

The role of Fraction Exhaled Nitric Oxide (FeNO) in asthma management: An Italian consensus statement on clinical and economic aspects

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ABSTRACT

Background: Chronic respiratory diseases cause significant global morbidity and mortality, with asthma being a major contributor. Globally, 461,000 asthma-related deaths and a prevalence of 262 million subjects were estimated in 2019. The objective of this paper is to summarize experts' opinions in the field of asthma to produce evidence on the clinical and economic impact of FeNO test in asthma management, as well as on its standard operational procedures.

Methods: The analysis conducted is based on a literature review of the FeNO test's role in asthma, focusing on its clinical and economic impact, strengths and limitations. Insights were gathered through interviews with ten Key Opinion Leaders in asthma management from various Italian regions. Their thoughts were summarized into key-messages and discussed in a joint meeting. A final document consolidating these discussions was outlined and approved by the experts involved.

Results: The FeNO test is crucial in the clinical management of asthma, aiding in phenotypic classification and guiding therapeutic decisions, particularly in severe cases. The value of FeNO assessment is supported by extensive literature evidence and recommended by international guidelines. Moreover, published economic analyses highlight the sustainability of the initial investment in FeNO technology thanks to a reduction of short-term medical costs for National Health Services by decreasing hospital admissions, specialist visits, and exacerbations related to asthma management. The test should be conducted at the first visit at the asthma centre and then regularly during follow-ups to monitor therapy adherence, adjust treatments, and predict response to drugs. FeNO testing facilitates early detection of bronchial inflammation, shortening the time for patients to access appropriate therapy. Despite its ease of use, interpreting the results requires specialist oversight due to potential confounding factors.

Conclusions: FeNO testing significantly improves asthma management by aiding in phenotyping, therapeutic strategy formulation, and monitoring. It enhances disease control, accelerates patient care, and offers economic benefits by reducing hospital admissions and treatment needs. However, practical and economic barriers can limit its adoption. Standardized test execution and result interpretation by specialists are essential for accurate patient management. The inclusion of FeNO assessment among exempt services for asthma patients would at last promote its equitable access.

Key words: Fraction Exhaled Nitric Oxide (FeNO), asthma, consensus, Italy

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Introduction

Chronic respiratory diseases (CRDs) are one of the main causes of mortality and morbidity worldwide, with asthma accounting for a huge part of them. The Global Burden of Diseases Study (GBD) 2019 reports 461,000 deaths due to asthma, a prevalent number of 262 million subjects and an incidence of 37.0 million cases [1-3]. In regard to the national context, the Italian Ministry of Health reported that in 2024 approximately 5% of the population, (approximately 3 million people), is affected by bronchial asthma, including 10% of severe asthmatic subjects (approximately 300,000 people). Furthermore, it is estimated that 87% and 77% of asthmatic patients have one or at least two comorbidities, respectively [4].

Asthma is a heterogeneous condition characterized by the presence of reversible airway obstruction and airway hyper-responsiveness typically resulting from type-2 (T2) inflammation. The pathology is characterized by respiratory symptoms such as wheezing, coughing, breathlessness, chest tightness and pain, associated with variable airflow obstruction, and often underlying inflammation [5-7]. The diagnosis of asthma does not rely on a single defining sign or symptom but rather requires a comprehensive and long-term evaluation of patient clinical (i.e. symptoms, exacerbations), functional (i.e. pulmonary function tests), inflammatory (i.e. eosinophils, total and specific IgE) and patient reported (i.e. ACQ, ACT, AQLQ, SGRQ) outcomes [5-7].

An additional relevant marker for T2 airway inflammation is Fractional Exhaled Nitric Oxide (FeNO), which refers to the fraction of exhaled nitric oxide that represents an inflammatory product in the lungs [5-7]. FeNO testing is a quantitative evaluation that has been suggested to support the diagnosis of asthma in individuals presenting with respiratory symptoms [7]. The FeNO test is performed by the patient inhaling up to total lung capacity and then exhaling for 10 seconds at an average flow of 50 ml/s. The test result is then shown from the device in approximately one minute [7].

In recent years, there has been considerable discussion regarding the relevance of FeNO testing in the diagnostic pathway of patients with suspected asthma. The objective of this paper is to summarize experts' opinions in the field of asthma to produce evidence on the clinical and economic impact of FeNO test in asthma management, as well as on its standard operational procedures.

Methods

The analysis was carried out starting from an extensive and updated literature review on the role of FeNO testing in asthma aimed at summarising its 1) strengths and limitations; 2) clinical and economic impact; 3) positioning of the test according to national and international guidelines; 4) use within the Italian medical context. The narrative review was performed in October 2023 using Medline/PubMed database to

search for consensus papers and reviews related to the role of FeNO test in asthma management. Furthermore, an analysis of international guidelines and Italian clinical pathways related to the management of subjects affected with asthma was conducted to retrieve indications related to recommendations on the use of the test.

The articles were analyzed by three researchers who independently analyzed the texts and extrapolated the concepts to be assigned to the topics reported upon. The concepts summarized were discussed in one-to-one semi-structured interviews administered by experts in health management and health economics, to ten Key Opinion Leaders (KOL) in the field of asthma (respiratory physicians, hospital pharmacists, patient association representatives and hospital managers) from 3 Italian regions (i.e. Campania, Lazio and Piedmont). During the interviews field notes were used to collect information. The data were analyzed abductively and themes were defined *a priori*. The researchers independently analyzed the text to identify key messages and disagreements were discussed together by researchers and solved referring to the interviews. The opinions collected were summarized in key messages and discussed in a joint meeting with all the experts involved to reach consensus. All the involved experts contributed to the drafting and approved the present final document.

Results

The results of the consensus are presented considering 5 main topics, each divided into sub-topics: the role of FeNO test in the patient's clinical pathway (phenotypic classification, therapeutic choice, monitoring, access to therapies, threshold values), organizational aspects (execution, organization, acquisition), patient's point of view (acceptance, understanding, exemption), use of the test at a primary care level and for telemonitoring. The results are summarized in Table 1.

Role of FeNO test in the patient's clinical pathway

PHENOTYPIC CLASSIFICATION

FeNO test should be performed in all subjects diagnosed with asthma to properly phenotype patients

and suspect the potential presence of upper airways comorbidities (i.e. nasal polyps), as recommended by international guidelines [5, 8-22]. In particular, it would be important to perform the test during the first visit at asthma centres.

Regarding this aspect, the European Respiratory Society (ERS) guidelines include FeNO testing in the diagnostic flow-chart for asthma phenotyping [17]. Also in subjects with severe asthma, FeNO test is useful for phenotypic diagnosis [5, 8-22].

THERAPEUTIC CHOICE

The result of FeNO test is useful for physicians to define the optimal therapeutic choice in subjects suffering from severe asthma and to predict the treatment effectiveness. FeNO is in fact recognized as a reliable biomarker to easily and quickly monitor the response to therapy and eventually switch the ongoing pharmacological regimen [14,16,18,19,21-24]. The test results can indicate when to switch from "on demand" therapies to continuous therapies [14,16,18,19,21-24]. In mild asthma the test can help to modulate therapies "as needed" and to predict exacerbations, particularly in non-symptomatic subjects. Being considered a "game changer" for its ability to predict exacerbations, centres prescribing biological drugs should necessarily be able to perform FeNO testing.

MONITORING

In subjects with T2 high values, FeNO test should be carried out regularly during follow-up visits to monitor therapeutic adherence and, consequently, re-evaluate the inhalation technique, as well as to evaluate the opportunity to change treatment dosage, guide the therapeutic choice for possible changes in therapy, to predict the therapeutic response, and foresee possible flare-ups [7,8,18,19,22,23].

ACCESS TO THERAPIES

Within the clinical pathway of subjects with asthma, FeNO test is useful thanks to its ability to identify bronchial inflammation at an early stage, allowing a significant reduction in the time to access therapy [14,16,18,19,21-24].

Table 1. Results of the analysis conducted

Topic / sub topic	Statement
Role of FeNO test in the patient's clinical pathway	
Phenotypic classification	<p>FeNO test should be performed in all subjects diagnosed with asthma to properly phenotype patients and suspect the potential presence of upper airways comorbidities.</p> <p>In subjects with severe asthma, FeNO test is useful for phenotypic diagnosis.</p>
Therapeutic choice	<p>The result of FeNO test is useful for physicians to define the optimal therapeutic choice in subjects suffering from severe asthma and to predict the treatment effectiveness.</p> <p>In mild asthma FeNO test can help to modulate therapies "as needed" and to predict exacerbations, particularly in non-symptomatic subjects.</p> <p>Centres prescribing biological drugs should necessarily be able to perform FeNO testing.</p>
Monitoring	In subjects with T2 high values, FeNO test should be carried out regularly during follow-up visits.
Access to therapies	FeNO test allow a significant reduction in the time to access therapy thanks to its ability to identify bronchial inflammation at an early stage.
Threshold values	The threshold values that should be considered to interpret the test results are those indicated in the American Thoracic Society (ATS) guidelines.
Organizational aspects	
Execution	<p>FeNO testing is simple to perform, requires no specific training, and is non-invasive.</p> <p>The test should be performed by a physician specialist, or with the supervision of a specialist.</p> <p>FeNO test, therefore, requires standardized execution and the results interpretation should be led by expert personnel.</p> <p>FeNO test is optimal for paediatric patients as it is non-invasive and independent of effort.</p>
Organization	<p>The execution of the test does not require changes in organizational terms.</p> <p>No processes' revision nor specific training to be provided to professionals are required.</p> <p>The only potential obstacle to the introduction of the technology is at a cultural level: acceptance of the new technology.</p>
Acquisition	<p>No new purchasing processes should be implemented at a hospital level for technology acquisition.</p> <p>Regarding hospital organisation, no problems are expected in the supply of the device and consumables.</p>
Patient's point of view	The test is well accepted by patients thanks to the ease of use, being non-invasive and fast.
Acceptance	Performing FeNO test helps patients to better understand asthma condition and to increase awareness on issues relating to inflammation and specific aspects of asthma.
Understanding	<p>Patients are more inclined to adhere to therapies following FeNO testing since they understand their implications.</p> <p>Carrying out the test facilitates communication between patients and their specialist physician.</p>
Exemption	The lack of inclusion of FeNO test among the exempt services for patients suffering from asthma represents a barrier to access the test and to its diffusion.
Use of the test at a primary care level and for telemonitoring	<p>FeNO test could be used for monitoring activities via home testing and telemonitoring.</p> <p>Although the test is easy to use and with a simple reading of the results, its use at a primary care level is not recommended, since it is part of the wider and complex context of patient and pathology management.</p>

THRESHOLD VALUES

The threshold values that should be considered to interpret the test results are those indicated in the American Thoracic Society (ATS) guidelines [13]. In detail, it is recommended that FeNO levels below 25 ppb (below 20 ppb in children) should be considered to suggest that eosinophilic inflammation and responsiveness to corticosteroids are unlikely. FeNO levels above 50 ppb (above 35 ppb in children) indicate that eosinophilic inflammation and responsiveness to corticosteroids in symptomatic patients are likely. FeNO values between 25 ppb and 50 ppb (20–35 ppb in children) should be interpreted with caution and considered within the clinical context.

Organizational aspects

EXECUTION

FeNO testing is simple to perform, requires no specific training, and is non-invasive [14,16]. Even if simple to be used, the test should be performed by a physician specialist, or with the supervision of a specialist. Indeed, the interpretation of its results has several confounding factors and requires an appropriate level of culture, experience and specialization [14,16,25].

FeNO test, therefore, requires standardized execution and the results interpretation should be led by expert personnel since values may vary based on patients' characteristics (e.g., age, weight, height, allergies, use of inhaled corticosteroids and smoking) [14,16]. The test is also optimal for paediatric patients as it is non-invasive and independent of effort.

ORGANIZATION

The execution of the test does not require changes in organizational terms, as no need to adapt spaces for the use of the device is necessary. No processes' revision nor specific training to be provided to professionals are required. It should be noted that space requirement and measurement results may vary between portable and "bench" analyzers [7,18].

The only obstacle to the introduction of the technology perceived by the experts involved is at a cultural

level, in terms of acceptance of the new technology whether it is not yet available within a hospital.

No additional procedures for quality assessment are necessary compared to the procedures commonly adopted within hospitals treating subjects affected with asthma.

ACQUISITION

Regarding technology acquisition, the purchasing processes are the same of those in use for similar technologies, which involve a multidimensional assessment by hospital committees or clinical engineering. Because of the low cost of the technology, it is not necessary to implement a tender.

The evaluation parameters for the purchase are clinical, technical, economic and organisational and in details, the parameters taken into consideration are related to safety, organizational aspects, interpretation of results, ease of use for the patient, sensitivity and specificity, visual feedback for the patient, compliance with the necessary technical characteristics, as well as the overall economic impact, the need to manage consumables, the ease of use for the operator and the training need.

Regarding the supply of consumables (disposable mouthpieces and filters), this is managed by the hospital pharmacy, in consideration of the small number of producers and the low price, a tender is not necessary.

Furthermore, given the relatively low cost of the technology, no critical economic factors for its acquisition are expected. Regarding consumables, the acquisition is limited to disposable filters and mouthpieces, with a low economic impact. Regarding hospital organisation, no problems are expected in the supply of the device and consumables.

Patient's point of view

ACCEPTANCE

The test is well accepted by patients thanks to the ease of use, being non-invasive and fast, characteristics that have been extensively discussed in literature [7,14,15,18,19,21–23,26]. If the patient is able to

coordinate with the technology in exhaling, no problems have been encountered in its implementation.

UNDERSTANDING

Performing FeNO test helps patients to better understand asthma condition and to increase awareness on issues relating to inflammation and specific aspects of asthma. Patients proved to be more inclined to adhere to therapies because they understood their implications, and carrying out the test facilitated communication with their specialist physician.

EXEMPTION

The lack of inclusion of FeNO test among the exempt services for patients suffering from asthma represents a barrier to access the test and to its diffusion. Some patients could not be able to face the expenditure required in out-of-pocket terms. This could result in inequity in access to care for people suffering from asthma.

FeNO test is considered crucial for proper patient management and should not be omitted in the patient's clinical pathway, despite the lack of exemption from payment.

USE OF THE TEST AT A PRIMARY CARE LEVEL AND FOR TELEMONITORING

FeNO test could be used for monitoring activities (e.g., via home testing and telemonitoring). The telemonitoring could be provided directly by hospital wards or at a primary care level. However, although the test is easy to use and with a simple reading of the results, its use at a primary care level is not recommended, since it is part of the wider and complex context of patient and pathology management. Therefore, the interpretative key of the test result should fit into this context and asthma specialists should be responsible for it [27].

Discussion

The expert panel agreed on the usefulness of FeNO testing for asthma phenotyping, as well as for defining therapeutic strategies and supporting monitoring with the evaluation of adherence. The prognostic

role of FeNO test is also confirmed in terms of provision of information on the risk of future severe exacerbations. Furthermore, FeNO testing could have a role in the assessment of asthma remission, measuring bronchial inflammation, along with the measurement of other clinical parameters. The use of the test can therefore improve the clinical management of the pathology but also speed up the process of access to care [8,9,11,12,14-16,18,19,21,22].

The test is characterized by non-invasiveness and ease of use both for physicians and patients [7,14,15,18,19,21-23,26]. FeNO test could be useful for patients for a better understanding of the pathology and of its consequences. Furthermore, for clinicians the test is informative and simple to use, and, from a hospital perspective, no critical organizational issues are expected in terms of acquisition and management of the technology. Among the limitations of the test, confounding factors and different characteristics and degrees of precision of the available devices should be considered [7,14,16,18]. Furthermore, it should be noted that, as reported in a study assessing three different nitric oxide analysers, the results of the tests obtained in adult subjects with and without chronic respiratory disorders showed a good correlation among devices, but only of moderate agreement [42]. Differences in terms of results among different devices should then be considered while defining the technology to be acquired considering that variability in performance can influence the results of the test [43].

It is fundamental for clinicians to reach an appropriate knowledge and experience in the field of nitric oxide related to asthma management in order to be extremely confident in the FeNO data reading and to avoid misleading interpretation.

In terms of economic impact, available literature reports that the initial investment required to purchase the technology leads to a reduction in direct medical costs already in the short term for National Health Services, due to asthma management with related lower hospital admissions, reduction in the need for specialist visits and exacerbations (the analyses published in literature were performed in Italy, Sweden, Great Britain, Spain, The Netherlands, United States, and Colombia) [7,12,16,18,19,26,28-41]. In detail, considering a study performed in the Italian context, an estimated reduction in annual direct medical costs

per patient of - 52.23 € (-13%) and possible total annual cost reduction between 102 and 204 million € compared to the management of patients not using FeNO testing are estimated [26].

The most recent guidelines for managing subjects affected with asthma no longer consider FeNO testing as an optional test and underline its usefulness in defining therapy choices and in case of uncertain diagnosis. Within the Italian context, clinical pathways implemented at regional and hospital levels (i.e., Regione Basilicata 2015; ASL Rieti 2019; Regione Campania 2021; Regione Piemonte 2021; AOU Careggi 2022) suggest the use of the test both in the diagnostic and treatment definition phase (although considered as optional in few cases) [5,13,17].

The reading of the test results should be carried out by expert personnel to guarantee its correct interpretation considering the complex framework and all the factors that characterize the patient condition [14,16]. It is also important to provide clear indications on the methodology to perform the test and standardize its use.

Conclusion

In conclusion, a joint action and close dialogue involving scientific societies, patient associations and institutions is highly needed to standardize the provision of the test throughout the national territory and to support the definition of minimum criteria for the identification of clinical centres eligible for the management of subjects affected with severe asthma.

References

1. Institute for Health Metrics and Evaluation. Findings from the Global Burden of Disease Study 2017. Seattle, WA: IHME 2018.
2. Viegi G, Maio S, Fasola S, Baldacci S. Global burden of chronic respiratory diseases. *J Aerosol Med Pulm Drug Deliv* 2020; 33: 171-7.
3. Shin YH, Hwang J, Kwon R, Lee SW, Kim MS, GBD 2019 Allergic Disorders Collaborators, et al. Global, regional, and national burden of allergic disorders and their risk factors in 204 countries and territories, from 1990 to 2019: a systematic analysis for the Global Burden of Disease Study 2019. *Allergy* 2023; 78: 2232-54.
4. Ministero della Salute, Alleanza contro le malattie respiratorie croniche GARD Italia. Asma grave. 2024. Available at: <https://www.salute.gov.it/portale/gard/dettaglioContenutiGard.jsp?lingua=italiano&id=5822&area=gard&menu=attivit>.
5. Global Initiative for Asthma. Global strategy for asthma management and prevention. 2024.
6. Kuo CR, Spears M, Haughney J, Smith A, Miller J, Bradshaw T, et al. Scottish consensus statement on the role of FeNO in adult asthma. *Respir Med* 2019; 155: 54-7.
7. Stonham C, Baxter N. FeNO testing for asthma diagnosis - a PCRS consensus. *Prim Care Respir Update* 2019; 1-5.
8. Alving K, Teague WG. Inflammatory markers to inform treatment of asthma with biologicals: FeNO versus blood eosinophils. *J Allergy Clin Immunol Pract* 2023; 11: 1221-3.
9. Bertolini F, Sprio AE, Baroso A, Riccardi E, Pizzimenti S, Carriero V, et al. Predictors of low and high exhaled nitric oxide values in asthma: a real-world study. *Respiration* 2022; 101: 746-56.
10. British Thoracic Society, Scottish Intercollegiate Guidelines Network. SIGN158, British guideline on the management of asthma: a national clinical guideline. 2003.
11. Busse WW, Wenzel SE, Casale TB, FitzGerald JM, Rice MS, Daizadeh N, et al. Baseline FeNO as a prognostic biomarker for subsequent severe asthma exacerbations in patients with uncontrolled, moderate-to-severe asthma receiving placebo in the LIBERTY ASTHMA QUEST study: a post-hoc analysis. *Lancet Respir Med* 2021; 9: 1165-73.
12. Darbà J, Ascanio M, Syk J, Alving K. Economic evaluation of the use of FeNO for the diagnosis and management of asthma patients in primary care in Sweden. *Clinicoecon Outcomes Res* 2021; 13: 289-97.
13. Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FeNO) for clinical applications. *Am J Respir Crit Care Med* 2011; 184: 602-15.
14. Guida G, Bagnasco D, Carriero V, Bertolini F, Ricciardolo FLM, Nicola S, et al. Critical evaluation of asthma biomarkers in clinical practice. *Front Med (Lausanne)* 2022; 9: 969243.
15. Heffler E, Carpagnano GE, Favero E, Guida G, Maniscalco M, Motta A, et al. Fractional exhaled nitric oxide (FeNO) in the management of asthma: a position paper of the Italian Respiratory Society (SIP/IRS) and Italian Society of Allergy, Asthma and Clinical Immunology (SIAAIC). *Multidiscip Respir Med* 2020; 15: 36.
16. Loewenthal L, Menzies-Gow A. FeNO in asthma. *Semin Respir Crit Care Med* 2022; 43: 635-45.
17. Louis R, Satia I, Ojanguren I, Schleich F, Bonini M, Tonia T, et al. European Respiratory Society guidelines for the diagnosis of asthma in adults. *Eur Respir J* 2022; 15: 2101585.
18. Marcos MC, Cisneros Serrano C. What is the added value of FeNO as T2 biomarker? *Front Allergy* 2022; 3: 957106.
19. Murugesan N, Saxena D, Dileep A, Adrish M, Hanania NA. Update on the role of FeNO in asthma management. *Diagnostics (Basel)* 2023; 13: 1428.
20. National Institute for Health and Care Excellence. Asthma: diagnosis, monitoring and chronic asthma management. 2017. Available at: www.nice.org.uk/guidance/ng80.

21. Ricciardolo FL, Sorbello V, Ciprandi G. FeNO as biomarker for asthma phenotyping and management. *Allergy Asthma Proc* 2015; 36: e1-8.
22. Ricciardolo FLM, Stufano S, Carriero V, Maniscalco M. Utilizzo della misura di ossido nitrico nell'aria espirata: un update. *Rass Patol App Respir* 2021; 36: 118-22.
23. Guida G, Carriero V, Bertolini F, Pizzimenti S, Heffler E, Paoletti G, et al. Exhaled nitric oxide in asthma: from diagnosis to management. *Curr Opin Allergy Clin Immunol* 2023; 23: 29-35.
24. Pavord ID, Deniz Y, Corren J, Casale TB, FitzGerald JM, Izuhara K, et al. Baseline FeNO independently predicts the dupilumab response in patients with moderate-to-severe asthma. *J Allergy Clin Immunol Pract* 2023; 11: 1213-20.
25. Holguin F, Comhair SA, Hazen SL, Powers RW, Khatri SS, Bleeker ER, et al. An association between L-arginine/asymmetric dimethyl arginine balance, obesity, and the age of asthma onset phenotype. *Am J Respir Crit Care Med* 2013; 187: 153-9.
26. Rognoni C, Milano C, Heffler E, Bonini M, Brussino L, Carpagano GE, et al. Economic impact of a more extensive use of FeNO testing on the Italian population with asthma. *Respir Res* 2023; 24: 147.
27. Wang R, Usmani OS, Chung KF, Sont J, Simpson A, Bonini M, et al. Domiciliary fractional exhaled nitric oxide and spirometry in monitoring asthma control and exacerbations. *J Allergy Clin Immunol Pract* 2023; 11: 1787-95.
28. Arnold RJG, Layton A, Massanari M. Cost impact of monitoring exhaled nitric oxide in asthma management. *Allergy Asthma Proc* 2018; 39: 338-44.
29. Beerthuizen T, Voorend-van Bergen S, van den Hout WB, Vaessen-Verberne AA, Brackel HJ, et al. Cost-effectiveness of FeNO-based and web-based monitoring in paediatric asthma management: a randomised controlled trial. *Thorax* 2017; 71: 607-13.
30. Berg J, Lindgren P. Economic evaluation of FeNO measurement in diagnosis and 1-year management of asthma in Germany. *Respir Med* 2008; 102: 219-31.
31. Brooks EA, Massanari M. Cost-effectiveness analysis of monitoring fractional exhaled nitric oxide (FeNO) in the management of asthma. *Manag Care* 2018; 27: 42-8.
32. Brooks EA, Massanari M, Hanania NA, Weiner DJ. Cost-effectiveness of fractional exhaled nitric oxide (FeNO) measurement in predicting response to omalizumab in asthma. *Clinicoecon Outcomes Res* 2019; 11: 301-7.
33. Buendía JA, Acuña-Cordero R, Rodriguez-Martinez CE. Cost utility of fractional exhaled nitric oxide monitoring for the management of children asthma. *Cost Eff Resour Alloc* 2021; 19: 33.
34. Buendía JA, Acuña-Cordero R, Rodriguez-Martinez CE. Analysis of the budget impact of fractional exhaled nitric oxide monitoring in the management of childhood asthma: the Colombian National Health System perspective. *J Investig Allergol Clin Immunol* 2022; 32: 200-5.
35. Bukstein D, Luskin AT, Brooks EA. Exhaled nitric oxide as a tool in managing and monitoring difficult-to-treat asthma. *Allergy Asthma Proc* 2011; 32: 185-92.
36. Honkoop PJ, Loijmans RJ, Termeer EH, Snoeck-Stroband JB, van den Hout WB, Bakker MJ, et al. Symptom- and fraction of exhaled nitric oxide-driven strategies for asthma control: a cluster-randomized trial in primary care. *J Allergy Clin Immunol* 2015; 135: 682-8.
37. LaForce C, Brooks E, Herje N, Dorinsky P, Rickard K. Impact of exhaled nitric oxide measurements on treatment decisions in an asthma specialty clinic. *Ann Allergy Asthma Immunol* 2014; 113: 619-23.
38. Massanari M, Brooks EA, Rickard KA, Roman AA. Investigation of the cost-effectiveness of FeNO measurement as a screening tool to detect omalizumab responsiveness in difficult-to-treat asthma patients. *Value Health* 2017; 20: A241.
39. Massanari M, Brooks EA, Rickard K, Roman AA. Cost-effectiveness of using FeNO in the management of asthma. *Value Health* 2017; 20: A241-A242.
40. Price D, Berg J, Lindgren P. An economic evaluation of NIOX MINO airway inflammation monitor in the United Kingdom. *Allergy* 2009; 64: 431-8.
41. Sabatelli L, Seppälä U, Sastre J, Crater G. Cost-effectiveness and budget impact of routine use of fractional exhaled nitric oxide monitoring for the management of adult asthma patients in Spain. *J Investig Allergol Clin Immunol* 2017; 27: 89-97.
42. Molino A, Fuschillo S, Mosella M, et al. Comparison of three different exhaled nitric oxide analyzers in chronic respiratory disorders. *J Breath Res* 2019; 13: 021002.
43. Maniscalco M, Vitale C, Vatrella A, Molino A, Bianco A, Mazzarella G. Fractional exhaled nitric oxide-measuring devices: technology update. *Med Devices (Auckl)* 2016; 9: 151-60.

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