Clinical Policy Title: Exhaled nitric oxide for diagnosis of lung disease

Clinical Policy Number: 07.01.04

Effective Date: June 1, 2014
Initial Review Date: February 19, 2014
Most Recent Review Date: November 16, 2016
Next Review Date: November 2017

Policy contains:
- Asthma.
- Fractional exhaled nitric oxide (FeNO).

Related policies:
None.

ABOUT THIS POLICY: Keystone First has developed clinical policies to assist with making coverage determinations. Keystone First’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by Keystone First when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Keystone First’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Keystone First’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Keystone First will update its clinical policies as necessary. Keystone First’s clinical policies are not guarantees of payment.

Coverage policy

Keystone First considers the measurement of fractional exhaled nitric oxide (FeNO) in the diagnosis and management of asthma and chronic lung disease to be investigational and, therefore, not medically necessary.

Limitations:

All other uses of FeNO testing are not medically necessary.

Alternative covered services:

Standard pulmonary function testing including, but not limited to, peak expiratory flows rate and spirometry.

Background
Nitric oxide (NO) is an important cellular signaling molecule involved in many physiological and pathological processes. Physiologically, NO causes vasodilatation and relaxation of smooth muscles. NO is synthesized from arginine by the actions of NO synthase (NOS). NOS activates cytosolic guanylate cyclase, which elevates intracellular levels of cyclic-guanosine 3’, 5’-monophosphate yielding NO and water. Three isoenzymes of NOS exist with a similar final common pathway. The inducible isoform, iNOS, is involved in immune response and produces NO as an immune defense mechanism. More NO is produced in the face of inflammatory processes and is reduced in the face of glucocorticosteroids.

**Exhaled nitric oxide:**

Because of its active role in pulmonary physiology, NO is present in exhaled breath in concentrations much higher than in the atmosphere. Higher levels of NO in exhaled air have been associated with a more exacerbation-prone phenotype in severe asthma. Since the diagnosis of asthma and other chronic lung disease is often not straightforward, diagnostic modalities that can strengthen the rationale for diagnosing asthma, chronic lung disease or other inflammatory conditions of the pulmonary system have been sought. The measurement of FeNO has been proposed as a biomarker of assessing inflammatory airways disease, including asthma.

**Searches**

Keystone First searched PubMed and the databases of:
- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on October 7, 2016. Search terms were: “exhaled nitric oxide,"lung diseases/diagnosis"[Mesh] and "nitric oxide"[Mesh].

We included:
- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews.**
- **Economic analyses, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**
Results of a number of observational studies have suggested higher levels of FeNO in patients with bronchospasm and atopy or eosinophilia, but the clinical use of FeNO testing remains controversial. There is an absence of a consistent, clinically validated protocol for interpretation of test results, and results of randomized controlled trials (RCTs) have not demonstrated the impact of FeNO testing on outcomes.

The American Thoracic Society (ATS) guidelines issued a strong recommendation for using FeNO testing to help identify the eosinophilic asthma phenotype in persons with mild-to-moderate asthma based on moderate quality of evidence, as this group is more likely to be steroid responsive than asthmatic patients who are neutrophilic, mixed or paucigranulocytic phenotypes (Dweik, 2011). The Society issued weak recommendations for FeNO testing to determine steroid responsiveness or establish an asthma diagnosis in situations where objective evidence is needed. The ATS did not indicate how FeNO testing would assist in patient management, since there are no recommendations for monitoring drug use or clinical patterns, nor did they recommend its use in critical care or for diagnosing other pulmonary conditions. The Global Initiative for Asthma (GINA) made no mention of the use of FeNO in the diagnosis or management of asthma in their guidance (GINA, 2012).

In persons with mild-to-moderate asthma, the ATS recommended specific cut points rather than reference values for interpreting FeNO levels, because multiple confounding factors and overlapping values found in subjects with and without asthma precluded the routine application of reference values in the clinical setting. These proposed cut points are based on low-to-moderate quality evidence (see Table 1; Dweik, 2011).

Table 1. ATS-defined cut points for FeNO levels by age and responsiveness

<table>
<thead>
<tr>
<th>Level of FeNO</th>
<th>Adults</th>
<th>Children</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low FeNO</td>
<td>&lt; 25 PPB*</td>
<td>&lt; 20 PPB</td>
<td>Less likely to be steroid responsive.</td>
</tr>
<tr>
<td>Moderate FeNO</td>
<td>25 – 50 PPB</td>
<td>20 – 35 PPB</td>
<td>Interpret cautiously.</td>
</tr>
<tr>
<td>High FeNO</td>
<td>&gt; 50 PPB</td>
<td>&gt; 35 PPB</td>
<td>Probably steroid responsive.</td>
</tr>
</tbody>
</table>

*PPB, parts per billion

In persons with severe asthma, FeNO testing remains controversial. A joint task force supported by the European Respiratory Society (ERS) and ATS issued a conditional recommendation suggesting clinicians not use FeNO testing to guide therapy in adults or children with severe asthma based on very low quality evidence available (Chung, 2014).

Policy update:

A 2014 practice guideline from the National Institute for Health and Care Excellence (NICE) recommends fractional exhaled nitric oxide as an option to help diagnose asthma in adults and children, but cautions that FeNO testing be done in combination with other options (NICE, 2014).
We identified two new systematic reviews (Lu, 2015; Bain, 2014), one update of a previously included review (Hayes, 2015) and one new guideline for this policy update (GINA, 2015). The new evidence is insufficient to support using FeNO as either an adjunct to, or as a replacement for, current testing. Results suggest moderate ability of FeNO to diagnose asthma, but the cutoff values used to interpret FeNO results vary widely. FeNO-guided treatment is associated with a reduction in the number of asthma exacerbations, but its effect on resource use and clinical outcomes has not been established. A uniform protocol for its interpretation such as that developed by the ATS should be evaluated in clinical trials to show that it provides useful information.

New guidance from GINA does not recommend FeNO testing for deciding whether to treat patients with possible asthma with inhaled corticosteroids (ICS) (GINA, 2015). FeNO has not been established for making a diagnosis of asthma, as it is increased in both eosinophilic asthma and non-asthma conditions (e.g., eosinophilic bronchitis, atopy and allergic rhinitis). FeNO is decreased in smokers and during bronchoconstriction, and may be increased or decreased during viral respiratory infections. In patients (mainly nonsmokers) with non-specific respiratory symptoms, a finding of FeNO greater than 50 PPB was associated with a good short-term response to ICS. However, there are no long-term studies examining the safety of withholding ICS in patients with low initial FeNO. Therefore, the clinical utility of FeNO remains controversial.

A systematic review of seven studies concluded that FeNO testing was effective in helping reduce adult asthma exacerbations, but had no impact on day-to-day clinical symptoms, end-of-study FeNO levels, or inhaled corticosteroid dose; the authors could not advocate FeNO to guide therapy (Petsky, 2016). In various systematic reviews, FeNO was also found to have only a moderate or equivocal ability, at best, to diagnose or predict management of asthma in children (Gomersal, 2016; Li 2015; and Tang, 2016).

A review of five studies showed FeNO, while able to assess airway inflammation, is not a good predictor of responsiveness to inhaled corticosteroids in patients with chronic cough (Song, 2016). Results from different types of hand-held electrochemical devices did not always agree (Harnan, 2015).

The most recent (2016) update added four new meta-analyses and systemic reviews in the “Summary of clinical evidence” section. Three new guidelines have been added, along with nine peer-reviewed reports, mostly published in the past year.

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guo (2016)</td>
<td>Key points:</td>
</tr>
<tr>
<td>Diagnostic accuracy of FeNO in asthma</td>
<td>- Meta-analysis of 25 studies (n=3983) patients testing accuracy of exhaled nitric oxide for diagnosing asthma.</td>
</tr>
<tr>
<td></td>
<td>- Sensitivity and specificity were 72% and 78% for all patients</td>
</tr>
<tr>
<td></td>
<td>- Report concludes that exhaled nitric oxide is accurate for diagnosing asthma in steroid-naïve or non-smoking patients, especially those with chronic cough.</td>
</tr>
<tr>
<td>Petsky (2016)</td>
<td>Key points:</td>
</tr>
<tr>
<td>Citation</td>
<td>Content, Methods, Recommendations</td>
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</tbody>
</table>
| Ability of FeNO to guide treatment of adult asthma | - Systematic review of seven studies, 1,546 adult asthma patients.  
- Patients who had FeNO had fewer exacerbations versus controls.  
- No differences between FeNO and control groups in day-to-day clinical symptoms, end-of-study FeNO levels, inhaled corticosteroid dose.  
- Authors conclude FeNO not helpful in guiding therapy in adults with asthma |
| Song (2016) Ability of FeNO to predict corticosteroid response in chronic cough | **Key points:**  
- Systematic review, five studies, patients with chronic cough.  
- Study design heterogeneous, difficult to combine study results.  
- Sensitivity range from 44 – 59%, specificity range from 63 – 97%.  
- FeNO testing not a good predictor of corticosteroid response. |
| Lu (2015) FeNO and asthma treatment in children | **Key points:**  
- Meta-analysis of six RCTs with 506 total subjects managed with FeNO-based treatment regimen and 511 total subjects managed using conventional markers.  
- No between-group differences in FeNO value (95% confidence interval [CI]: -0.31, 0.1), change from baseline in forced expired volume in one second (FEV1) (95% CI: -0.07 to 0.20), or steroid use (95% CI: -0.67 to 1.80).  
- FeNO group was associated with a lower frequency of greater than one asthma exacerbation (95% CI: 0.532 to 0.895).  
- Little clinical benefit of a FeNO-guided treatment regimen, although it may decrease asthma exacerbations.  
- Findings support guideline-based asthma management and diagnosis. |
| Bain (2014) Cochrane review Managing asthma in pregnancy | **Key points:**  
- Systematic review included one RCT (220 nonsmoking, pregnant women) of FeNO-based algorithm vs. a clinical guideline-based algorithm to adjust inhaled corticosteroid therapy.  
- Overall quality: high with low risk of bias.  
- FeNO-based algorithm significantly reduced asthma exacerbations (RR 0.61; 95% CI 0.41 to 0.90); trended towards fewer neonatal hospitalizations (RR 0.46; 95% CI 0.21 to 1.02; 214 infants); may improve some quality of life scores, use of inhaled corticosteroids and long-acting beta-agonists; may lower use of short-acting beta-agonists; may be associated with fewer infants with recurrent episodes of bronchiolitis in their first year of life, and trended towards fewer episodes of croup in infants.  
- While a FeNO-based algorithm reduced exacerbations, the effects on perinatal outcomes were less certain, and thus widespread implementation is not yet appropriate.  
- Future trials must be sufficiently powered, and well-designed, to allow differences in important outcomes for mothers and babies to be detected. The impact on health services requires evaluation. |
| Donohue (2013) Measuring asthma exacerbations | **Key points:**  
- Meta-analysis of three RCTs, comparing FeNO-based and clinically-based adult asthma management programs.  
- Rate of exacerbations measured using both types of algorithms.  
- Asthma exacerbation rate significantly reduced using FeNO-based algorithm. |
| Hayes (2013, updated 2015) | **Key points:** |
FeNO measurement for diagnosis of asthma

- Systematic review evaluating FeNO as an adjunct indicator (seven RCTs) or replacement indicator (three RCTs).
- FeNO testing is noninvasive and poses no direct risk to patient safety.
- FeNO may have moderate or moderately high sensitivity and specificity for the diagnosis of asthma. However, cutoff values used for interpretation of FeNO measurements vary widely.
- FeNO test cannot be considered suitable for routine clinical use until a uniform protocol for its interpretation has been established and evaluated in clinical trials demonstrating clinical benefit.

Dweik (2011)

ATS guideline

Key points:

- Consensus panel from ATS that reviewed the literature using evidence weighting.
- Recommended the use of FeNO in diagnosis of eosinophilic airway inflammation (strong recommendation, moderate quality of evidence).
- Recommended use of FeNO in determining the likelihood of steroid responsiveness (strong recommendation, low quality of evidence).
- Suggests FeNO be used to support the diagnosis of asthma in situations where objective evidence is needed (weak recommendation, moderate quality of evidence).

Glossary

**Bronchodilation** — Relaxation of the muscles around the bronchial tubes, causing the airways to open further.

**Fractional exhaled nitric oxide (FeNO)** — A test measuring the fraction of exhaled nitric oxide in the exhaled air of the patient. The test is purported to measure the degree of inflammatory response from the airway, as in eosinophilic asthma.

**Inhaled nitric oxide (INO)** — Use of nitric oxide as reported therapy for premature infants with respiratory failure, or other conditions.

**Nitric oxide** — A simple molecule with one atom each of nitrogen and oxygen. It is produced in the body as a result of enzyme reactions and is a potent regulator of vasodilatation and bronchodilation.

**Vasodilatation** — Relaxation of the small muscles within the artery wall, causing the artery to open to a wider diameter.

References

**Professional society guidelines/other:**


**Peer-reviewed references:**


**CMS National Coverage Determinations (NCDs):**
No NCDs identified as of the writing of this policy.

**Local Coverage Determinations (LCDs):**

No LCDs identified as of the writing of this policy.

**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

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