



Could home based FeNO measurements breathe new life into asthma management?

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Asthma is the most prevalent chronic respiratory disease in the world, affecting an estimated 235 million people [1,2]. In Australia, where detailed current estimates are available, the cost of asthma was estimated to be US\$8 800 per patient, per annum. These costs not only include health system costs and productivity losses but importantly the total burden of disease associated with suffering, premature death and loss of quality of life [3]. These high costs are replicated around the globe.

While existing and affordable interventions are effective in treating or preventing much of the burden of asthma [2], ineffective implementation of these interventions is limiting their performance and it has been recently suggested that a plateau in asthma control has been reached [4]. It is well-established that the most effective interventions are linked to a personalised asthma action plan, and such plans have underpinned international asthma management guidelines for decades [5, 6]. These plans are co-designed by the patient and health professional and provide individuals with advice on how to respond to deterioration in their asthma.

Randomised controlled trials have provided overwhelming evidence that personalised asthma action plans significantly improve all aspects of asthma health [7], reducing the risk of hospitalisation, emergency department presentations, doctor consultations, exacerbations and school and work absenteeism [8, 9]. However, implementation of these plans by health professionals and uptake by patients is low [10, 11].

Consequently, personalised asthma action plans have not had the expected effect on the burden-of-disease that was predicted from the available evidence.

Much effort has been put into understanding why personalised asthma action plans are not as popular with patients and doctors as would be predicted from the excellent outcomes associated with their use in the clinical trial setting. One possible reason is that their success relies on the patient monitoring their own symptoms, recognising signs of deterioration and then feeling sufficiently empowered to take action.

Symptoms are often complex, qualitative, and non-specific indicators of changes in asthma status and a subset of patients commonly fail to fully appreciate their worsening [12, 13]. Accordingly, a patient's perception of their own symptoms may not be sufficient to trigger the appropriate response dictated by their asthma action plan. To assist patients objectively monitor their asthma symptoms, lung function tests suitable for home use, including peak expiratory flow (PEF) and forced expiratory volume (FEV), have been developed. Whilst providing quantitative results, these tests require a high level of patient effort to obtain good-quality results. As a result, few people wish to monitor lung function routinely [7] and, in the home setting, these tests are generally associated with low compliance [14-17]. The combination of uncertain perception of symptoms and low compliance with existing quantitative tests most likely contributes to the poor uptake and use of personalised asthma action plans.

There is much enthusiasm for the inclusion of digital recording technology within personalised asthma action plans to allow patients to readily compare daily symptoms and/or lung function measurements and therefore detect worsening of their asthma control [10, 18]. Whilst technology will undoubtedly increase uptake and compliance with asthma management plans, it is unrealistic to expect more than incremental improvements as a result of their implementation alone.

We suggest that to improve the use and compliance of personalised asthma action plans there is a need for easy to use, quantitative monitoring systems that can be used as an alternative to home-based lung function tests.

Quantitative data is required to minimise the need for patient judgment, or support the patient's own judgement, enabling them to respond to changes in the state of their asthma on an as-required basis and in the absence of immediate professional oversight. The systems also need to be affordable and easy to use, to ensure compliance, and ideally linked to digital recording technology. Such tools may drive a revolution in asthma self-management akin to that which occurred in diabetes management when blood glucose biosensors became available.

Objective measures of asthma, aside from lung function tests, currently used clinically to support asthma diagnosis or management include Fractional exhaled Nitric Oxide (FeNO), serum total IgE, and sputum or blood eosinophil counts [19]. In addition, much effort is being invested into finding and characterising other biomarkers of asthma phenotypes. However, at this stage such alternatives are still in the developmental stage.

Of the currently available options, we suggest that FeNO measurement has the greatest potential as a home management tool for the main reason that the other options require complicated protocols and high levels of technical expertise to obtain good quality data. Measurement of FeNO is non-invasive and requires lower levels of patient cooperation than the maximal effort manoeuvres required for peak flow or spirometry lung function

tests. Given that FeNO tests are easier for the patient to carry out than peak flow or spirometry could make FeNO more suitable for a home based monitoring tool.

There have now been a number of randomised clinical trials assessing the advantage of using FeNO in asthma management. The findings of these studies is equivocal and as a result the medical community is divided on the benefit of FeNO measurement in clinical practise. Despite this controversy American Thoracic Society (ATS) and the National Institute for Health and Care Excellence (NICE) both recommend the use of clinic-based FeNO for diagnosis of asthma.

Recent Cochrane reviews identified a number of unbiased randomised controlled trials that assessed the use of FeNO in asthma management [20, 21]. We would like to highlight some key points about the clinical trials included in these reviews and where the results of these trials have implications for regular home-based FeNO monitoring.

The vast majority of these trials measured FeNO in a clinical setting on a regular, but lengthy time period. Furthermore, these trials assessed the advantage of using FeNO in addition to well-proven outcomes such as symptom monitoring and spirometry. The expectation of these studies was that the addition of FeNO measurements would further improve clinical care, and therefore asthma management outcomes, when compared to clinical care alone. Frequently, this was not proven to be the case.

A small number of randomised trials have directly compared FeNO-driven asthma management to that of standard clinical practice. The results from these studies suggested that FeNO-driven asthma management can be successful is equivalent to

standard asthma management [22-26]. The benefits measured in these trials have included a significantly reduction in the number of asthma exacerbations [23, 24, 27] or asthma control at significantly lower inhaled corticosteroid doses [22]. In pregnant women, FeNO-driven asthma management reduced the asthma exacerbation rate significantly, improved quality of life in women, and reduced the rate of hospitalisations in their infants in comparison to controls [23].

To determine if a home-based FeNO system would provide quantitative data from which an individual could make asthma management decisions requires clinical trials investigating asthma management based on *daily* FeNO measurements. Current published trials taking daily FeNO measurements include those where FeNO data was used to guide the minimal inhaled corticosteroid dose [27] or minimal oral steroid dose [28] required to achieve asthma control. Both studies assessed the benefit of FeNO *in addition to* symptom monitoring and spirometry guided by clinical expertise. As with the above mentioned studies using less frequent FeNO measurements, neither found that FeNO added benefit above that of standard clinical practices

A detailed analysis of the single daily FeNO measurements from one of the studies [26] suggested that moderate exacerbations could be predicted based on increases in an individual's FeNO in the days prior to the onset of an exacerbation [29]. Studies have shown that early intervention at this early stage reduces the severity of exacerbations, the number of hospitalizations and the length of stay in hospital [30].

We therefore propose that we should reframe the protocols for the use of FeNO in asthma management to be based around daily measurements compared to an

individual's best measures (i.e baseline when asthma is well controlled) rather than comparing a irregular FeNO results (i.e. at annual clinical reviews) against a population average.

It is well known that FeNO varies according to a wide variety of factors including age, height, smoking status, diet, allergen exposure, rhinovirus infection, air pollution and possibly exercise [31]. This variation is often used as an argument against the use of FeNO in clinical practise. It is possible that much of the variation seen within the population can be reduced by monitoring changes in an individual's baseline on a daily basis. Factors which lead to variation within the individual, such as diet and exercise, will require patient education to ensure, for example, that the patient takes measurements prior to eating or exercising and after sleep.

The benefit of using changes in an individual's daily FeNO to guide asthma management needs to be tested in specifically designed clinical trials. Comprehensive testing requires an affordable FeNO measuring device. To date, a lack of such devices has limited the testing of home FeNO measurement for asthma management.

Gold-standard, laboratory based devices use chemiluminescent sensors that measure the quantity of light released from the reaction of NO with ozone. The sensors are extremely sensitive (1 ppb limit of detection), accurate (± 1 ppb), and selective for NO. However, these devices are expensive (US\$20,000–\$45,000), bulky (≈ 25 kg), and require technical expertise and frequent calibration [32].

Devices that measure electrochemical oxidation or reduction of NO can be made significantly smaller and at a lower cost than those based on chemiluminescence. There are a number of commercially available devices which are portable (weighing under 1 kg), user-friendly, and do not require calibration. These devices are technically adequate for home-based monitoring as demonstrated by at least three clinical trials [22, 24, 26].

While these existing commercially-available electrochemical FeNO devices have dramatically broadened the scope of FeNO use to the home and will now allow clinical testing of the concept of use of FeNO to support personalized asthma action plans, their cost per test (around US\$20–\$40) remains too high for routine uptake as a daily monitoring device in the home.

The cost per test for a home based devices would likely need to be reduced to a similar cost per test as that of the blood glucose monitors used to manage diabetes (around US\$1). Similarly, improvements in accuracy to levels at least half that of the current electrochemical sensors is required to increase the ability to predict future exacerbations [29].

In addition to the above sensors, there are a considerable number of unique nitric oxide sensors in development including those based on different laser technologies [33] or biomimetic systems [34]. Furthermore, whilst not yet described in the scientific literature or in clinical trials there are a number of new products coming onto the market specifically targeting monitoring FeNO in the home. We hope that by

highlighting the potential of FeNO in the home setting that this will drive research into further development and testing of existing or new FeNO sensing technologies.

In conclusion, we believe that by taking FeNO measurements from the clinic to the home, and developing a FeNO test that is affordable enough to allow daily measurements, patients will be able to access quantifiable data to assist them to monitor their asthma. This will empower them to implement their asthma action plan as required and lead to significant improvements in asthma control and quality of life. While this is undoubtedly not the only answer to the complex problem of compliance, it has the potential to be an important addition. The use of FeNO to manage asthma in the home requires clinical testing and is reliant on the development of user-friendly, cost-effective measuring devices, which allow frequent measurements to be taken. The development of such devices may lead to the same exponential improvements in compliance of self-management plans for asthma as seen in other chronic diseases, such as diabetes [35].

References

1. World Health Organisation. Asthma. 2018.
<http://www.who.int/respiratory/asthma/en/>
2. Soriano JB, Abajobir AA, Abate KH, et al. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015 *Lancet Respir Med*. 2017;5:691–706.
3. Asthma Australia and National Asthma Council Australia, The hidden cost of asthma. Deloitte Access Economics report Online 2015.
<https://www2.deloitte.com/au/en/pages/economics/articles/hidden-cost-asthma.html>
4. O'Byrne PM, Jenkins C, Bateman ED. The paradoxes of asthma management: time for a new approach? *Eur Respir J*. 2017;50:1701103.
5. Woolcock A, Rubinfeld A, Seale J, et al. Asthma management plan. *Med J Australia*. 1989;151:650–653.
6. British Thoracic Society, Research Unit of the Royal Colleges of Physicians for London, Kings Fund Centre, National Asthma Campaign. Guidelines for management of asthma in adults: 1-chronic persistent asthma. *Brit Med J*. 1990;301:651–653.
7. Pinnock H. Supported self-management for asthma. *Breathe*. 2015;11:98–109.
8. Gibson PG, Powell H, Coughlan J, et al. Self-management education and regular practitioner review for adults with asthma. *Cochrane Database Syst Rev*. 2003;1:CD001117.
9. Taylor SJC, Pinnock H, Epiphaniou E, et al. A rapid synthesis of the evidence on interventions supporting self-management for people with long-term conditions: PRISMS – Practical systematic review of self-management support for long-term conditions. *Health Serv Deliv Res*. 2014;2:1–191.
10. Ring N, Booth H, Wilson C, et al. The 'viscous cycle' of personalised asthma action plan implementation in primary care: a qualitative study of patients and health professionals' views. *BMC Fam Pract*. 2015;16:145–156.
11. Asthma UK. Annual Asthma Survey 2016 Report.
<https://www.asthma.org.uk/share/?rid=3690>
12. Kendrick AH, Higgs CM, Whitfield MJ, Laszlo G. Accuracy of perception of severity of asthma: patients treated in general practice. *BMJ*. 1993;307:422–424.
13. Ignacio-Garcia JM, Gonzalez-Santos P. Asthma self-management education program by home monitoring of peak expiratory flow. *Am J Respir Crit Care Med*. 1995;151:353–359.

14. Côté J, Cartier A, Malo JL, Rouleau M, Boulet LP. Compliance with peak expiratory flow monitoring in home management of asthma. *Chest*. 1998;113:968–972.
15. Wensley DC, Silverman M. The quality of home spirometry in school children with asthma. *Thorax*. 2001;56:183–185.
16. van der Meer V, Rijkers-Mutsaerts ER, Sterk PJ, et al. Compliance and reliability of electronic PEF monitoring in adolescents with asthma. *Thorax*. 2006;61:457–458.
17. Feldman JM, McQuaid EL, Klein RB, et al. Symptom perception and functional morbidity across a 1-year follow-up in pediatric asthma. *Pediatr Pulmonol*. 2007;42:339–347.
18. Asthma UK. 2016. Connected asthma: how technology will transform care. <https://www.asthma.org.uk/globalassets/get-involved/external-affairs-campaigns/publications/connected-asthma/connected-asthma---aug-2016.pdf>
19. Sánchez-García S, Habernau Mena A, Quirce S. Biomarkers in inflammometry pediatric asthma: utility in daily clinical practice. *Eur Clin Respir J*. 2017;4:DOI: 10.1080/20018525.2017.1356160.
20. Petsky HL, Kew KM, Turner C, Kynaston JA, Chang AB. Exhaled nitric oxide to guide asthma treatment for adults. *Cochrane Database of Systematic Reviews* 2015, Issue 1. Art. No.: CD011440. DOI: 10.1002/14651858.CD011440.
21. Petsky HL, Kew KM, Chang AB. Exhaled nitric oxide levels to guide treatment for children with asthma. *Cochrane Database of Systematic Reviews* 2016, Issue 11. Art. No.: CD011439. DOI: 10.1002/14651858.CD011439.pub2
22. Smith AD, Cowan JO, Brassett KP, Herbison GP, Taylor DR. Use of exhaled nitric oxide measurements to guide treatment in chronic asthma. *N Engl J Med*. 2005;352:2163–2173.
23. Powell H, Murphy VE, Taylor DR, et al. Management of asthma in pregnancy guided by measurement of fraction of exhaled nitric oxide: a double-blind, randomised controlled trial. *Lancet*. 2011;378:983–990.
24. Syk J, Malinowski A, Johansson G, et al. Anti-inflammatory treatment of atopic asthma guided by exhaled nitric oxide: a randomized, controlled trial. *J Allergy Clin Immunol Pract*. 2013;1:639–648.
25. Petsky HL, Li A, Au CT, Kynaston JA, Turner C, Chang AB. Management based on exhaled nitric oxide levels adjusted for atopy reduces asthma exacerbations in children: A dual centre randomised controlled trial. *Pediatric Pulmonol*. 2014;50:535–543.
26. Peirsman EJ, Carvelli TJ, Hage PY, et al. Exhaled nitric oxide in childhood allergic asthma management: A randomised controlled trial. *Pediatr Pulmonol*. 2014;49:624–631.

27. De Jongste JC, Carraro S, Hop WC et al. Daily telemonitoring of exhaled nitric oxide and symptoms in the treatment of childhood asthma. *Am J Respir Crit Care Med*. 2009;179:93–97.
28. Hashimoto S, Brinke AT, Roldaan AC, et al. Internet-based tapering of oral corticosteroids in severe asthma: a pragmatic randomised controlled trial. *Thorax*. 2011;66:514–520.
29. van der Valk RJ, Baraldi E, Stern G, Frey U, de Jongste JC. Daily exhaled nitric oxide measurements and asthma exacerbations in children. *Allergy*. 2012;67:265–271.
30. Cristescu SM, Mandon J, Harren FJM, Merilainen P, Hogman M. Methods of NO detection in exhaled breath. *J Breath Res*. 2013;7:017104.
31. Bjermer L, Alving K, Diamant Z, Magnussen H, Pavord I, Piacentini G, Price D, Roche N, Sastre J, Thomas M, Usmani O. Current evidence and future research needs for FeNO measurement in respiratory disease. *Respir Med*. 2014;108:830–841.
32. Maniscalco M, Lundberg JO. Hand-held nitric oxide sensor NIOX MINO for the monitoring of respiratory disorders. *Expert Rev Respir Med*. 2010;4:715–721.
33. Maniscalco M, Vitale C, Vatrella A, Molino A, Bianco A, Mazzearella G. Fractional exhaled nitric oxide-measuring devices: technology update. *Med Devices*. 2016;9:151–160.
34. Musameh MM, Dunn CJ, Uddin MH, Sutherland TD, Rapson TD. Silk provides a new avenue for third generation biosensors: Sensitive, stable and selective electrochemical detection of nitric oxide. *Biosens Bioelectron*. 2018;103:26–31.
35. Gibson PG, Talbot PI, Toneguzzi RC, et al. Self-management, autonomy, and quality of life in asthma. *Chest*. 1995;107:1003–1008.

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Declaration of interest

TDS and TDR have developed a nitric oxide sensor. The authors alone are responsible for the content and writing of the paper.

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