Exhaled nitric oxide (eNO) measurements with the new evernoa® device, through a extended range of eNO levels, are valid and reproducible

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Exhaled nitric oxide (eNO) is a biomarker that suggest type T 2 airway inflammation, with potential applications in respiratory allergic diseases, including asthma diagnosis, patient phenotyping supporting a good response to some biologics and corticosteroids and assessment of adherence to this therapy [1, 2] . Although numerous publications analyse clinical uses ofeNO, few studies provide data on whether measurementsperformed with different devices are valid and comparable [3]. The aim of this study was to compare the usability and the clinical validity, accuracy, reproducibility and degree of agreement between FENO measurements made with the Niox Vero (Circassia, Oxford, United Kingdom), which is the reference technique, performing very well in comparison with the more accurate measurements provided by electrochemiluminescence [4]and the evernoa® eNO analyser (Eversens, Pamplona, Spain)–both of whichare based on electrochemical sensors. Both devices followthe recommendations of the American Thoracic Society/European Respiratory Society [5] but evernoa makes the measurements by a simpler manoeuvre not requiring a previous inhalation through the device. A more accurate description of these devices can be foundon the supplementary material.

The study design was single-centre, cross-sectional with randomized measurements. 196 patients (18 to 74 years old) were included, of which the great majority (76%) had an allergic asthma phenotype, 10 % had a non-allergic eosinophilic phenotype and only 4% had non-eosinophilic asthma. The rest of the patients (10%) suffer from allergic rhinitis. Half of the asthmatics were being treated with inhaled corticosteroids.

To consider the greater variability of measurements at a higher concentration of eNO, the population was selected according to 2 groups and 3 classes: Group 1, Class 1: Subjects with FENO values <20 ppb. Group 1, Class 2: Subjects with FENO values 20-50 ppb. Group 2, Class 3: Subjects with FENO values> 50 ppb. The average of the measurements made with NIOX Vero were considered as the true reference value. All participants made two determinations in each of the devices in a randomized manner and in accordance with the recommendations of the ATS/ERS [5], with intervals of one minute between them. The number of attempts needed to obtain the measurements was recorded, as well

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as an overall rate of the patients of the simplicity and general experience with both devices. The correlation between the measures carried out (r Pearson) was studied, as well as the classification capacity, of grouping in values below or above the clinical cut-off point of 50 ppb, using the kappa index. On the other hand, the degree of concordance between both devices, the repeatability of both by the Bland Altman test and the bias at 50 ppb were estimated. [6]. Finally, the concordance analysis was extended by means of a Deming regression, since it considers the measurement error introduced by both devices estimated from areproducibility study of the measurement systems [7].

The measurement range was between 5 and 300 ppb, which is the measuring range of both devices. 30% of the subjects had an eNO greater than 50 ppb and 9% higher than 100 ppb. Despite lacking previous experience, 99% of users successfully tested with evernoa compared to 96.6% of users using Niox Vero for the first time [8]. A more detailed description of the usability aspects of the equipment is found in the supplementary material.

The correlation between the measurements with both devices was excellent (Pearson r 0.943, p <0.001). The classification capacity of the evernoa®with respect to that of NIOX VERO to classify the subjects in groups 1 or 2 (greater or less than 50 ppb) was also very good, obtaining a Kappa index of 0.7610.The results of concordance between both devices(Bland-Altman test) were excellent with an average difference between them of 2.44 ppb being homogeneous in all over the range of measurements (Fig. 1 A). The repeatability of evernoa showed concordance limits of 6.04 and -7.53 ppb versus 6.68 and -7.38 ppb of NIOX, which suggests that evernoa repeatability, is discreetly better (Fig. 1B, 1C)

A balanced Deming regression [7] was carried out with a value of the measurement error ratio(λ) estimated from two studies of the reproducibility of data obtained with the devices.The slope of the regression is 0.904 I.C. (0.851; 0.956) and the ordinate at the origin is 2.71 I.C. (-1,182; 5,523), beingthe results obtained with evernoa® slightly lower than those of NIOX, although there is a high degree of concordance between the two devices (see supplementary material). The bias for the level of greatest clinical relevance (50 ppb) is -2,634 ppb value that is within the specifications of evernoa (± 3 ppb) and is considered suitable for use in the diagnosis of asthma [9].

To conclude, our results guarantee the ease of use and the quality of the measurements obtained with evernoa® in terms of diagnostic accuracy, repeatability, truthfulness and concordance with the reference equipment, which indicates its suitability for the measurement of eNO.

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Conflicts of interest:
Dr.A. OLAGUIBEL reports grants from FONDOS FEDER, grants from GOBIERNO DE NAVARRA, during the conduct of the study.
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Dr. IRAOLA reports grants from FONDOS FEDER, grants from GOBIERNO DE NAVARRA, during the conduct of the study.
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Dr. ALVAREZ PUEBLA has nothing to disclose.
Dr. TABAR has nothing to disclose.
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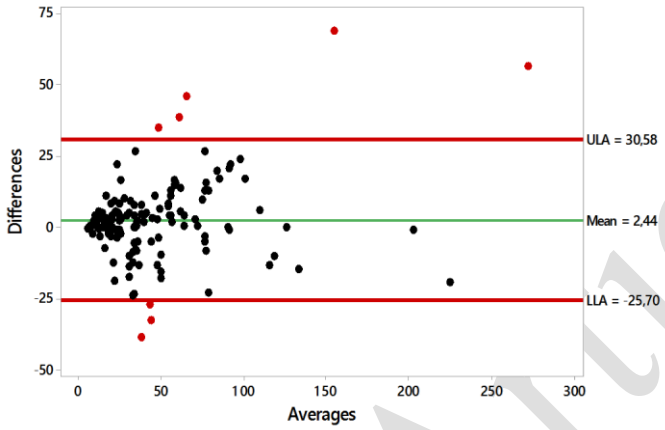
REFERENCES

1. Pavord ID, Afzalnia S, Menzies-Gow A, Heaney LG. The current and future role of biomarkers in type 2 cytokine-mediated asthma management. Clinical & Experimental Allergy. 2017;47:148-60.
2. Karrasch S, Linde K, Rucker G, Sommer H,Karsch-Völk M,Kleijnen J,et al. Accuracy of FENO for diagnosing asthma: a systematic review. Thorax. 2017;72:109-16.
3. Taylor DR. Exhaled Nitric Oxide: Still Alive, Not Laid to Rest. Am J RespirCrit Care Med 2009;179:88-9.
4. Fortuna AM, Feixas T, Casan P. Measurement of fraction of exhaled nitric oxide with the portable NIOX-MINO monitor in healthy adults. Arch Bronconeumol. 2007;43:176-9.
5. ATS/ERS Recommendations for Standardized Procedures for the Online and Offline Measurement of Exhaled Lower Respiratory Nitric Oxide and Nasal Nitric Oxide, 2005. Am J RespirCrit Care Med. 2005;171:912-30.

6. Bland JM, Altman DG. Agreement Between Methods of Measurement with Multiple Observations Per Individual. Journal of Biopharmaceutical Statistics. 2007;17:571-82.
7. Linnet K.Evaluation of Regression Procedures for Methods Comparison Studies. CLINICALCHEMISTRY.1993:39:22-4.
8. Alving K, Anolik R, Crater G, LaForce CF, Rickard K. Validation of a New Portable Exhaled Nitric OxideAnalyzer, NIOX VERO: Randomized Studiesin Asthma. Pulmonary Therapy. 2017;3: 207–18
9. Guo Z, Wang Y, Xing G, Wang X. Diagnostic accuracy of fractional exhaled nitric oxide in asthma: a systematic review and meta-analysis of prospective studies. Journal of Asthma. 2016;53:404-12.

Figure1. Analysis of agreement betweenmeasurements (Bland-Altman plot): Differences between both measurements performed with each device (y axis) vs means of both measurements(x axis). A: evernoa vs Niox Vero. B: evernoareproducibility. C: Niox Vero reproducibility.

1. A



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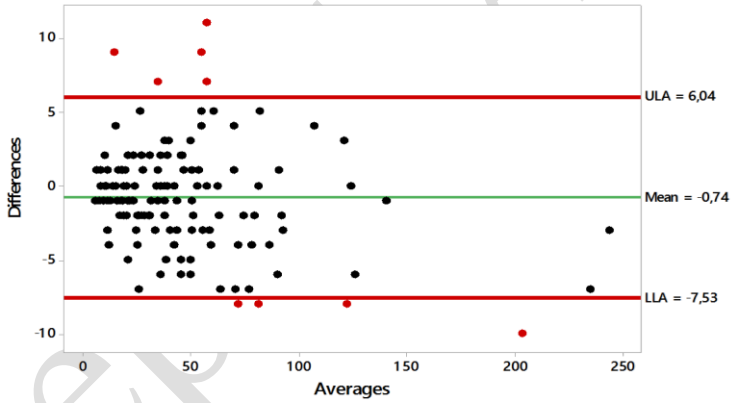
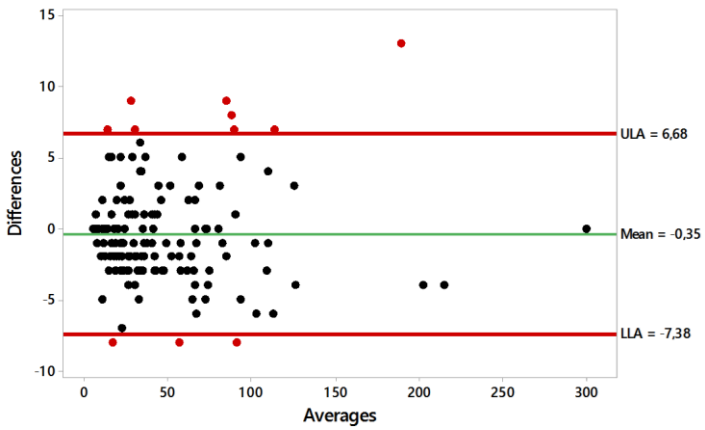


1. C



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