



## Nitrogen offset in N<sub>2</sub> multiple washout method

*From the authors:*

Thank you for the opportunity to respond to the correspondence by J.G. Nielsen from Innovision about our recent paper [1]. We would like to respond with a few points to address any concerns that may have arisen from his comments amongst colleagues at cystic fibrosis centres using the Exhalyzer D (Eco Medics, Dürnten, Switzerland).

It is well established that the lung clearance index (LCI) values obtained from different devices are not interchangeable; the data we presented continue to emphasise that message.

J.G. Nielson is concerned that the higher LCI value obtained with the Exhalyzer D “makes the patient appear sicker” than they are. This is only the case if one judges the value against an inappropriate reference range from a different piece of equipment. Reference ranges specific to devices and gases are needed. These are being collated at present for the Exhalyzer D by our group and have recently been published by others [2].

The use of LCI in our centre is solely as an outcome measure of disease progression or therapeutic intervention. It is also the purpose of its use across the cystic fibrosis trial networks mentioned by J.G. Nielsen. What is needed in these situations is a measure with good clinimetrics [3], which relates to other understood measures or biomarkers, which reflects clinical change, and which is repeatable and reproducible. This is not the same as a requirement for accuracy or purity of measurement, which is required by those studying fundamental physiology.

The Exhalyzer D nitrogen washout has proven itself both practical in multicentre studies and sensitive to therapeutic response in the trial setting [4]. The standardisation, certification and over-reading processes put in place by the core facilities in Europe, North America and Australia [5] make it an increasingly attractive outcome measure for both academic and industrial sponsors designing drug trials for cystic fibrosis.

Irrespective of gas type, we do need to understand any offset in order to improve the multiple breath washout (MBW) technique and MBW's use as an outcome measure. This will likely involve more complicated lung models, and comparison of devices with minimal software and hardware differences, all having had appropriate *in vitro* and *in vivo* validation.

We look forward to independent research groups performing further work to improve the technique, including investigating whether a correction for the offset present can or should be applied.

**Katie J. Bayfield**<sup>1,2,3,4</sup>, **Eric Alton**<sup>1,2</sup>, **Samantha Irving**<sup>1,2</sup>, **Andrew Bush**<sup>1,2</sup> and **Jane C. Davies**<sup>1,2,3</sup>

<sup>1</sup>Imperial College London, London, UK. <sup>2</sup>Royal Brompton and Harefield NHS Foundation Trust, London, UK. <sup>3</sup>European Cystic Fibrosis Society Clinical Trials Network, Lung Clearance Index Core Facility, London, UK. <sup>4</sup>The Children's Hospital at Westmead, Sydney, Australia.

Correspondence: Katie J. Bayfield, The Children's Hospital at Westmead, Locked Bag 4001, Westmead 2145, NSW, Australia. E-mail: [katie.bayfield@health.nsw.gov.au](mailto:katie.bayfield@health.nsw.gov.au)

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