IEHP UM Subcommittee Approved Authorization Guidelines

Measurement of the Fractional Exhaled Nitric Oxide (FE\textsubscript{NO}) Concentration for the Diagnosis and Management of Asthma and Other Pulmonary Disorders

**IEHP Policy:**
Based on a review of the currently available literature, there is insufficient evidence to support the use of FE\textsubscript{NO} measurement in the diagnosis or management of asthma or other pulmonary disorders. Therefore, the IEHP UM Subcommittee concurred not to endorse FE\textsubscript{NO} as a covered benefit at this time.

**MEDICARE**: As of April 22, 2014, Medicare does not have a National Coverage Determination (NCD) or a Local Coverage Determination (LCD) for California for the measurement of FE\textsubscript{NO} (Fractional Exhaled Nitric Oxide Concentration) for the diagnosis or management of asthma or other pulmonary disorders.

**MEDI-CAL**: CPT code 95012 is the appropriate code describing Exhaled Nitric Oxide Measurement. According to the Medi-Cal Benefit Manual, this procedure is not a covered benefit. Additional searches of the Medi-Cal website failed to detect any documents regarding this test such as relevant guidelines, medical reviews or policy statements.

**APOLLO GUIDELINES 2013**: “Exhaled nitrous oxide had not been demonstrated to be clinically useful in the management of asthma or other inflammatory airway disorders. It is considered to be experimental and therefore not covered”.

**AETNA**: “Aetna considers measurement of exhaled nitric oxide experimental and investigational for assessment of asthma, lung cancer, other pulmonary diseases (e.g., COPD, pulmonary tuberculosis, sino-nasal disease) and all other conditions because of insufficient evidence of its effectiveness”.

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BLUE SHIELD OF CALIFORNIA 5:
“…there is insufficient evidence through lack of studies to determine the effect of exhaled nitric oxide and exhaled breath condensate tests on health outcomes, and require further investigation. These tests are therefore considered investigational”.

CIGNA 6:
“Cigna does not cover the measurement of exhaled nitric oxide or exhaled breath condensate for any indication, including the management of asthma and/or other respiratory disorders, because it is considered experimental, investigational or unproven due to insufficient evidence of beneficial health outcomes”.

BACKGROUND:

The Biochemistry of Nitric Oxide (NO) in Mammalian Systems 7, 8:
NO is a gaseous molecule present in virtually all mammalian organ systems. It is produced by the action of the enzyme Nitric Oxide Synthase (NOS) on the amino acid L-arginine. One isoform of this enzyme is inducible by inflammatory cytokines and inhibited by glucocorticoids. Thus, NO has been investigated as a surrogate biomarker of underlying inflammation in various diseases.

The Biological Effects of NO in the Human Airway 7, 8:
In the lungs, NO is a bronchodilator; it causes relaxation of bronchial smooth muscles. It is also thought to have anti-inflammatory properties due to its action as an antioxidant.

The Clinical Role of Measuring Exhaled Nitric Oxide 7, 8:
Patients with asthma and other inflammatory respiratory disorders including COPD have abnormally elevated levels of NO in their exhaled breath. The observation that FE\textsubscript{NO} levels in asthmatics decrease following treatment with inhaled corticosteroids has led to the theory that FE\textsubscript{NO} may be a useful biological marker of inflammation in patients with inflammatory respiratory conditions. As a surrogate marker of inflammation and oxidative stress, FE\textsubscript{NO} is suggested to have many useful clinical applications for diagnosing and monitoring asthma, COPD, cystic fibrosis, lung cancer, and other conditions. FE\textsubscript{NO} is currently being used to diagnose disease and identify patients who are likely responders to anti-inflammatory treatment. It is also believed to be useful for monitoring compliance with medications and permitting dose tailoring to avoid inaccurate dosing. Measurement of FE\textsubscript{NO} levels is less cumbersome and invasive than current techniques for monitoring the status of underlying inflammation such as bronchoscopy (with lavage and biopsy), or analysis by induced sputum. Therefore, there has been interest in noninvasive techniques such as FE\textsubscript{NO} to assess underlying pathogenic chronic inflammation.

Interpretation of Exhaled NO in Asthma 7, 8:
Initial studies of FE\textsubscript{NO} in asthma used reference ranges to define normal and abnormal values. However, it has been difficult to determine appropriate reference ranges as healthy individuals
sometimes fall outside the “normal” range and individuals with asthma occasionally fall within the range. Rather than develop reference ranges based on the varied combinations of these characteristics, a simpler method of using cut-points has been proposed in the American Thoracic Society (ATS) Clinical Practice Guideline for Interpretation of \( \text{FENO} \) \(^{11}\). Caution needs to be used in interpreting \( \text{FENO} \) levels as several factors including age, sex, atopy and cigarette smoking can influence the level of exhaled nitric oxide.

**Use of Exhaled NO for the Diagnosis and Characterization of Asthma** \(^8\):
Patients with asthma have higher concentrations of NO in their exhaled air than do non-asthmatic subjects. Exhaled NO levels rise in association with acute airway inflammation, sputum eosinophilia, viral upper respiratory infections, and other clinical parameters associated with deteriorating asthma control. Intermediate of high \( \text{FENO} \) levels are associated with asthma, wheeze and asthma exacerbations.

**Use of Exhaled NO as a Guide to Therapy** \(^8\):
While \( \text{FENO} \) levels generally predict which patients will respond to inhaled glucocorticoid therapy, the largest trials and a systematic review did not find sufficient evidence to support routine use of \( \text{FENO} \) to guide asthma therapy \(^{12,13,14}\). The systematic review compared trials of asthma therapy guided by \( \text{FENO} \) with those in which guidance was based on standard measures (symptoms with or without spirometry/peak flow) \(^8\). This analysis was hampered by variations between studies in the definition of asthma exacerbations, algorithms for adjustment of medication, and cut-off values for increasing or decreasing therapy. In contrast, a subsequent meta-analysis that included an additional study found that the rate of exacerbations was significantly reduced in a \( \text{FENO} \)-based asthma management algorithm compared with a clinically-based algorithm \(^{15}\).

**Research Review and Summary** \(^7,8\):
According to the ECRI Institute’s March 2014 Health Technology Assessment Information Service Hotline Response, which was based on an extensive search of numerous sources (including PubMed, the Cochrane Library, and selected web-based documents) and included a review of abstracts published between January 1, 2009 and March 25, 2014, a total of 141 documents relevant to this topic were found. Among these studies, there was a mixture of positive, negative and inconclusive results regarding the usefulness and effectiveness of \( \text{FENO} \) as a tool to diagnose and monitor inflammatory airway disease \(^7\). Similar results were obtained by a 2014 Up-to-Date review of the literature authored by Raed A. Dweik, MD, FACP, FCCP \(^8\). According to this review, several studies found a benefit to using \( \text{FENO} \) as a tool to guide asthma therapy while several others did not find such as benefit. Please refer to the bibliography in this document for references regarding both negative \(^{12,13,16,17}\) and positive \(^{18,19,20}\) studies.

**Concerns with the research studies regarding measurement of exhaled NO** \(^21\):
The overall strength of the available evidence is moderate due to: limitations in study design, heterogeneous patient populations, variable methodological and treatment protocols, different
outcome measures, wide variations in threshold values of exhaled NO, and a lack of studies that evaluated whether exhaled NO resulted in improved long-term health outcomes including effects on long-term asthma control or improved quality of life. Additional studies are needed to clarify the role of exhaled NO breath testing in clinical practice.

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Revised:

Bibliography:


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