Medical Policy

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

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Policy Number: 524
BCBSA Reference Number: 2.01.61
NCD/LCD: NA

Related Policies
None

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity
Medicare HMO BlueSM and Medicare PPO BlueSM Members

Measurement of exhaled or nasal nitric oxide in the diagnosis and management of asthma and other respiratory disorders, including but not limited to chronic obstructive pulmonary disease and chronic cough, is INVESTIGATIONAL.

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

Prior Authorization Information

Pre-service approval is required for all inpatient services for all products. See below for situations where prior authorization may be required or may not be required for outpatient services.

Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.
N/A indicates that this service is primarily performed in an inpatient setting.

<table>
<thead>
<tr>
<th>Outpatient</th>
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<tbody>
<tr>
<td>Commercial Managed Care (HMO and POS)</td>
<td>This is not a covered service.</td>
</tr>
<tr>
<td>Commercial PPO and Indemnity</td>
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<tr>
<td>Medicare HMO BlueSM</td>
<td>This is not a covered service.</td>
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<tr>
<td>Medicare PPO BlueSM</td>
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</table>
CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The following CPT codes are considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

### CPT Codes

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>83987</td>
<td>pH; exhaled breath condensate</td>
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<tr>
<td>95012</td>
<td>Nitric oxide expired gas determination</td>
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### Description

#### Asthma Overview

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 1 second (FEV\textsubscript{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.

#### Fractional Exhaled Nitric Oxide and Exhaled Breath Condensate

Two proposed strategies are the measurement of exhaled nitric oxide (NO) and the evaluation of exhaled breath condensate. NO 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 NO-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 NO (FeNO) is best measured at an exhaled rate of 50 mL per second (FeNO 50 mL/s) maintained within 10% for more than 6 seconds at an oral pressure between 5 and 20 cm H\textsubscript{2}O.(1)

Results are expressed as the NO concentration in parts per billion (ppb), based on the mean of 2 or 3 values.

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.

**Clinical Uses of FeNO and EBC**

Measurements of FeNO have particularly been associated with an eosinophilic asthma phenotype. Eosinophilic asthma is a subtype of severe asthma associated with sputum and serum eosinophilia, along with later-onset asthma. Until recently, most asthma management strategies did not depend on the recognition or diagnosis of a particular subtype. However, 2 anti-interleukin 5 inhibitors have been approved by the Food and Drug Administration (FDA) for the treatment of severe asthma with an eosinophilic phenotype, mepolizumab and reslizumab.

A 2015 Cochrane review compared the evidence for mepolizumab and placebo for asthma. The review included 8 studies (total N=1707 patients). One randomized controlled trial (RCT) used FeNO as 1 potential criterion for eosinophilic asthma (Pavord et al, 2012). In another RCT, the criteria for eosinophilic asthma was a prior diagnosis of eosinophilic asthma or evidence of eosinophilic inflammation, but criteria for the diagnosis are not provided (Ortega et al, 2014). Overall, the Cochrane review concluded: “It is not possible to draw firm conclusions from this review with respect to the role of mepolizumab in patients with asthma. Our confidence in the results of this review are limited by the fact that the intravenous route is not currently licensed for mepolizumab, and the evidence for the currently licensed subcutaneous route is limited to a single study in participants with severe eosinophilic asthma.”

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, cystic fibrosis, allergic rhinitis, pulmonary hypertension, and primary ciliary dyskinesia.

**Summary**

Evaluation of exhaled nitric oxide (NO) and exhaled breath condensate (EBC) are proposed as techniques to diagnose and monitor asthma and other respiratory conditions. There are commercially available devices for measuring NO in expired breath and various laboratory techniques for evaluating components of EBC.

For individuals who have suspected asthma or suspected eosinophilic asthma who receive measurement of fractional exhaled nitric oxide (FeNO), the evidence includes multiple retrospective and prospective studies of diagnostic accuracy, along with systematic reviews of those studies. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbid events, and functional outcomes. There is a large volume of reports on the sensitivity and specificity of FeNO in asthma diagnosis. The available evidence is limited by the use of wide variability in FeNO cutoff levels used to diagnose asthma and wide variability in sensitivity and specificity for asthma diagnosis. The accuracy of the cutoffs recommended by the American Thoracic Society guidelines has not been evaluated in the diagnosis of asthma. In addition, no studies were identified that evaluated whether use of FeNO improved the accuracy of asthma diagnosis compared with clinical diagnosis. For use of FeNO in the diagnosis of eosinophilic asthma, using the criterion standard of sputum eosinophilia, the diagnostic accuracy is moderate. The evidence is insufficient to determine the effect of the technology on health outcomes.

For individuals who have asthma and who receive medication management directed by FeNO, the evidence includes multiple randomized controlled trials (RCTs). Relevant outcomes are symptoms, change in disease status, morbid events, and functional outcomes. The available RCTs evaluating the use of FeNO tests for the management of patients have not consistently found improvement in health outcomes. A 2012 meta-analysis of 6 RCTs did not find significantly improved outcomes (eg, a lower rate of asthma exacerbations, lower symptom scores) when medication dose was tailored to FeNO level. By contrast, a subsequent meta-analysis found statistically significant reductions in asthma exacerbations in...
patients managed with FeNO measurements. RCTs in various populations published since 2012 have had mixed findings. An additional RCT that demonstrated improvements in asthma control with a FeNO-based management approach compared clinical management targeting “partial control,” although not with a clinical management approach targeting complete control. Some available evidence suggests that a FeNO-based algorithm for adjusting inhaled corticosteroid doses may be associated with modest improvements in asthma exacerbations, but additional studies are needed. The evidence is insufficient to determine the effect of the technology on health outcomes.

For individuals who have suspected or confirmed respiratory disorders other than asthma who receive measurement of FeNO, the evidence includes 1 crossover trial and observational studies. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbid events, and functional outcomes. The available evidence for the use of FeNO for respiratory disorders other than asthma is limited by heterogeneity in the conditions evaluated and uncertainty about the potential clinical use. The evidence is insufficient to determine the effect of the technology on health outcomes.

For individuals who have suspected or confirmed respiratory disorders who receive measurement of EBC, the evidence includes observational studies reporting on the association between various EBC components and disease severity. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbid events, and functional outcomes. There is considerable variability in the particular EBC components measured and criteria for standardized measurements. The evidence is insufficient to determine the effect of the technology on health outcomes.

Policy History

<table>
<thead>
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<td>12/2015</td>
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<tr>
<td>3/2015</td>
<td>New references added from BCBSA National medical policy.</td>
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<tr>
<td>7/2014</td>
<td>Updated Coding section with ICD10 procedure and diagnosis codes, effective 10/2015.</td>
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<tr>
<td>2/2013</td>
<td>New references from BCBSA National medical policy.</td>
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Information Pertaining to All Blue Cross Blue Shield Medical Policies
Click on any of the following terms to access the relevant information:
- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines

References


49. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Exhaled nitric oxide monitoring as a guide to treatment decisions in chronic asthma. TEC Assessments. 2005;Volume 20, Tab 17.


66. O’Connor GT, Reibman J. Inhaled corticosteroid dose adjustment in mild persistent asthma. JAMA. Sep 12 2012;308(10):1036-1037. PMID 22968893


84. Keskin O, Balaban S, Keskin M, et al. Relationship between exhaled leukotriene and 8-isoprostane levels and asthma severity, asthma control level, and asthma control test score. Allergol Immunopathol (Madr). May-Jun 2014;42(3):191-197. PMID 23265270


