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, 2017
Next Review Date: November 2018

Related policies:
None.

ABOUT THIS POLICY: Select Health of South Carolina has developed clinical policies to assist with making coverage determinations. Select Health of South Carolina’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 Select Health of South Carolina 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. Select Health of South Carolina’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. Select Health of South Carolina’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Select Health of South Carolina will update its clinical policies as necessary. Select Health of South Carolina’s clinical policies are not guarantees of payment.

Coverage policy

Select Health of South Carolina considers the measurement of fractional exhaled nitric oxide in the diagnosis and management of asthma and chronic lung disease to be investigational and, therefore, not medically necessary.

Limitations:

All other uses of fractional exhaled nitric oxide 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 is an important cellular signaling molecule involved in many physiological and pathological
processes. Physiologically, nitric oxide causes vasodilatation and relaxation of smooth muscles; controls blood flow to tissues; regulates binding and release of oxygen to hemoglobin; controls oxygen supply to mitochondria; and kills parasites, viruses, and tumors (MedicineNet, 2017).

Because of its active role in pulmonary physiology, nitric oxide is present in exhaled breath in concentrations much higher than in the atmosphere. Higher levels of nitric oxide in exhaled air have been associated with a more exacerbation-prone phenotype in severe asthma (Taylor, 2006). 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 fractional exhaled nitric oxide has been proposed as a biomarker of assessing inflammatory airways disease, including asthma.

A 2014 practice guideline from the National Institute for Health and Care Excellence recommends fractional exhaled nitric oxide as an option to help diagnose asthma in adults and children, but cautions that testing be done in combination with other options (NICE, 2014).

The American Thoracic Society guidelines issued a strong recommendation for using fractional exhaled nitric oxide 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 fractional exhaled nitric oxide testing to determine steroid responsiveness or establish an asthma diagnosis in situations where objective evidence is needed.

The American Thoracic Society did not indicate how 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 made no mention of the use of testing in the diagnosis or management of asthma in their guidance (GINA, 2012). New guidance from the Global Initiative for Asthma does not recommend testing for deciding whether to treat patients with possible asthma with inhaled corticosteroids (GINA, 2015).

In persons with mild-to-moderate asthma, the American Thoracic Society recommended specific cut points rather than reference values for interpreting fractional exhaled nitric oxide testing 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 fractional exhaled nitric oxide levels by age and responsiveness

<table>
<thead>
<tr>
<th>Level</th>
<th>Adults</th>
<th>Children</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>&lt; 25 PPB*</td>
<td>&lt; 20 PPB</td>
<td>Less likely to be steroid responsive.</td>
</tr>
<tr>
<td>Moderate</td>
<td>25 – 50 PPB</td>
<td>20 – 35 PPB</td>
<td>Interpret cautiously.</td>
</tr>
<tr>
<td>High</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, fractional exhaled nitric oxide testing remains controversial. A joint task force supported by the European Respiratory Society and American Thoracic Society issued a conditional recommendation suggesting clinicians not use testing to guide therapy in adults or children with severe asthma based on very low quality evidence available (Chung, 2014).

**Searches**

Select Health of South Carolina 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 17, 2017. Search terms were: “exhaled nitric oxide,"lung diseases/diagnosis" and "nitric oxide".

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 fractional exhaled nitric oxide in patients with bronchospasm and atopy or eosinophilia, but the clinical use of testing remains controversial. There is an absence of a consistent, clinically validated protocol for interpretation of test results, and results of randomized controlled trials have not demonstrated the impact of fractional exhaled nitric oxide testing on outcomes.

Several systematic reviews on fractional exhaled nitric oxide testing and treatment were located in the peer-reviewed literature:

1. A Hayes review of 13 studies concluded that sensitivity and specificity were only moderate, and thus the accuracy of exhaled nitric oxide for diagnosing asthma varied widely (Hayes, 2017a).
2. A Hayes review of 17 studies of monitoring asthma using exhaled nitric oxide found low quality of evidence that produced highly inconsistent results and uncertain benefits (Hayes, 2017b).

3. A review of 21 studies (n=4691) revealed sensitivity and specificity rates of 78 and 74 percent for exhaled nitric oxide, deemed “insufficient for diagnosing asthma” (Li, 2015).

4. A review of 6 studies (n=1017) compared monitoring of asthma treatment with fractional exhaled nitric oxide and conventional methods; no differences were observed, leading authors to support use of guideline-based asthma management and diagnosis (Lu, 2015).

5. An analysis of eight studies of children (n=2933) found asthma sensitivity and specificity of 79 and 81 percent, which authors described as a “moderate diagnostic performance” (Tang, 2016).

6. A review of seven trials some evidence of accurate nitric oxide monitoring of childhood asthma, mostly not significant, and with a “potential benefit equivocal” (Gomersal, 2016).

7. A review of eight trials (n=1181) of pregnant women with asthma included a trial of 220 women that found a fractional nitric oxide-based algorithm reduced asthma exacerbations and neonatal hospital stays; and in two other trials, improved quality of life and use of long-acting beta agonists, while reducing episodes of croup and bronchiolitis to infants (Bain, 2014).

8. A Cochrane review of nine studies of children and adults compared use of fractional nitric oxide-based algorithms and sputum eosinophils. The latter had fewer exacerbations and a lower increase in their mean daily dose of inhaled corticosteroids, but did not alter the day-to-day clinical symptoms or inhaled corticosteroid doses; authors were unable to advocate routine use of either type of analysis (Petsky, 2016a), which upheld similar results of an earlier Cochrane review (Petsky, 2009).

9. A systematic review of six studies showed no significant differences for health-related quality of life or asthma control from fractional exhaled nitric oxide measurement. It did show a significant reduction in exacerbations of asthma of any severity, but no reduction for severe exacerbations (Essat, 2016).

10. A meta-analysis of 25 studies (n=3983) showed sensitivity and specificity of fractional exhaled nitric oxide for asthma to be 72 and 78 percent. Results were significant for smokers, non-smokers, and patients with chronic cough and allergic rhinitis, leading authors to state that the method was accurate for diagnosing asthma (Guo, 2016).

11. A review of five studies showed that sensitivity and specificity levels were insufficiently low for fractional exhaled nitric oxide to accurately predict inhaled corticosteroid responsiveness to a chronic cough (Song, 2017).
Fractional exhaled nitric oxide 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). Fractional exhaled nitric oxide 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 greater than 50 parts per billion was associated with a good short-term response to inhaled corticosteroids. However, there are no long-term studies examining the safety of withholding inhaled corticosteroids in patients with low initial fractional exhaled nitric oxide. Therefore, the clinical utility of this approach remains controversial.

A systematic review of 12 studies, including children, adolescents, and adults, analyzed the extent to which ethnicity of the patient influences fractional exhaled nitric oxide. In 10 of the studies, ethnicity was found to be a significant factor, and thus reference ranges by ethnic group need to be developed (Blake, 2017).

Policy updates:

A total of one guideline/other and five peer-reviewed references were added to this policy, and one guideline/other and three peer-reviewed references were removed in 2017.

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guo (2016)</td>
<td><strong>Key points:</strong></td>
</tr>
</tbody>
</table>
| Diagnostic accuracy of FeNO in asthma | • Meta-analysis of 25 studies (n=3983) patients testing accuracy of exhaled nitric oxide for diagnosing asthma.  
• Sensitivity and specificity were 72% and 78% for all patients  
• Report concludes that exhaled nitric oxide is accurate for diagnosing asthma in steroid-naïve or non-smoking patients, especially those with chronic cough. |
| Petsky (2016) | **Key points:**                   |
| 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)  | **Key points:**                   |
| Ability of FeNO to predict corticosteroid response in chronic cough | • 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. |
<p>| Lu (2015)    | <strong>Key points:</strong>                   |</p>
<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
</thead>
</table>
| FeNO and asthma treatment in children | - 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. |
| Hayes (2015) FeNO measurement for diagnosis of asthma | **Key points:**  
- 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. |

References

**Professional society guidelines/other:**

Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and


**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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