Society does not include a recommendation on how to use exhaled nitric oxide levels in the diagnosis of asthma. The joint statement does suggest that there are inter- and intra-subject variability and variability among devices. The Schneider et al and Pedrosa et al studies found similar optimal cut-offs (46 ppb and 40 ppb, respectively) using the NIOX MINO, but this cut-off differs from other studies e.g., a cut-off of 18 ppb in the Sivan study conducted with children using a different device. Another study conducted with children who had asthma, allergic rhinitis or both used ROC analysis and found that the optimal cut-off for discriminating between patients with bronchial hyperactivity from those with absent or borderline bronchial hyperactivity was 32 ppb of nitric oxide.
In 2010, Selby et al published a study from the U.K. that evaluated the reproducibility of exhaled nitric oxide measurements in young people. The study included 494 teenagers from an unselected birth cohort, aged 16-18, and 65 asthma patients between the ages of 6 and 17. Paired readings were obtained from each participant. The mean within-participant difference in FeNO (second reading minus the first reading) was 1.37 ppb (95% confidence interval [CI] = -7.61 to 10.34 ppb); this difference was statistically significant, p<0.001. When participants with high FeNO values (above 75 ppb) were excluded, there was a lower mean within-participant difference, 0.90 ppm (95% CI= -4.89 to 6.70 ppb). Among the 71 participant with asthma, the mean within-participant difference in FeNO in the two measurements was 2.37 ppb (95% CI= -11.38 to 16.12 ppb). When FeNO values were categorized as low, normal, intermediate or high (using different values for participants under 12 years and 12 years or older), the findings were reproducible. That is there were no statistically significant differences in the categorization using the first and second measurement.

Management
A Cochrane review was published in 2009 (update of 2008 review) that identified studies comparing outcomes in asthma patients whose medication adjustments were managed based on exhaled nitric oxide levels compared to clinical symptoms (with or without spirometry/peak flow). Six randomized controlled trials were identified, including the two that were previously included in the TEC Assessment as well as four additional studies, Shaw et al 2007, Fritsch et al 2006, Szeffler et al 2008 and de Jongst et al 2009. Four studies included children or adolescents, one included only adults and the sixth included both adolescents and adults. Two studies were double-blind and the other four were single-blind. Five studies used hospital-based FeNO measurements and one used a portable at-home NO analyzer. Four studies measured FeNO at a flow rate of 50 mL/S. When findings for the two studies that included adults and/or adolescents were pooled (Shaw et al 2007 and Smith et al 2005), total n=197, there was not a significant difference in the number of patients experiencing an exacerbation (odds ratio [OR] =0.85, 95% CI =0.30 to 2.43) or the occurrence of any exacerbation (mean difference= -0.14, 95% CI = -0.41 to 0.12). There was also no significant difference in symptom scores (mean difference of -0.14 [95% CI=-0.42 to 0.14]). Findings from three of the four pediatric trials were pooled, total n=782 (Pijnenburg et al 2005, Szeffler et al 2008, and de Jongst et al 2009). As with the adult studies, there was not a significant difference in the number of patients experiencing an exacerbation (OR=0.75, 95% CI=0.55 to 1.01). Another pooled analysis of these three studies found a statistically significantly higher dose of inhaled corticosteroid at the final study visit in patients managed using exhaled nitric oxide levels (mean difference=140.2, 95% CI=28.9-251.4). A pooled analysis of two of the studies (Szeffler et al 2008 and de Jongst et al 2009, total n=631) did not find a significant difference in symptom scores when patients were managed with and without measurement of exhaled nitric oxide (mean difference=0.04, 95% CI= -0.11 to 0.20). Findings on the number of patients experiencing an exacerbation were not pooled for the pediatric studies. The authors of the Cochrane review concluded, “Tailoring the dose of inhaled corticosteroids based on exhaled nitric oxide in comparison to clinical symptoms was carried out in different ways in the six studies and found only modest benefit at best and potentially higher doses of inhaled corticosteroids in children. The role of utilizing exhaled nitric oxide to tailor the dose of inhaled corticosteroids cannot be routinely recommended for clinical practice at this stage and remains uncertain”.
In 2009, de Jongste et al published an open-label randomized study that included 151 children with atopic asthma. They were randomized to have medication adjustments based on either symptom monitoring alone or symptom monitoring plus measurement of exhaled nitric oxide levels. The study consisted of six periods of three weeks and a final period of 12 weeks. Adjusted for baseline levels, there was not a significant difference between groups for the primary outcome, the percentage of symptom-free days in the last 12 weeks of the study; p=0.065. (Numbers of symptom-free days were not reported). In addition, using Kaplan-Meier survival analysis, there was no significant between-group difference in the composite outcome: time to first prednisone course, emergency visit or hospitalization (p=0.43).

A 2010 review by Barnes et al stated that the published trials comparing exhaled NO measurement as an add-on to clinical guideline management had substantial design issues that may limit their validity. For example, the authors question the adequacy of the cut-points used for determining a positive test. They mention that, due to inter-individual variability in exhaled NO levels, use of individual cut-points as determined by baseline assessment, or measuring change from baseline may be more valid than use of a fixed cut point. In addition, the authors state that the choice of outcome variables is important. They assert that asthma exacerbations may be the most relevant primary outcome but that was not consistently the case in the published studies. The authors concluded, “The true value of FeNO in improving asthma control and reducing exacerbations has yet to be tested rigorously.” Another 2010 review, by Kercsmar, discussed the six randomized trials described above and made the following conclusion, “…the reported results are quite consistent: the routine use of FeNO as a guide to chronic adjustment of anti-inflammatory treatment in asthma offers little benefit. None of the studies demonstrate a clear improvement in asthma control, significant reduction in exacerbations or a lower ICS burden when FeNO is used, compared to, or in addition to standard clinical measures.”

**Exhaled Breath Condensate**
A 2010 study by Antus et al compared exhaled breath condensate in 58 patients (20 with asthma and 38 with COPD) hospitalized for exacerbations and 36 health controls (18 smokers and 18 non-smokers). The EBC pH was significantly lower in patients with asthma exacerbations (all non-smokers) at hospital admission compared to non-smoking controls (6.2 vs. 6.4, p<0.001). The pH of EBC in asthma patients increased during the hospital stay and was similar to that of non-smoking controls at discharge. Contrary to investigators’ expectations, EBC pH values in ex-smoking COPD patients (n=17) did not differ significantly from non-smoking controls, either at hospital admission or discharge (mean pH not reported). Similarly, pH values in EBC samples from smoking COPD patients (n=21) at admission and discharge (mean of 6.3 at both times) did not differ significantly from smoking controls (mean pH=6.31, p>0.05). None of the above studies address how assessment of EBC could be useful in clinical practice.

**January 2012 Update**
**Management**
In 2011, Powell et al in Australia published a double-blind RCT evaluating FeNO for guiding treatment decisions in pregnant non-smoking women with asthma. Eligibility included being between 12 and 20 weeks’ of gestation and using inhaled therapy for asthma within the past year. Women were randomized to a FeNO algorithm to adjust therapy (n=111) or a clinical guideline
algorithm that did not include FeNO measurement (n=109). The FeNO algorithm appeared to be devised by the study investigators. According to the algorithm, the cut-off for reducing the dose of inhaled corticosteroids was less than 16 ppb, and the cut-off for dose increase was at least 30 ppb. Both treatment groups also had their symptoms assessed by the Asthma Control Questionnaire (ACQ), and ACQ scores were utilized in both medication adjustment algorithms. A total of 203 of 220 women (92%) completed the study; analysis was intention to treat. The primary study outcome was the total number of asthma exacerbations during pregnancy (and after study enrollment) for which the patient sought medical attention. The mean total exacerbation rate was significantly lower in the FeNO group (0.29 per pregnancy) compared to the control group (0.62 per pregnancy), p=0.01. Overall, 28 (25%) of women in the FeNO group and 45 (41%) in the control group had at least one exacerbation; the difference between groups was statistically significant, p=0.01. Among the secondary outcomes, there were significantly fewer unplanned doctors visits in the FeNO group (mean of 0.26 per patient) than the control group (mean of 0.56 per patient), p=0.002.

The Powell study demonstrates a potential benefit to using a treatment algorithm that incorporates FeNO levels. However, this trial is prone to many of the same limitations as previous trials of FeNO management algorithms. Most importantly, patients in each group end up on differing regimens of medications according to the algorithm followed. It is then difficult to isolate the effect of the algorithm from the efficacy of the medications themselves. For example, if a FeNO algorithm uses a lenient cut-off point for increasing inhaled corticosteroids, then the FeNO group will likely end up on higher doses of inhaled steroids. Improved outcomes are then more likely to be due to the efficacious effect of inhaled steroids, rather than the inclusion of FeNO in the algorithm. In the Powell study, the cut-off point for increasing inhaled steroids was lowered compared to previous algorithms, thus resulting in more patients being started on inhaled steroids. Together with this, the control group was treated by an algorithm that differed from current treatment guidelines in at least two important ways, both which resulted in less intensive treatment compared to treatment guidelines. The net effect of these algorithms was that more patients in the FeNO group received both long-acting beta-agonists and inhaled corticosteroids, although patients treated with inhaled steroids in the control group were treated at higher doses. Therefore, the differences in outcomes may be due to differences in treatment regimens that could have been achieved with or without the use of FeNO in the guidelines.

January 2013 Update

Asthma Diagnosis

The sensitivity and specificity of FeNO for the diagnosis of asthma is dependent upon the cutoff point that is used. To date, the optimal cutoff point remains undefined, and this has been the focus of some of the published studies on using FeNO in the diagnosis of asthma.

Most recently, in 2012, Malinovschi and colleagues in Denmark evaluated 282 individuals with symptoms suggestive of asthma. Study participants were part of a sample of 10,400 individuals aged 14-44 randomly selected from the civil registration list in Denmark. Individuals were eligible for the study if they had at least two symptoms suggestive of asthma. FeNO was measured with the NIOX MINO device and patients were examined by a respiratory specialist to determine the clinical diagnosis of asthma. Among the 282 participants, 112 were current smokers, One hundred eight never smoked and 62 were ex-smokers. According to clinical
evaluation, 96 of 282 (34%) had asthma, 32 smokers, Forty-five never smokers and 19 ex-smokers. The authors examined different cut-offs of FeNO to determine the value with the optimal sensitivity and specificity for diagnosing asthma. They proposed a cutoff of 17ppb in current smokers (56.3% sensitivity and 82.5% specificity), 15ppb in never smokers (77.8% sensitivity and 63.5% specificity) and 22ppb in ex-smokers 63.2% sensitivity and 86.1% specificity.

Another 2012 study, by Schleich and colleagues in Belgium, prospectively evaluated 174 individuals with suspected asthma who were referred for a methacholine challenge and who were not currently receiving inhaled corticosteroids (ICS). FeNO was measured with a NIOX device set at a flow rate of 50 ml/s. According to the methacholine challenge test findings, 82 of 174 (47%) of participants were diagnosed with asthma (i.e., provocative concentration of methacholine [PC20M] was 16 mg/ml or lower). FeNO was significantly higher in patients with a positive methacholine challenge (19 ppb) than a negative challenge test (15 ppb), p<0.05. Receiver operating characteristic (ROC) analysis found that a FeNO cutoff of 34 ppb best predicted the outcome of the methacholine challenge test (sensitivity 35.4%, specificity 95.4%).

Woo and colleagues in Korea also published a study in 2012 using prospectively collected data on 245 consecutive steroid-native children with respiratory symptoms suggestive of asthma. FeNO was measured using the NIOX MINO and lung function tests were performed with spirometry. Asthma was diagnosed in 167 (68%) of participants. Using ROC analysis, the investigators found that the optimal cutoff for FeNO in diagnosing asthma was 22ppb which provided 56.9% sensitivity and 87.2% specificity. At a cutoff of 42ppt, the specificity was 100%, but the sensitivity was very low, 23.4%.

A 2011 clinical practice guideline from the American Thoracic Society (ATS) (described in more detail and critically appraised in the section on Practice Guidelines and Position Statements) recommended FeNO cutoff values for predicting the presence of eosinophilic inflammation. Many, but not all, patients with asthma will have eosinophilic inflammation. The guidelines recommended that FeNO less than 25 ppb (<20ppb in children) be used to indicate that eosinophilic inflammation is less likely, and that FeNO greater than 50ppb (>35ppb in children) be used to indicate that eosinophilic inflammation is more likely. The sensitivity and specificity of these recommended cutoffs have not been evaluated in published studies for the diagnosis of asthma.

Conclusions
Numerous studies have evaluated measurement of FeNO as a tool to aid in the diagnosis of asthma. The optimal cutoff of FeNO for diagnosing asthma has varied among studies; studies determining the optimal cutoff of FeNO are still being published as of 2012. There is still no validated standardized cutoff of FeNO to use for diagnosing asthma. As a result, it is not possible to determine the true sensitivity and specificity of the test for diagnosing asthma. Available studies tend to report low to moderate sensitivity and moderate to high specificity, but with wide variability among studies that may be related to different cutoff levels used. Due to these limitations, it is not possible to determine whether exhaled NO has incremental utility for diagnosing asthma compared to the usual clinical evaluation.
FeNO Level as Predictor of Medication Therapy Response in Asthma Patients

The 2011 clinical practice guideline from the ATS recommended the use of FeNO to determine the likelihood of response to steroids in individuals with chronic respiratory symptoms that are possibly due to airway inflammation. Three studies were cited in the guideline in support of this recommendation: all used data from randomized controlled trials (RCTs). In a 2002 open-label trial, Szefler and colleagues randomized 30 asthma patients to one of two types of ICS. There was a higher rate of response to ICS (defined as an increase in forced expiratory volume in one second [FEV1] of at least 15%) in individuals with higher baseline FeNO (median 17.6ppb) compared to lower baseline FeNO (median 11.1ppb). Other factors associated with a response to ICS in this study included high bronchodilator reversibility and a low FEV1/forced vital capacity ratio before treatment. In 2005, Smith and colleagues conducted a single-blind placebo-controlled trial of inhaled fluticasone in 60 patients presenting with undiagnosed respiratory symptoms. Steroid response was defined as an increase in FEV1 of at least 12% or an increase in peak morning flow (over the previous seven days) of 15% or greater. In the 52 (87%) patients who completed the study, steroid response was significantly higher in patients with the highest FeNO quartile at baseline (over 47ppb) for both of the study endpoints. In addition, a baseline FeNO of over 47ppb had a 67% sensitivity and 78% specificity for predicting response to steroids, when defined as an increase in FEV1. When response to steroids was defined as an increase in peak morning flow, there was an 82% sensitivity and 81% specificity for predicting response.

The third study cited in the ATS guideline in support of FeNO for predicting response to corticosteroids was published by Knuffman and colleagues in 2009. The study was a planned post hoc analysis of data from an RCT comparing different treatment regimens in children with asthma. The authors evaluated predictors of long-term response to treatment in 191 children who received either fluticasone or montelukast. In a multivariate analysis, statistically significant predictors of a better ACD response to fluticasone over montelukast were a baseline FeNO of at least 25ppb (p=0.01) and a parental history of asthma (p=0.02).

All of these three studies found significant associations between baseline FeNO and response to inhaled corticosteroids. It is worth noting, however, that the authors of two of the above studies (Smith et al and Szefler et al) have also published RCTs evaluating FeNO measurement for guiding treatment decisions for patients with asthma. Neither of those RCTs found better health outcomes e.g., exacerbation rates when FeNO was used to manage patients. (The RCTs are described in more detail in a later section of the policy).

No additional recent trials were identified in the 2012 literature update that specifically addressed the association between baseline FeNO and subsequent response to ICS.

Conclusions

Several studies have found a statistically significant association between baseline FeNO and response to inhaled corticosteroids. The number of studies addressing this topic is small and they have used different cutoff points for FeNO and different definitions of the outcome, i.e., response to steroids. As a result, there is uncertainty as to the degree of association between FeNO and response to steroids, as well as uncertainty in the optimal cutoff point that should be used for this purpose. It is also not clear that the ability to predict responsiveness to steroids will result in
management changes. Inhaled steroids are a mainstay of treatment of asthma and have been associated with a variety of health outcome benefits. Therefore, it may not be defensible to withhold inhaled steroids for symptomatic asthmatics even if there is evidence for reduced responsiveness.

Management
In 2012,Petsky and colleagues published a meta-analysis of RCTs evaluating the use of tailoring asthma treatment based on levels of eosinophilic markers (exhaled NO or sputum eosinophils) compared to clinical symptoms (with or without spirometry/peak flow). The study combined two Cochrane reviews including a 2009 review on exhaled NO. Updated literature searches were not performed. As in the 2009 Cochrane review, the 2012 review identified a total six RCTs on FeNO. In addition to the two RCTs described above in the section on the TEC Assessment, the studies were Shaw et al 2007, Fritsch et al 2006, Szefler et al 2008, and de Jongste et al 2009.

The primary outcome of the meta-analysis was the difference in the number of patients in each group who had asthma exacerbations during follow-up. A pooled analysis of two of the pediatric studies (Pijnenburg et al 2005 and Szefler et al 2008) did not find a significant difference in symptom scores between patients managed with and without FeNO measurement (mean difference: 0.13; 95% CI: -0.32-0.57).

There were, however, statistically significant differences between groups in the final dose of ICS although the direction of this relationship was different in adults and children. In adults, patients who had their medication doses adjusted based on exhaled NO levels had a significantly lower final dose of ICS than those in the control group (pooled analysis of two studies: mean difference: -450ug budesonide equivalent, 95% CI: -677 to -223). In contrast, children in the FeNO group had a significantly higher dose of ICS compared to the control group (pooled analysis of three studies, mean difference: 140ug, 95% CI: 29 to 251).

Three additional, more recent RCTs were identified in literature searches for policy updates. Two of these had findings similar to the Petsky systematic review. In 2012, an RCT by Pike and colleagues in the U.K. included 90 children with severe asthma. Medication management decisions were based on clinical symptoms (i.e., standard management) (n=46) or clinical symptoms and FeNO levels (n=44). In the standard management group, therapy was increased if symptoms were poorly controlled or decreased if symptoms were well-controlled for three months. Medications were given according to a stepped care algorithm consistent with British clinical guidelines. In the exhaled NO group, when symptoms were poorly controlled and FeNO was less than 25ppb, long-acting beta-agonist therapy (LABA) was maximized before ICS was increased. If FeNO was at least 25ppb or doubled from baseline, ICS was increased. ICS was decreased if symptoms were well-controlled for three months (as in the standard care group) or if FeNo was 15ppb or lower and symptoms were controlled. Seventy-seven of 90 (86%) of participants completed the 12-month study; analysis was intention to treat. During the follow-up period, Thirty-seven (84.1%) of the patients in the FeNO group and 38 (82.6%) of the patients in the standard care group experienced at least one asthma exacerbation. The proportion of children with exacerbations did not differ significantly between groups, p=0.85. Five (11.4%) children in the FeNO group and three (6.5%) in the standard care group experienced a severe exacerbation;
the difference between groups was not statistically significant, p=0.42. In addition, there was not a significant difference between groups in the initial ICS dose, the final ICS dose and the change in ICS during the study. Median final dose of ICS was 800 mcg in the FeNO group and 500 mcg in the standard management group.

Also in 2012, Calhoun and colleagues published a multicenter trial funded by the National Institutes of Health (NIH) known as the Best Adjustment Strategy for Asthma in the Long Term (BASALT) trial. The study included 342 adults with mild to moderate persistent asthma that was well or partially controlled by low-dose ICS. Participants were randomized to one of two strategies for medication adjustment: 1) adjusted by physicians at clinic visits (every six weeks) according to NIH clinical guidelines; 2) adjusted according to levels of exhaled NO at clinic visits (every six weeks); or 3) adjusted by patients on a day-to-day basis based on their symptoms. The third strategy involved patients using an inhaler that contained corticosteroids whenever they used an inhaler containing a short-term beta-agonist for symptom relief. No details were provided in the article or supplemental material regarding how steroid dose was adjusted according to FeNO level. A total of 290 of 342 randomized patients completed the nine month study; analysis was intention to treat. The primary study outcome was time to first treatment failure according to pre-defined criteria. The nine-month Kaplan-Meier first treatment failure rate did not differ significantly among the three groups. The rates were 22% (97.5% CI: 14% to 33%) in the physician-directed medication adjustment group, 20% (97.5% CI: 13% to 30%) in the exhaled NO medication adjustment group and 15% (97.5% CI: 9% to 25%) in the symptom-based medication adjustment group. The failure rate in the physician-based and exhaled NO-based medication adjustment groups were not significantly different (hazard ratio: 1.2, 95.5% CI: 0.6 to 2.3). Secondary outcomes, including measures of lung function and asthma symptoms, also did not differ significantly among groups. The mean monthly dose of ICS was significantly higher in both the physician-directed medication adjustment group (1610 ug) and the exhaled NO-based medication adjustment group (1617 ug) compared to the patient-based symptom medication adjustment groups (832 ug, p=0.01 for both comparisons). An editorial accompanying the publication of the BASALT trial noted that, given the trials findings, it is difficult to recommend routine monitoring of exhaled NO in adults with mild to moderate asthma.

The third RCT, conducted by Powell and colleagues, found improved outcomes in pregnant women with asthma managed with an algorithm including FeNO.

Conclusions
Numerous RCTs comparing management of asthma with and without FeNO have been published. These studies are heterogenous in terms of the patient populations, the FeNO cutoff levels, and the protocol for management of patients in the control group. A meta-analysis of the six RCTs did not find significantly improved outcomes (e.g., a lower rate of asthma exacerbations, lower symptom scores) when medication dose was tailored to FeNO level. Two subsequent RCTs, including a large multicenter NIH-funded trial, had similar findings of no benefit. One recent RCT in pregnant women did find a lower rate of asthma exacerbations in women managed with an algorithm that included FeNo measurement compared to an algorithm without FeNo. However, in that RCT, it was difficult to determine that improved outcomes were
due to FeNO measurement and not to other factors such as dose of medication. Efficacy of this treatment algorithm has not been confirmed in other studies.

Respiratory Conditions Other than Asthma
Management
No controlled studies were identified that compared health outcomes in patients with COPD or other respiratory diseases whose treatment was managed with and without FeNO measurement.

Exhaled Breath Condensate
In general, it appears from the published literature that exhaled breath condensate (EBC) is at an earlier stage of development compared to exhaled NO. A 2012 review by Davis and colleagues noted that this is due, in part, to the fact that FeNO is a single biomarker and EBC is a matrix that contains so many potential biomarkers that research efforts have thus far been spread among numerous of these markers. In addition, several review articles note that before routine clinical use in the diagnosis and management of respiratory disorders can be considered, the following issues must be resolved: Standardization of collection and storage techniques:

- Effect of dilution of respiratory droplets by water vapor;
- Effect of contamination from oral and retropharyngeal mucosa;
- Variability in EBC assays for certain substances, including assay kits for the same biomarker and kit lot numbers from the same manufacturer;
- Lack of gold standard for determining absolute concentrations of airway lining fluid non-volatile constituents to compare with EBC;
- Lack of normative values specific to each potential EBC biomarker.

Asthma Severity
Several studies have been published on components of exhaled breath condensate (EBC) and their relationship with asthma severity. A 2011 study by Liu and colleagues, the Severe Asthma Research Program, was a multicenter study funded by the National Institutes of Health. This study had the largest sample size with 572 patients. Study participants consisted of 250 patients with severe asthma, 291 patients with non-severe asthma and 51 healthy controls. Samples of EBC were collected at baseline and were analyzed for pH levels. Overall, the median pH of asthma patients (two groups combined), 7.94, did not differ significantly from the median pH of controls, 7.90, p=0.80. However, the median pH of patients with non-severe asthma, 7.90, was significantly lower than patients with severe asthma, 8.02 (p-value not reported).

A 2012 cross-sectional study by Karakoc and colleagues in Turkey evaluated 42 children; 20 with persistent asthma (Group 1); 10 with intermittent asthma (Group 2) and 12 healthy controls (Group 3). EBC was collected from all participants and levels of matrix metalloprotease (MMP-9) and tissue inhibitors of metalloproteinases (TIMP-1) levels were analyzed. Mean MMP-9 of EBC levels was 57.7 ng/ml, 35.4 ng/ml and 30.6 ng/ml in Groups 1, 2 and 3, respectively. Levels were significantly higher in children with persistent asthma and intermittent asthma compared to controls. There were no significant differences among Groups in levels of TIMP-1 of EBC.

In 2011, Piotrowski and colleagues in Poland prospectively studied adult patients with asthma. The study included 27 patients with severe asthma who were receiving treatment (Group 1), 16 newly diagnosed and never-treated asthma patients (Group 2) and 11 health controls.
(Group 3). At baseline and at weeks four and eight, EBC was collected and patients underwent spirometry and other tests of asthma severity. Patients were able to take all medications needed to control symptoms throughout the study. Levels of 8-isoprostane (8-IP) in breath condensate were analyzed. At baseline, the median level of 8-IP was 4.67 pg/ml, 6.93 pg/ml and 3.80 pg/ml in Groups 1, 2 and 3, respectively. There were no statistically significant differences among groups in 8-IP levels. In addition, 8-IP levels did not significantly correlate with asthma severity measures, including the number of symptom-free days, FEV1 reversibility and scores on the asthma control test (ACT). In this study, 8-IP in EBC was not found to be a useful marker of asthma severity.

Conclusions
There is limited evidence on the use of EBC for determining asthma severity. The available evidence is insufficient to form conclusions on the utility of EBC for this purpose.

Respiratory Conditions Other than Asthma
There is little published literature on EBC levels in patients with respiratory disorders other than asthma.

Summary
Evaluation of exhaled nitric oxide and exhaled breath condensate are proposed as techniques to diagnose and monitor asthma and other respiratory conditions. Several prospective studies have addressed FeNO measurement; however, there is still no standardized and validated cut-off to use for diagnosing asthma.

Multiple randomized controlled studies have evaluated the use of FeNO tests for the management of patients and have not consistently found improvement in health outcomes. Moreover, a 2012 metaanalysis pooling results of studies evaluating FeNO in the management of patients with asthma found a high degree of variability among studies and did not recommend routine use of FeNO in clinical practice. A 2011 RCT of pregnant women with asthma found better outcomes in the group managed using a FeNO algorithm than standard care. In this study, as in many others, there are concerns that differences in treatment regimens that arise as a result of different algorithms may confound the outcomes, particularly in cases where the control algorithm may lead to undertreatment. However, two subsequent RCTs, one in children with asthma and the other in adults with asthma, reported no improvement in outcomes associated with FENO-based treatment algorithms.

There is less evidence on the utility of FeNO for the diagnosis and management of other respiratory disorders. There are also few studies on exhaled breath condensate evaluation for the diagnosis and treatment of asthma and other conditions. Thus, the evidence is insufficient to determine the effect of exhaled nitric oxide and exhaled breath condensate tests on health outcomes, and the tests are considered investigational.

Practice Guidelines and Position Statements
In 2011, the American Thoracic Society (ATS) published a clinical practice guideline on interpretation of FeNO levels. The guideline was critically appraised using criteria developed by the Institute of Medicine (IOM) which includes eight standards. The guideline was judged to not
adequately meet the following standards: Standard 3: guideline development group composition; Standard 4: clinical practice guideline-systematic review intersection; Standard 5: Establishing evidence foundation for and rating strength of recommendations; and Standard 7: external review.

The ATS guideline included the following strong recommendations (if not otherwise stated, the recommendations apply to asthma patients):

- 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 recommend accounting for age as a factor affecting FENO in children younger than 12 years of age (strong recommendation, high quality of evidence).
- We recommend that low FENO less than 25 ppb (<20 ppb in children) be used to indicate that eosinophilic inflammation and responsiveness to corticosteroids are less likely (strong recommendation, moderate quality of evidence).
- We recommend that FENO greater than 50 ppb (>35 ppb in children) be used to indicate that eosinophilic inflammation and, in symptomatic patients, responsiveness to corticosteroids are likely (strong recommendation, moderate quality of evidence).
- We recommend that FENO values between 25 ppb and 50 ppb (20–35 ppb in children) should be interpreted cautiously and with reference to the clinical context. (strong recommendation, low quality of evidence).
- We recommend accounting for persistent and/or high allergen exposure as a factor associated with higher levels of FENO (strong 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).

**Key Words:**
Asthma, nitric oxide, NIOX, Breathmeter, exhaled breath condensate pH, exhaled breath condensate, EBC, NIOX MINO

**Approved by Governing Bodies:**
In 2003, the U.S. Food and Drug Administration (FDA) cleared for marketing the Nitric Oxide Monitoring System (NIOX) (Aerocrine; Sweden) with 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 ages of four years, 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. The main differences between this new device and the NIOX are that the NIOX MINO is hand-held and portable and that it is not suitable for children under age seven years.

Breathmeter (Ekipstech), another device to measure exhaled nitric oxide using laser spectroscopy. As of November 2010, the Breathmeter is only available for research only and has not yet received FDA approval or clearance.

The RTube Exhaled Breath Condensate collection system (Respiratory Research, Inc) is registered with the FDA as a Class I device that collects expired gas. Respiratory Research has a proprietary gas-standardized pH assay, which, when performed by the company, is considered a laboratory-developed test.

**Benefit Application:**
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply
FEP contracts: Special benefit consideration may apply. Refer to member’s benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

**Current Coding:**
CPT codes:

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**Previous Coding:**
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**References:**


83. www.aerocrine.com

**Policy History:**
Medical Policy Group, June 2004 (1)
Medical Policy Administration Committee, July 2004
Available for comment July 12-August 25, 2004
Medical Policy Group, June 2005 (1)
Medical Policy Group, June 2006 (1)
Medical Policy Administration Committee, June 2006
Available for comment July 5-August 18, 2006
Medical Policy Group, June 2007 (1)
Medical Policy Group, December 2009 (1)
Medical Policy Administration Committee, December 2009
Available for comment December 23, 2009-February 4, 2010
Medical Policy Group, December 2010 (1): Description updated, Key Points updated, Approved Governing Bodies, no policy statement change
Medical Policy Group, January 2012 (1): Policy retitled to include exhaled breath condensate; Update to Key Points and References related to MPP update; no change in policy statement

Medical Policy Panel, January 2014

Medical Policy Group, January 2014 (3): Updates to Description, Policy Statement, Key Points, Governing Bodies, & References; policy statements updated to include the word “diagnosis”

Available for comment January 23 through March 7, 2014

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.