The interest in asthma biomarkers has increased markedly over the past 15-20 years. In the early 1990s, the original description of the fraction of exhaled nitric oxide (FeNO) as a marker of airway inflammation in asthma greatly stimulated the research interest in this marker. To date, there are more than 3,500 articles published on FeNO, and over 300 articles are published each year - a figure which is still increasing (see Fig. 1). The discovery of FeNO also stimulated the search for other biomarkers in exhaled breath, for example exhaled breath condensate and volatile organic compounds. However, FeNO is by far the most clinically validated biomarker of all these proposed non-invasive markers in exhaled breath, and instruments for FeNO measurement are now small and portable.

Asthma is a truly heterogenous condition, with different underlying pathophysologies, or endotypes, leading to different treatment response characteristics. Biomarkers can help define these endotypes and, thus, will enable more personalised asthma treatment. For example, it is well established that FeNO is a much stronger predictor of corticosteroid responsiveness than spirometry. Despite all the available evidence on FeNO measurement in the management of asthma, the inclusion of this biomarker in asthma guidelines has been very slow. In April 2014, the British National Institute for Health and Care Excellence (NICE) published a guidance document on the use of FeNO devices based on a very thorough health technology assessment performed by the University of Sheffield and commissioned by NICE, as well as having input from different stakeholders (http://www.nice.org.uk/dg12). NICE clearly states that FeNO measurements provide added value in both the diagnosis and therapy monitoring of adults and children with suspected or established asthma, at least in the UK context. Almost simultaneous to this report, an update of the Global Initiative for Asthma (GINA) report was published (http://www.ginasthma.org). In contrast to the recommendations by NICE, this group concludes that FeNO cannot be recommended in the diagnosis and therapy monitoring of asthma patients. Explanations for the different conclusions may be that GINA has a global perspective whereas NICE looks at UK conditions, but possibly also that different methodologies are used when clinical guidelines are written compared to health technology assessments.

**Study results**

One argument against the clinical use of FeNO has been that some early randomised, controlled trials evaluating the effect of FeNO-guided asthma treatment on the rate of asthma attacks have been non-significant, and an early meta-analysis of these studies was likewise negative. However, study design issues have been highlighted, and it has been recognised that it is more complicated to study the clinical effect of introducing a diagnostic procedure than the effect of a drug over placebo. With better insight into these problems, later trials have been positive, and this has rendered an updated meta-analysis on studies in adult patients to show a weighted average reduction in asthma attacks.

![Fig. 1 Publications found on PubMed when performing a search on exhaled and nitric oxide. The first publications 1991-93 are all from Karolinska Institutet, Stockholm, Sweden](image)

![Fig. 2 Rate of asthma exacerbations (number of exacerbations per patient over the study period) in adult algorithm-based clinical trials using FeNO measurement versus traditional methods for asthma management.](image)
In a pan-European collaboration, we aim to address outstanding issues on the clinical use of biomarkers in asthma. This international group has recently published an updated review on FeNO measurement, including future research needs. The group also plans for new studies on FeNO measurement with submissions to Horizon 2020, both with and without collaboration with industry, to further support the inclusion of FeNO in clinical asthma guidelines. The focus will be on real-life studies to be able to incorporate all the dimensions of a diagnostic procedure in clinical practice.

### Future research

We have recently discussed in this forum that FeNO and blood eosinophil (B-Eos) count have additive predictive effects on asthma morbidity and, thus, are not interchangeable (see Science & Technology 9). The first study was population-based, and we have now moved on to examine this in the MIDAS cohort of young asthma patients. In this study, we could show that FeNO and B-Eos have a strong additive predictive effect on bronchial hyper-responsiveness. In the same patient cohort, we are presently studying the inflammatory profile in patients with non-atopic versus atopic asthma. In this work we have utilised a new platform which enables the sensitive measurement of 92 inflammatory molecules in a small blood sample using PCR technology (Fig. 3). In pilot experiments, we have seen that the inflammatory profile is markedly different in these two groups of asthma patients using principal component analysis. The results strongly indicate that the two patient groups should respond differently to treatment, whereas treatment is normally not differentiated in clinical practice today.

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UPPSALA UNIVERSITY

Kjell Alving
Professor of Respiratory Pharmacology
Department of Women’s and Children’s Health
Uppsala University Hospital

tel: +46 70 659 8870
kjell.alving@kbh.uu.se
www.kbh.uu.se

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