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

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Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for measurement of exhaled nitric oxide and exhaled breath condensate. This is considered investigational.

When Policy Topic is covered

Not Applicable

When Policy Topic is not covered

Measurement of exhaled nitric oxide is considered **investigational** in the diagnosis and management of asthma and other respiratory disorders including but not limited to chronic obstructive pulmonary disease and chronic cough.

Measurement of exhaled breath condensate is considered **investigational** in the diagnosis and management of asthma and other respiratory disorders including but not limited to chronic obstructive pulmonary disease and chronic cough.

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.

Background

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 FEV1 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 proposed strategies are the measurement of exhaled nitric oxide 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. In biologic tissues, nitric oxide is unstable, limiting measurement. However, in the gas phase, nitric oxide is fairly stable, permitting its measurement in exhaled air. Exhaled nitric oxide 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 and European Respiratory Society, 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) maintained within 10% for more than 6 seconds at an oral pressure between 5 and 20 cm H2O. (1) Results are expressed as the nitric oxide concentration in parts per billion (ppb) based on the mean of 2 or 3 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 nitric oxide 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 managing patients with chronic obstructive pulmonary disease, cystic fibrosis, allergic rhinitis and primary ciliary dyskinesia.

Regulatory Status
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 age of 4, as measurement requires patient cooperation. NIOX should not be used in critical care, emergency care or in anesthesiology." In March 2008, the NIOX MINO was cleared for marketing. 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 7 years.

The RTube™ Exhaled Breath Condensate collection system (Respiratory Research Inc.) and the ECoScreen EBC collection system (CareFusion, Germany) are registered with FDA as a Class I devices that collect expired gas. Respiratory Research has a proprietary gas-standardized pH assay, which, when performed by the company, is considered a laboratory-developed test.

Rationale

An initial literature search was performed in 2003. The policy was updated regularly with a literature review using MEDLINE, the most recent through December 10, 2013. Evaluation of the tests for diagnosis requires that the test findings are reproducible on test-retest and that the test is reasonably accurate compared to a validated reference standard. Assessment of the clinical role of exhaled nitric oxide (NO) and exhaled breath condensate (EBC) tests requires controlled studies of those managed conventionally compared to those whose management was additionally directed by test measurements. Following is a summary of literature to date.

Exhaled Nitric Oxide

Asthma

Reproducibility of fractional concentration of exhaled nitric oxide (FeNO) measurements

In 2010, Selby and colleagues published a study from the UK that evaluated the reproducibility of exhaled NO measurements in young people. (2) The study included 494 teenagers, aged 16-18 years, from an unselected birth cohort and 65 asthma patients between the ages of 6 and 17 years. Paired readings were obtained from each participant. The mean within-participant difference in FeNO (second reading minus the first reading) was 1.37 parts per billion (ppb) (95% confidence interval [CI], -7.61 to 10.34 ppb); this difference was statistically significant; p less than 0.001. When participants with high FeNO values (above 75 ppb) were excluded, there was a lower mean within-participant difference, 0.90 ppb (95% CI, - 4.89 to 6.70 ppb). Among the 71 participants with asthma, the mean within-participant difference in FeNO in the 2 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 younger than age 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.

Does FeNO aid in the diagnosis of asthma in individuals with signs or symptoms of asthma?

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.

In 2013, See and Christiani published an evaluation of reference ranges for FeNO evaluated with the NIOX MINO for a representative sample of the U.S. population aged 6 through 80 years that was derived from the National Health and Nutrition Examination Survey (NHANES, 2007-2010).(3) They report that the range of FeNO values (5th-95th percentile) was 3.5–36.5 ppb for children younger than age 12 years and 3.5–39 ppb for individuals from 12-80 years of age and conclude that a reasonable upper limit of “normal” values for FeNO, as represented by 95% of the general population is 36 ppb for children younger than age 12 years and 39 for older individuals.

In 2013, Schneider and colleagues in Germany reported findings from a prospective diagnostic study of 393 patients presenting to a pulmonology practice with signs/symptoms suggestive of obstructive airway disease.(4) FeNO was measured with the NIOX MINO device at a flow rate of 50 mL/s. Asthma was diagnosed based on bronchial provocation or bronchodilator testing. Among all 393 participants, receiver operating characteristic (ROC) analysis found that a FeNO cutoff of 25 ppb had the highest sum of sensitivity/specificity (sensitivity 49% and specificity 75%). The authors also evaluated the influence of inflammatory cell predominance in first morning sputum on the accuracy of FeNO in diagnosing asthma. Among the subset of 128 patients who provided sputum, when patients with a neutrophilic predominance on Giemsa-stained sputum smear slides were excluded, the highest sum of sensitivity and specificity was reached at a FeNO cutoff of 23 ppb (sensitivity 67% and specificity 77%).

Also in 2013, Katsoulis and colleagues in Greece reported findings from an evaluation of 112 individuals aged 22-37 years recruited from an outpatient clinic setting who endorsed at least one symptom of asthma and had a negative bronchodilator test.(5) FeNO was measured with the NIOX MINO device at a flow rate of 50 mL/s. Asthma was diagnosed based on methacholine challenge. ROC analysis found that a FeNO cutoff of 32 best predicted bronchial hyper-reactivity on methacholine challenge (sensitivity 47% and specificity 85%).

Sverrild and colleagues in Denmark reported results from a *post hoc* analysis of a random-sample population study of 238 individuals aged 14-24 years who underwent mannitol challenge and FeNO measurement using the NIOX.(6) Asthma was diagnosed based on assessment of a respiratory specialist and airway hyper-responsiveness was defined as a positive result on a mannitol challenge. Among 180 subjects who were not active smokers or on an inhaled corticosteroid, ROC analysis found that a FeNO cutoff of 25 ppb best predicted airway hyper-responsiveness (sensitivity 86% and specificity 84%).

In 2012, Malinovschi and colleagues in Denmark evaluated 282 individuals with symptoms suggestive of asthma. (7) Study participants were part of a sample of 10,400 individuals aged 14-44 years randomly selected from the civil registration list in Denmark. Individuals were eligible for the study if they had at least 2 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, 108 never smoked and 62 were ex-smokers. According to clinical evaluation, 96 of 282 (34%) had asthma, 32 smokers, 45 never smokers, and 19 ex-smokers. The authors examined different cutoffs of FeNO to determine the value with the optimal sensitivity and specificity for diagnosing asthma. They proposed a cutoff of 17 ppb in current smokers (56.3% sensitivity and 82.5% specificity), 15 ppb in never smokers (77.8% sensitivity and 63.5% specificity), and 22 ppb 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). (8) 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 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-naïve children with respiratory symptoms suggestive of asthma. (9) 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 22 ppb, which provided 56.9% sensitivity and 87.2% specificity. At a cutoff of 42 parts per trillion (ppt), the specificity was 100%, but the sensitivity was very low, 23.4%.

Other representative studies include one using the NIOX MINO device that was published in 2010 by Pedrosa and colleagues in Spain. (10) The study included 114 individuals at least 14 years-old who 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 findings, 35 patients (31%) were diagnosed with asthma. FeNO levels were significantly higher in individuals diagnosed with asthma (mean 58 ppb) than in non-asthmatic patients (mean ppb 30 ppb); $p<0.001$. Using ROC analysis, the cutoff point with maximum sensitivity (74.3%) and specificity (72.5%) for diagnosing asthma was a FeNO value of 40 ppb. A 2010 study conducted in Italy included 280 children with asthma, allergic rhinitis or both. (11) The authors used ROC analysis and found that the optimal cutoff for discriminating between patients with bronchial hyperactivity from those with absent or borderline bronchial hyperactivity was 32 ppb of NO. , In 2009, Schneider and colleagues in Germany published data on 160 patients with symptoms suspicious of asthma. (12) All patients underwent measurement of exhaled NO. The reference standard was a stepwise series of tests, beginning with spirometry. Those with forced expiratory volume in one second (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 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 NO 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 NO at a cutoff of 46 ppb. Among patients with unsuspicious spirometry findings (n=101), 49 had asthma. The optimal cutoff of exhaled

NO in this subgroup was also 46 ppb; the sensitivity of exhaled NO was 35%, and the specificity was 90%.

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. (13) Many, but not all, patients with asthma will have eosinophilic inflammation. The guidelines recommended that FeNO less than 25 ppb (<20 ppb in children) be used to indicate that eosinophilic inflammation is less likely and that FeNO greater than 50 ppb (>35 ppb in children) be used to indicate that eosinophilic inflammation is more likely. Based on their assessment of U.S. population-based normal ranges for FeNO, See and Christiani concluded that the ATS thresholds are reasonable to use for clinical decisionmaking.(3) However, the sensitivity and specificity of these recommended cutoffs have not been evaluated in published studies for the diagnosis of asthma.

Section Summary:
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 2013. 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, different study populations, and different "criterion standards" for asthma diagnosis. . Given these limitations, it is not possible to evaluate whether the use of FeNO levels in clinical practice improves the accuracy of diagnosing asthma.

Does FeNO level predict response to medication therapy in patients with asthma?
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. (13) 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 1 of 2 types of inhaled corticosteroids (ICS). (14) 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 17.6 ppb) compared to lower baseline FeNO (median 11.1 ppb). 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. (15) Steroid response was defined as an increase in FEV1 of at least 12% or an increase in peak morning flow (over the previous 7 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 47 ppb) for both of the study end points. In addition, a baseline FeNO of over 47 ppb 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. (16) 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 asthma control days (ACD) response to fluticasone over montelukast were a baseline FeNO of at least 25 ppb (p=0.01) and a parental history of asthma (p=0.02).

All of these 3 studies found significant associations between baseline FeNO and response to inhaled corticosteroids. It is worth noting, however, that the authors of 2 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).
Following the ATS clinical practice guideline publication, several trials have been published that addressed the association between FeNO and subsequent response to ICS. Anderson et al. conducted a randomized crossover trial in 21 patients with persistent asthma and elevated FeNO levels (>30 ppb) receiving ICS at baseline.(17) Following an ICS washout period, subjects were randomized to either low-or high-dose inhaled fluticasone, with a 2-week ICS washout period followed by crossover to the other arm. The primary outcome was diurnal household FeNO level measured by the NIOX MINO device. Analysis was performed on a per protocol basis. The authors reported significant improvements in FeNO compared with baseline for both morning and evening values, with a dose-dependent effect: morning FeNO decreased from baseline 71 ppb to 34 ppb for those receiving the lower dose ICS and to 27 ppb for those receiving the higher dose ICS; evening FeNO decreased from baseline 67 ppb to 31 ppb for those receiving the lower dose ICS and to 22 ppb for those receiving the higher dose ICS. While this study suggests that ICS dose is associated with FeNO levels, it is limited by its small size; furthermore, it does not address the question of FeNO's role in predicting ICS response *ex ante.*

Section Summary:
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 asthmatic patients even if there is evidence for reduced responsiveness. Further study into the use of FeNOs in tailoring dosing of ICS and in asthma step-up or step-down therapy is needed.

Does measurement FeNO to guide treatment decisions in patients with asthma improve health outcomes?
In 2005, a TEC Assessment was published on exhaled NO monitoring for guiding treatment decisions in patients with chronic asthma. (18) The assessment identified 2 randomized controlled trials; both were published in 2005. Smith and colleagues reported that equivalent outcomes (e.g. exacerbations, pulmonary function) were achieved in the group managed using exhaled NO measurements compared to the group managed using conventional guidelines (19) The FeNO group, however, used lower doses of ICS at the end of the study. Pijnenburg and colleagues found similar changes in steroid dose and FEV1 in groups managed with and without FeNO measurements. (20) Bronchial hyper reactivity, an intermediate outcome, improved more in the FeNO group. The TEC Assessment concluded that the available evidence did not permit the conclusion that use of NO monitoring to guide treatment decisions in asthma leads to improved outcomes.

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). (21) The study combined 2 Cochrane reviews including a 2009 review on exhaled NO. (22) Updated literature searches were not performed. As in the 2009 Cochrane review, the 2012 review identified a total 6 RCTs on FeNO. In addition to the 2 RCTs described above in the section on the TEC Assessment, the studies were Shaw et al. 2007, (23) Fritsch et al. 2006, (24) Szefler et al. 2008, (25) and de Jongste et al. 2009. (26) Four of the 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 4 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.

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. When findings for the 2 FeNO studies that included adults and/or adolescents were pooled (Shaw et al. 2007 and Smith et al. 2005), 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). There was also no significant difference in symptom scores (mean difference of -0.10 [95% CI, -0.33 to 0.12]). Findings from 3 of the 4 pediatric trials were pooled, Pijnenburg et al. 2005, (20) Szefler et al. 2008, (25) and de Jongste et al. 2009 (26). 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). A pooled analysis of 2 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 2 studies: mean difference= -450 ug 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 3 studies, mean difference=140 ug, 95% CI, 29 to 251).

Following the Petsky systematic review, 5 additional RCTs evaluating the use of FeNO as part of an asthma management strategy have been identified with mixed findings about the benefit of using FeNO as part of an asthma treatment algorithm.

In 2013, Syk et al. in Sweden published the results from a randomized controlled trial of FeNO-based asthma management in a primary care setting among 187 nonsmoking patients aged 18-64 with asthma requiring regular ICS use. (27) Subjects were randomized to a FeNO-guided management group or a control group and followed for one year. In the control group, treatment with an algorithm of escalating doses of inhaled corticosteroid (budesonide, fluticasone, or mometasone), with the addition of a leukotriene receptor antagonist (LTRA) at higher doses, was based on the discretion of the treating physician. In the FeNO-guided group, ICS and LTRA therapies were adjusted according to the same stepwise treatment plan as the control group, but with treatment decisions based on FeNO level. The algorithm for women was as follows: one step down for FeNO <19 ppb; no change for FeNO from 19-23 ppb; one step up for FeNO ≥24 ppb; and 2 steps up for FeNO ≥30 ppb. The algorithm for men was: one step down for FeNO <21 ppb; no change for FeNO from 21-25 ppb; one step up for FeNO ≥26 ppb; and 2 steps up for FeNO ≥32 ppb. The study's primary outcome was changes in the mini Asthma Quality of Life Questionnaire (mAQLQ), with secondary outcomes of change in Asthma Control Questionnaire (ACQ) score, exacerbation frequency, lung function, quality-of-life score, and medication use. For the primary study outcome, there was no significant difference between groups on the change in the mAQLQ score (0.23 [interquartile range 0.07-0.73] in the FeNO-guided group vs. 0.07 [interquartile range -0.20- 0.80] in the control group, p=0.197). On secondary outcomes, the frequency of exacerbations was significantly lower in the FeNO-guided group than in the control group (0.22 vs. 0.41 exacerbations/patient/year, p=0.024). The change in ACQ score was significantly higher in the FeNO-guided group than in the control group (-0.17 [interquartile range -0.67-0.17] in the FeNO-guided group vs 0 [-0.33-0.50] in the control group, p=0.045. Other secondary outcomes did not show any significant differences. (The authors state that the mean ICS dose did not differ between the 2 groups, but statistics are not provided. Strengths of this study include a primary care-based setting, allowing results to be generalized to the setting in which most asthmatics are treated, a relatively large sample size, and a clearly outlined algorithm for how asthma therapy was adjusted. Limitations include the fact that the analysis was not intent-to-treat and the article does not provide details about the statistical comparisons to support several of its conclusions.

Also in 2013, Peirsman et al. in Belgium reported results from an industry-sponsored randomized single-blind controlled trial of a FeNO-based asthma management strategy among 99 children aged 5-14 years with persistent allergic asthma.(28) Similar to the Syk study, subjects were randomized to a

FeNO-guided management group or a control group and followed for one year. In the control group, treatment was guided by the Global Initiative for Asthma (GINA) guidelines on the basis of symptom reporting every 3 months. Details about who made decisions about treatment were not provided. In the FeNO-guided management group, FeNO measurements and the degree of symptom control were used to guide therapy based on a treatment algorithm. Using a classification of controlled asthma (FENO of <20 ppb and no symptoms), partly controlled asthma (FENO of <20 ppb with symptoms), or uncontrolled asthma (FENO of >20 ppb), ICS, LTRA, and long-acting beta-2 agonist therapies were stepped up or down on each visit. The primary outcome was symptom-free days; secondary outcomes were exacerbations, unscheduled asthma-related contact, hospital or emergency department admissions, and nonattendance at school. The authors found no significant differences between the treatment and control group on the primary outcome of symptom-free days, as recorded by symptom diary; the ability to detect a difference in this outcome may have been limited by a considerable amount of missing data, with 10 children failing to provide data for >85% of days. On secondary outcomes, the FeNO-guided group had significantly fewer asthma exacerbations (18 vs. 35 exacerbations/year, p=0.02) but no differences on emergency department visits, hospital admissions, or time missed from school. While there was no difference between the median cumulative daily ICS doses between the groups, the FeNO group demonstrated a greater change in ICS dose from the beginning to the end of the study compared with the control group (0 mcg vs. +100 mcg, p=0.016).

In 2012, an RCT by Pike and colleagues in the U.K. included 90 children with severe asthma. (29) 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 3 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 25 ppb, long-acting beta-agonist therapy (LABA) was maximized before ICS was increased. If FeNO was at least 25 ppb or doubled from baseline, ICS was increased. ICS was decreased if symptoms were well-controlled for 3 months (as in the standard care group) or if FeNO was 15 ppb 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, 37 (84.1%) of patients in the FeNO group and 38 (82.6%) of 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 3 (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. (30) 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 2 strategies for medication adjustment: 1) adjusted by physicians at clinic visits (every 6 weeks) according to NIH clinical guidelines; 2) adjusted according to levels of exhaled NO at clinic visits (every 6 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 9-month study; analysis was intention to treat. The primary study outcome was time to first treatment failure according to predefined criteria. The 9-month Kaplan-Meier first treatment failure rate did not differ significantly among the 3 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 trial findings, it is difficult to recommend routine monitoring of exhaled NO in adults with mild to moderate asthma. (31)

The third RCT, conducted by Powell and colleagues, found improved outcomes in pregnant women with asthma managed with an algorithm including FeNO. (32) Eligibility included being between 12 and 20 weeks' gestation a non-smoker 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 cutoff for reducing the dose of ICS was less than 16 ppb, and the cutoff 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, Peirsman, and Syk studies demonstrate potential benefits to using a treatment algorithm that incorporates FeNO levels, particularly regarding exacerbation frequency. However, limitations of these trials include the fact that 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 cutoff point for increasing ICS, then the FeNO group will likely end up on higher doses of ICS. Improved outcomes are then more likely to be due to the efficacious effect of ICS, rather than the inclusion of FeNO in the algorithm. In the Powell study, (32) for example, the cutoff point for increasing ICS was lowered compared to previous algorithms, thus resulting in more patients being started this medication. Additionally, the control group was treated by an algorithm that differed from current treatment guidelines in at least 2 important ways, both which resulted in less intensive treatment compared with treatment guidelines. The net effect of these algorithms was that more patients in the FeNO group received both long-acting beta-agonists and ICS, 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.

Section Summary:
Numerous RCTs comparing management of asthma with and without FeNO have been published. These studies are heterogeneous 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 6 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. Three RCTs, one in adults, one in children, and one in pregnant women, found a lower rate of asthma exacerbations in subjects managed with an algorithm that included FeNO measurement compared to an algorithm without FeNO. Most of the RCTs use a relatively low cutoff value for FENO, thereby leading to an overall increase in ICS use among patients managed with a FeNO-based algorithm. As such, it is difficult to determine whether the improved outcomes in the treatment group are the result of increased doses of ICS in patients who were

undertreated at the outset of the trials, or to the impact of FENO-guided management in improving tailored therapy.

Respiratory conditions other than asthma

Does FeNO aid in the diagnosis of respiratory disorders other than asthma?

Rouhos and colleagues in Finland published a study in 2011 on repeatability of FeNO measurements in 20 patients with stable chronic obstructive pulmonary disease (COPD) and 20 healthy controls. (33) FeNO was measured 3 times in each individual; a baseline measurement and measurements 10 minutes and 24 hours after baseline. In COPD patients, median FeNO values were 15.2 ppb at baseline, 17.4 ppb 10 minutes later, and 14.5 ppb 24 hours later. In healthy controls, corresponding median FeNO values were 15.6 ppb, 19.6 ppb, and 15.7 ppb. Differences between the baseline and 24-hour measurements in both groups were not statistically significant. FeNO values 10 minutes after baseline were significantly higher than the 24-hour measurement in both groups; the authors attributed this difference to the fact that patients did not rinse their mouths with sodium bicarbonate between the baseline and 10-minute measurements.

Does FeNO level predict response to medication therapy in patients with respiratory conditions other than asthma?

A double-blind crossover trial by Dummer and colleagues evaluated the ability of exhaled NO test results to predict corticosteroid response in chronic obstructive pulmonary disease (COPD). (34) The study included 65 patients with COPD who were 45 years or older, were previous smokers with at least a 10- pack a year history, had persistent symptoms of chronic airflow obstruction, had a postbronchodilator 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 comorbidities and those taking regular corticosteroids or had used oral corticosteroids for exacerbations more than twice during the past 6 months were excluded. Treatments, given in random order, were 30 mg/d of prednisone or placebo for 3 weeks; there was a 4-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 3 primary outcomes, 6-minute walk distance (6MWD and FEV1) increased significantly from baseline with prednisone compared to placebo. There was a nonsignificant decrease in the third primary outcome, score on the St. George's Respiratory Questionnaire (SGRQ). The correlation between baseline fraction of exhaled NO 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 of exhaled NO cutoff of 50 ppb, 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 NO 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 NO test results.

A prospective uncontrolled study by Prieto and colleagues assessed the utility of exhaled nitric oxide measurement for predicting response to ICS in patients with chronic cough. (35) The study included 43 patients with cough of at least 8 weeks' duration who were non-smokers and did not have a history of other lung disease. Patients were evaluated at baseline and after 4 weeks of treatment with inhaled fluticasone propionate 100 µg 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 FeNO cutoff, the sensitivity was 53% and the specificity was 63%. The authors concluded that exhaled NO is not an adequate predictor of treatment response.

Does measurement of FeNO improve health outcomes when used to guide treatment decisions in patients with respiratory disorders other than asthma?

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. (36) 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 (36-40):

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.

Are components of EBC useful as markers of asthma severity?

Similar to FeNO, EBC has been associated with asthma severity. In 2013, Thomas and colleagues conducted a systematic review of studies assessing the association components of EBC with pediatric asthma.(41) They identified 46 papers that measured at least one EBC marker in asthma, allergy, and atopy in children up to age 18 years. Most studies were cross-sectional, but there was wide variation in the definitions used to identify children with asthma and the collection devices and assays for EBC components. Studies reviewed evaluated multiple specific EBC components, including hydrogen ions, NO, glutathione and aldehydes, hydrogen peroxide, eicosanoids (including prostaglandins and leukotrienes), and cytokines (including interleukins in the TH2 pathway and interferon gamma). The authors note that hydrogen ions and markers of oxidative stress, including hydrogen peroxide and oxides of nitrogen, were most consistently associated with asthma severity. Eicosanoids and cytokines demonstrated more variable results, but were frequently elevated in the EBC of patients with asthma. Overall, the authors conclude that while EBC has the potential to aid diagnosis of asthma and evaluate inflammation in pediatric asthma, further studies on EBC collection and interpretation techniques are needed.

Among adults, a number of 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. (42) Study participants consisted of 250 patients with severe asthma, 291 patients with nonsevere 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 (2 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).

In 2011, Piotrowski and colleagues in Poland prospectively studied adult patients with asthma. (44) 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 4 and 8, 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.
Are components of EBC useful as markers of respiratory disorders other than asthma?
There is little published literature on EBC levels in patients with respiratory disorders other than asthma. A 2010 study by Antus and colleagues evaluated EBC in 58 hospitalized patients (20 with asthma and 38 with COPD) and 36 healthy controls (18 smokers and 18 non-smokers). (45) 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, respectively, $p<0.001$). 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 exsmoking COPD patients (n=17) did not differ significantly from nonsmoking controls, either at hospital admission or discharge. Similarly, pH values in EBC samples from smoking COPD patients (n=21) at admission and discharge did not differ significantly from smoking controls.

Are components of EBC useful in guiding treatment decisions for patients with asthma or other respiratory disorders?

No controlled studies were identified that evaluated the role of EBC tests in the management of asthma or other respiratory disorders. Uncontrolled studies include a 2009 case series investigating whether components of EBC could predict response to steroid treatment in patients with asthma. (46) 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 µg fluticasone propionate/d). 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 whether EBC measurement could improve patient management or health outcomes.

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers
In response to requests, input was received through 3 physician specialty societies (1 specialty society submitted 2 reviews) and 5 academic medical centers when this policy was under review in 2012. While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted. Input was mixed on whether measurement of exhaled NO is considered investigational in the diagnosis and management of asthma and other respiratory disorders. There was consensus that measurement of exhaled breath condensate is considered investigational in the diagnosis and management of asthma and other respiratory disorders. Input was mixed on additional questions posed to reviewers including whether there is a well-accepted cutoff for FeNO, whether FeNO levels would affect their decision regarding prescribing inhaled corticosteroids, whether there is published evidence that using FeNO measurements to guide treatment improves health outcomes and whether recommendations in ATS guidelines are supported by evidence.

Summary
Evaluation of exhaled nitric oxide and exhaled breath condensate are proposed as techniques to diagnose and monitor asthma and/or other respiratory conditions. While several prospective studies have addressed FeNO measurement for the diagnosis of asthma, there is still no standardized and validated cutoff to use in clinical care. Therefore, it is not possible to determine the accuracy of FENO for the diagnosis of asthma with certainty.

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 meta-analysis that pooled results of studies evaluating FeNO in the management of asthma found a high degree of variability among studies and did not recommend routine use of FeNO in clinical practice. Following that meta-analysis, 5 RCTs have compared the use of FeNO-based treatment algorithms to routine care for asthma, 2 among children, 2 among a general adult population, and one among pregnant women. Three studies report an improvement in some outcomes associated with FeNO-based treatment algorithms, while 2 demonstrated no clinical improvement. For the studies reporting benefit, improvement is mainly reported in the frequency of exacerbations, and there is generally no improvement reported in measures of overall disease activity or quality of life on standardized asthma measures.

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 these tests are therefore considered investigational.

Practice Guidelines and Position Statements

American Thoracic Society: In 2011, the ATS published a clinical practice guideline on interpretation of FeNO levels. (13) The guideline was critically appraised using criteria developed by the Institute of Medicine (IOM) which includes 8 standards. (47) 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).

American Thoracic Society/European Respiratory Society: A 2009 statement includes the following key points on exhaled nitric oxide:

> "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. Due to logistic and cost issues, FeNO is the only biomarker likely to have a role in primary care-based asthma studies, although

it is possible that with technological improvements, other techniques including sputum induction could have a role in the medium term." (1)

National Heart Lung and Blood Institute (NHLBI): Their 2007 expert panel guidelines for the diagnosis and management of asthma state:

> "Use of minimally invasive markers ("biomarkers") to monitor asthma control and guide treatment decisions for therapy is of increasing interest. Some markers, such as spirometry measures, are currently and widely used in clinical care; others, such as sputum eosinophils and FeNO, may also be useful, but they require further evaluation in both children and adults before they can be recommended as clinical tools for routine asthma management (Evidence D)."
>
> "The Expert Panel recommends some minimally invasive markers for monitoring asthma control, such as spirometry and airway hyper-responsiveness, that are appropriately used, currently and widely, in asthma care (Evidence B). 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 (Evidence D)." (48)

Medicare National Coverage

No national coverage determination.

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Billing Coding/Physician Documentation Information

83987 pH; exhaled breath condensate
94799 Unlisted pulmonary service or procedure
95012 Nitric oxide expired gas determination

Code 0140T was deleted effective 1/1/2010 and replaced with CPT code 83987. 0064T was deleted effective 1/1/2010 and was not replaced with a Category I CPT code.

Additional Policy Key Words

N/A

Policy Implementation/Update Information

3/1/07 New policy; considered investigational.
9/1/07 No policy statement changes.
3/1/08 No policy statement changes.
9/1/08 No policy statement changes.
3/1/09 No policy statement changes.
9/1/09 No policy statement changes.
3/1/10 Existing policy statement divided into two statements; one for exhaled nitric oxide, the other for exhaled breath condensate; examples of other respiratory disorders also added to policy statements. Both techniques remain investigational. Coding updated.
9/1/10 No policy statement changes.
3/1/11 No policy statement changes.

9/1/11	No policy statement changes.
3/1/12	In first policy statement, “exhaled or nasal nitric oxide” changed to “exhaled nitric oxide”; otherwise policy statements unchanged.
9/1/12	No policy statement changes.
3/1/13	No policy statement changes.
9/1/13	No policy statement changes.
3/1/14	No policy statement changes. Mention of the Breathmeter device removed from policy (no FDA clearance, no specific code). Added unlisted cpt code.
9/1/14	No policy statement changes.
