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Point-of-care biomarkers in asthma management: time to move forward

To the Editor,

The Global Initiative for Asthma (GINA) report was primarily intended as a strategy document and not a clinical guideline. However, the 2014 update moved the report towards a "practical, clinical practice-centred document", and has in many countries formed a basis for national guidelines. A possible limitation of the GINA report is its primary focus on evidence coming from randomised controlled trials, potentially leading to the omission of clinically important data coming from real-life and observational studies, and in conclusions based on highly-selected asthmatic patients, fulfilling strict study inclusion criteria.

The interest in biomarkers for clinical decision making has grown exponentially over the last 10-15 years in parallel to increasing evidence that asthma is a heterogeneous condition with different underlying pathophysiology, and with different responses to treatment¹. Biomarkers can help identify these different phenotypes and endotypes, and subsequent treatment response to standard treatment or targeted therapeutic options with biologicals. In this capacity, they complement symptom scoring and lung function measurement in asthma management. For example, fractional exhaled nitric oxide (FeNO), which is a marker of type-2 driven inflammation within the bronchial mucosa², has been shown to be a much stronger predictor of corticosteroid responsiveness in patients with symptoms suggestive of asthma than other more routinely used methods,

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such as spirometry³. Another reason for the increased interest in asthma biomarkers – evidenced by approximately 5,000 scientific articles published on exhaled NO – is the extensive development of regulator-approved devices for quick and non-invasive FeNO measurement⁴. Likewise, blood eosinophil (B-Eos) count, a biomarker that has been widely available for quite some time although scarcely used, is presently undergoing a renaissance in interest including the development of point-of-care devices⁵. Ample evidence exists of a strong association between elevated blood eosinophils and increased risk of asthma exacerbations¹. Interestingly, simultaneously elevated FeNO and B-Eos count add the risk of asthma attacks and asthma morbidity, independently of each other⁶. Thus, although elevated B-Eos count and FeNO often occur together, they represent different parts of the type-2 inflammatory pathway, with FeNO being particularly linked to the IL-4/IL-13 pathway². Some confounders have been recognized for FeNO, primarily smoking, rhinovirus infections and nitrate intake, but measures to handle these in the clinic have been suggested⁴. Little is known about confounders for B-Eos count, except a marked circadian variation.

Despite the emerging data on the utility of B-Eos count and an increasing number of studies investigating the applicability of FeNO measurement in routine clinical management of asthma⁴, the incorporation of biomarkers into guidelines remains slow. The latest 2019 GINA report (<https://ginasthma.org/gina-reports>), recommends the use of FeNO to aid phenotyping of severe asthma and to differentiate COPD from asthma, but not as an aid to diagnosis or management of less severe asthma. Furthermore, it suggests that elevated FeNO in preschool children with recurrent coughing and wheezing predicts asthma later in the life. In contrast, lung function measurements, which are of little use in distinguishing between asthma endotypes, have been adopted and are routinely featured in all guidelines.

In 2014, the National Institute for Health and Care Excellence (NICE) in the United Kingdom published a guidance document for the clinical use of FeNO measurement in patients with asthma (<http://www.nice.org.uk/dg12/evidence>). This thorough health technology assessment, incorporating a detailed cost-effectiveness analysis, identified important clinical utilities of FeNO measurement in patients with suspected or established

asthma. In November 2017, NICE published their new clinical guidelines focusing on the diagnosis, monitoring and chronic asthma management (<https://www.nice.org.uk/guidance/ng80>). These guidelines were developed using a pragmatic approach, with the consideration of both real-life and observational studies as well as more strict randomized controlled trials. The conclusions were to recommend FeNO measurement and spirometry to be used as initial assessments in all patients in whom asthma is suspected, and propose FeNO measurement to be considered in the management of patients with asthma who remain symptomatic despite inhaled corticosteroid treatment.

Thus, NICE and GINA have come to substantially different conclusions on the utility of FeNO in clinical practice. This demonstrates that examination of evidence by two different expert groups can yield different recommendations at the same time. Further explanations for the different conclusions drawn may reflect different perspectives of the respective experts: UK-focused in the case of NICE *versus* GINA's more global perspective. It is also possible that potentially practical advantages of FeNO measurement (for example ease of use, reproducibility, cost-effectiveness, at least in the UK context) and availability of detailed practice guidelines may have been weighted differently by the GINA and NICE committees.

We hope that the contrasting guidelines will stimulate further clinical research on the use of simple and accessible point-of-care biomarkers (such as FeNO and blood eosinophils) for determining the inflammatory endotype, their link to targeted treatment responsiveness and the potential to assess future risk of exacerbations and lung function decline. It is of note that large pragmatic studies in primary care have shown that FeNO-guided management reduces the rate of asthma exacerbations⁷, is cost effective and improves asthma control while minimising corticosteroid use⁸. Furthermore, FeNO strongly predicted symptomatic response to inhaled corticosteroids in those with unclear evidence of asthma in terms of bronchial reversibility in a randomised trial set in both primary and secondary care⁹. Additional real-life studies would be useful to complement these encouraging observations and to provide consistent advice for clinicians managing asthma.

In conclusion, there is an increasing need for clinical biomarkers to better stratify patients according to their inflammatory phenotype or endotype. FeNO measurement shows promise in the diagnosis and management of asthma, particularly to predict potential response to inhaled corticosteroid treatment, and, in combination with B-Eos count, to assess future risk. Furthermore, both biomarkers should be used to indicate responsiveness to new type-2 targeted treatment (dupilumab) in severe asthma, according to the European Medicines Agency (<https://www.ema.europa.eu/en/news/new-add-treatment-patients-severe-asthma>), and they will be useful in the future development of other biological drugs in asthma. To enable adequate inclusion of biomarkers in asthma guidelines for the broad benefit of patients and society, guidelines should consider all available evidence, including both real-life studies and randomised controlled trials.

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Authors' contributions

Kjell Alving wrote the first version of the manuscript. All authors have read and contributed to the manuscript, and approved the final version of the manuscript.

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