

ORIGINAL RESEARCH

Cost-Effectiveness Analysis of Monitoring Fractional Exhaled Nitric Oxide (FeNO) in the Management of Asthma

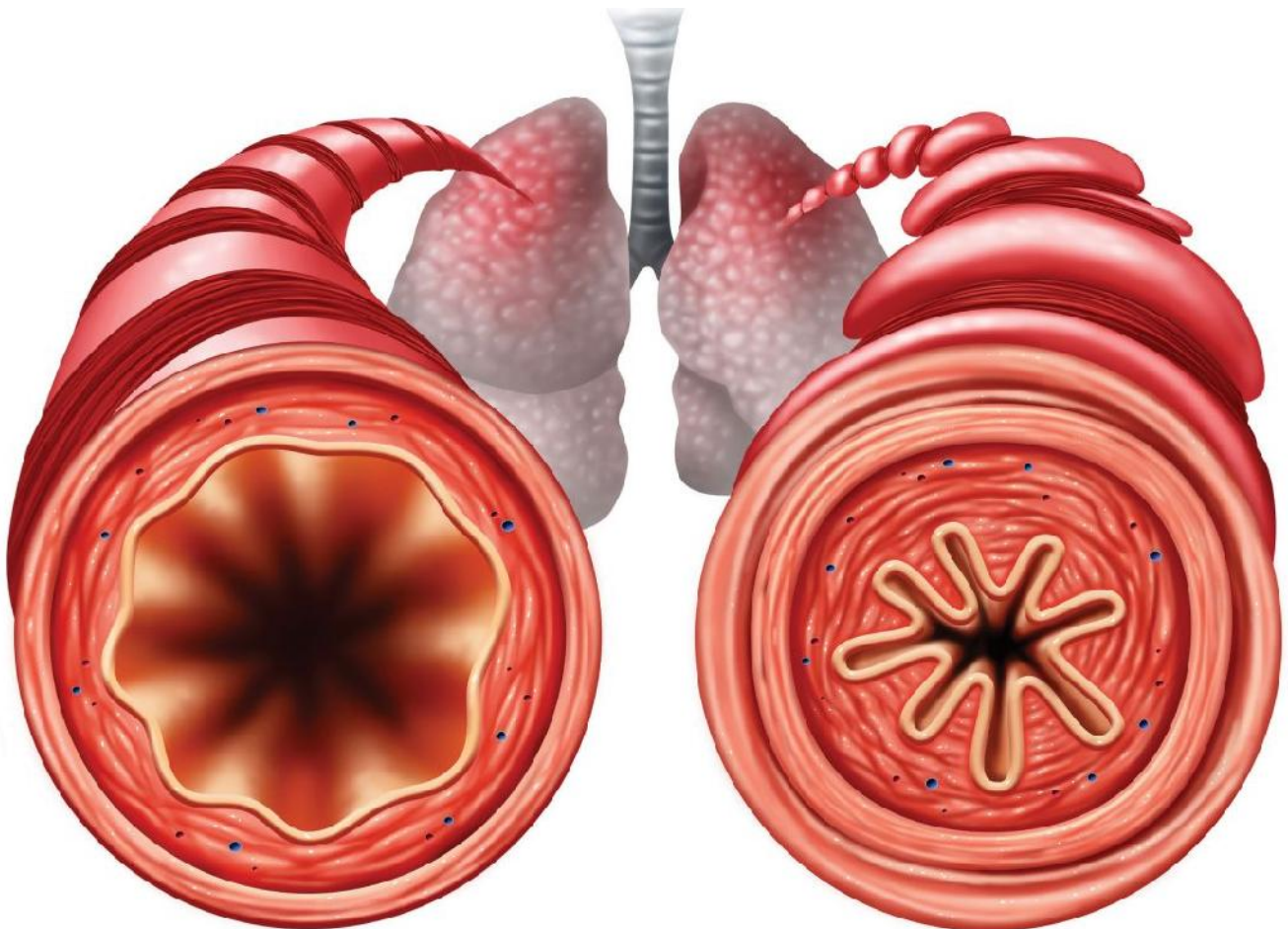
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Abstract

Purpose: Current asthma guidelines combine treatment, follow-up, and reevaluation to manage asthma control, reduce impairment, and decrease risk of morbidity in patients. Clinical use of biomarkers, such as fractional exhaled nitric oxide (FeNO), along with standard management can provide clinicians with improved ability to recognize airway inflammation, optimize drug therapy, and potentially increase asthma control. Our objective is to examine the impact of FeNO monitoring on the cost effectiveness of asthma management compared with management without FeNO. Sensitivity analyses further examine the impact of FeNO monitoring on patients with varying levels of severity and exacerbations.

Design and Methods: A decision-tree analysis of estimated outcomes and costs associated with annual management of asthma was utilized to simulate asthma management and treatment cost scenarios, comparing estimated 12-month costs and outcomes using the following treatment alternatives: (1) current standard of care (SOC) or (2) FeNO utilized in conjunction with the current SOC. Costs were estimated from the perspective of the health care payer; cost effectiveness was estimated as cost per quality-adjusted life year (QALY).

Results: FeNO in conjunction with SOC guidelines has decreased expected per-patient annual expenditure (\$2,228) and increased expected per-patient annual QALYs (0.844) compared with SOC alone (\$2,637 and 0.767). FeNO monitoring with SOC resulted in decreased annual costs and increased annual QALYs compared with SOC alone, and this difference was consistent through all one-way sensitivity analyses.

Conclusion: Our analysis revealed that FeNO monitoring to guide asthma management is cost effective and could result in increased QALYs and decreased health care costs associated with asthma management.

Introduction

According to the CDC National Health Interview Survey (NHIS), 18.4 million (7.6%) adults and 6.2 million (8.4%) children under 18 were living with asthma in the United States in 2015 (CDC 2017). Asthma management is complex and supported by national guidelines that initially were created to emphasize the importance of treating the inflammatory nature of the disease to improve patient outcomes (NAEPP 1991, NAEPP 1997, NAEPP 2007). These guidelines include recommendations for initial diagnosis and treatment to achieve asthma control, as well as continuing follow-up care to adjust treatment and maintain control. Asthma control focuses on reducing impairment (frequency and intensity of symptoms) and decreasing risk (likelihood of future attacks). Achieving and maintaining asthma control requires providing appropriate medication, addressing environmental factors that cause exacerbations and increase symptoms, helping patients learn self-management skills, and monitoring the disease to assess how well it is being controlled and adjust therapy accordingly. Asthma guidelines such as those published by the American Thoracic Society (ATS) and the National Institute for Health and Care Excellence (NICE) in the United Kingdom recommend periodic assessment and management of symptoms to prevent exacerbations, the most severe of

which can lead to hospitalization, increased health care utilization, and increased cost (Dweik 2011, NICE 2017).

Fractional exhaled nitric oxide (FeNO)

NO (nitric oxide) has long been known to be critical in understanding the cardiovascular system (SoRelle 1998) and as a biomarker for many inflammatory disease states (Mian 2013); subsequent research has clarified the role of exhaled NO in airway inflammation and asthma physiology. The concentration of NO in exhaled breath, or fractional exhaled nitric oxide (FeNO), is a simple, noninvasive measurement that can be used as a biomarker in the assessment of inflammatory airway diseases. Testing can be performed in any clinical setting and the cost is less than that of spirometry. Evidence to support the clinical and economic value of monitoring FeNO in asthma management is considerable (Arnold 2018). FeNO monitoring aids in diagnosis of asthma and can identify patients with Th2/Type 2 airway inflammation (Pakhale 2011, Wagener 2015). It can also help to determine steroid responsiveness and optimize the dose of inhaled corticosteroids (Price 2013, LaForce 2014) and reveal inhaled corticosteroid treatment nonadherence (Klok 2014, McNicholl 2012). FeNO monitoring reduces the likelihood of exacerbations in patients at risk of future events (Morten 2016, Petsky 2016b). According to recent data from Petsky et al. (2016b), when FeNO monitoring is incorporated into asthma management, the risk of exacerbation is reduced by 40%–50%, and monitoring is recommended for some subgroups, although not universally. FeNO monitoring also aids in identifying people with asthma who may be candidates for treatment with a biologic such as omalizumab, mepolizumab, or reslizumab (Hekking 2015, Kupczyk 2014, Hanania 2013).

FeNO, asthma, and clinical recommendations

In 2011, the ATS published a clinical practice guideline, Interpretation of Exhaled Nitric Oxide Levels (FeNO) for Clinical Applications (Dweik 2011). This guideline provides evidence-based recommendations for the use and interpretation of exhaled NO measurements in clinical practice. In 2012, this guideline was also formally endorsed and supported by the American College of Allergy, Asthma, and Immunology and the American Academy of Allergy, Asthma, and Immunology. FeNO has also been included in the most recent guidelines in the United Kingdom after NICE recommended FeNO measurement to help diagnose and manage asthma in most adults and children (NICE 2017).

Coincident with the release of the latest asthma guidelines from NICE, the Agency for Healthcare Research and Quality (AHRQ) has released a comprehensive, evidence-based assessment of the use of FeNO in the diagnosis and management of asthma. AHRQ found that FeNO measurements can help in monitoring response to anti-inflammatory or long-term control medications, including dose titration, weaning, or treatment adherence. The agency also found that asthma management algorithms incorporating FeNO testing reduced the risk of exacerbations and possibly the risk of exacerbations requiring oral steroids. However, the

agency concluded that it does not affect other outcomes, such as hospitalization, quality of life, asthma control, or FEV1% predicted (Wang 2017).

Study objective

Our study objective is to evaluate the hypothesis that FeNO monitoring is a cost-effective strategy to guide asthma management as compared to alternative methods. The cost effectiveness of monitoring FeNO in asthma management as compared to an alternative clinical asthma management without FeNO assessments was assessed from the payer perspective. In addition to evaluating the cost effectiveness of FeNO assessments in asthma management through base-case and one-way sensitivity analyses, we also evaluated the impact of FeNO assessments on theoretical cohorts of asthmatic patients with varying frequencies of exacerbations and FeNO measurements per year.

Methods

Our cost-effectiveness analysis used an expected-value, decision-analytic model to compare the estimated 12-month costs and outcomes associated with asthma management using the current standard of care (SOC) in asthma management or SOC with FeNO monitoring. As patients progress through the model simulation they begin with either SOC or FeNO in conjunction with SOC, and the condition may be well controlled or symptoms may worsen. If symptoms worsen through exacerbation, patients proceed to either mild-to-moderate or severe exacerbations. Patients having a mild-to-moderate exacerbation may either visit a physician's office or an outpatient facility. Patients having a severe exacerbation may either visit a physician's office or outpatient facility, or experience hospitalization.

Model assumptions

Model assumptions (Table 1) regarding patient treatments and costs from a health care payer perspective were drawn from the current literature on the topic. The following assumptions were made: all patients entering the model are nonsmoking adults, diagnosed with mild to severe asthma, and are seen in both primary and secondary care. An average patient would receive inhaled corticosteroid (ICS) and long-acting beta-agonist as maintenance therapy. Additionally, we assumed that in both management pathways a patient's asthma could either be successfully controlled by therapy or the patient could suffer an exacerbation.

Table 1
Model assumptions

Variable description	Base case value	Reference
Likelihood of exacerbation using FeNO for management	0.307	Donohue 2013
Likelihood of exacerbation using	0.580	Donohue 2013

standard care guidelines for asthma management		
Likelihood that exacerbations will be severe	0.060	Peirsman 2014
Likelihood that mild-to-moderate asthma exacerbations will be treated at an ED or urgent care center	0.500	Expert opinion
Likelihood that FeNO patient experiencing severe asthma exacerbations will be treated at an ED or urgent care center	0.750	Andersson 2001
Likelihood that standard care patient experiencing a severe exacerbation will require hospitalization	0.230	Green 2002
Reduction in ICS dose observed in FeNO group as compared to standard care group*	0.125	Petsky 2016a, Petsky 2016b
Reduction in risk of hospitalization for severe exacerbations observed in FeNO group as compared to standard care group*	0.860	Petsky 2016a, Petsky 2016b
Reduction in risk of exacerbations due to FeNO use	0.470	Donohue 2013
Cost assumptions		
Cost of FeNO	\$23.20	Private payer payment estimated as 120% of 2016 Medicare national average reimbursement for CPT code 95012 (FeNO measurement) (\$19.33)
Cost of spirometry	\$43.82	Private payer payment estimated as 120% of 2016 Medicare national average reimbursement for CPT code 94010 (spirometry) (\$36.52)
Annual cost of asthma medications for patients managed with FeNO	\$1,449.38	Assume reduction in cost of ICS only; assume cost of beta-agonists is same as for standard care; updated to 2016 US\$; RedBook and medshealth.com
Annual cost of asthma medications using standard care guidelines	\$1,686.28	Average cost of maintenance therapy for ICS + beta-agonist; updated to 2016 US\$; RedBook and medshealth.com
Cost per asthma management visits	\$88.08	Private payer payment estimated as 120% of 2016 Medicare national average reimbursement for CPT code 99213; assumption made that each visit for maintenance will be a Level III visit (\$73.40)
Cost per office visit for asthma exacerbation	\$129.76	Private payer payment estimated as 120% of 2016 Medicare national average reimbursement for CPT code

99214; assumption made that each visit for exacerbation will be a Level IV visit (\$108.13)

Cost of ED visit for asthma exacerbation	\$730.69	Barnett 2011; updated to 2016 US\$
Cost of rescue medications for moderate-to-severe exacerbations	\$22.99	Average cost of rescue drug cost for exacerbation; assume combination of oral steroids and short-acting beta-agonist; updated to 2016 US\$; RedBook and medshealth.com
Variable description	Base case value	Reference
Cost of rescue medications for mild-to-moderate exacerbations	\$14.99	Average cost of rescue drug cost for exacerbation; assume addition of short-acting beta-agonist; updated to 2016 US\$; RedBook and medshealth.com
Average hospital cost for asthma admission due to exacerbation	\$6,951.42	Mean hospital costs based on HCUP 2011 National statistics for asthma, principal diagnosis only; (\$6,600 based on 2011; http://www.hcup-us.ahrq.gov/reports/statbriefs/sb169-Asthma-Trends-Hospital-Stays.pdf ; updated to 2016 US\$)
Other assumptions		
Annual number of check-ups for asthma management	2	Expert opinion; assumption made that well controlled asthma will result in 2 office visits per year; this number is modifiable
Average annual number of exacerbations	2	Jayaram 2006
Utility value of asthma patients with good control	0.91	Honkoop 2015
Utility value of asthma patients with mildly reduced control	0.89	Honkoop 2015
Utility value of asthma patients with moderately reduced control	0.65	Szende 2004
Utility value of asthma patients with poor control	0.52	Szende 2004

*Differences were not statistically significant

CPT=Current Procedural Terminology, ED=emergency department, HCUP=Healthcare Cost and Utilization Project, ICS=inhaled corticosteroid

Exacerbations were divided into mild-to-moderate or severe to capture different levels of resource use. Mild-to-moderate exacerbations were defined as requiring only short-acting beta-agonists and severe exacerbations as requiring oral steroids. The final model assumption specified that the only patients who could require hospitalization would be in the severe exacerbation pathway. Treatment effectiveness was measured as quality-adjusted life years (QALYs).

Cost data

The decision analytic model, inputs, and supporting analyses were conducted utilizing recommendations from the U.S. Panel on Cost-Effectiveness in Health and Medicine (Sanders 2016). A comprehensive literature review was performed to assess data on costs and outcomes after both SOC treatment and FeNO in conjunction with SOC treatment related to asthma management.

Costs presented represent direct medical costs to the health care system relating to asthma management, including those for medication, ambulatory care, and hospitalizations. The cost estimates were derived from the peer-reviewed literature and U.S. Medicare values.

Some cost-related examples consist of FeNO costs; asthma management SOC including spirometry costs; annual costs of asthma medication for management strategies including and excluding FeNO; costs of asthma management visits to physician offices or emergency departments; rescue medications for exacerbation costs; and the annual hospital cost for asthma admission due to exacerbation.

Costs in the literature were converted to 2016 U.S. dollars using a cumulative inflation rate based on the Consumer Price Index for medical care services. Private payer payment was estimated as 120% of the 2016 Medicare national average reimbursement; drug costs were obtained from the 2016 RedBook and medshealth.com.

Hospital costs were estimated based on AHRQ's Healthcare Cost and Utilization Project (HCUP) 2011 national statistics for asthma. All costs were estimated from the health care payer perspective.

Utilities and transition probabilities

The patient outcome of interest for our analysis is a common disease burden measurement, the total QALYs experienced by the patient over the course of a 12-month period. Using QALYs as the treatment effectiveness parameter, our model evaluated cost effectiveness of two management strategies as cost per QALY. Four utility values were taken into account (Honkoop 2015, Szende 2004): asthma patients with good control; asthma patients with mildly reduced control; asthma patients with moderately reduced control; and asthma patients with poor control. Empirical evidence highlights the impact of FeNO on asthma management--related utility values in ICS dose reduction, reduction in hospitalization risk for severe exacerbations, and exacerbation risk reduction (Petsky 2016a, Petsky 2016b, Donohue 2013). Transition probabilities governing movement through the decision tree were obtained from peer-reviewed literature. Movement through the decision tree is governed by the success or failure of primary asthma management strategies; likelihood of mild-to-moderate or severe exacerbation; and likelihood of severe exacerbation warranting a visit to a physician office, outpatient facility, or hospitalization.

In order to demonstrate the robustness of the preliminary results, a series of one-way sensitivity analyses were performed using TreeAge. One-way sensitivity analyses consisted of

the manipulation of individual key variables by increasing and decreasing values by 15% to determine the impact these changes may have upon the cost-effectiveness findings.

Results

The principal effectiveness outcome is annual QALY associated with each asthma management strategy compared to the previous strategy when strategies are ordered by cost. A strategy is dominated when another strategy is both less costly and more effective. Conversely, a strategy is dominant when it both costs less and is more effective.

Base case and sensitivity analysis

Comparison of the 12-month average individual medical costs and QALYs between SOC asthma management alone and FeNO measurement utilized in conjunction with SOC asthma management reveals that FeNO in conjunction with standard management guidelines dominates standard management guidelines in both decreased costs per patient (\$2,637 vs. \$2,228) and increased effectiveness (0.844 vs. 0.767 QALYs). Additionally, FeNO in conjunction with SOC costs less per QALY when compared with SOC alone (\$2,640 vs. \$3,440).

Our analysis suggests that FeNO monitoring in addition to SOC is the more cost-effective strategy when compared with SOC alone and may be a preferable strategy for the management of asthma. Our preliminary results are supported by additional sensitivity analyses, conducted on all model variables; for each model variable, the values were allowed to vary individually up or down by 15% from the base case value provided in Table 1. In these analyses, no threshold values were identified. FeNO in conjunction with SOC remained the dominant asthma strategy across all sensitivity analyses performed.

Additionally, we examined the impact of FeNO monitoring on the cost of asthma management among asthma patients with infrequent and frequent exacerbations, as shown in Tables 2 and 3, respectively. In a theoretical population of people with asthma with infrequent exacerbations (Table 2), annual per patient costs of standard management with FeNO were less than those of standard management alone, with annual per-patient cost savings ranging between \$72 and \$217. In a theoretical population of people with frequent exacerbations (Table 3), FeNO showed an even greater benefit with annual per patient cost savings from FeNO monitoring ranging between \$316 and \$1,331, dependent on the assumed annual frequency of exacerbations and the assumed frequency of FeNO measurements.

Table 2
Impact of FeNO on cost of asthma management in patients with infrequent exacerbations

Annual number of exacerbations	0.25	0.25	0.50	0.50	1	1
Annual number of FeNO measurements	1	2	1	2	2	4
Per patient annual cost of SOC asthma management	\$1,904	\$2,036	\$1,990	\$2,122	\$2,294	\$2,557
Per patient annual cost of FeNO in addition to SOC	\$1,809	\$1,964	\$1,847	\$2,002	\$2,077	\$2,387

asthma management

Annual cost savings due to FeNO	\$95	\$72	\$143	\$120	\$217	\$170
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Red type indicates high and low ends of the range of savings from FeNO monitoring

Table 3**Impact of FeNO on cost of asthma management in patients with frequent exacerbations**

Annual number of exacerbations	2	2	4	4	6	8
Annual number of FeNO measurements	4	6	8	10	10	12
Per patient annual cost of SOC asthma management	\$2,901	\$3,165	\$4,115	\$4,379	\$5,066	\$6,016
Per patient annual cost of FeNO in addition to SOC asthma management	\$2,538	\$2,849	\$3,461	\$3,771	\$4,073	\$4,685
Annual cost savings due to FeNO	\$363	\$316	\$654	\$608	\$993	\$1,331

SOC=standard of care. Red type indicates high and low ends of the range of savings from FeNO monitoring

Discussion

Our cost-effectiveness model suggests that the use of FeNO monitoring to guide asthma management is a cost-effective strategy compared with current SOC alone because the addition of FeNO monitoring increases QALYs and reduces health care costs. In the base case analysis, FeNO in conjunction with SOC dominates SOC; asthma management that included FeNO monitoring strategy was less costly and provided greater QALYs. Sensitivity analyses showed these results to be robust to changes in the cost of asthma medications, exacerbations, treatment, and health utility associated with mild, moderate, or severe exacerbations. They were also robust with respect to costs for health care providers, ED visits, and hospital admissions.

Our cost-effectiveness model was constructed according to the recommendations of the U.S. Panel on Cost-Effectiveness in Health and Medicine and has its own intrinsic methodological strengths as an interactive model.

There are, however, some limitations. Our model was conducted from the health care payer perspective, which may not account for indirect costs related to asthma management that would be addressed from other cost perspectives. Additionally, our model's timeframe was short term—one year. It also included a simplified presentation of “average” clinical responses as the basis for ICS dose and hospitalization values, although the Cochrane reviews of the use of FeNO levels to guide treatment of children or adults with asthma did not find statistically significant differences (Petsky 2016a, Petsky 2016b).

Additional studies involving the use of FeNO monitoring in asthma management are recommended to provide additional data and insight, including additional cost-effectiveness

analysis from provider and patient perspectives as well as cost data from other countries. However, this cost-effectiveness analysis may serve as a model for the advancement of health care system and insurer policy, and ultimately, clinical practice regarding the use of FeNO to improve asthma management.

Glossary

AHRQ	Agency for Healthcare Research and Quality
ATS	American Thoracic Society
FeNO	fractional exhaled nitric oxide
QALY	quality-adjusted life year
SOC	standard of care

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