

**Aerocrine Commentary on:**

**An Official American Thoracic Society/European Respiratory Society Statement:**

**Asthma Control and Exacerbations**

Standardizing Endpoints for Clinical Asthma Trials and Clinical Practice

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An official American Thoracic Society (ATS)/European Respiratory Society (ERS) joint statement was published on July 1, 2009 [1]. The Task Force behind this statement was established in 2004. Its work has been based on a narrative literature review, primarily a structured literature search on asthma control, severity and exacerbations between 1998 and 2004. Its goal has been to: "provide recommendations about standardization of outcomes relating to asthma control, severity, and exacerbations in clinical trials and clinical practice, for adults and children aged 6 years and older." This commentary is intended to summarize the role of biomarkers, and specifically, the fraction of exhaled nitric oxide (F<sub>E</sub>NO) in the ATS/ERS statement.

The definitions of asthma control, severity and exacerbations were developed by the same Task Force as above, as reported in 2008 [2]. Essentially, asthma severity should refer to the intensity of treatment required to control the patient's condition. Asthma control refers to the extent to which the manifestations of asthma are reduced or removed by treatment. The latter includes two components; the level of current clinical asthma control in terms of, for example, symptoms and quality of life, and the risk of future adverse events, such as exacerbations and accelerated decline in lung function. Furthermore, severe and moderate asthma exacerbations were defined, whereas a definition of mild asthma exacerbations was not considered justifiable.

The current definition of asthma covers four domains: symptoms, variable airway obstruction, airway hyperresponsiveness (AHR), and airway inflammation. In the present ATS/ERS statement, biomarkers of airway inflammation (induced sputum and exhaled NO) are described as central outcome variables, alongside lung function and bronchial provocation testing, symptom questionnaires and diaries, and quality-of-life questionnaires. Of course, having access to measurements for all domains would be optimal, but in primary care, diagnosis is often based only on symptoms that may lead to incorrect diagnosis. One reason for relying primarily on symptoms is given in the Task Force report: "The current safety recommendations for bronchial provocation testing (for measurement of AHR) preclude its use in most primary care settings." The Task Force also concludes that "due to logistic and cost issues, F<sub>E</sub>NO is the only biomarker (of airway inflammation) likely to play a role in primary-care based asthma studies..." This would leave the primary care physician with symptoms, lung function measurements and exhaled NO to diagnose patients with symptoms suggestive of asthma. The conclusions continue, "normal lung function does not exclude a diagnosis of asthma." Together, this strongly suggests that measurements of airway inflammation should be part of the basis of asthma diagnosis, and moreover, the statement regarding clinical practice is: "Where possible, biomarkers should be employed to provide information about underlying airway inflammation, a domain of the asthma 'syndrome' that would not otherwise be available to the clinician." Specifically, the Task Force states the following for the use of F<sub>E</sub>NO in clinical practice: "F<sub>E</sub>NO measurements may be used as a surrogate marker for eosinophilic airway inflammation. They may be used to evaluate the potential for response to corticosteroid treatment." It further concluded that: "F<sub>E</sub>NO is a prototype for the application of biomarkers in children with asthma, and may be helpful in decisions on starting and stopping ICS (inhaled corticosteroids), and perhaps monitoring medication effects."

There has been a shift in recent guidelines to incorporate future risk in the assessment of asthma control [3]. This is very important since "even in patients thought to have mild asthma, the rates of severe asthma exacerbations have been shown to be much higher than expected." The report continued, "while current poor control predicts future poor control and health care utilization, there is increasing awareness that other pathological and physiological measures, independent of

the level of current clinical control, predict future risk. For example, exhaled nitric oxide has been used as a 'predictor' of loss of asthma control." The statement regards the use of biomarkers as a predictor of future risk as desirable (like AHR), and pre-bronchodilator FEV<sub>1</sub> as essential, and that biomarkers would "allow assessment of discrepancies with the observed level of clinical control, e.g. with masking by LABA monotherapy." Again, since bronchial provocation testing is not generally feasible, and pre-bronchodilator FEV<sub>1</sub> is highly variable, the incorporation of FE<sub>NO</sub> measurements to assess future risk should be obvious. This is further supported by van Veen et al [4], who showed that persistently high FE<sub>NO</sub>, in spite of high-dose ICS treatment, predicts long-term lung function decline in patients with difficult-to-treat asthma. This study was published in May 2008, unfortunately too late to be considered in the present ATS/ERS statement.

The Task Force also offers future directions in its report. Particularly, it foresees an even more important role for biomarkers in the future. For example, the report states that "emerging work on biomarkers suggests that several measures of airway inflammation should be evaluated [in a similar way] for inclusion in composite control scores," and that, "biomarkers may ultimately prove to be [more] appropriate in asthma, particularly for some phenotypes. This approach is already accepted for patients with poor perception of airway obstruction. The possibility needs to be envisaged that, in the future, a well-validated biomarker might override symptoms as the basis for treatment decisions: while not ignoring the burden of symptoms to patients, we ought not to be locked in to the definitions of asthma control provided in this document, or the current stepwise approach to treatment."

Thus, in regard to the role of exhaled NO in clinical practice, **the following conclusions can be drawn** from the ATS/ERS statement on Asthma Control and Exacerbations:

1. Exhaled NO may be used as a surrogate marker for eosinophilic airway inflammation, and as such, be helpful in diagnosis and treatment decisions in asthma. Especially, exhaled NO may be used to evaluate the potential for response to corticosteroid treatment.
2. Exhaled NO may be used to predict the risk of future adverse events regardless of current clinical control.
3. With emerging work, the role of biomarkers is anticipated to be even more important in future guidelines, even overriding symptoms as the basis for treatment decisions.

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#### References

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