Exhaled nitric oxide for diagnosis and management of lung disease

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Policy contains: Asthma, fractional exhaled nitric oxide.

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Coverage policy

The measurement of fractional exhaled nitric oxide in the diagnosis and management (monitoring response to long-term control therapy) of asthma and eosinophilic airway inflammation for members five years of age and older is clinically proven, and therefore medically necessary (National Institute of Health and Care Excellence, 2020).

Limitations

All other uses of fractional exhaled nitric oxide are investigational/not clinically proven, and therefore 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 vasodilation 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 (Shiel, 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 National Institute for Health and Care Excellence guideline states fractional exhaled nitric oxide concentrations of 40 and 35 parts per billion are considered positive for persons over age 17 and 5-16, respectively. The guideline also states that fractional exhaled nitric oxide 1) should not be used as a routine means of monitoring asthma, and 2) should be used as an option to monitor patients who are still symptomatic after using corticosteroids (National Institute for Health and Care Excellence, 2014 and 2020).

One report acknowledged the ability of fractional exhaled nitric oxide as a marker of T-helper cell type 2-mediated allergic airway inflammation in asthma, and that point-of-care testing can play a role in managing patients with asthma. Coverage and reimbursement issues are discussed (Mummadi, 2016).

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. American Thoracic Society-defined cut points for fractional exhaled nitric oxide levels by age and responsiveness

Level	Adults	Children	Recommendations
Low	< 25 PPB*	< 20 PPB	Less likely to be steroid responsive.
Moderate	25 – 50 PPB	20 – 35 PPB	Interpret cautiously.
High	> 50 PPB	> 35 PPB	Probably steroid responsive.

*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).

Findings

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 (National Institute for Health and Care Excellence, 2014). A 2020 update to this guideline states that unwell persons with suspected cases of asthma (based on results of fractional

exhaled nitric oxide testing) should be treated immediately (National Institute for Health and Care Excellence, 2020).

The American Thoracic Society 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. New guidance from the Initiative does not recommend testing for deciding whether to treat patients with possible asthma with inhaled corticosteroids (Global Initiative for Asthma, 2018).

The most recent update to the National Heart, Lung, and Blood Advisory Council's National Asthma Education and Prevention Program guideline includes a recommendation that fractional exhaled nitric oxide testing be used to assist in diagnosis and monitoring of symptoms, but not alone to diagnose or monitor asthma (Cloutier, 2020).

A Japanese guideline lists concentration of nitric oxide in exhaled breath is listed as one of five indicators for asthma diagnosis in children (Arakawa, 2018). A Swiss guideline notes the growing evidence that fractional concentration of exhaled nitric oxide may be useful for monitoring response and adherence to anti-inflammatory treatment in patients with eosinophilic asthma. However, the fact that this level is high in eosinophilic bronchitis, atopy, and allergic rhinitis makes exhaled nitric oxide of limited value in diagnosing asthma (Rothe, 2018).

Results of a number of observational studies have suggested using 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.

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

- A review of 21 studies (n = 4,691) revealed sensitivity and specificity rates of 78% and 74% for exhaled nitric oxide, deemed "insufficient for diagnosing asthma" (Li, 2015).

- A review of six studies (n = 1,017) 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).

- An analysis of eight studies of children (n = 2,933) found asthma sensitivity and specificity of 79% and

81%, which authors described as a “moderate diagnostic performance” (Tang, 2016).

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

- A review of eight trials (n = 1,181) 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).

- 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 these 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, 2016b; Petsky, 2016a), which upheld similar results of an earlier Cochrane review (Petsky, 2009).

- A systematic review of six studies showed no difference in exacerbations of adults and children with asthma for fractional exhaled nitric oxide versus controls. Authors conclude that tailoring asthma treatment based on exhaled nitric oxide has not been shown to be effective (Petsky, 2012).

- A systematic review of six studies showed no significant differences from the norm for health-related quality of life or asthma control using 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).

- A meta-analysis of 25 studies (n = 3,983) showed sensitivity and specificity of fractional exhaled nitric oxide for asthma to be 72% and 78%. 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).

- 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).

- A systematic review/meta-analysis of 26 studies (n = 4,518), mostly with low risk of bias, revealed sensitivity and specificity of 0.65 and 0.82 of exhaled nitric oxide’s ability to diagnose asthma. Sensitivity, but not specificity, varied significantly by device (Karrasch, 2017).

- A systematic review/meta-analysis of 16 studies of fractional exhaled nitric oxide-based management determined persons with asthma who received the test had significantly fewer exacerbations (adult and child Odds Ratios = 0.60 and 0.58). No significant group differences were observed for daily inhaled corticosteroids dose (at end of study), asthma control or lung function (Petsky, 2018).

- In a review of 43 studies (n = 13,747), including adults and children age 5–18, use of fractional exhaled nitric oxide testing increased the odds of having a positive asthma test 2.80 to 7.00 fold. Using cutoffs of <20, 20–30, 30–40, ≥40 parts per billion, respectively, testing had sensitivities of 0.80, 0.69, 0.53 and 0.41 and specificities of 0.64, 0.78, 0.85, and 0.93 (Wang, 2017).

- In a meta-analysis of three studies, the rate of exacerbations were significantly reduced in favor of fractional exhaled nitric oxide-based asthma management (Donohue, 2013).

- In a review of 27 studies, measurements of exhaled nitric oxide revealed considerable uncertainty on its use, in terms of equivalence of devices, and difficulty in interpreting evidence for diagnosis (Harnan, 2015).

- A review of the utility of fractionated exhaled nitric oxide in managing asthma describes the procedure as a validated, noninvasive biomarker for T2-driven airway inflammation that correlates with sputum eosinophils at or greater than 3% across various asthma phenotypes, and that the medical literature supports its use as a biomarker in asthma (Arnold, 2018).

- A meta-analysis of 19 studies analyzed levels of fractionated exhaled nitric oxide patients with stable chronic obstructive pulmonary disease and healthy controls. Those with the disease had higher levels, as did those who did not smoke (both $P < .05$). The study found no difference in levels between smoking patients and controls ($P = .85$) (Gong, 2020).

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/meta-analysis of 11 studies (n = 4,645) showed the average concentration difference of fractional exhaled nitric oxide between preterm-born and term-born infants was -0.74 parts per billion. For six studies (n = 444) with chronic lung disease, preterm exhaled nitric oxide was -2.82 less (neither significant), suggesting this measure may be an alternative mechanism to eosinophilic inflammation for symptoms (Course, 2019).

A systematic review of 22 studies revealed that fractional exhaled nitric oxide is lower in smoking than in non-smoking asthmatics, but higher in untreated smoking asthmatics than healthy smokers. Data is not sufficient to create guidelines on using exhaled nitric oxide in smokers (Ahovuo-Saloranta, 2019).

References

On January 12, 2021, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “exhaled nitric oxide, "lung diseases/diagnosis" and "nitric oxide." We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

2/2014: initial review date and clinical policy effective date: 6/2014

2/2015: Policy references updated.

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