ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES

Fractional Exhaled Nitric Oxide Testing for the Diagnosis and Management of Asthma

A Health Technology Assessment

JULY 2024

Ontario Health

Key Messages

What Is This Health Technology Assessment About?

Asthma is a chronic respiratory disease that interferes with a person's breathing. Common symptoms of asthma include coughing, wheezing, and chest tightness. The severity of symptoms can vary from minor to life-threatening and can change over time. Although asthma has no cure, its symptoms can be controlled. Asthma is diagnosed using a review of the patient's medical history, a physical exam, and a lung function test that measures the strength of a person's breathing. Although asthma has no cure, its symptoms can be controlled. Asthma is diagnosed using a review of the patient's medical history, a physical exam, and a lung function test that measures the strength of a person's breathing.

Nitric oxide is a gas that is present at low levels in the lungs but that may be present in larger quantities when the airways are inflamed (a condition that is often associated with asthma). The fractional exhaled nitric oxide (FeNO) test may help in the diagnosis and management of asthma by measuring the amount of nitric oxide in the breath.

This health technology assessment looked at how accurate, effective, and cost-effective FeNO testing is for children and adults who have or may have asthma. It also looked at the budget impact of publicly funding FeNO testing and at the experiences, preferences, and values of people with asthma.

What Did This Health Technology Assessment Find?

For asthma diagnosis, we found that FeNO testing was more reliable in correctly identifying people who have asthma (i.e., low number of false positives) and therefore a positive result on the test could be used in addition to standard testing to "rule in" an asthma diagnosis in both children and adults. FeNO testing was less reliable in correctly identifying people who do not have the condition (i.e., high number of false negatives), so a negative result could not be used to "rule out" an asthma diagnosis. Using FeNO testing to help monitor and manage asthma resulted in a reduction in the number of people who experienced worsening symptoms in children and adults, but it made little to no difference in improving other health outcomes like medication use, hospital visits, and quality of life.

We found that using FeNO testing in addition to standard testing in asthma diagnosis is cost-effective compared to standard testing in children, and in adults when a higher FeNO cut-off is applied. We estimated that publicly funding FeNO testing over the next 5 years for asthma diagnosis would cost about $0.10 million to $0.22 million for children and $1.19 million to $1.61 million for adults (depending on the testing method adopted). We found that including FeNO testing in the monitoring and management of asthma would be more costly and have a minimal impact on health-related quality of life in both children and adults. We estimate that publicly funding FeNO testing to monitor and manage asthma over the next 5 years would cost about $22.37 million for children and $196 million for adults.

People we spoke with were unaware if they had experience with FeNO testing because of its similarity to other types of asthma testing, but they expressed valuing the potential of FeNO testing to provide more information about their condition as well as aid in the diagnosis and management of asthma.

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Abstract

Background

Asthma is a common respiratory disease characterized by airflow obstruction caused by inflammation and narrowing of the airways. Nitric oxide is a gas that is present at low levels in the lungs, but that is elevated in the presence of airway inflammation. Fractional exhaled nitric oxide (FeNO) testing may help in the diagnosis and management of asthma by measuring the amount of nitric oxide in the breath. We conducted a health technology assessment of FeNO testing for the diagnosis and management of asthma in children and adults, which included an evaluation of the accuracy, effectiveness, cost-effectiveness, the budget impact of publicly funding FeNO testing, and patient preferences and values.

Methods

We performed a systematic literature search of the clinical evidence. We assessed the risk of bias of each included study using the Quality Assessment of Diagnostic Accuracy Studies tool, version 2 (QUADAS-2) and of each systematic review using the Risk of Bias Assessment Tool for Systematic Reviews (ROBIS). We evaluated the quality of the body of evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. We performed a systematic economic literature search and conducted cost–utility analyses with a 20-year time horizon from a public payer perspective. We also analyzed the budget impact of publicly funding FeNO testing in children and adults in Ontario. To contextualize the potential value of FeNO testing, we spoke with people with asthma and their care partners.

Results

We included 48 primary studies assessing the diagnostic accuracy of FeNO testing and 2 reviews evaluating the effectiveness of FeNO testing for asthma management in the clinical evidence review. The use of FeNO testing for the diagnosis of asthma reported variable (~30% to 90%) sensitivities (GRADE: Very low) and consistently high (~70% to 100%) specificities (GRADE: Low) in children and adults. FeNO testing for asthma management likely reduced exacerbations in children (GRADE: Moderate) and adults (GRADE: Moderate), lowered oral corticosteroid use in children (GRADE: Moderate), and slightly improved lung function in a mixed population (GRADE: Moderate), but little to no improvement was seen in other outcomes. We found that, for asthma diagnosis, FeNO testing in addition to standard testing is cost-effective in children, with an incremental cost-effectiveness ratio (ICER) of $6,192 per quality-adjusted life-year (QALY) gained. FeNO testing is not cost-effective for asthma diagnosis in adults except when a higher FeNO cut-off is applied. For asthma management, the ICER of FeNO testing compared with standard care alone is $103,893 per QALY gained in children and $200,135 per QALY gained in adults. Publicly funding FeNO testing as an adjunct to standard testing for asthma diagnosis over the next 5 years would cost about $0.10 million to $0.22 million for children and $1.19 million to $1.61 million for adults over the next 5 years, and for asthma management would cost about $22.37 million for children and $195.99 million for adults over the next 5 years. Participants were unaware if they had experience with FeNO testing because of its similarity to other types of asthma testing, but they reported valuing the potential of FeNO testing to provide more information about their condition as well as aid in the diagnosis and management. Barriers to access include lack of awareness and the limited availability of FeNO testing across the province.

Conclusions

We found that FeNO testing had good diagnostic specificity (i.e., low false positive rate), supporting its use as an adjunct to standard testing to help rule-in an asthma diagnosis in both children and adults. FeNO testing to monitor and manage asthma likely resulted in a reduction in the number of people who experienced exacerbations and used oral corticosteroids, but may make little to no difference in improving other health outcomes. FeNO testing is likely cost-effective as an additional test to support the diagnosis of asthma in children, as well as in adults when a higher FeNO cut-off is applied, but is likely not cost-effective as an additional test to monitor and manage asthma in both children and adults. We estimate that publicly funding FeNO testing as an adjunct to standard testing for asthma diagnosis in Ontario would result in additional costs of $0.10 million to $0.22 million for children and $1.19 million to $1.61 million for adults over the next 5 years. For monitoring and managing asthma, FeNO testing would result in additional costs of $22.37 million for children and $195.99 million for adults over the next 5 years. People we spoke with were unaware if they had experience with FeNO testing because of its similarity to other types of asthma testing, but they reported valuing the potential of FeNO testing to provide more information about their condition as well as aid in the diagnosis and management of asthma.

Table of Contents

List of Tables

List of Figures

Objective

This health technology assessment evaluates the accuracy, effectiveness, and cost-effectiveness of fractional exhaled nitric oxide (FeNO) testing for the diagnosis and management of children and adults with asthma. It also evaluates the budget impact of publicly funding FeNO testing and the experiences, preferences, and values of people with asthma.

Background

Health Condition

Asthma is a chronic respiratory disease characterized by variable airflow obstruction. People with asthma are more sensitive to airway stimuli that can cause inflammation of the lungs, narrowing of the airways, and an increase in mucus production, making it difficult to breathe. Other common symptoms of asthma include coughing, wheezing, and chest tightness. The severity of asthma symptoms can vary from minor to life-threatening and can fluctuate over time. Although asthma has no cure, its symptoms can be controlled.[1,2]

As research has progressed, the understanding of the molecular pathways of asthma has expanded and clinical decision-making has advanced accordingly. Although long thought to be a single disease, recent studies have focused on asthma's heterogeneity.[3,4] Asthma is now considered an umbrella term that describes a complex condition with distinct disease pathways (endotypes) further grouped by common clinical characteristics (phenotypes).[4,5]

Asthma is commonly classified into two broad endotypes: type 2 (T2)-high and T2-low asthma. The more commonly occurring T2-high endotype is characterized by the presence of eosinophilic airway inflammation. There are several T2-high asthma phenotypes described in the literature with related but distinct mechanisms of action, while T2-low asthma phenotypes are still poorly understood and may be manifested by neutrophils, bacteria, or endothelial dysfunction.[5]

The complexity of asthma and the clinical diversity in people with asthma means there may not be one standard test or care pathway that works for all, which is an important consideration when developing best practices for diagnosis and treatment in this population.

Clinical Need and Population of Interest

Asthma is the most common respiratory condition and the third most common chronic condition in Canada. Asthma affects 3.8 million people in Canada, of which 850,000 are children under the age of 14. On average, 317 people in Canada are newly diagnosed with asthma every day and 250 lose their lives to asthma each year.[6]

In Ontario, 1,073,600 people over 12 years of age reported being diagnosed by a health professional as having asthma in 2020.[7] The annual incidence of asthma in the province has declined from about 9% to 4% from 1996 to 2018, while the prevalence of asthma has grown from about 9% to 16% in the same period.[8] These numbers suggest that although fewer people are being diagnosed with asthma each year, more people are living with asthma for longer. The rate of hospitalization and emergency department

visits related to asthma, as well as the number of OHIP claims are on a steady drop over the last 20 years. Asthma mortality (1.1 per 100,000 people in Ontario in 2000) has been cut in half, to about 0.55 per 100, 000 in 2018.[8]

Although these numbers suggest that asthma care in Ontario is improving, concerns remain around misdiagnosis and poor control of the disease. In a 2017 study, 33% of people who were diagnosed with asthma did not actually have asthma when objective tests were administered and medication tapered off,[9] highlighting the importance of objective testing to prevent unnecessary treatment and health care spending. In addition, a study from 2011[10] suggested that over 50% of people with asthma in Canada do not have good control of the disease. Poor asthma control increases the burden on the health care system and contributes to lowered quality of life.[1,11]

Current Clinical Care Pathways

Asthma care can be divided into two broad categories: diagnosis and management. Ontario Health has published quality standards for the diagnosis and management of asthma in children[12] and in adults[13] in the primary care setting for the province, as summarized below.

Diagnosis

Asthma diagnosis in primary care generally consists of 3 components: a person's medical history, a physical exam, and an objective lung function test (simplified clinical pathway adapted from Ontario's Primary Care Asthma Program[2] shown in Figure 1). In Ontario, spirometry is the preferred objective test. Spirometry is a pulmonary function test that measures the speed and amount of air exhaled in one forced breath and can show reversible airflow obstruction. The test is performed before and after an inhaled bronchodilator. First to demonstrate that airway obstruction exists, and second to show that the airway obstruction is reversed with the administration of inhaled mediation. If spirometry is not available, peak expiratory flow measurements can be used as an alternative method to support a diagnosis of asthma by assessing airflow variation over a period (e.g., 2 weeks).

A diagnosis of asthma is supported by the successful airway reversibility or improvement in peak flow in response to bronchodilator administration, but a negative spirometry result does not rule out asthma. Spirometry testing can have low sensitivity, and it is estimated that as many as 60% of people who have asthma have also had normal or inconclusive spirometry tests.[14] In these instances, a positive challenge test (also known as a bronchial provocation test) is used to confirm an asthma diagnosis.

The methacholine challenge test is the most used bronchial provocation test in Ontario, and it is the most complicated of the lung function tests. It measures airflow at baseline and after inhaling increasing doses of methacholine (which mimics the histamines released during an allergic reaction) to test hyperresponsiveness. The methacholine challenge test requires preparation (e.g., inhaled corticosteroids should be withheld for 4–8 weeks prior to administering) and can cause increased symptoms or a negative reaction.

Although objective testing is universally recommended, sometimes asthma diagnoses are made on clinical assessment alone, which can lead to misdiagnosis (both over and underdiagnosis). In the case of acute or severe symptoms or long wait times, treatment or trial medication may be prescribed immediately based on clinician assessment, but a follow-up objective test to confirm the asthma diagnosis is highly recommended. It should be noted that there are some scenarios in which this recommendation may not be feasible due to barriers such as age, illness, or distance from a testing site.

There are three points in the current care pathway where additional objective testing may help improve asthma diagnosis: 1) before spirometry as an initial test when assessing clinical symptoms in office, 2) with spirometry during the same lab visit, or 3) after a normal or inconclusive spirometry result and before a challenge test is considered (Figure 1).

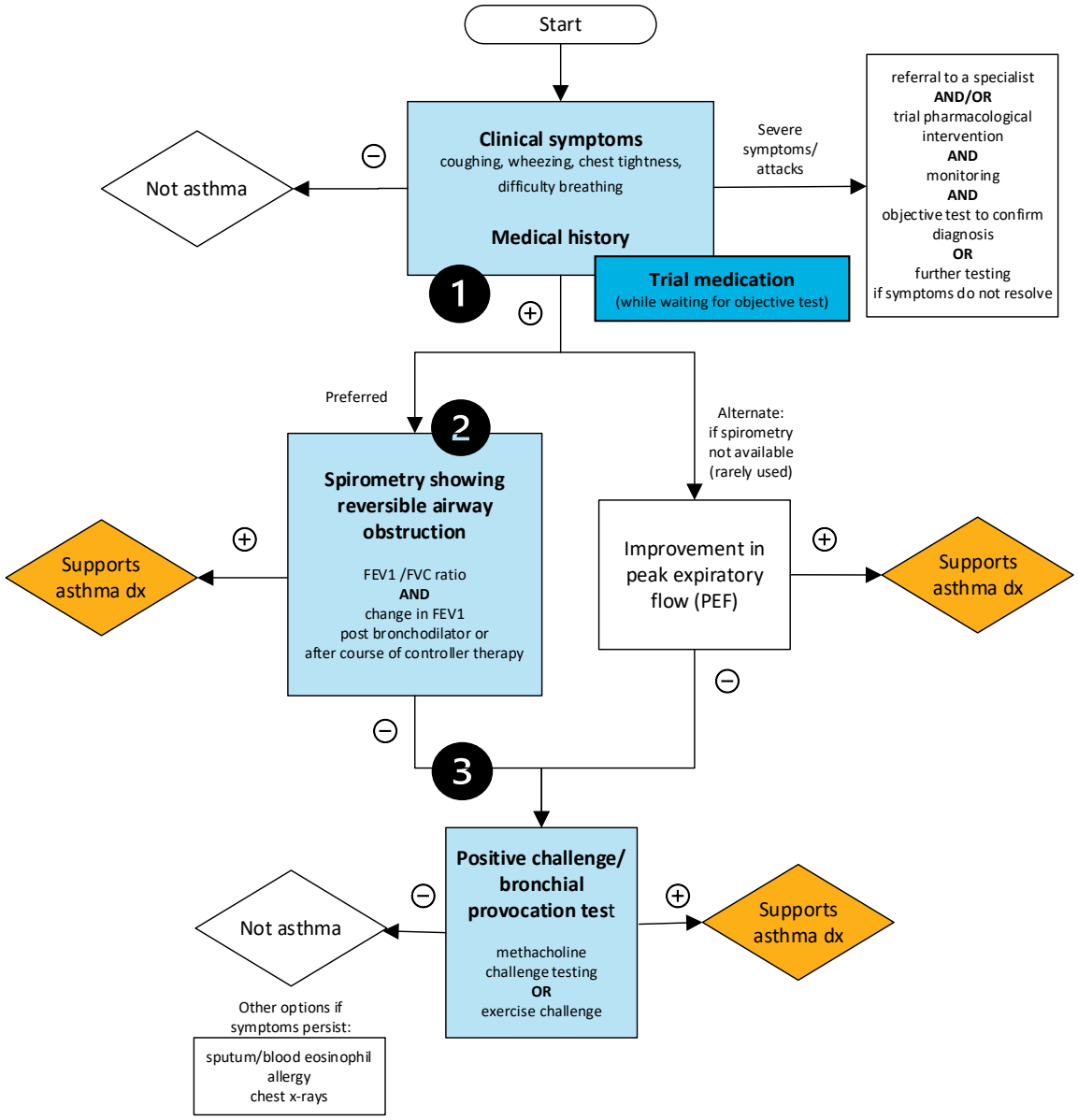


Figure 1: Asthma Diagnosis Pathway for Primary Care in Ontario

Chart showing the diagnostic pathway followed by a patient suspected of having asthma. First, a person presents with physical symptoms (coughing, wheezing, chest tightness, difficulty breathing). Depending on the severity, they may be put on medication immediately, before objective testing is completed. The preferred next step is spirometry. If spirometry is negative, then they would undergo a positive challenge/bronchial provocation test. If both are negative, then asthma is ruled out.

Management

Asthma management in primary care involves a combination of education with the development of an asthma action plan, pharmacological intervention, and regular monitoring and assessment of asthma control. Referral to specialized care (e.g., respirologist, allergist, therapist, asthma educator) is considered in the case of asthma that is severe, difficult to diagnose, uncontrolled, or results in acute exacerbations or hospital admissions.

People with asthma and their care partners are educated in several areas to support self-management. Areas addressed include medication adherence and inhaler technique, smoking cessation counselling, management of comorbidities, and identifying and avoiding triggers to prevent exacerbations. A written individualized asthma action plan, developed in collaboration with a health care professional, outlines ways to maintain asthma control and how to identify and respond when experiencing a period of uncontrolled asthma.

Medications and devices are offered to those with a confirmed asthma diagnosis based on their current level of asthma control; treatment is escalated and de-escalated as needed. To effectively prescribe and adjust medications, it is important that asthma control indicators (e.g., symptoms, lung function, and airway inflammation) are assessed on a regular basis. Ontario Health's Quality Standard[13] suggests validated symptom control questionnaires as well as spirometry be conducted at least annually to assess changes in control and to predict the likelihood of exacerbations. People with uncontrolled moderate to severe asthma who are in the care of specialists should have their inflammation assessed using sputum eosinophil levels.

Although the recommended symptom control questionnaires can be readily administered by primary care physicians, our clinical experts noted that yearly spirometry measurements are not always accessible and that there is a growing gap between current practice and the recommended yearly testing. According to experts, the wait time for a test, especially following the pandemic, can be 3 to 4 months in certain parts of the province (if available at all), which can make it challenging to effectively monitor, adjust, and control asthma in Ontario.

Health Technology Under Review

Nitric oxide is an endogenous gaseous molecule that is present at low levels in healthy individuals, but these levels can be elevated in the presence of airway inflammation and can decrease in response to corticosteroids. By measuring the level of nitric oxide in the lungs, fractional exhaled nitric oxide (FeNO) tests can help diagnose airway inflammation (mostly as a rule-in test using established cut-off values in parts per billion [ppb]) and predict responsiveness to medication.[15,16] Although acceptable cut-offs vary between devices and administrators, people with uncontrolled or undiagnosed symptomatic asthma generally have FeNO levels above 25 ppb in children and 30 ppb in adults. However, some international guidelines recommend the use of cut-offs greater than 35 ppb in children and 45 ppb in adults (see Table 1 for guideline recommendations).[17,18]

Table 1: Optimal FeNO Cutoff Values Recommended by Clinical Guidelines

Clinical guidelines	Recommended FeNO Cutoff
NICE, 2017[19]	In adults (aged ≥ 17 years), a FeNO level ≥ 40 ppb In children (aged 5–16 years), a FeNO level ≥ 35 ppb
US NHLBI, 2020[20]	In adults: • < 25 ppb is considered negative • 25–50 ppb is considered inconclusive • > 50 ppb is considered positive In children (aged 5–12 years): • < 20 ppb is considered negative • 20–35 ppb is considered inconclusive • > 35 ppb is considered positive
European Respiratory Society, 2022[21]	A cutoff value of 40 ppb offers the best compromise between sensitivity and specificity, while a cutoff of 50 ppb has a high specificity (> 90%) and is supportive of a diagnosis of asthma A FeNO value < 40 ppb does not rule out asthma and similarly high FeNO levels themselves do not define asthma

Abbreviation: FeNO, fractional exhaled nitric oxide; NHLBI, National Heart, Lung, and Blood Institute; NICE, National Institute for Health and Care Excellence.

A FeNO test is a relatively quick and non-invasive test that can be used by most people over 5 years of age[22] (some children under age 8 struggle to use the test). When administering the test, individuals are asked to gently blow into a disposable handheld device attached to a base with a digital display that displays the NO level. It is recommended that the test be administered by a health care professional with sufficient training as the device requires calibration and the use of an acceptable expiratory flow rate and exhalation period. The benefits of the FeNO testing devices are that they can be administered in most health care settings without extensive training, are non-invasive, and provide immediate results to support asthma care decisions.[23]

It is important to note that, unlike traditional lung function tests that measure airway obstruction or hyperresponsiveness, FeNO tests measure elevated NO caused by inflammation in the lungs. Elevated NO is not present in all asthma phenotypes and is also not unique to asthma. Some factors (e.g., smoking, infection) can lower NO levels in people with asthma, while other non-asthma conditions (e.g., bronchitis) can cause an increase in NO levels.[17,23-25]

There are two types of FeNO devices available for use. Stationary devices usually measure FeNO levels using chemiluminescence techniques and include the NIOX Flex and Ecomedics analyser CLD 88, while handheld devices measure FeNO levels using an electrochemical system like the NIOX Mino, NIOX Vero, NObreath, and Vivatmo pro devices.[16,26]

Regulatory Information

Health Canada has approved the following portable FeNO devices for use by trained health care providers to monitor and manage airway inflammation and response to therapy in people (approximately > 7 year of age) with diagnosed asthma, as an adjunct to the established clinical and laboratory assessments:

1. The NIOX VERO system (Licence No: 98844)
2. The NIOX MINO airway inflammation monitor (Licence No: 80559)

FeNO devices are currently not indicated for use as a diagnostic tool by Health Canada. In addition, they are not recommended for use in critical care, emergency care, or in anesthesiology (Medical Devices Directorate, Health Canada; email communication, July 21, 2022).

Ontario, Canadian, and International Context

Although licensed for use in Canada, FeNO testing is not commonly used in Ontario. Hospitals choosing to use the test cover the cost of the device, as well as clinician and technician fees, through their hospital-specific budgets or by billing patients directly for the service. Similarly in Quebec, a study team reached out to 7 local hospitals and found only 2 perform FeNO testing: 1 for routine management along with standard asthma care and the other for phenotyping of severe asthma, prescription of biologic agents, and assessment of adherence to treatment.[27]

The 2012 Canadian Thoracic Society (CTS) assessed the use of FeNO testing for the management of asthma and did not find sufficient evidence to recommend the routine use of the test, but did suggest FeNO testing could be used to characterize severe asthma phenotypes to help guide management decisions in this population. The CTS did not conduct an evaluation of the accuracy of FeNO testing as a diagnostic tool, but it was noted as a question for future exploration.[28-30]

Internationally, FeNO testing has been widely used for asthma diagnosis and management standards of care (Figure 2) with varying indications for use across different guidelines and geographical areas. The latest European Respiratory Society guideline recommends the use of FeNO testing for the diagnosis of asthma following an uncertain spirometry and bronchodilator reversibility test in adults and as a first-line test in children.[21,31] The National Institute for Health and Care Excellence (NICE) also recommends the use of FeNO testing as a first-line test combined with spirometry in adults, but for children, only if there is diagnostic uncertainty after an initial test.[19] Finally, the American National Heart, Lung, and Blood Institute (NHLBI) recommends the measurement of FeNO levels in both children and adults only if the diagnosis of asthma is uncertain after initial assessment or if spirometry cannot be performed.[20] Clinical guidelines recommending FeNO testing for the diagnosis of asthma in children and adults have also been published by groups in Mexico[32] and Korea.[33]

Conversely, the 2021 Global Initiative for Asthma (GINA) guideline update recommends against FeNO testing as a diagnostic tool for asthma but, like the CTS guidelines, supports its use to phenotype people with severe asthma and as an indicator of response to treatment.[24] NICE also does not recommend the routine use of FeNO testing to monitor asthma control, but recognizes the test as an option to manage asthma in people who are symptomatic despite using inhaled corticosteroids.[19] The American Thoracic Society (ATS) guidelines are more broadly supportive of the use of FeNO testing in the management of people with asthma who are considering treatment in addition to usual care,[34] and the NHLBI guidelines

state that FeNO testing should be used only as part of an ongoing monitoring and management strategy and never in isolation.[20]

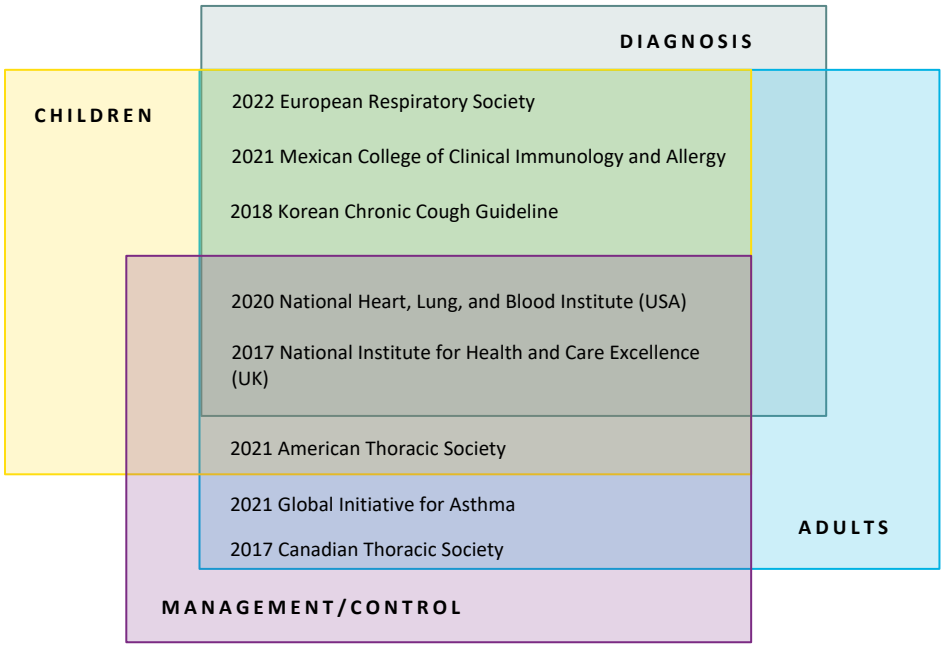


Figure 2: International Clinical Guidelines, Which Include FeNO Testing for Asthma Diagnosis and Management in Children and Adults

Chart showing different society guidelines, divided by category. For diagnosis of children and adults, the Korean Clinical Cough Guideline (2018), the Mexican College of Clinical Immunology and Allergy guideline (2021), and the European Respiratory Society guideline (2022). For diagnosis and management for children and adults, the National Institute for Health and Care Excellence guideline (2017) and the National Heart, Lung, and Blood Institute guideline (2020). For management for children and adults, the American Thoracic Society guideline (2021). For management for adults, the Canadian Thoracic Society guideline (2017) and the Global Initiative for Asthma guideline (2021).

Equity Context

We use the PROGRESS-Plus framework[35] to help explicitly consider health equity in our health technology assessments. PROGRESS-Plus is a health equity framework used to identify population and individual characteristics across which health inequities may exist. These characteristics include place of residence; race or ethnicity, culture or language; gender or sex; disability; occupation; religion; education; socioeconomic status; social capital; and other key characteristics that stratify health opportunities and outcomes. We considered equity issues across the different categories in the PROGRESS-Plus framework and did not identify any potential health inequities related to the use of FeNO testing in Ontario. However, timely access to specialists and objective testing labs to diagnose and manage asthma can be a challenge in certain geographical locations, impacting the care received by the residents of these areas. Currently, FeNO testing is not part of standard care for asthma, but if FeNO testing is found to be effective, it will make another objective test available to Ontarians and potentially offer improved access to care.

Expert Consultation

We engaged with experts in the areas of asthma diagnosis and management, including relevant associations, primary care physicians, respirologists and those with experience using FeNO testing and/or knowledge of the research literature, to help inform our understanding of aspects of the health technology and our methodologies and to contextualize the evidence.

PROSPERO Registration

This health technology assessment has been registered in PROSPERO, the international prospective register of systematic reviews (CRD42023389649), available at crd.york.ac.uk/PROSPERO.

Clinical Evidence

Research Questions

1. What is the diagnostic accuracy of fractional exhaled nitric oxide (FeNO) testing (alone or as an add-on) compared with standard testing used for diagnosis in people with suspected asthma?

2. What is the clinical effectiveness of using FeNO testing (alone or as an add-on) compared with standard care to monitor and manage people with diagnosed asthma?

Methods

Clinical Literature Search

We performed a clinical literature search on October 6, 2022, to retrieve studies published from January 1, 2010, until the search date, to address both research questions. The starting date limit was chosen in consultation with clinical experts considering the number of existing published reviews capturing older evidence that can be leveraged and the recent updates made to international guidelines. We used the Ovid interface in the following databases: MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and the National Health Service Economic Evaluation Database (NHS EED). We used the EBSCOhost interface to search the Cumulative Index to Nursing & Allied Health Literature (CINAHL).

A medical librarian developed the search strategies using controlled vocabulary (e.g., Medical Subject Headings) and relevant keywords. The final search strategy was peer-reviewed using the PRESS Checklist.[36]

We created database auto-alerts in MEDLINE, Embase, and CINAHL and monitored them until May 2023. We also performed a targeted grey literature search of the International HTA Database, the websites of health technology assessment organizations and regulatory agencies, and clinical trial and systematic review registries, following a standard list of sites developed internally. See Appendix 1 for our literature search strategies, including all search terms.

Literature Screening

Two reviewers screened titles and abstracts to assess the eligibility of a sample of 100 citations to validate the inclusion and exclusion criteria of both research questions (below). A single reviewer then screened all remaining citations using Covidence[37] and then obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. A single reviewer then examined the full-text articles and selected studies eligible for inclusion.

Review Approach

There was a single literature search conducted; however, the inclusion criteria and methods differed between the 2 research questions. Question 1 focused on the diagnosis of asthma with a defined index test, target condition, and reference standard. Question 2 specified the relevant intervention and comparators as inclusion criteria.

We took a hierarchical approach to the screening process, prioritizing systematic reviews (including meta-analyses and health technology assessments that included a systematic review) of studies that matched our research questions. In this report, we will first present the eligibility criteria and methods for research question 1, followed by the methods used for research question 2.

Research Question 1: Asthma Diagnosis

Eligibility Criteria

Studies

Inclusion Criteria

- English-language full-text publications
- Systematic reviews or health technology assessments published since January 1, 2010
- Diagnostic accuracy studies published after the search date of the latest review (2018)

Exclusion Criteria

- Animal and in vitro studies
- Non-systematic reviews, narrative reviews, non-comparative studies, conference abstracts, editorials, letters, case reports, and commentaries

Participants

Inclusion Criteria

- People over 5 years of age presenting with clinical symptoms suggestive of asthma (e.g., shortness of breath, chest tightness, wheezing, and/or cough)

Exclusion Criteria

- Children 5 years of age or younger (who are judged too young to undergo objective testing) and people previously diagnosed with asthma and/or receiving treatment for asthma during objective testing

Index Tests

Investigational Test

- FeNO, measured with an acceptable expiratory flow rate and exhalation time for the device being used
- Use of co-interventions (e.g., education, lung function tests, etc.) to be included if there is equal access in each group

Comparators

- Pulmonary function tests, including any combination of spirometry, bronchodilator reversibility, peak expiratory flow variability, challenge tests, induced sputum

Target Condition

- Asthma diagnosis

Reference Standard

- Clinician diagnosis of asthma (with or without objective testing)

Accuracy Measures

- Sensitivity
- Specificity
- Positive/negative predictive values (secondary)

Test Cut-Off

- Positive and negative results for tests defined by study authors

Data Extraction

We extracted relevant data on study characteristics and risk-of-bias items using a data form to collect information on the following:

- Source (e.g., citation information, study type)
- Methods (e.g., objective, study design, country of conduct, clinical setting, population, index test, reference standards, risk-of-bias items)
- Outcomes (e.g., number of participants, asthma prevalence, diagnostic accuracy outcomes measured, unit of measurement, test cut-off values)

Statistical Analysis

One reviewer assessed the presence and extent of heterogeneity and considered this when interpreting the results. Due to significant variation in study design and eligibility criteria in the included studies, a meta-analysis was not deemed appropriate and a narrative summary and analysis of results was reported.

Subgroup Analyses

We planned to report subgroup analyses of the following groups, if possible: age (children, adults), severe/hard to diagnose asthma (as defined and reported in the studies), smoking status, pregnancy status, diagnostic reference standards, study design, clinical setting, and/or timing of intervention to see if these subgroups can explain the differences seen in the data and to highlight gaps in the current literature. We were able to subgroup by age (i.e., children, adults, mixed ages) and present a narrative summary of the following subgroups: studies of low risk of bias and high applicability to Ontario, asthma sub-populations, clinical settings, device brand/manufacturers, timing of FeNO interventions, and diagnostic reference standards. We were not able to analyze subgroups by severity, smoking status, or pregnancy status as they were not well reported in the included studies.

Critical Appraisal of Evidence

We assessed the risk of bias using QUADAS-2 for diagnostic accuracy studies. We then evaluated the quality of the body of evidence for each outcome according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) handbook. The body of evidence was assessed based on the following considerations: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The overall rating reflects our certainty in the evidence.

Research Question 2: Asthma Management

Eligibility Criteria

Studies

Inclusion Criteria

- English-language full-text publications
- Systematic reviews or health technology assessments published since January 1, 2010

Exclusion Criteria

- Animal and in vitro studies
- Non-systematic reviews, narrative reviews, non-comparative studies, conference abstracts, editorials, letters, case reports, and commentaries

Participants

Inclusion Criteria

- People over 5 years of age with clinician-diagnosed asthma (with or without objective testing) that is controlled or uncontrolled

Exclusion Criteria

- Children 5 years of age or younger (who are judged too young to undergo objective testing) and people without an asthma diagnosis

Interventions

Inclusion Criteria

- FeNO, measured with an acceptable expiratory flow rate and exhalation time for the device being used for asthma monitoring and management
- Use of co-interventions (e.g., education, lung function tests, etc.) to be included if there is equal access in each group

Exclusion Criteria

- Expiratory flow rate or exhalation time less than the recommended cut-offs for the device, co-interventions only offered to one group, use of nasal or alveolar NO

Comparators

Inclusion Criteria

- Asthma management strategies without the use of FeNO testing (including any combination of clinical symptom assessment, asthma control questionnaires, education interventions, lung function tests, airway inflammation tests, challenge tests, etc.)

Exclusion criteria

- Management strategies that include FeNO testing

Outcome Measures

- Asthma control assessed through:
  - Asthma Control Test [ACT]
  - Asthma Control Questionnaire [ACQ]
  - Lung function tests
  - Airway inflammation tests
  - Use/adjustment/stoppage of inhaled corticosteroids
  - Exacerbation rate
  - Use of oral corticosteroids
  - ED/unscheduled hospitalizations due to asthma
  - Symptom-free days
  - Time off work/school
  - Quality of life measures

Data Extraction

We extracted relevant data on review characteristics and risk-of-bias items using a data form to collect information on the following:

- Source (e.g., citation information, study type)
- Methods (e.g., objective, study design, country of conduct, population, intervention, comparators, risk-of-bias items)
- Outcomes (e.g., asthma control outcomes measured, outcome definition and source of information, number of participants, unit of measurement, variance)

Statistical Analysis

We identified recent reviews that answered this research question and we reported their meta-analysis and narrative results. If reviews combined results for children and adults, we conducted a population-based sensitivity analysis by pooling studies in children and adults separately using the Meta Analysis Shiny App.[38]

Subgroup Analyses

We planned to report subgroup analyses of the following groups: age (children, adults), severe/hard to diagnose asthma (as defined and reported in the studies), smoking status, pregnancy status, diagnostic reference standards, study design, clinical setting and/or timing of intervention to see if these subgroups can explain the differences seen in the data and to highlight gaps in the current literature. We were able to present data only by age (i.e., children and adults) and were unable to present any other equity-related subgroup analysis because information on the effect of asthma management including FeNO testing across different populations was not reported in the included systematic reviews.

Critical Appraisal of Evidence

We assessed the risk of bias of the included systematic reviews using the Risk of Bias in Systematic Reviews (ROBIS) tool (Appendix 6). When the reviews included the quality of the body of evidence for each outcome according to the GRADE handbook,[39] it was reported in the HTA. The body of evidence was assessed based on the following considerations: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The overall rating reflects our certainty in the evidence.

Equity Considerations

We sought but did not identify any equity considerations relevant to the effect of FeNO testing in asthma management across different populations defined by the PROGRESS-Plus categories.[40] However, equity considerations may exist that were not identified as part of our analysis.

Results

Clinical Literature Search

The clinical literature search yielded 4,196 citations, including grey literature results and after the removal of duplicates, published between January 1, 2010, and October 6, 2022. We did not identify additional eligible studies from other sources, including database alerts (monitored until May 2023). Figure 3 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the clinical systematic review.

Asthma Diagnosis

In total, we identified 15 recent systematic reviews that met our inclusion criteria. However, we did not feel the eligibility criteria of any one review fit our research question or the Ontario context, and the overlap of included primary studies across the reviews was poor. See Appendix 2 for a table of the distribution and overlap of the 110 primary studies included across the 15 reviews. We decided to leverage the primary studies from these reviews and re-screen using our own eligibility criteria. We included 46 primary studies from these systematic reviews (see Appendix 7 for a list of studies excluded, with reasons for exclusion) and updated the list by including relevant studies published after 2018 (the search date of the most recent systematic review) from our literature search. We found an additional 27 studies, for a total of 73 studies of diagnostic accuracy.

Asthma Management

In total, we identified 8 recent systematic reviews (and 3 companion reports) that met our inclusion criteria.

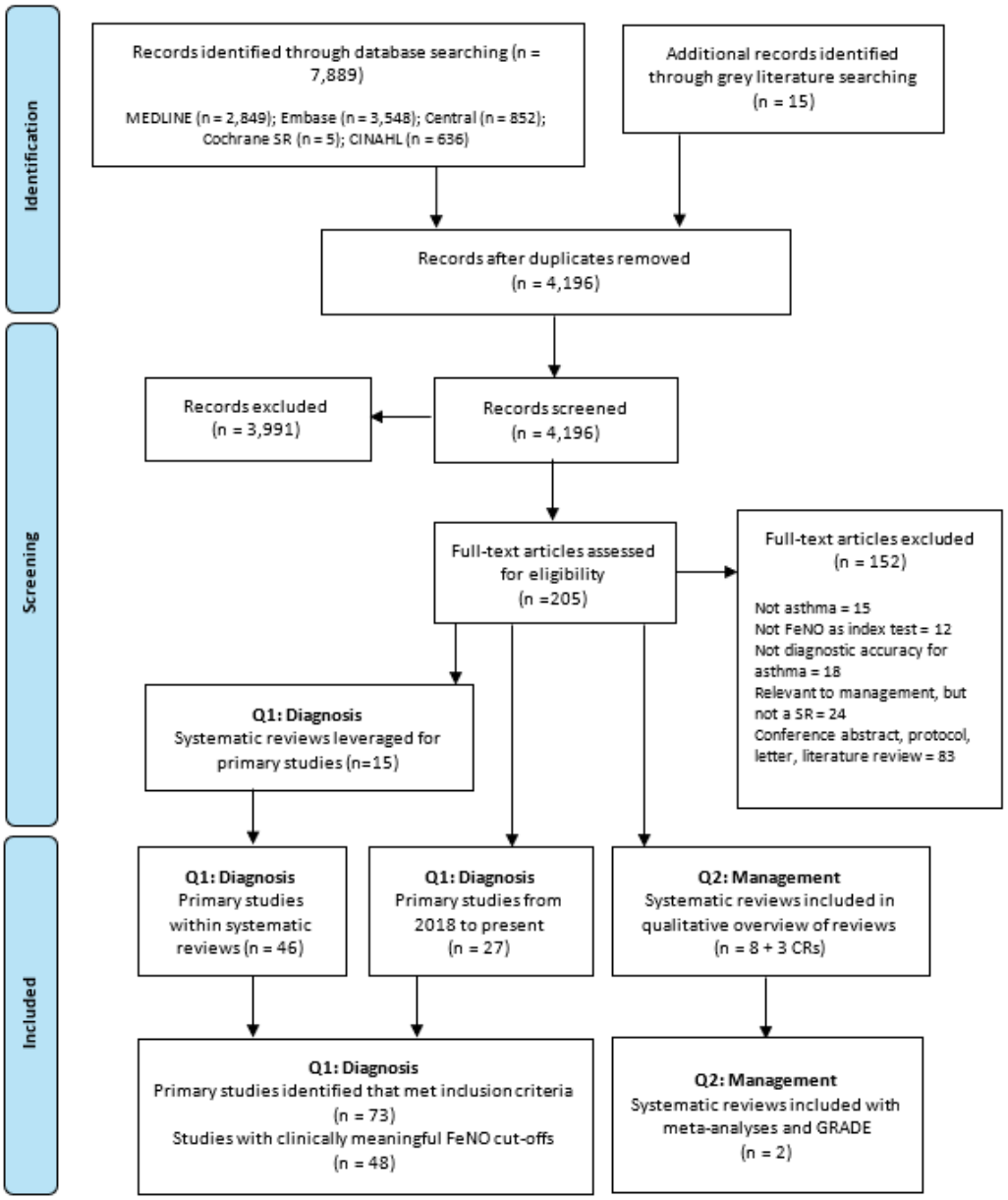


Figure 3: PRISMA Flow Diagram – Clinical Systematic Review

PRISMA flow diagram showing the clinical systematic review. The search of the clinical literature yielded 4,196 citations published between January 2010 and October 2022, including grey literature searches and after duplicates were removed. We screened the abstracts of the 4,196 identified studies and excluded 3,991. We assessed the full text of 205 articles and excluded a further 152. In the end, we included 73 primary studies for the diagnostic accuracy qualitative synthesis (Q1) and 8 systematic reviews (with 3 companion reports) for the management qualitative synthesis (Q2).

Abbreviations: CR, companion report; FeNO, fractional exhaled nitric oxide; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; SR, systematic review.

Source: Adapted from Page et al.[41]

Asthma Diagnosis

Characteristics of All Identified Studies

There were 73 primary studies identified that met the eligibility criteria. A summary of the characteristics of these studies can be found in Appendix 4. They were conducted in children (n = 21), adults (n = 40), and a mix of both populations (n = 12) to evaluate the accuracy of FeNO testing as a diagnostic tool for people with suspected asthma. The studies were published from 1999 to 2022 in different countries, with the majority from China (n = 10), Germany (n = 8), Japan (n = 7), and Poland (n = 5). Almost all studies were set in hospital or specialist clinics and, although the majority included people suspected of all asthma, some studies focused on specific asthma subgroups (i.e., cough variant asthma [n = 5], chest tightness variant asthma [n = 1], bronchial asthma [n = 4], and asthma in people with allergic rhinitis [n = 2]). The FeNO device brands most often reported in the studies were NIOX (n = 44), followed by Sievers (n = 9), CLD88 (n = 4), and NObreath (n = 2). The reference standards used in the identified studies were also heterogeneous and included spirometry with reversibility and bronchoprovocation using methacholine (n = 14), spirometry with reversibility and other forms of bronchoprovocation (n = 8), spirometry with reversibility (n = 6), and self-reported asthma diagnosis, symptoms, and medications used (n = 6).

The main outcomes of interest are the sensitivity (%) and specificity (%) of FeNO testing. The secondary outcomes, where available, were positive and negative predictive values. Detailed information on the characteristics and findings for each identified study are presented in Appendix 5.

The distribution of the sensitivities and specificities of the 73 identified studies are presented by population in Figure 4. The FeNO test sensitivities reported fall across nearly all ranges, with the largest group of studies reported in the range of 0% to 50%, with a smaller spike later in the distribution. For studies in either children or adults, this second most reported sensitivity range is 81% to 90%. Most studies with mixed populations not discernible by age report sensitivities within the range of 71% to 80%.

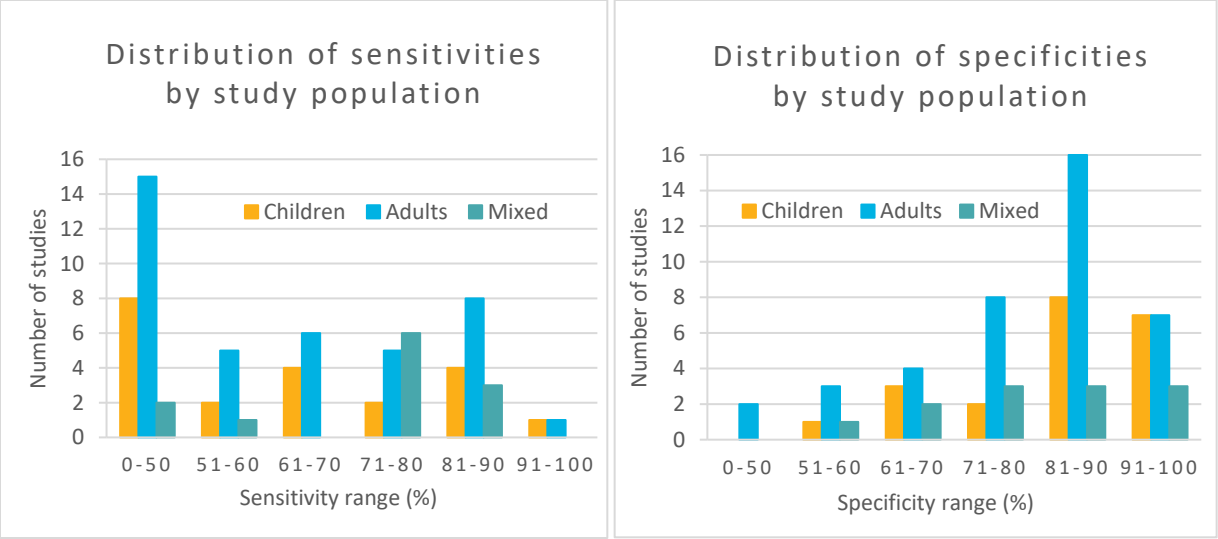


Figure 4: Distribution of Sensitivities and Specificities by Study Population (n = 73)

Bar charts showing distribution by study population of sensitivities and specificities in children, adults, and mixed populations. The largest category of studies in sensitivities for children and adults are in the 0% to 50% range and, for mixed populations, the 71% to 80% range. Most studies found sensitivities between 81% and 100%.

The specificities reported for the FeNO device follow a normal curve, with a skew towards higher specificity. Most studies across all populations report specificities within the 81% to 90% range, with almost no studies showing a specificity less than 50%. The second most common range was 91% to 100%, followed by 71% to 80%.

Selection of Included Studies Based on FeNO Cut-Off Levels

The FeNO cut-off levels reported in the studies ranged widely (> 7 to > 64 ppb). Of the 73 identified studies, 25 used cut-off values lower than those generally found in people with asthma (< 20 ppb in children; < 25 ppb in adults) and were not considered relevant for inclusion in our analysis.

Therefore, the focus of our analysis and findings is on the remaining 48 studies (15 in children, 26 studies in adults, and 7 mixed studies) evaluating clinically meaningful cut-offs as recommended by guidelines and clinical experts (> 35 ppb in children and > 45 ppb in adults), as well as FeNO cut-off levels that fall in between and that may potentially support an asthma diagnosis but should be interpreted within the clinical context (i.e., ≥ 20 to 35 ppb in children and ≥ 25 to 45 ppb in adults).

Risk of Bias in the Included Studies

We assessed the quality of the 48 included studies and their applicability to the Ontario healthcare context using the QUADAS-2 tool (Appendix 6, Table A5). For applicability to Ontario, we specifically considered study recency, whether a NIOX brand device (approved in Canada) was used, timing of the intervention, whether the reference standard included the spirometry and methacholine challenge tests (reflecting standard practice in Ontario), and whether limitations were placed on the type of asthma included. While there were general concerns with bias due to poor reporting of patient selection, blinding, and reference standards, several studies in children and in adults were found to represent good reporting quality with low applicability concerns. The certainty of evidence from the studies was

assessed using GRADE and was rated as Very low for sensitivity (downgraded for risk of bias, imprecision, and inconsistency) and Low for the reported specificity values (downgraded for risk of bias and imprecision) (Appendix 6, Table A7).

Findings of Included Studies

All 48 included studies were plotted using false positive rates (i.e., 100 − specificity) on the x-axis and sensitivities on the y-axis (see Figure 5 and Table 2). Except for a few outliers, most studies for all populations reported sensitivity values between 30% and 90% and specificity values greater than 70% (boundaries denoted on the figure by black dashed lines).

Seven studies including both children and adults were grouped in the mixed category in Figure 5.[42-48] Sensitivities in this group ranged from 35% to 78.6%, with a median of 74.3%. Specificities were between 60% and 95%, with a median value of 89%.

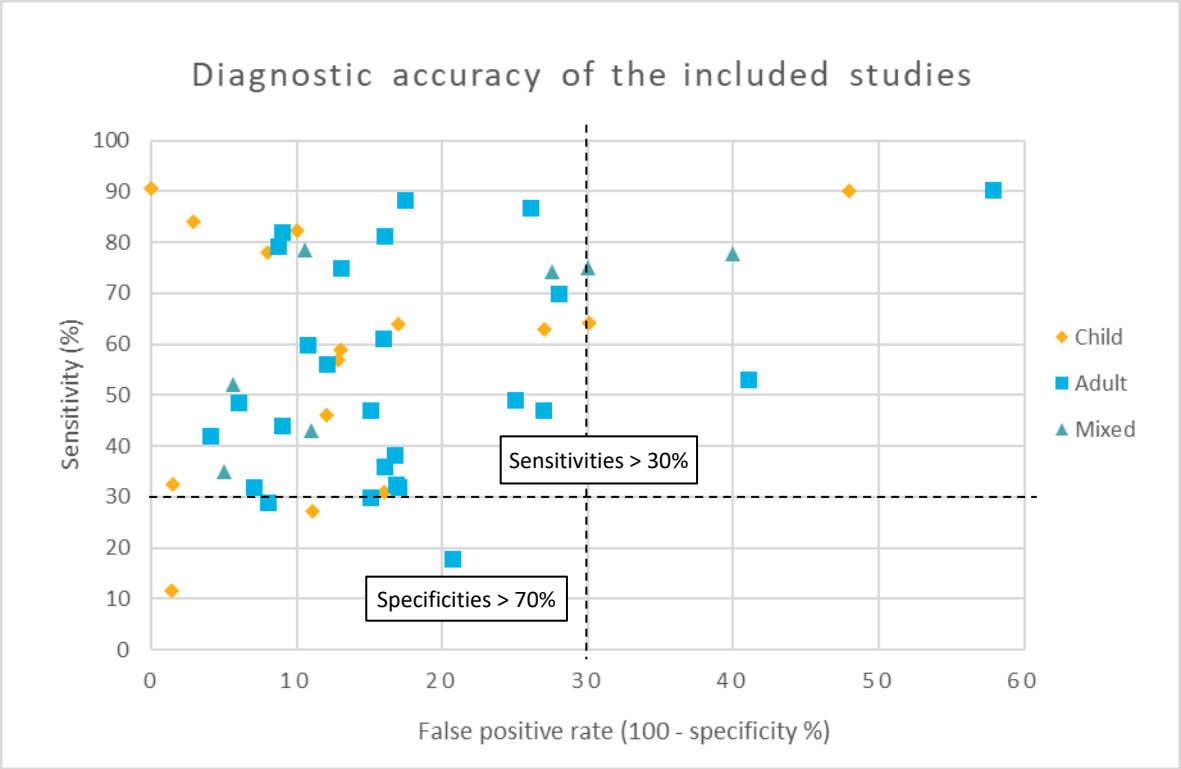


Figure 5: Diagnostic Accuracy (Sensitivity and False Positive Rates) in All Included Studies (n = 48)

Quadrant chart showing the diagnostic accuracy of 48 included studies with children, adult, or mixed populations. 44 studies found a sensitivity ≥ 30%, while 44 studies showed a false positive rate (100 – specificity) ≤ 30%. (None of the four studies showing ≤ 30% sensitivity also showed ≥ 30% false positive.)

Children aged 5 to 18 years with FeNO cut-off levels from 20 to 35 ppb were reported in 15 studies.[49-63] Sensitivities ranged from 11.6% to 90.7%, with a median sensitivity of 59%. the specificities ranged from 52% to 100%, with a median value of 88%. No studies reported optimal FeNO cut-off levels (> 35 ppb; Figure 6).

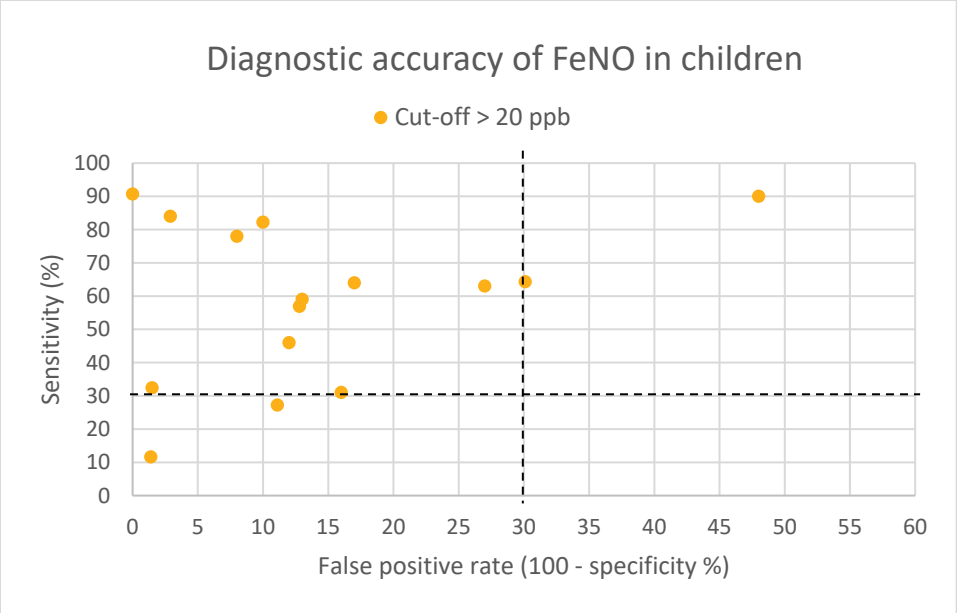


Figure 6: Diagnostic Accuracy in Studies of Children Aged 5–18 Years (n = 15)

Quadrant chart showing the diagnostic accuracy of 15 studies in children. 11 studies showed sensitivity rates ≥ 40%, while 14 studies showed false positive rates (100 – specificity) ≤ 30%.

Adults aged 18 and older with FeNO cut-off levels from 25 to 45 ppb were reported in 21 studies.[64-84] Sensitivities ranged from 17.9% to 88.3%, with a median sensitivity of 49%. Specificities ranged from 59% to 94%, with a median value of 84%. Five studies reported FeNO cut-off levels > 45 ppb, with sensitivities ranging from 29% to 90.4%, with a median of 42%, and specificities ranging from 42.2% to 96%, with median value of 92% (Figure 7).[85-89]

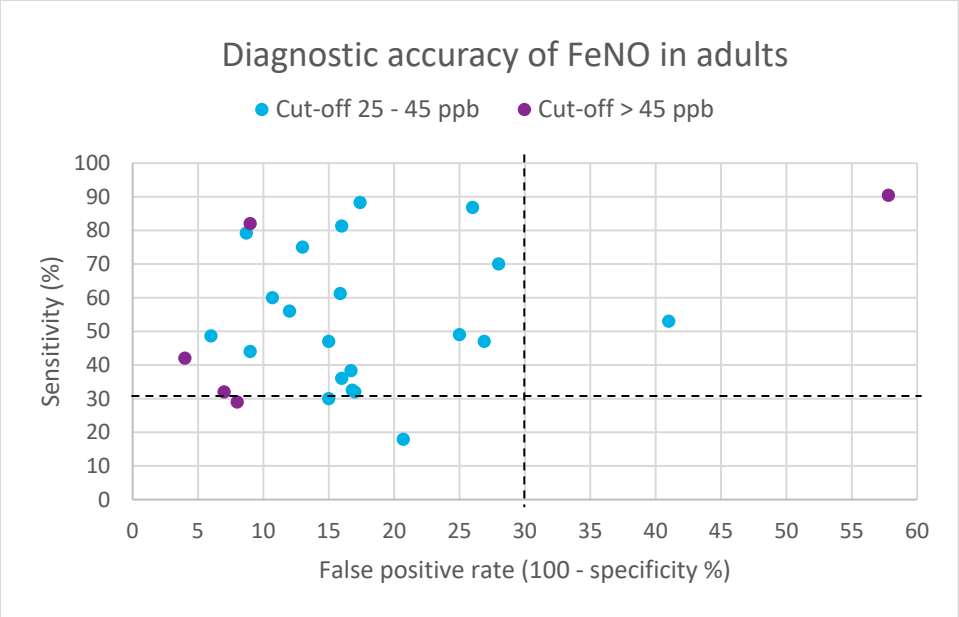


Figure 7: Diagnostic Accuracy in Studies of Adults Aged Over 18 Years (n = 26)

Quadrant chart showing the diagnostic accuracy of 26 studies in adults. 18 studies showed sensitivity rates ≥ 40%, while 25 studies showed false positive rates (100 – specificity) ≤ 30%.

Subgroups/Scenarios

Given the heterogeneity in study characteristics across the included studies, we explored different subgroups to identify factors that may explain the variation seen in the reported sensitivity and specificity ranges. These subgroups were identified during scoping and in consultation with clinical experts.

Low Risk of Bias and High Applicability to Ontario

Six recent studies were identified with low risk of bias and good relevance to the Ontario asthma care context (based on the population, FeNO device, cut-off values, reference standards and recency of publication). The sensitivity and specificity ranges reported in these studies are narrower and more consistent than the ranges seen in all included studies (Table 2). These values were used as inputs in the asthma diagnosis economic model presented in Tables 7 and 8.

Two studies of children were conducted in Switzerland by de Jong et al in 2019[50] and 2020.[57] The authors reported sensitivities of 59% and 46% and specificities of 87% and 88%, respectively. A third study focusing on atopic asthma using a cut-off > 25 ppb reported a sensitivity of 31% and specificity of 84%.[58]

Three studies of adults evaluated the diagnostic accuracy of FeNO testing compared to spirometry and bronchoprovocation in an asthma/specialist clinic. In 2023 in Belgium, Louis et al[73] reported a sensitivity of 32% and a specificity of 83% using a cut-off > 33 ppb. In Germany, Schneider et al[70] and Kellerer et al[90] reported sensitivities of 44% and 32.5% and specificities of 91% and 83.2%, respectively.

Table 2: Summary of Diagnostic Accuracy Findings by Population, FeNO Cut-Off Levels, Risk of Bias and Applicability to Ontario

Subgroups	Number of studies	Sensitivity median (%)	Sensitivity range (%)	Specificity median (%)	Specificity range (%)	Certainty of the evidence (GRADE)
Children (15 studies)						
Cut-off 20–35 ppb	15	59	11.6–90.7	88	52–100	Sensitivity: ⨁ Very low due to risk of bias, inconsistency, and imprecision Specificity: ⨁⨁ Low due to risk of bias and imprecision
Low risk of bias + High applicability to Ontario	3	46	31–59	87	84–88	—
Adults (26 studies)						
Cut-off 25–45 ppb	21	49	17.9–88.3	84	59–94	Sensitivity: ⨁ Very low due to risk of bias, inconsistency, and imprecision Specificity: ⨁⨁ Low due to risk of bias and imprecision
Low risk of bias + High applicability to Ontario	3	32.5	32–44	83.2	83–91	—
Cut-off > 45 ppb	5	42	29–90.4	92	42.2–96	Sensitivity: ⨁ Very low due to risk of bias, inconsistency, and imprecision Specificity: ⨁⨁ Low due to risk of bias and imprecision
Mixed (7)						
Cut-off > 20 ppb	7	74.3	35–78.6	89	60–95	Sensitivity: ⨁ Very low due to risk of bias, inconsistency, and imprecision Specificity: ⨁⨁ Low due to risk of bias and imprecision

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation Working Group criteria*; ppb, parts per billion.*

Asthma Sub-populations

Some studies focused on specific asthma subgroups, resulting in sensitivities and specificities different from the ranges described above. In children, Feng et al[91] focused on patients with chest-tightness variant asthma, comparing FeNO testing to a reference standard of spirometry and exercise challenge testing and found much higher sensitivity (74%) and lower specificity (70%) values. In adults, a similar effect can be seen in a study by Matsunaga et al[92] that includes smokers and people with allergic rhinitis. The sensitivity reported in this study is among the highest of all the included studies.

Clinical Setting

Most studies were conducted in specialist settings; however, 3 studies in adults evaluated the use of FeNO testing in primary care. Of note is a recent study conducted in a primary care setting by Drake et al[83] using methods comparable to Ontario's asthma diagnosis pathway. This study had some risk of bias concerns (unclear patient selection methods), but reported a sensitivity of 56%, which is slightly higher than the median of all adult studies, and a comparable specificity of 88%.

Device Brand/Manufacturer

The diagnostic accuracy, particularly sensitivity, reported in studies using the Sievers FeNO device were generally much higher than those reported in studies using the NIOX brand devices approved for use in Ontario. Four included studies (1 child, 3 adults)[52,69,78,82] used Sievers and reported a range of sensitivities from 75% to 90% (median 87.6%) and a specificity range of 52% to 87% (median 78.3%). One study in this group is also the oldest included study (Chatkin, 1999)[69] and the only one conducted in Canada.

Another recent study with low risk of bias concerns using the NObreath device in adults (Fard, 2021)[81] reported a sensitivity and specificity slightly higher than the median values (48.6% and 94%, respectively).

Timing of FeNO Tests Compared to Other Tests

A study conducted by Jeppegaard et al[65] in Denmark tested the use of FeNO testing at a third follow-up visit after spirometry was used in the first visit and methacholine challenge test used in the second, which is different from most studies where FeNO was administered prior to spirometry. The resulting sensitivity and specificity were 70% and 72%, respectively.

Reference Standards

The reference standard typically reported in the included studies involved spirometry (with or without reversibility) with some form of bronchoprovocation. In 2022, Baranski et al[54] recruited children from a primary school in Poland and compared the use of FeNO with a cut-off level > 25 ppb with a reference standard of spirometry alone. The reported sensitivity of 27.2% is one of the lowest in our included studies, and the specificity of 88.9% is comparable to the other studies in this population (children).

Asthma Management

Characteristics of Included Systematic Reviews

Eight recent reviews were identified that met the eligibility criteria (Table 3). These reviews, published between 2016 and 2021, compared an asthma management strategy with FeNO testing to standard care and reported on at least 1 of the 10 outcomes of interest. Three of the reviews included only studies in children, 1 included only studies in adults, and 4 reviews included a combination of studies in children and adults. In the 7 reviews that included children, 4 included meta-analyses with pooled estimates of relevant outcomes, 2 of which conducted GRADE assessments for the certainty of evidence by outcome. In the 5 reviews that included adults, 2 included meta-analyses, both of which included GRADE assessments. Appendix 3, Table A2 lists the outcomes reported in the reviews that conducted meta-analyses.

Risk of Bias in the Included Reviews

The ROBIS tool was used to assess the potential risk of bias in the 8 identified reviews (Appendix 6; Table A5). Bias in eligibility criteria was deemed low. Identification and selection of studies was generally good (with search dates and sources reported in Table 3). However, some reviews limited their searches to published randomized controlled trials (RCTs). These reviews were not penalized because the final list of included studies, regardless of study design limits, were similar across the reviews (with the exception of the review by Wang et al,[93] which imposed no language limit). All reviews except Lu et al[94] conducted a risk of bias assessment on individual studies, but most did not use GRADE to appraise the certainty of evidence. The overall risk of bias was considered low in 4 reviews,[34,93,95,96] high for 1 (due to no risk of bias or quality assessment),[94] and unclear in 3 (with narrative synthesis and no quality appraisal of the certainty of evidence by outcome).[97-99]

Table 3: Characteristics of Relevant Systematic Reviews

Author, year, country	Review design and analyses	Search dates and sources	Intervention	Comparator(s)	Included studies	Relevant outcomes assessed	Quality assessed
Children only							
Wang et al, 2020[93] China	SR with MA	Inception to March 31, 2020 PubMed, Web of Science, Cochrane Library, China Biology Medicine Database, China National Knowledge Infrastructure, Wanfang Data, and reference lists of relevant SRs	FeNO-guided asthma management with or without other strategies	Asthma mx based on symptoms, spirometry, need for rescue treatment, exacerbations, activity, and guidelines	23 RCTs	Asthma/symptom control ICS dose, exacerbations	ROB for RCTs
Gomersal et al, 2016[99] United Kingdom	SR with narrative	Inception to November 2014 MEDLINE; Cochrane Database of Systematic Reviews; Science Citation Index Expanded (SCIE); Conference Proceedings Citation Index – Science (CPCI-S): Web of Science, and several trial registries	FeNO-guided (NIOX MINO, NIOX VERO, NObreath) asthma management following ATS guidelines	Asthma mx strategy not including FeNO testing	7 RCTs	Asthma/symptom control, ICS dose, exacerbations (acute), OCS use	ROB for RCTs
Lu et al, 2015[94] China (companion review: Jartti et al, 2012,[100] Finland)	SR with MA	Inception to November 2013 PubMed and Cochrane CENTRAL databases	FeNO-based asthma mx strategy	Conventional/standard methods without FeNO testing	6 RCTs	Lung function, ICS dose, exacerbations	NONE, publication bias through funnel plots

Author, year, country	Review design and analyses	Search dates and sources	Intervention	Comparator(s)	Included studies	Relevant outcomes assessed	Quality assessed
Children and adults							
Khatri et al, 2021[34] United States	SR with MA (part of HTA)	January 2016 to July 2019 (leveraging Wang et al, 2017[96]) Medline, Embase, and Cochrane Central databases	FeNO-based care	Usual care (without FeNO testing)	20 RCTs	Asthma/symptom control, lung function, airway inflammation, ICS dose, exacerbations, OCS dose, ED/unscheduled visits, symptom-free days, time off, quality of life	ROB for RCTs + GRADE for strength of evidence by outcome
Petsky et al, 2012,[101] 2016,[102] 2018[95] Australia	SR with MA	Inception to February 2017 Cochrane Airways Group Specialised Register of Trials, the Cochrane Central Register of Controlled Trials (CENTRAL), Medline, EMBASE, and reference hand searching	Adjustment of asthma medications based on FeNO levels	Adjustment according to clinical symptoms without FeNO testing (and with or without spirometry/peak flow)	16 RCTs (7 in adults, 9 in children)	Asthma/symptom control, lung function, ICS dose, exacerbation, quality of life	ROB for RCTs + GRADE for strength of evidence by outcome
Harnan et al, 2015[97] United Kingdom	SR with narrative, and exploratory MA where possible	Inception to September 2013 MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, Science Citation Index Expanded, Conference Proceedings Citation Index, and trial registries	FeNO-guided management	Any other management strategy that does not use FeNO measurements	13 RCTs (6 in adults, 7 in children)	Asthma/symptom control, ICS use, exacerbation, OCS use, ED/unscheduled visits, quality of life	ROB for RCTs

Author, year, country	Review design and analyses	Search dates and sources	Intervention	Comparator(s)	Included studies	Relevant outcomes assessed	Quality assessed
Wang et al, 2017[96] United States	SR with narrative	Inception to 2017 MEDLINE, EMBASE, Cochrane Central Databases, and SciVerse Scopus, references lists, trials registries, and grey literature sources	FeNO measurement	Standard monitoring methods of asthma made by health care providers	58 studies (7 RCTs, 34 nonrandomized longitudinal, and 17 cross-sectional)	Asthma/symptom control, exacerbation	ROB for RCTs + Newcastle-Ottawa for observational + SOE graded based on the EPC Methods Guide on Comparative Effectiveness Reviews
Adults only							
Essat et al, 2016[98] United Kingdom	SR with narrative and, MA where possible	2009 to April 2013, with updates in September and November 2013 13 electronic databases and research registers were searched (including MEDLINE and the Cochrane Library)	FeNO measured according ATS guidelines with or without other indicators of asthma control	Any other management strategy that does not use FeNO measurements	Adults (6 RCTs: 3 from previous SRs + 3 newly identified)	Acute exacerbations (including oral corticosteroids), unscheduled hospitalizations and ER visits, ICS use, asthma control, HRQoL/mortality	ROB for RCTs

Abbreviations: ATS, American Thoracic Society; ED, emergency department; GRADE, Grading of Recommendations Assessment, Development, and Evaluation Working Group; HRQoL, health-related quality of life; HTA, health technology assessment; ICS, inhaled corticosteroids; MA, meta-analyses; mx, management; OCS, oral corticosteroids; ROB, risk of bias; RCT, randomized controlled trials; SOE, strength of evidence; SR, systematic review.

Findings of Included Systematic Reviews

From the 8 reviews identified, we assessed 4 to have low potential risk of bias. Three of those reviews included meta-analyses and pooled effects, of which 2 (Khatri et al[34] and Petsky et al[95]) reported GRADE assessments on the certainty of evidence by outcome. These two reviews collectively include all 10 outcomes of interest for both children and adults (Table 4). The findings from these reviews were also used as inputs in the asthma management economic model, (Tables 39 and 40). Relevant findings from all 8 reviews are summarized in the following clinical narrative synthesis.

Table 4: Main Results by Outcome from Systematic Reviews with GRADE Assessment

Outcome description	Population	Author, year	Number of RCTs in analysis	Results[a]	GRADE assessment
Asthma control					
Asthma Control Test	Children	Khatri et al, 2021[34]	2	MD: 0.40 (–0.49 to 1.28; *P* = NR)	⨁⨁ Low
		Petsky et al, 2018[95]	2	MD: 0.14 (–0.18 to 0.47; *P* = 0.39)	NR
	Adults	Petsky et al, 2018[95]	4	MD: –0.08 (–0.18 to 0.01; *P* = 0.09)	NR
Asthma Control Questionnaire	Adult	Khatri et al, 2021[34]	3	MD: –0.01 (–0.19 to 0.16; *P* = NR)	⨁⨁⨁ Moderate
Lung function					
FEV_1 (percent change)	Combined	Khatri et al, 2021[34]	9	MD: 1.11 (0.02 to 2.21)	⨁⨁⨁ Moderate
		Petsky et al, 2018[95]	NR	While FEV_1 was reported in all studies, data points were not provided; authors reported finding no difference between participants	NR
Airway inflammation					
Blood eosinophil count (percentage)	Combined	Khatri et al, 2021[34]	3	Results could not be combined because of differences in reporting; however, no differences were identified in the peripheral blood eosinophil count	NR
Inhaled corticosteroid dose					
Varying medications and doses	Combined	Khatri et al, 2021[34]	15	Most studies (n = 9) showed no difference in ICS use. There was evidence of increased ICS use in some studies (n = 4) and less ICS use in others (n = 2).	NR
ICS dose (mcg) at final visit	Children	Petsky et al, 2018[95]	3	MD: 65.88 (–86.71 to 218.47; *P* = 0.40)	⨁⨁⨁ Moderate
	Adults	Petsky et al, 2018[95]	4	MD: –147.15 (–380.85 to 86.56; *P* = 0.22)	⨁ Very low

Outcome description	Population	Author, year	Number of RCTs in analysis	Results[a]	GRADE assessment
Exacerbations					
No. of patients with ≥ 1 exacerbations over the study period	Combined	Khatri et al, 2021[34]	10	RR: 0.72 (0.56 to 0.93; *P* = NR)	⊕⊕⊕ Moderate
	Children	Khatri et al, 2021[34]	6	RR: 0.70 (0.51 to 0.96)[b]	—
		Petsky et al, 2018[95]	8	OR: 0.58 (0.45 to 0.76, *P* < 0.0001)	⊕⊕⊕ Moderate
	Adult	Khatri et al, 2021[34]	3	RR: 0.77 (0.47 to 1.27)[b]	—
		Petsky et al, 2018[95]	5	OR: 0.60 (0.43 to 0.84, *P* = 0.003)	⊕⊕⊕ Moderate
Asthma exacerbation frequency or rate (No./year)	Combined	Khatri et al, 2021[34]	7	MD: –0.15 (–0.28 to –0.03; *P* = NR)	⊕⊕ Low
	Children	Khatri et al, 2021[34]	1	MD: –1.02 (–1.60 to –0.44)[b]	—
		Petsky et al, 2018[95]	4	MD: –0.37 (–0.8 to 0.06)	⊕ Very low
	Adult	Khatri et al, 2021[34]	5	MD: –0.12 (–0.21 to –0.03)[b]	—
		Petsky et al, 2018[95]	5	RR: 0.59 (0.45 to 0.76)	⊕⊕⊕ Moderate
Oral corticosteroid use					
No. of patients	Combined	Khatri et al, 2021[34]	6	RR: 0.79 (0.65 to 0.95; *P* = NR)	⊕⊕⊕ Moderate
	Children	Khatri et al, 2021[34]	5	RR: 0.77 (0.63 to 0.94)[b]	—
	Adult	Khatri et al, 2021[34]	1	RR: 0.90 (0.48 to 1.68)[b]	—
ER/unscheduled hospital visits					
No. of visits	Children	Khatri et al, 2021[34]	3	RR: 0.67 (0.36 to 1.23)	⊕⊕ Low

Outcome description	Population	Author, year	Number of RCTs in analysis	Results[a]	GRADE assessment
Hospitalizations					
Asthma hospitalizations (frequency)	Combined	Khatri et al, 2021[34]	5	RR: 0.78 (0.36 to 1.70; *P* = NR)	⨁⨁⨁ Moderate
	Children	Khatri et al, 2021[34]	2	RR: 0.82 (0.36 to 1.86) [b]	—
	Adult	Khatri et al, 2021[34]	1	RR: 0.54 (0.05 to 5.91) [b]	—
Symptom-free days					
Frequency	Combined	Khatri et al, 2021[34]	2	Both studies reported numeric improvements in the frequency of symptom-free days; however, these results were not statistically significant	NR
Time off from school/work					
Days missed (frequency)	Combined	Khatri et al, 2021[34]	1	MD: –1.6 (–6.01 to 2.81; *P* = NR)	⨁⨁ Low
Quality of life					
Asthma-related quality of life scores	Combined	Khatri et al, 2021[34]	3	None of the studies showed a significant difference in quality of life with the intervention	NR
	Children	Petsky et al, 2018[95]	3	MD: 0.09 (–0.08 to 0.26, *P* = 0.29)	NR
	Adults	Petsky et al, 2018[95]	2	MD: 0.00 (–0.01 to 0.01, *P* = 0.99)	NR

Abbreviations: FEV_1, forced expiratory volume in 1 second; GRADE, Grading of Recommendations Assessment, Development, and Evaluation Working Group; ICS, inhaled corticosteroids; MD, mean difference; NR, not reported; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk.

[a]As reported by systematic reviews, unless otherwise stated.

[b]Our calculations.

Asthma/Symptom Control

Khatri et al[34] and Petsky et al[95] reported no statistically significant difference between asthma management including FeNO testing and control groups in the ACT and ACQ scores (reported in both children and adults, Table 4). Another review in children (Wang X, 2020)[93] reported on the rate of symptom control, which also showed no significant difference between groups (relative risk [RR] = 1.09; 95% CI: 0.99–1.20; *P* = 0.07).

Additionally, the narrative summaries from two other reviews (Harnan, 2015 and Wang Z, 2017)[96,97] reported no significant change between groups in asthma control or in the ability to differentiate patients who are well-controlled from those who are not.

Lung Function and Airway Inflammation

Percent change in forced expiratory volume in 1 second (FEV_1) was reported in 9 studies in Khatri, 2021[34], where the pooled estimate for children and adults found an overall improvement in lung function when FeNO-based care was used, but the effect size was small (MD = 1.11%, 95% CI: 0.02–2.21; GRADE: Moderate). There was some heterogeneity in the studies, but pediatric and adult studies were equally represented in the results. In Petsky[95], however, a narrative summary of FEV_1 was provided and all studies found no difference between participants who had treatment adjusted to FeNO testing in comparison with the control group.

In addition, one review in children alone reported FEV_1 in 4 studies at both baseline and final visit.[94] The difference in FEV_1 percent change was similar in the FeNO testing–based and control groups (MD = 0.07%, 95% CI: −0.07 to 0.20).

Three studies reported the percentage of blood eosinophils, and found no difference between the groups.[34]

Inhaled Corticosteroid Dose

Khatri et al[34] did not pool data for inhaled corticosteroid (ICS) dosing due to the different medications and doses reported across studies. Instead, they provided a narrative summary, concluding that most of the studies showed no difference in ICS use, while others showed evidence of increased or decreased ICS use. Petsky, 2018[95] conducted a meta-analysis and found no statistically significant group differences in the final ICS dose for children (3 RCTs; GRADE: Moderate) or adults (4 RCTs; GRADE: Very low).

Two reviews in children alone also reported ICS dose, with mixed results.[93,94] Although FeNO testing–based groups may be associated with greater ICS use, this finding did not reach statistical significance. Similarly, Essat et al[98] included 4 studies in adults alone that were in favour of FeNO-guided management; however, the pooled standardized mean difference (SMD) of −0.24 (−0.56 to 0.07) was not statistically significant. Harnan et al[97] identified one study in pregnant participants that found the change in mean values from baseline to final visit for ICS use was a statistically significant decrease of 210 mcg/d in the FeNO testing–based intervention arm in this sub-population.

Exacerbations

Khatri et al, 2021[34] included 10 studies reporting the number of patients with one or more exacerbations in each group. The number of patients experiencing exacerbations in the groups that received FeNO testing–based care was significantly lower (RR = 0.72; 95% CI: 0.56–0.93), translating to an average of 111 fewer exacerbations per 1,000 individuals (GRADE: Moderate). When we conducted our own population-based sensitivity analyses in children and adults separately, the difference in children remained significant (RR = 0.70; 95% CI: 0.51–0.96); however, the difference in adults was not significant (RR = 0.77; 95% CI: 0.47–1.27).

Petsky et al[95] also found that in the group receiving treatment adjusted according to FeNO testing, the number of participants with one or more exacerbations during the study follow-up period was significantly lower than in the control group in 8 RCTs of children (OR = 0.58, 95% CI: 0.45–0.76; GRADE: Moderate) and in 5 RCTs that included adults (OR = 0.60, 95% CI: 0.43–0.84; GRADE: Moderate).

Khatri et al[34] included 11 studies evaluating exacerbation frequency in adults and children. In the 7 studies reporting variance, the authors found a significant reduction in the frequency of asthma exacerbations using FeNO testing–based care (MD = −0.15, 95% CI: −0.28 to −0.03; GRADE: Low). When we conducted our own population-based sensitivity analyses in children and adults separately, the difference remained significant in both groups (in children, MD −1.02 [−1.60 to −0.44]; in adults, MD: −0.12 [−0.21 to −0.03]).

Petsky et al[95] reported that the exacerbation rate (number of exacerbations per 52 weeks) in the group receiving FeNO testing–adjusted care was significantly lower than controls in adults (RR = 0.59, 95% CI: 0.45–0.76; GRADE: Moderate), but that there was no statistically significant difference between groups in children.

Several reviews also found that exacerbations were less likely in the FeNO testing–based management groups in children and adults. Wang et al[93] reported a meta-analysis of 8 trials showing that FeNO testing–guided care could significantly reduce the proportion of children with asthma exacerbations (RR = 0.73, 95% CI: 0.63–0.84) and it could lower exacerbation frequency (SMD: −1.57, 95% CI: −2.25 to −0.88). Lu et al[94] similarly found the percentage of children experiencing exacerbations was significantly lower in the FeNO groups compared with the control groups (OR = 0.690, 95% CI: 0.532–0.895). Essat et al[98] reported a composite of all exacerbations in adults that also favored FeNO testing–based care (RR = 0.53, 95% CI: 0.46–0.61; $P < 0.00001$). Severe exacerbations were less likely with FeNO testing–based care (RR 0.80, 95% CI: 0.63–1.02; $P = 0.08$), but this finding was not statistically significant.

Finally, Harnan et al[97] reported on the composite outcome of all exacerbations in a pregnancy subgroup in which the number of exacerbations was statistically significantly reduced in the FeNO testing arm (RR = 0.496, 95% CI: 0.325–0.755).

Oral Corticosteroid Use

In Khatri et al[34], 6 studies (5 in children, 1 in adults) reported the number of patients who used oral corticosteroids (OCS) in each treatment arm and found the number of patients treated with OCS was significantly reduced when FeNO testing–based care was used (RR = 0.79; 95% CI: 0.65–0.95; GRADE: Moderate). This translates to 69 fewer individuals using corticosteroids per 1,000 individuals treated with FeNO testing–based care (95% CI: 115 fewer to 16 fewer). We conducted our own population-based analyses in children and adults separately. Children continued to show lowered use of OCS in the FeNO testing–based care group (RR = 0.77; 95% CI: 0.63–0.94). FeNO testing–based care was associated with a lowered use of OCS in adults, but the difference was not statistically significant (RR = 0.90; 95% CI: 0.48–1.68).

In a review of studies in children (Gomersal, 2016)[99], all 4 trials reported improvement in exacerbations, resulting in OCS use when using FeNO testing, but only 2 of those 4 trials showed a statistically significant difference between groups. Meanwhile, in a review of adult studies (Essat, 2016)[98], 2 studies reported opposite directions of effect for the outcome of severe exacerbations resulting in the use of OCS.

Emergency Room Visits and Hospitalizations

Khatri et al[34] reported on emergency department and unscheduled health care visits in 3 trials. The authors reported a reduction when using FeNO testing–based care in children (RR = 0.67; 95% CI: 0.37–1.22; GRADE: Low), although this was not statistically significant.

Khatri et al[34] included 5 trials that reported on hospitalizations due to asthma. Three were pooled and the authors found no significant difference in frequency of hospitalizations in children and adults (RR = 0.78; 95% CI: 0.36–1.70; GRADE: Moderate). When we conducted our own analyses to separate the results in children and adults, there continued to be no statistically significant difference between groups.

Two other reviews (Harnan, 2015 and Essat M, 2016)[97,98] found that unscheduled health care utilization and hospitalizations showed some improvement using FeNO management, but the differences between groups were not statistically significant.

Symptom-Free Days and Time Off from School or Work

Narratively, Khatri et al[34] reported a numeric improvement in the frequency of symptom-free days in 2 studies; however, the results were not statistically significant and no GRADE assessment was reported for this outcome. Similarly, Wang et al[93] identified 3 trials in children that showed no statistically significant difference in the rate of symptom-free days between FeNO testing–based care and the control group. Time off was addressed only in one study in Khatri, which showed 1.6 fewer days off in the FeNO group, but this difference was not statistically significant (GRADE: Low).

Asthma-Related Quality of Life

Khatri et al[34] reported on 3 trials (1 in children, 2 in adults) evaluating quality of life. None showed a statistically significant difference in the groups that used FeNO testing (no GRADE reported). Likewise, in the Petsky review[95], there were no statistically significant group differences in asthma quality of life scores for the FeNO testing–based studies in children (n = 1) or in adults (n = 2). Wang et al[93] included three studies and Gomersal et al[99] included one reporting the effects of FeNO testing on pediatric quality of life, but no statistical difference was found between groups in either review.

Essat et al[98] reported on health-related quality of life (HRQoL) in 3 trials of adults with asthma. The pooled analysis of 2 studies reported no significant difference in global symptom scores (standardised mean difference: 0.00 (95% CI: −0.20 to 0.20); *P* = 0.96), but 1 study reported a statistically significant difference in the symptoms score (*P* = 0.041) with a between-group difference in change from baseline of 0.10 in favour of FeNO management.

Ongoing Studies

We are aware that there are some RCTs showing the usefulness of FeNO testing to define subgroups that help identify individuals with better response to biologics, for example:

- Menzies-Gow A, Corren J, Bourdin A, Chupp G, Israel E, Wechsler ME, et al. Tezepelumab in adults and adolescents with severe, uncontrolled asthma. N Engl J Med. 2021; 384(19):1800–09

Discussion

FeNO testing is proposed as an easy-to-perform objective test to improve diagnostic testing of people suspected of having asthma, in addition to existing clinical and laboratory assessments. It is suggested as a potential add-on test 1) before spirometry testing (likely in an office setting) prior to putting a patient on trial medication, 2) with spirometry testing in the same laboratory visit, or 3) after spirometry testing to help confirm uncertain or inconclusive findings.

The addition of FeNO testing could potentially alleviate the need for some bronchial provocation tests such as the methacholine challenge test, which can be complex, more costly, and carries a risk for patients. After diagnosis of asthma by a clinician, patients often require regular monitoring to ensure adequate management of symptoms (e.g., exacerbations), as well as to adjust therapy. Ontario standards suggest the use of validation questionnaires, annual spirometry, and other lab-based tests for inflammation; however, the clinical experts we consulted indicated that this is not always possible due to access and wait times. Thus FeNO testing is also proposed as an additional test in the toolkit to support ongoing monitoring and management of asthma.

For question 1 (asthma diagnosis), we included 48 primary studies that evaluated the diagnostic accuracy of FeNO testing and reported sensitivity and specificity values. These studies were identified by leveraging primary studies in systematic reviews[31,103-105 21,25,106-114] and conducting an updated search of the literature. The sensitivity of FeNO to detect airway inflammation in support of an asthma diagnosis was low and inconsistent across the studies. Most of the studies were conducted in specialist care settings with spirometry and bronchoprovocation as the reference standard. Subgroup analyses suggest studies that use different device brands (such as Sievers or Nobreath, which are not currently approved for use in Canada) or that focus on a specific sub-population of asthma (e.g., chest variant asthma, asthma with allergic rhinitis) reported relatively higher sensitivity results than did studies we identified as most applicable to Ontario. This potentially explains the variation in values seen in the data. The specificity values reported for FeNO testing, however, were consistently high across studies in both children and adults, as well as in the subgroups examined. The clinical evidence supports the use of FeNO testing as a potential rule-in test to complement spirometry testing and may be a reasonable step to consider before methacholine challenge testing.

For question 2 (asthma management), we included 8 systematic reviews[34,93-99] of children and adults demonstrating that asthma management strategies that include FeNO testing can improve some asthma outcomes. In children, the evidence supports the use of FeNO-adjusted asthma care to reduce exacerbations and also reduce the number of patients treated with oral corticosteroids (these outcomes often occur together).

In adults, the use of asthma strategies that included FeNO testing resulted in a lower number of exacerbations and lower exacerbation rates. In this case, there was only 1 study that reported oral corticosteroid use in adults, and the difference between groups was not significant. The evidence also suggests a small improvement in lung function with management strategies that included FeNO testing when studies in children and adults were combined (with equal representation of both populations).

Other asthma control outcomes (e.g., ACT scores, ICS dose/use, number of ED visits) also report slight benefits to using FeNO testing, but these differences were not statistically significant. The data for outcomes such as hospitalizations, days missed from school or work, and quality of life suggest that management strategies that included FeNO testing did not convey additional benefit over control and sometimes there was a lack of studies evaluating these outcomes in the reviews.

Strengths and Limitations

The overall strength of our report is that it includes a comprehensive review of the literature in children and adults seeking to understand the diagnostic accuracy of FeNO testing, as well as its clinical effectiveness in managing asthma.

The reported optimal FeNO cut-off levels ranged from > 7 to > 64 ppb in the 73 studies we identified reporting on the diagnostic accuracy of FENO testing for asthma. Only 6 of these studies reported optimal cut-offs recommended by clinicians and guidelines. As a result, in addition to clinically meaningful cut-offs, we also considered 42 studies with a range of cut-offs with slightly lower certainty that may or may not be useful in the diagnosis of asthma. Some studies presented diagnostic accuracy outcomes for multiple cut-off values, but only one was selected from each study to be included in our review. For the most part, we selected the cut-off labeled as having the "optimal" diagnostic accuracy by study authors, which often was not one of the higher cut-offs reported. Heterogeneity was also present due to the inclusion of different sub-populations of asthma, clinical settings, device brands, reference standard tests, and timing of tests. It was therefore inappropriate to pool the data, but we were able to explore differences in these studies through subgroup analyses.

In the management of asthma literature, we conducted an overview of reviews, reporting existing pooled analyses of results with assessments of certainty conducted by the review authors. In one review[34] that combined studies of all ages, we were able to conduct our own subgroup analyses in children and adults; however, our ability to conduct other subgroup analyses was limited. In addition, the follow-up periods used in the included studies were able to detect changes in short term outcomes such as exacerbations and resulting oral corticosteroid use; however, a longer study period may be required to see the full effect of uncontrolled asthma on lung function and quality of life and to detect rarer outcomes like hospitalizations due to asthma.

Conclusions

Asthma Diagnosis

- Studies of children and adults using FeNO testing for the diagnosis of asthma reported low and variable sensitivities compared with a reference standard, with most studies reporting values greater than 30% and less than 90% (GRADE: Very low)
    - The variability in sensitivities may be due to the inclusion of studies with different cut-offs, asthma sub-populations, FeNO device brands, reference standards, and clinical settings
- Studies of children and adults using FeNO testing for the diagnosis of asthma reported consistently high specificities compared with a reference standard, with most studies reporting values greater than 70% (GRADE: Low), supporting the use of FENO as an additional test to help rule-in the diagnosis of asthma

Asthma Management

Based on an overview of reviews in children with diagnosed asthma, compared with standard care alone, including FeNO testing in the monitoring and management of asthma:

- Likely decreases the number of patients experiencing exacerbations (asthma attacks or other sudden worsening of symptoms; GRADE: Moderate) and the use of oral corticosteroids (GRADE: Moderate)
- May result in little to no difference in asthma and symptom control (GRADE: Low), inhaled corticosteroid dose (GRADE: Moderate), emergency department visits (GRADE: Low),

hospitalizations due to asthma (GRADE: not reported), and asthma-related quality of life (GRADE: not reported).

Based on an overview of reviews in adults with diagnosed asthma, compared with standard care alone, including FeNO testing in the monitoring and management of asthma:

- Likely decreases the number of patients experiencing exacerbations (asthma attacks or other sudden worsening of symptoms; GRADE: Moderate) and the exacerbation rate (GRADE: Moderate)
- May result in little to no difference in asthma and symptom control (GRADE: Moderate), inhaled corticosteroid dose (GRADE: Very low), use of oral corticosteroids (GRADE: not reported), hospitalizations due to asthma (GRADE: not reported), and asthma-related quality of life (GRADE: not reported)

Based on an overview of reviews that combined children and adults with diagnosed asthma, including FeNO testing in the monitoring and management of asthma:

- Likely results in a small improvement in lung function (GRADE: Moderate)
- May result in little to no difference in blood eosinophil count (GRADE: Low), days missed from school or work (GRADE: Low), and frequency of symptom-free days (GRADE: not reported)

Economic Evidence

Research Questions

1. What is the cost-effectiveness of fractional exhaled nitric oxide (FeNO) testing (alone or as an add-on) compared with standard testing used for diagnosis in people with suspected asthma?
2. What is the cost-effectiveness of FeNO testing (alone or as an add-on) compared with standard care to monitor and manage people with diagnosed asthma?

Methods

Economic Literature Search

We performed an economic literature search on October 3, 2022, to retrieve studies published from inception until the search date. To retrieve relevant studies, we developed a search using the clinical search strategy with an economic and costing filter applied.

We created database auto-alerts in MEDLINE and Embase, and CINAHL and monitored them until May 2023. We also performed a targeted grey literature search of health technology assessment agency websites, clinical trial and systematic review registries, and the Tufts Cost-Effectiveness Analysis Registry. See the Clinical Literature Search, above, for further details on methods and sources used. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

Research Question 1: Asthma Diagnosis

Studies

Inclusion Criteria

- English-language full-text publications
- Cost–benefit analyses, cost-effectiveness analyses, cost-minimization analyses, or cost–utility analyses

Exclusion Criteria

- Studies where the outcomes of interest are not reported or cannot be extracted
- Non-systematic reviews, editorials, case reports, commentaries, conference abstracts, letters, and unpublished studies
- Non-comparative costing studies, feasibility analyses

Population

Inclusion Criteria

- People over 5 years of age presenting with clinical symptoms suggestive of asthma (e.g., shortness of breath, chest tightness, wheezing, and/or cough)

Exclusion Criteria

- Children 5 years of age or younger (who are judged unable to undergo objective testing) and people previously diagnosed with asthma and/or receiving treatment for asthma during objective testing

Interventions

- FeNO measured with an acceptable expiratory flow rate (e.g., 50 ml/s) and exhalation time (e.g., ≥ 6 s for children and ≥ 10 s for adults) for the device being used
- Use of co-interventions (e.g., physical exam, other lung function tests, etc.) to be included if equal access in each group

Comparators

- Pulmonary function tests including any combination of spirometry, bronchodilator reversibility, peak expiratory flow variability, challenge tests, induced sputum
- Clinician diagnosis of asthma (with or without objective testing)

Outcome Measures

- Costs
- Health outcomes (e.g., quality-adjusted life-years)
- Incremental costs
- Incremental effectiveness
- Incremental cost-effectiveness ratios

Research Question 2: Asthma Management

Studies

Inclusion Criteria

- English-language full-text publications
- Cost–benefit analyses, cost-effectiveness analyses, cost-minimization analyses, or cost–utility analyses

Exclusion Criteria

- Studies where the outcomes of interest are not reported or cannot be extracted

- Non-systematic reviews, editorials, case reports, commentaries, conference abstracts, letters, and unpublished studies
- Non-comparative costing studies, feasibility analyses

Population

Inclusion Criteria

- People over 5 years of age with clinician-diagnosed asthma (with or without objective testing) that is controlled or uncontrolled.

Exclusion Criteria

- Children aged 5 years or younger (who are judged unable to undergo objective testing) and people without an asthma diagnosis

Interventions

Inclusion Criteria

- FeNO measured with an acceptable expiratory flow rate and exhalation time for the device being used for asthma monitoring and management
- Use of co-interventions (e.g., education, lung function tests, etc.) to be included if there is equal access in each group

Exclusion Criteria

- Expiratory flow rate or exhalation time less than the recommended cut-off for the device; co-interventions only offered to 1 group; use of nasal or alveolar NO

Comparators

Inclusion Criteria

- Asthma management strategies without the use of FeNO testing (including any combination of clinical symptom assessment, asthma control questionnaires, education interventions, lung function tests, airway inflammation tests, challenge tests, etc.)

Exclusion Criteria

- Management strategy includes FeNO testing

Outcome Measures

- Costs
- Health outcomes (e.g., quality-adjusted life-years)
- Incremental costs
- Incremental effectiveness
- Incremental cost-effectiveness ratios

Literature Screening

One reviewer conducted an initial screening of titles and abstracts and then obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. The reviewers then examined the full-text articles and selected studies eligible for inclusion. The reviewer also examined reference lists of included studies for any additional eligible studies not identified through the search.

Data Extraction

We extracted relevant data on study characteristics and outcomes to collect information about the following:

- Source (e.g., citation information, study type)
- Methods (e.g., study design, analytic technique, perspective, time horizon, population, intervention[s], comparator[s])
- Outcomes (e.g., health outcomes, costs, incremental cost-effectiveness ratios)

Study Applicability and Limitations

We determined the usefulness of each identified study for decision-making by applying a modified quality appraisal checklist for economic evaluations originally developed by the National Institute for Health and Care Excellence (NICE) in the United Kingdom.[115] The NICE checklist has two sections: the first is for assessing study applicability, and the second is for assessing study limitations. We modified the wording of the questions of the first section to make it specific to Ontario. Using this checklist, we assessed the applicability of each study to the research question (directly, partially, or not applicable). Next, we assessed the limitations (minor, potentially serious, or very serious) of the studies that we found to be applicable.

Results

Economic Literature Search

The economic literature search yielded 389 citations, including grey literature results and the removal of duplicates, published from inception until October 03, 2022. We identified 30 additional studies from other sources, for a total of 276 after removing duplicates. In total, we identified 7 studies that met our inclusion criteria. Figure 8 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the economic systematic review.

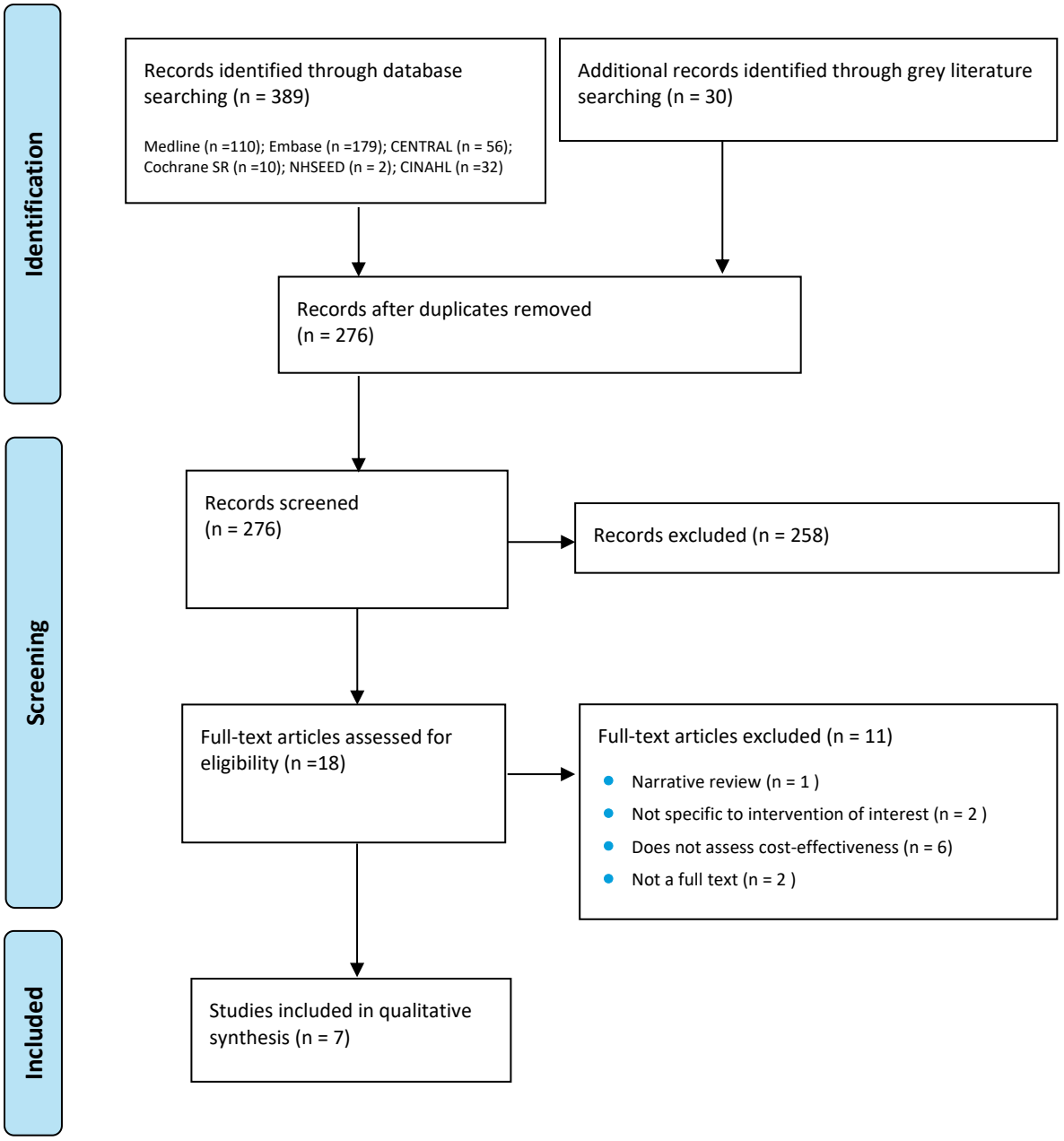


Figure 8: PRISMA Flow Diagram – Economic Systematic Review

PRISMA flow diagram showing the economic systematic review. The search of the economic literature yielded 389 citations published from database inception, until October 3, 2023. We identified 30 additional eligible studies from other sources. After removing duplicates, we screened the abstracts of 276 studies and excluded 258. We assessed the full text of 18 articles and excluded a further 11. In the end, we included 7 articles in the qualitative synthesis.

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

Source: Adapted from Page et al.[41]

Overview of Included Economic Studies

We identified a total of 7 published economic studies that met our inclusion criteria.[110,116-121] Four studies assessed the use of FeNO testing for both diagnosis and management of asthma,[19,116,119,120] and 3 assessed the use of FeNO testing for the management of asthma only.[117,118,121] None of the included studies was conducted from the Canadian perspective. Most were conducted from different national payer or societal perspectives: 2 from the United Kingdom,[97,120] and 1 each from Sweden,[119] Germany,[116] Spain,[121] the United States,[117] and Colombia.[118]

For the studies with both diagnostic and management models, 2 included only adults,[116,120] while the remaining 2 included both children and adults.[97,119] For the studies on asthma management only 1 study included children only,[118] while 2 included adults only.[117,121] Most studies included people with mild to severe asthma who were seen in primary and secondary care settings.[117,118,120] Two studies included a general population seen in primary care settings only[119,121] and another study included children with mild to moderate allergic asthma.[118]

All included studies conducted model-based analyses to predict possible outcomes and associated costs. Decision tree structures were used for all diagnostic models,[97,116,120] and 3 management models,[116,120,121] while 2 studies used Markov structures for their management models.[97,118] Two studies did not report the model structure clearly.[117,119]

For the diagnostic models, only 1 study clearly stated that they applied a 5-year time horizon,[97] while the time horizons for the remaining studies were unclear, but seem related to the time from presentation to correct diagnosis.[116,119,120] For the management models, most studies adopted a 1-year time horizon,[116-118,120,121] while 1 study used a lifetime horizon.[97]

A health care payer perspective was used by all but 1 study, which took a societal perspective.[118] Most studies included the cost of testing, health care, or laboratory visits for diagnosis and control, hospitalization, exacerbation, and medications. The FeNO testing device considered in the studies varied. For example, Price et al[120] considered FeNO testing using the NIOX MINO device, while Harnan et al[97] considered testing using NIOX MINO, NIOX VERO, and NObreath devices, although they assumed an equivalent effectiveness for all devices. See Table 5 for a summary of the results of the economic literature review.

Results for Asthma Diagnosis

For asthma diagnosis, 2 studies presented only a comparative cost-analysis,[116,120] while 1 study conducted a budget impact analysis.[119] Health outcomes were not explicitly reported in the published analyses. In their base-case analysis, these 3 studies investigated FeNO testing as a single replacement strategy compared with the standard care (standard diagnosis guidelines). The 2 cost-analysis studies used a blended comparison that included relative frequency weights assigned to each test used in standard diagnosis.[116,120]

Both cost-analysis studies included only adult patients and were conducted by the same group. It was found that in Germany, using FeNO testing for diagnosis would be more costly than standard care (an additional €12 per patient EUR; 95% CI: €9 to €14),[116] although they found in the UK that using FeNO testing would be less costly (a savings of £43 GBP per patient).[120] The sensitivity analyses by Price et al[120] showed that the parameters of the diagnostic model were robust over a wide range of values, except when the reimbursement price of NIOX MINO was increased by 200%. These studies also considered the

combination of FeNO testing with a standard diagnostic test in different scenario analyses. When FeNO testing was combined with a lung functioning test (FEV_1), the cost was £42 GBP higher than standard tests alone.[120] However, when FeNO testing was combined with spirometry, compared with bronchoprovocation and spirometry together, there was a cost-savings of €62 EUR associated with the FeNO testing strategy.[116]

Darba et al[119] considered the budget impact of the progressive introduction of FeNO testing in primary care in Sweden. Over a 4-year period (2021–2023), the economic burden of asthma diagnosis became lower with FeNO testing, resulting in a total savings of 128,429,100 SEK in adult patients (495 kr per patient), and 99,147,258 SEK in paediatric patients (1,679 kr per patient) in the final year of the study.

The study by Harnan et al[97] was the only cost–utility analysis for asthma diagnosis that included both adults and children. The authors investigated FeNO testing alone or as an adjunctive test to standard care (standard diagnosis guidelines) versus standard care alone. The authors concluded that either alone or as an adjunctive test, FeNO testing using the NIOX MINO and NIOX VERO devices were dominated by FeNO testing using the NObreath device. The NObreath device had a lower cost, while all FeNO devices were assumed to have the same test accuracy. FeNO testing with the NObreath device plus bronchodilator reversibility dominated all competing strategies (less costly and more effective), with the exception of airway hyper-responsiveness (MCT), which produced slightly higher quality-adjusted life years (QALYs), but at a higher cost. The incremental cost-effectiveness of MCT compared with FeNO testing plus bronchodilator reversibility was expected to be approximately £1.125 million GBP per QALY gained. Sensitivity analyses showed that the model's results were most sensitive to assumptions about the duration of time required to resolve misdiagnoses, assumptions about health losses incurred by patients who are FNs, and the costs of asthma treatment.

Results for Asthma Management

For asthma management, 3 studies investigated FeNO testing as a single strategy compared to standard care,[116,120] and 4 investigated FeNO testing combined with standard treatment versus standard treatment alone.[19,117,121] All studies concluded that FeNO testing (alone or as a combined strategy with standard treatment) would be a cost-effective or cost-saving strategy compared to standard treatment alone in the adult population.

Berg and Lindgren[116] compared FeNO testing alone to spirometry based on standard asthma management guidelines in Germany over a 1-year time horizon, while Price et al[120] compared FeNO measurement with lung function testing, as recommended by the asthma management guidelines in the United Kingdom for adults with different levels of asthma severity. These studies found that, for adults with mild-to-severe asthma, cost-savings were €30 EUR and £341 GBP per patient per year, and €160 EUR and £554 GBP for patients with moderate to severe asthma, respectively. Berg and Lindgren[116] found the results of 1-way sensitivity analysis showed that FeNO testing remained the dominant strategy (less costly and more effective) compared with standard of care across most key baseline parameters, except when the number of monitoring visits increases to 6 visits per year, if the cost of the FeNO device increases by 50%, or if asthma costs, excluding the device, decrease by 50%. Second-order stochastic sensitivity analyses showed uncertainty in the clinical benefit. Price et al[120] also found that, for asthma management, the model was robust and FeNO testing remained the dominant strategy in all sensitivity analyses. However, in a scenario where FeNO testing was combined with lung function testing, the incremental cost-effectiveness ratio (ICER) would be £279 GBP per QALY when compared with standard care guidelines without FeNO testing.

Darba et al[119] also evaluated FeNO testing alone with standard care tests individually. Compared with spirometry and reversibility testing, allergy testing, and blood eosinophil count, FeNO testing was dominant (less costly and more effective); however, compared to methacholine challenge testing, FeNO testing was less costly but also less effective (ICER not reported). FeNO testing was found to be cost saving due to its reduced use of resources, represented by fewer visits to the primary care general practitioner (GP) when compared to the standard care tests.

When looking at FeNO testing combined with standard care, compared with standard care alone, Brooks and Massanari[117] found this resulted in decreased annual costs ($2,228 vs. $2,637 USD) and increased annual QALYs (0.844 vs. 0.767). This difference was consistent through all 1-way sensitivity analyses. Similarly, Sabatelli et al[121] found that adding FeNO testing to standard care for management of asthma saved €62.53 GBP per patient per year in the adult population and improved QALYs by 0.026 per patient yearly. Harnan et al[97] also found that, for adults, FeNO monitoring using NObreath in addition to standard care guidelines was most likely to be cost-effective (probability = 0.82).

For children, FeNO testing was found to be more costly than standard care in 1 study,[97] but cost-saving compared with standard care in another.[118] Buendia et al[118] included patients between 4 and 18 years of age with mild to moderate allergic asthma. The analysis was carried out from a societal perspective. Cost data were obtained from a retrospective study on asthma from a tertiary center in Medellin, Colombia. The authors found that asthma management with FeNO testing was associated with a lower total cost than standard care (average cost per patient: $1,333 vs. $1,452 USD) and higher QALYs (average per patient: 0.93 vs. 0.92), while the probability that FeNO testing is cost-effective compared with standard care exceeded 99% for all willingness-to-pay values. They concluded better outcomes were due to a reduction in the likelihood of asthma exacerbations and suboptimal asthma control.

Harnan et al,[97] however, found that, at a willingness to pay of £20,000 GBP per QALY, use of standard treatment guidelines alone is likely most cost-effective (probability = 0.99) in children. For the management of asthma, similar to the results of their analysis in adults, FeNO testing was expected to produce a small incremental QALY compared with standard treatment guidelines alone. The ICER for NObreath versus standard treatment guidelines was expected to be £45,200 GBP per QALY gained. This was due to the projected ICS use for the FeNO testing groups. Sensitivity analyses showed that the ICER results were sensitive to the changes in ICS use over time and the number of nurse visits for FeNO testing.

Table 5: Results of Economic Literature Review – Summary

Author, year, country	Analytic technique, study design, perspective, time horizon	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
Berg and Lindgren, 2008,[116] Germany	Type of analysis: Cost-analysis and cost–utility Study design: Model based, decision trees Perspective: German healthcare payer Time horizon: Management model: 1 year Cost: Euro (year NR) Discount rate: NA	Patients (assumed adults) with mild to severe asthma who are seen in both primary and secondary care	Intervention: FeNO testing (NIOX MINO) (as a replacement) Comparator: <u>Diagnostic model</u> Standard diagnostic (spirometry, reversibility testing, bronchial provocation, sputum eosinophil count) <u>Management model</u> Standard treatment guidelines (spirometry)	<u>Diagnostic model</u> Intervention: NR Comparator: NR MD: NR Management model Mild to severe patients Intervention: 0.781 QALYs Comparator: 0.726 QALYs MD: 0.055 QALYs MD from SA: 0.029 (–0.144 to 0.205) QALYs Mild to severe patients Intervention: NR Comparator: NR MD from SA: 0.003 (–0.017 to 0.025) QALYs	<u>EUR</u> Diagnostic model (patient/year) Intervention: €38 Comparator: €26 MD: €12Management model Mild to severe patients Intervention: €949 Comparator: €981 MD: –€32 MD from SA: –€24 (–96 to 41) Moderate to severe asthma: Intervention: €949 Comparator: €981	<u>Diagnostic model</u> Diagnosis based on FeNO measurement compared with standard testing cost and additional €12/patient (95% CI: €9 to €14) The largest impact in one-way sensitivity analyses from: • Reimbursement price of FeNO device • Cost of standard testing • FeNO vs. bronchoprovocation + spirometry • -FeNO + spirometry vs. bronchoprovocation + spirometry <u>Management model</u> FeNO measurement dominates standard care guidelines Second-order stochastic sensitivity analysis show results are uncertain

Author, year, country	Analytic technique, study design, perspective, time horizon	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
					MD: –€161 MD from SA: –€110 (–297 to 26)	
Brooks and Massanari, 2018[117] United States	Type of analysis: Cost–utility Study design: Model based, decision trees? Perspective: healthcare payer Time horizon: Management model: 1 year Cost: $2,016 USD Discount rate: NA	Non-smoking adults, diagnosed with mild to severe asthma, seen in both primary and secondary care centres	Intervention: FeNO testing in conjunction with SOC Comparator: current SOC in asthma management	<u>Management model</u> Intervention: 0.844 QALYs Comparator: 0.767 QALYs MD: NR	<u>USD</u> Management model Intervention: $2,228 Comparator: $2,637 MD: NR	FeNO testing in conjunction with standard care guidelines dominates standard care guidelines
Buendia et al, 2021,[118] Colombia	Type of analysis: Cost–utility Study design: Model based, Markov model Perspective: societal Time horizon: Management model: 1 year	Aged between 4 and 18 year with mild to moderate allergic asthma	Intervention: FeNO testing in conjunction with SOC Comparator: current SOC	<u>Management model</u> Intervention mean: 0.9395 QALYs (0.93–0.94) Comparator mean: 0.9233 QALYs (0.91–0.92) MD: 0.016	<u>USD</u> Management model Intervention mean: $1,333.57 ($1,331 to $1,335) Comparator mean: $1,452.38 ($1,449 to $1,454) MD: –$118.81	FeNO testing used in asthma management dominated standard asthma management Probabilistic sensitivity analysis found 53.82% of simulations fell in quadrant 2 (lower cost, high QALYs) and 45.97% fell in quadrant 1 (high cost, high QALYs)

Author, year, country	Analytic technique, study design, perspective, time horizon	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
	Cost: USD (year NR) Discount rate: NA					
Darba et al, 2021,[119] Sweden	Type of analysis: Cost-analysis and budget impact Study design: Model based, structure unclear Perspective: Swedish healthcare payer Time horizon: Diagnostic model: 4–year budget impact Management model: NR Cost: 2019 SEK Discount rate: NA	10,421,400 residents in primary health care in Sweden	Intervention: <u>Diagnostic model</u> FeNO measurement compared individually with each test Management model FeNO measurement compared individually with each diagnostic test Comparator: standard diagnostic tests used in Swedish primary care • Spirometry and reversibility testing • Methacholine challenge test • Allergy testing • Blood eosinophil count	<u>Diagnostic model</u> NR Management model Test effectiveness FeNO testing: 0.68 Spirometry and reversibility test: 0.35 Methacholine challenge test: 0.88 Allergy test: 0.42 Blood eosinophil count: 0.21 Mean Difference: FeNO vs. spirometry and reversibility test: 0.33 FeNO vs. methacholine challenge test: –0.20 FeNO vs. allergy test: 0.26	<u>SEK</u> Diagnostic model Budget impact from 2020 to 2023 Economic burden with FeNO testing: Adults: 4,461 million to 5,285 million Pediatric: 909 million to 1,015 million Economic burden without FeNO: Adults: 4,450 million to 5,414 million Pediatric: 907 million to 1,115 million Mean Difference: Adults: 10 million to–128 million Pediatrics: 2 million to –99 million	<u>Diagnostic model</u> Adding FeNO testing in clinical practice costs SEK 672 less per patient (saving 495 per adult patient, and 1,679 per pediatric patient) The largest impact on savings with FeNO diagnosis was determined using one-way sensitivity analyses: • Asthma prevalence • Cost of FeNO test • Cost of standard testing <u>Management model</u> FeNO vs. spirometry and reversibility test: dominant FeNO vs. methacholine challenge test: less effective, less costly FeNO vs. allergy test: dominant

Author, year, country	Analytic technique, study design, perspective, time horizon	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
				FeNO vs. blood eosinophil count: 0.47	Management model FeNO testing: 7,906 Spirometry and reversibility test: 11,921 Methacholine challenge test: 15,747 Allergy test: 10,311 Blood eosinophil count: 10,087 Mean Difference: FeNO vs. spirometry and reversibility test: –4,016 FeNO vs. methacholine challenge test: –7,842 FeNO vs. allergy test: –2,406 FeNO vs. blood eosinophil count: –2,181	FeNO vs. blood eosinophil count: dominant One-way sensitivity analyses for management model showed FeNO remained dominant compared with all other tests except methacholine challenge test for all parameter changes (SN, SP, prevalence test, and treatment costs) PSA not done

Author, year, country	Analytic technique, study design, perspective, time horizon	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
Harnan et al, 2015,[97] United Kingdom	Type of analysis: Cost–utility Study design: Model based, decision tree and Markov model Perspective: UK healthcare payer Time horizon: Diagnostic model: 5 year Management model: lifetime Cost: 2012/13 GBP Discount rate: 3.5%	<u>Diagnostic model</u> People (children and adults) with symptoms of asthma seen in primary and secondary care in England and Wales Management model Children (aged 5–17) and adults (≥ 18) who have been diagnosed with asthma	Intervention: FeNO measurement Comparator: standard care for the diagnosis and management of asthma	<u>Diagnostic model</u> Airway hyper-responsiveness (MCT): 4.2834 QALYs FeNO + bronchodilator reversibility (NObreath): 4.2829 QALYs FeNO + sputum induction (NObreath): 4.2812 QALYs FeNO + FEV_1 (NObreath): 4.2783 QALYs Sputum induction: 4.2774 QALYs FeNO (NObreath): 4.2771 QALYs FeNO (NIOX VERO): 4.2771 QALYs FeNO (NIOX MINO): 4.2771 QALYs PEF: 4.2719 QALYs Bronchodilator reversibility: 4.2710 QALYs FEV_1/FVC: 4.2686 QALYs Management model (children)	<u>GBP</u> Diagnostic model Airway hyper-responsiveness (MCT): £1,226.00 FeNO + bronchodilator reversibility (NObreath): £686.08 FeNO + sputum induction (NObreath): £1,265.78 FeNO + FEV_1 (NObreath): £810.14 Sputum induction: £1,328.28 FeNO (NObreath): £819.94 FeNO (NIOX VERO): £821.47 FeNO (NIOX MINO): £822.18 PEF: £877.91 Bronchodilator reversibility: £886.27 FEV_1/FVC: £907.71	<u>Diagnostic model</u> Airway hyper-responsiveness (MCT): £1,125,074/QALY GBP FeNO + bronchodilator reversibility (NObreath): -- FeNO + sputum induction (NObreath): dominated FeNO + FEV_1 (NObreath): dominated Sputum induction: dominated FeNO (NObreath): dominated FeNO (NIOX VERO): dominated FeNO (NIOX MINO): dominated PEF: dominated Bronchodilator reversibility: dominated FEV_1/FVC: dominated At a WTP of £20,000 per QALY gained, FeNO plus bronchodilator reversibility

Author, year, country	Analytic technique, study design, perspective, time horizon	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
				Guidelines plus FeNO (NObreath): 23.6767 QALYs Guidelines plus FeNO (NIOX VERO): 23.6767 QALYs Guidelines plus FeNO (NIOX MINO): 23.6767 QALYs Guidelines: 23.6261 QALYs Mean Difference: Guidelines plus FeNO (NObreath) vs. guidelines: 0.0506 Management model (adults) Guidelines plus FeNO monitoring (NObreath): 21.9397 QALYs Guidelines plus FeNO monitoring (NIOX VERO): 21.9397 QALYs Guidelines plus FeNO monitoring (NIOX MINO): 21.9397 QALYs Guidelines: 21.9018 QALYs Mean Difference:	Management model (children) Guidelines plus FeNO (NObreath): £8,148.59 Guidelines plus FeNO (NIOX VERO): £8,314.30 Guidelines plus FeNO (NIOX MINO): £8,391.53 Guidelines: £5,860.06 Mean Difference: Guidelines plus FeNO (NObreath) vs. guidelines: £2,288.53 Management model (adults) Guidelines plus FeNO monitoring (NObreath): £7,377.61 Guidelines plus FeNO monitoring (NIOX VERO): £7,535.43 Guidelines plus FeNO monitoring (NIOX MINO): £7,608.99 Guidelines: £7,296.30	(using NObreath) is likely most cost-effective (probability = 0.98). Across the majority of the DSA scenarios, the results are maintained <u>Management model (children)</u> Guidelines plus FeNO (NObreath) vs. guidelines: £45,213 GBP/QALY Guidelines plus FeNO (NIOX VERO): dominated Guidelines plus FeNO (NIOX MINO): dominated At a WTP of £20,000 GBP per QALY gained, use of guidelines alone is likely most cost-effective (probability = 0.99). <u>Management model (adults)</u> Guidelines plus FeNO monitoring (NObreath) vs. guidelines: £2,146 GBP/QALY Guidelines plus FeNO monitoring (NIOX VERO): dominated

Author, year, country	Analytic technique, study design, perspective, time horizon	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
				Guidelines plus FeNO monitoring (NObreath) vs. guidelines: 0.0379	Mean Difference: Guidelines plus FeNO monitoring (NObreath) vs. guidelines: £81.31	Guidelines plus FeNO monitoring (NIOX MINO): dominated At a WTP of £20,000 GBP per QALY gained, FeNO monitoring using NObreath plus guidelines is likely most cost-effective (probability = 0.82) Results from the DSA analysis are similar to those produced using the probabilistic model
Price et al, 2009,[120] United Kingdom	Type of analysis: Diagnostic model: cost-analysis Management model: cost–utility Study design: Model-based, decision trees Perspective: UK healthcare payer Time horizon: Diagnostic model: unclear, presentation to correct diagnosis	Nonsmoking adults with mild to severe asthma seen in both primary and secondary care	Intervention: FeNO measurement (NIOX MINO) Comparator: <u>Diagnostic model</u> Blended comparison of standard diagnostic tests: (1) lung function test, (2) reversibility test, (3) bronchial Provocation, and (4) sputum eosinophil count <u>Management model</u> Standard care lung function testing	<u>Diagnostic model</u> Intervention: NR Comparator: NR Mean difference: NR Management model Mild to severe asthma: Intervention mean: 0.785 QALYs Comparator mean: 0.726 QALYs	<u>GBP</u> Diagnostic model (per patient) Intervention mean: £29 Comparator mean: £72 MDD: –£43 Management model (per patient per year) Mild to severe asthma: Intervention mean: £666 Comparator mean: £1,007	<u>Diagnostic model</u> FeNO measurement alone is less costly (£43 GBP/patient) and more accurate than standard diagnostic methods FeNO testing remained cost-saving across one-way sensitivity analyses except: • FeNO testing cost +200% • FeNO combined with FEV_1 vs. standard testing <u>Management model</u>

Author, year, country	Analytic technique, study design, perspective, time horizon	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
	Management model: 1 year Cost: 2005 GBP Discount rate: NA			Mean Difference: 0.059 QALYs Moderate to severe asthma: MD: 0.004 QALYs	MD: –£341 Moderate to severe asthma MD: –£554	FeNO measurement compared to lung function testing was a dominant strategy (annual cost-savings of £341 GBP and 0.059 QALYs gained for people with mild to severe asthma and a cost-savings of £554 and 0.004 QALYs gained for those with moderate to severe asthma FeNO testing remained dominant across one-way sensitivity analyses except when adding FeNO with lung function vs. lung function (£279 GBP per QALY) PSA not done
Sabatelli et al, 2017,[121] Spain	Type of analysis: Cost-effectiveness and budget impact Study design: Model based, decision tree Perspective: Spanish healthcare payer	100,000 people with asthma aged ≥ 15 year in primary care settings	Intervention: FeNO testing in conjunction with SOC Comparator: current SOC	<u>Management model</u> Intervention mean: 0.802 QALYs Comparator mean: 0.776 QALYs MD: 0.026 QALYs	<u>EUR</u> Management model (per patient) Intervention mean: €790.05 Comparator mean: €852.58 MD: –€62.53	FeNO monitoring in addition to asthma management guidelines dominated standard asthma management guidelines alone (0.026 QALYs gained, with a cost-savings of €62.53 EUR per patient) PSA: at a threshold of €30,000 EUR, FeNO added to SOC was cost-effective in 998/1,000 runs and

Author, year, country	Analytic technique, study design, perspective, time horizon	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
	Time horizon: Management model: 1 year Cost: 2012 Euro Discount rate: NA					cost-saving in 874/1,000 runs One-way sensitivity analysis: FeNO in addition to SOC was dominant for all parameter changes Budget impact of FeNO monitoring in Spain for varying uptake rates (20% to 100%) ranged from a yearly savings of nearly €26 million to €129 million

Abbreviations: DSA, deterministic sensitivity analysis; MCT, methacholine challenge testing; MD, mean difference; NA, not applicable; NR, not reported; PEF, peak expiratory flow; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; SA, sensitivity analysis; SN, sensitivity; SOC, standard of care; SP, specificity; WTP, willingness to pay.
*Dominant indicates the intervention is less costly and more effective.

Applicability and Limitations of the Included Studies

Appendix Table A8 provides the results of the quality appraisal checklist for economic evaluations applied to the included studies. One study was not applicable,[119] while 6 were partially applicable to the research question.[97,116-118,120,121] The concerns related to applicability mainly arise from 3 sources: standard care practices that are different for Ontario, variability in the modeling structures, and strong assumptions on the impact of misdiagnosis.

We did not assess the limitations of these studies as they were considered not directly applicable.

Discussion

We identified 7 economic studies that evaluated the cost-effectiveness of FeNO testing for the diagnosis and/or management of asthma. Based on the studies on FeNO testing for asthma diagnosis included in this review, the cost-effectiveness results of FeNO testing (alone or as an add-on test to standard diagnostic testing) compared with standard care alone was uncertain. The results of the studies on FeNO testing for asthma management included in this review were also uncertain. FeNO testing combined with standard treatment guidelines in asthma management was not cost-effective compared to standard treatment guidelines alone among children of 5 years of age or older in 1 study,[97] while another study showed the opposite results.[118] All[116,117,119-121] but 1 study[97] concluded FeNO testing compared with standard treatment guidelines was cost-saving for asthma management in adults.

The literature suggests that the cost-effectiveness of FeNO testing might depend on how the test was used and the comparator. Treatment strategies varied across the included studies. FeNO testing was assessed as both a stand-alone test and as an adjunct to standard diagnosis and management. Additionally, for the diagnosis of asthma, some studies evaluated FeNO testing against a blended comparator by assigning frequency weights to each test used in the local standard diagnosis practice,[116,120] while others compared FeNO testing individually as a single strategy or in combination with tests in standard care.[97] The cost of asthma diagnosis was also different, depending how the test was used. Heterogeneity of clinical practice in asthma diagnosis and management across countries likely impacted modeling results. There are also likely differences in clinical practices between those jurisdictions and Canada.

There was variability in the management model structures and health states included in the analyses. Three management models were constructed using a decision tree structure,[116,120,121] while 2 studies used Markov structures.[97,118] The model structure used in 2 studies was unclear.[117,119] Additionally, in the management models with Markov structure, different health states were included in some of the analyses. Some studies used shorter cycle lengths and patients could move between well-controlled, sub-optimal control, and asthma exacerbations in their model. In the model by Harnan et al,[97] 2 states were captured (diagnosed asthma and dead), and asthma exacerbations were captured through disutility. Therefore, the cost and utility parameters related to asthma and how these parameters are modelled may influence the results.

The impact of misdiagnosis and its correction was fully considered in a few analyses, but they relied on strong assumptions. For example, Buendia et al[118] assumed that all misdiagnoses are resolved by the next episode of testing. However, it is unclear which tests were used or how many follow-up visits would be required. Evidence indicates that it is often months or years before a misdiagnosis is corrected, if at all, in some people. Misdiagnoses may incur unnecessary treatment costs and health losses. In many

studies, the negative health consequences (e.g., QALY losses) associated with incorrect diagnoses are not quantified in the model.[120] Many of the models also did not account for the potential health benefits associated with improved accuracy of diagnosis.

Conclusions

We identified a total of 7 published economic studies for FeNO testing, 4 of which assessed the use of FeNO testing for both diagnosis and management of asthma, and another 3 assessed the use of FeNO testing for the management of asthma. However, no study was directly applicable to either of our research questions and the results were mixed. To determine the cost-effectiveness of FeNO testing in the Ontario setting, we decided to conduct a primary economic evaluation that incorporates Ontario-specific clinical pathways and uses the latest clinical evidence and costs to inform the model parameters.

Primary Economic Evaluation – Asthma Diagnosis

Research Question

From the perspective of the Ontario Ministry of Health, what is the cost-effectiveness of FeNO testing compared with standard testing used for diagnosis in people with suspected asthma?

Methods

The information presented in this report follows the reporting standards set out by the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.[122] The content of this report is based on a previously developed economic project plan.

Type of Analysis

For the reference case, we conducted a probabilistic cost–utility analysis as recommended by the Canadian Agency for Drugs and Technologies in Health (CADTH) guidelines for economic evaluation.[123] We used QALYs as the effectiveness outcome. QALYs consider both the person's survival and quality of life (e.g., 1 QALY represents 1 year of perfect health). A generic outcome measure such as the QALY allows decision-makers to make comparisons across conditions and interventions. We also conducted a cost-effectiveness analysis with outcomes expressed in natural units, such as the numbers of true positive, false positive, true negative, and false negative diagnoses.

Population of Interest

For the diagnosis of asthma, the population of interest consists of individuals presenting with clinical symptoms suggestive of asthma (e.g., shortness of breath, chest tightness, wheezing, and/or cough). They may or may not have true underlying asthma. We conducted analyses for children (aged 5–17 years) and adults (aged ≥ 18 years) separately because they have different diagnostic pathways, health-related quality of life (HRQoL), health resource use, and costs. The starting age for the children model was 5 years, to reflect the eligible population, and the starting age of the adult model was 40 years, based on the average age seen in the clinical trials in this population.

Subgroup Analysis

We did not conduct an equity-related subgroup analysis due to the limited data available.

Perspective

We conducted this analysis from the perspective of the Ontario Ministry of Health.

Interventions and Comparators

Comparators

As mentioned in the Background, above, asthma diagnosis in primary care is based on medical history, physical examination, and objective lung function tests. In Ontario, spirometry showing reversible airflow obstruction is the preferred objective test. Successful airway reversibility or improvement in peak flow in response to bronchodilator administration supports a diagnosis of asthma, but a negative spirometry result does not rule out asthma. For those who have normal or inconclusive spirometry tests, a positive challenge test (also known as bronchial provocation test) is used to confirm an asthma diagnosis.[12,124]

Interventions

FeNO testing is a relatively quick and non-invasive test that can be used in both children (aged 5–17 years) and adults (aged ≥ 18 years) as an addition to standard testing.[22] As indicated in the clinical review, the FeNO test should be administered by a health care professional as the device requires calibration and the use of an acceptable expiratory flow rate and exhalation period. The benefits of FeNO devices are that they can be administered in most health care settings, are non-invasive, and provide immediate results to support asthma care decisions.[23] For the reference case analysis, we assumed that FeNO testing for asthma diagnosis would be done in the special care setting (specialist's office) or in the laboratory.

Two portable FeNO devices have been approved for use by Health Canada: the NIOX VERO system and the NIOX MINO airway inflammation monitor. Although the devices may have slightly different diagnostic accuracy, for simplicity we assumed that the diagnostic accuracy is similar between devices. In clinical guidelines,[19-21] the optimal cutoff values for FeNO testing vary (Table 5):

- We used a cutoff value of 33 ppb for our reference case analysis in adults, based on the available clinical data.[73] We examined the accuracy of FeNO testing at a higher cutoff value of 50 ppb for our scenario analysis
- We used a cutoff value of 21 ppb for our reference case analysis in children, based on the available clinical data[50]

We evaluated two diagnostic testing strategies involving FeNO testing (Table 6):

- The first strategy is conducting a spirometry test and then moving on to FeNO testing if the spirometry test result is negative (the sequential testing strategy). Bronchial provocation is conducted if the result of FeNO testing is negative
- The second strategy is conducting FeNO testing at the same time as spirometry (the combined testing strategy). FeNO testing and spirometry can be done in 1 visit at either a specialist's office or in the laboratory. Bronchial provocation is conducted if the results of FeNO testing and spirometry are both negative

More details about the testing strategies are provided in the model structure section.

Table 6: Population, Interventions, Comparators, and Outcomes Evaluated in the Diagnostic Model

Decision problem	Patient population	Interventions	Comparator	Outcomes
Diagnosis	Individuals presenting with clinical symptoms suggestive of asthma (e.g., shortness of breath, chest tightness, wheezing, and/or cough) • Children (aged 5–17 years) • Adults (aged ≥ 18 years)	2 diagnostic strategies involving FeNO as an add-on test to standard testing • Sequential testing strategy • Combined testing strategy	Standard testing without FeNO (spirometry, bronchial provocation test)	Total costs, QALYs, and incremental cost per QALY gained Numbers of TP, FP, FN, and TN diagnosis

Abbreviations: FeNO, fractional exhaled nitric oxide; FN, false negative; FP, false positive; QALY, quality-adjusted life years; TN, true negative; TP, true positive.

Time Horizon and Discounting

We applied a 20-year time horizon in our reference case analysis. Since asthma is a chronic condition, a 20-year time horizon would allow the long-term effects of FeNO testing on costs and clinical outcomes to be captured. In accordance with CADTH guidelines,[125] we applied an annual discount rate of 1.5% to both costs and QALYs incurred after the first year. We also applied a shorter time horizon (10 years) in a scenario analysis.

Model Structure

We based our diagnostic model on the recommended standard practice in Ontario and clinical guidelines. The diagnostic model consists of 2 parts: a decision tree (Figure 9) and four Markov models (Figure 10, A–D). Using test sensitivity, specificity, and pre-test probability of asthma in the defined population, the decision tree calculates the proportion of patients that will receive true positive, false positive, false negative, or true negative diagnoses. After that, patients would enter different Markov models based on the type of diagnosis to track the long-term costs and health outcomes.

We developed a decision tree model to reflect the following three possible diagnostic strategies of asthma in Ontario (Figure 9). In each case, the diagnosis, whether positive or negative, can be either true or false.

Standard Tests

Currently in Ontario, a person who is suspected by their primary care provider of having asthma would be referred to take a spirometry test. If they test positive with spirometry, they are diagnosed as having asthma and would receive treatment as appropriate. If they test negative with spirometry, they would receive a bronchial provocation test. If they test positive with the bronchial provocation test, they would be diagnosed as having asthma and receive treatment as appropriate. If the person tests negative with a bronchial provocation test, they would not receive asthma treatment.

FeNO and Spirometry Sequential Testing Strategy

A person with suspected asthma would be referred to take a spirometry test. If they test positive with spirometry, they would be diagnosed as having asthma and receive treatment for asthma. If the test is negative or inconclusive, they would receive FeNO testing for further diagnosis. If they test positive with FeNO, they would be diagnosed as having asthma and receive treatment for asthma. If they test negative with FeNO, they would receive a bronchial provocation test for further diagnosis. If they test positive with a bronchial provocation test, they would be diagnosed as having asthma and receive treatment as appropriate. Otherwise, they would be diagnosed as not having asthma and receive no treatment.

FeNO and Spirometry Combined Testing Strategy

FeNO and spirometry tests would be conducted in the same visit. If the person tests positive with either FeNO or spirometry, they would be diagnosed as having asthma and receive treatment as appropriate. If they test negative with both FeNO and spirometry, they would receive a bronchial provocation test for further diagnosis. If they test positive with a bronchial provocation test, they would be diagnosed as having asthma and receive treatment as appropriate. Otherwise, they would be diagnosed as not having asthma and receive no treatment.

In all strategies, a person could be correctly or incorrectly diagnosed with asthma (true positive [TP] or false negative [FN]). Similarly, a person without asthma could be correctly or incorrectly diagnosed (true negative [TN] or false positive [FP]).

A person who receives a TP diagnosis would enter the Markov model depicted in Figure 10A. All patients start in the "correctly treated asthma" health state and remain there until they die. Within the "correctly treated asthma" state, people will receive asthma treatment; some may experience an exacerbation.

A person who receives a FP diagnosis would enter the Markov model depicted in Figure 10B, which consists of three health states: (1) "non-asthma conditions, incorrectly treated for asthma," (2) "non-asthma conditions," and (3) dead. All patients start in the "non-asthma conditions, incorrectly treated for asthma" health state of the model. They experience the quality of life of people without asthma, the QALY losses are due to the false positive diagnosis and the cost of additional diagnostic testing to correct the misdiagnosis, as well as the cost of unnecessary treatment for asthma.

Based on expert consultation (Dr. Gupta, email communication, September 18 2023) and the published literature (Harnan et al),[97] a FP diagnosis may require about 2 to 5 years to be corrected. Some FP diagnoses last for many years. In our model, we assumed a FP diagnosis would be corrected after a period of at least 2 but no more than 5 years. For simplicity, we assumed that the rate of FP diagnoses being corrected would remain constant each year. This yearly rate was subsequently converted into a monthly transition probability ($p = 0.08$) and populated in the model. Once a false diagnosis is corrected, the person would move to the "non-asthma conditions" health state. People in this health state may incur other treatment costs from their underlying health condition. However, we did not include non-asthma treatment costs in the reference case because there are a wide range of non-asthma conditions and any cost estimate would be outside the scope of this analysis. During any model cycle, a patient could die and move to the "dead" health state (Figure 10D). We also conducted a scenario analysis in which the duration for correcting a FP diagnosis is 10 years.

A person who receives a FN diagnosis would enter the Markov model depicted in Figure 10C, which consists of three health states: (1) "undiagnosed and untreated for asthma," (2) "treated asthma," and (3) dead. All patients start in the "undiagnosed and untreated asthma" health state of the model. They experience the quality-of-life of people with asthma, the QALY losses due to incorrect diagnosis (false negatives), and the costs of additional diagnostic tests, additional visits to a family doctor to correct misdiagnosis, and the cost of exacerbations due to uncontrolled asthma. Because the asthma goes untreated, there is a higher risk of asthma exacerbation in these patients compared with people in the TP group who are treated for asthma.

We assumed that the misdiagnosis would be corrected either when an exacerbation occurs as a result of uncontrolled asthma, or after 5 years have passed (we assumed that all FN diagnoses would be corrected by Year 5). At this point, they move to the "treated asthma" state. People in the "treated asthma" state receive asthma treatment, and a small proportion of them may experience exacerbations. During any model cycle, a patient could die and move to the "dead" state (Figure 10C).

A person who receives a TN diagnosis would enter the Markov model depicted in Figure 10D, which consists of two health states: (1) "non-asthma conditions" and (2) "dead." All patients start in the "non-asthma conditions" health state and experience the quality-of-life of people without asthma and incur only the cost of additional diagnostic tests. In this health state, people may incur other treatment costs for their underlying health condition. However, we did not include non-asthma treatment costs in the reference case because there are a wide range of non-asthma conditions and cost estimates would be outside the scope of this analysis. During any model cycle, a patient could die and enter the "dead" health state (Figure 10D).

The cycle length of the Markov model is 1 month. The starting age for an adult entering the Markov model is 40 (this is the most common age in published studies).[73,126] The starting age for a child entering the Markov model is 5.[127]

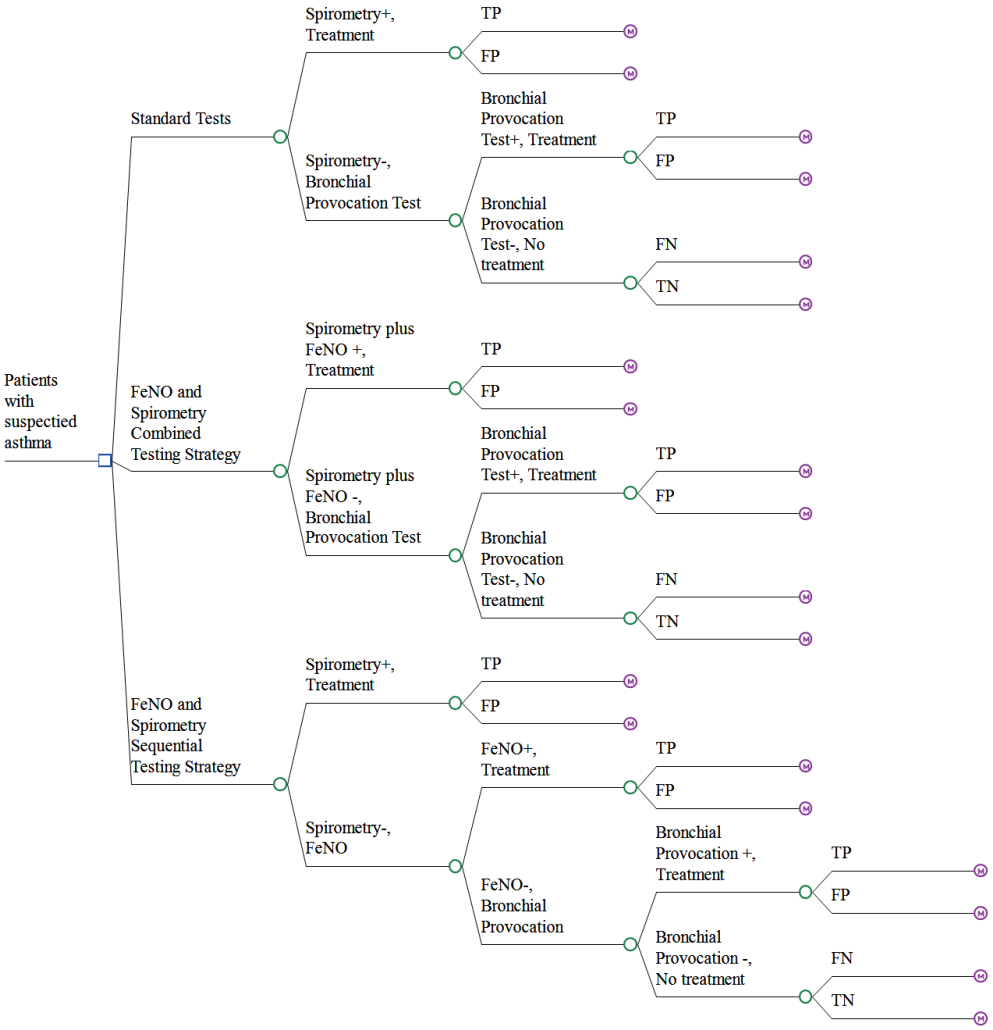
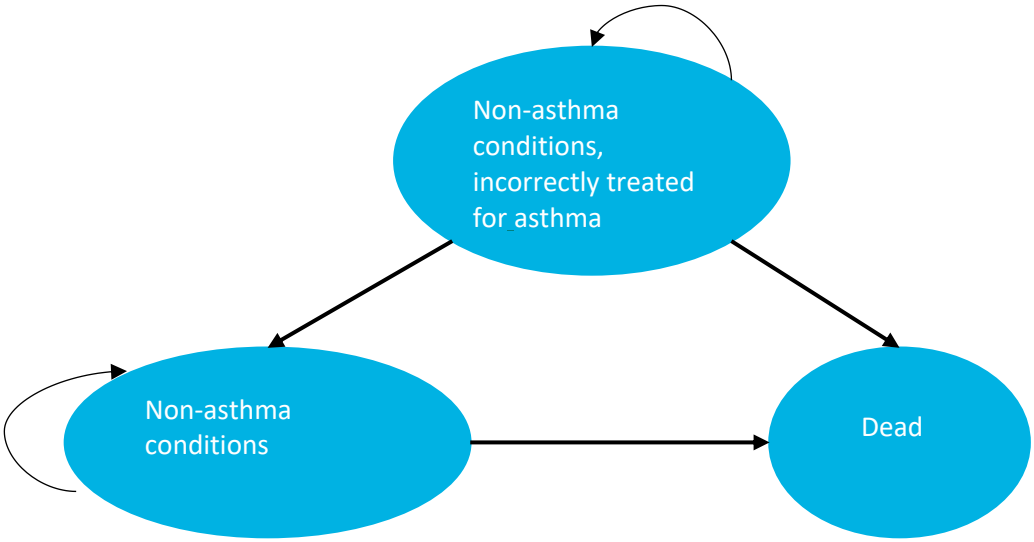


Figure 9: Asthma Diagnostic Model Structure

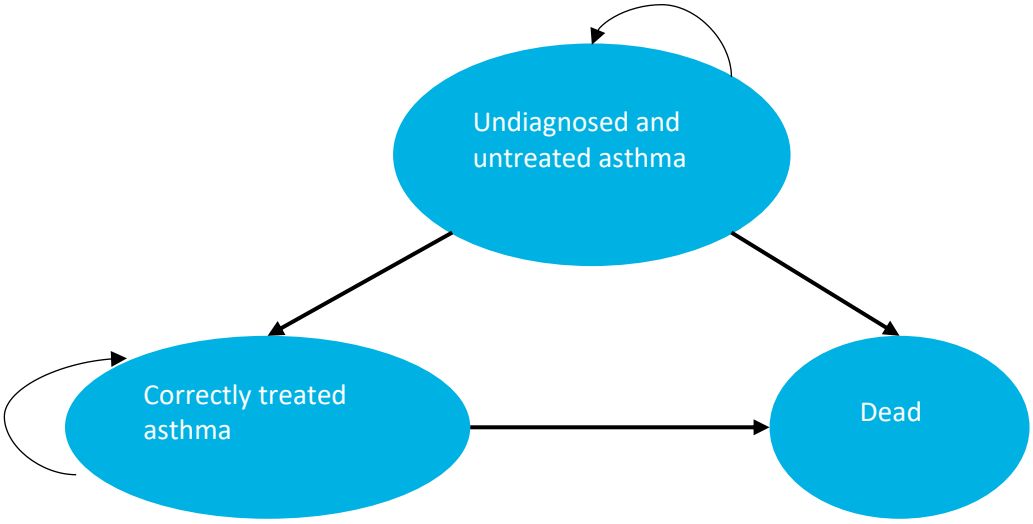
Decision tree of the asthma diagnostic model structure showing people with suspected asthma receiving 1 of 3 treatment protocols (standard care, FeNO and spirometry combined, and FeNO and spirometry sequential), eventually leading to TP, FP, TN, or FN results.

A: Markov Model for True Positive Diagnoses

B: Markov Model for False Positive Diagnoses



C: Markov Model for False Negative Diagnoses



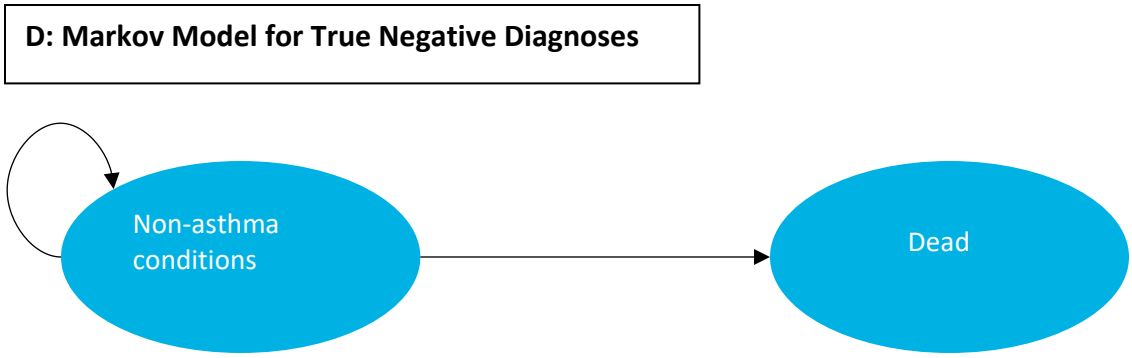


Figure 10: Markov Models for Asthma Diagnoses

Footnotes: Although exacerbations were not shown in the diagram, the model captured the costs and QALY losses due to exacerbations. Due to the fact these exacerbations were temporary (e.g., an exacerbation could last for a few days or up to a month), we did not specifically assign a health state for exacerbations.
Markov model showing the possible states for people with asthma diagnoses. In part A, people with a true positive diagnosis are in the correctly treated asthma state until they move to the dead state. In part B, people with a false positive diagnosis may be in 1 of 3 states – non-asthma conditions incorrectly treated for asthma state, non-asthma conditions state, and dead. In part C, people with a false negative diagnosis are in the undiagnosed and untreated asthma state, the correctly treated asthma state, or dead. In part D, people with a true negative diagnosis are in the non-asthma conditions state or dead.

Main Assumptions

For simplicity, we assumed that, on average, all incorrect diagnoses (false negatives and false positives) would be corrected after 5 years (60 months) in the reference case analysis. In the scenario analyses, we assumed all incorrect diagnoses would be resolved after 10 years. Moreover, there would be additional costs incurred for correcting these wrong diagnoses (e.g., physician's visits and additional diagnostic testing).

A person with a false negative diagnosis would remain misdiagnosed for a maximum of 5 years if an exacerbation does not occur. However, they might experience an increased rate of exacerbations because their asthma condition might be uncontrolled due to the incorrect diagnosis. After an exacerbation, a patient with a false negative would be correctly identified as having asthma and would be correctly treated. If an exacerbation does not occur, a patient with a false negative diagnosis would remain misdiagnosed for a maximum of 5 years.

As seen in the clinical section, above, asthma-related mortality is relatively low. We, therefore, assumed that improved diagnostic accuracy has no impact on mortality within the time horizon of the model. People would follow age-specific mortality.

FeNO testing, spirometry, and bronchial provocation testing would be conducted in a specialist office or a laboratory. All tests would be conducted by a specialist (i.e., a respirologist). A referral by a primary care physician would be needed for tests such as spirometry. For simplicity, we assumed that different FeNO devices would have the same sensitivity and specificity. FeNO was conditionally independent from other tests. As FeNO testing is the only test in the model that measures inflammation of the airways, a person's FeNO count is unlikely to be dependent on the results of other tests.[19]

Clinical Outcomes and Utility Parameters

We used several types of input parameters to populate the model:

- Prevalence of asthma (i.e., pre-test probability) among patients (children and adults) with suspected asthma
- Sensitivity and specificity of different diagnostic tests (FeNO testing, spirometry, bronchial provocation test)
- Natural history of asthma (mortality, baseline risk of exacerbation)
- Health state utilities (i.e., quality of life)

The pre-test probability of asthma and the diagnostic accuracy of different tests were determined based on the clinical evidence review, which included a total of 48 primary studies on diagnostic accuracy. We selected the studies considered most applicable to the Ontario setting. We specifically considered study recency, whether a NIOX brand device (approved for use in Canada) was used, timing of the intervention, whether the reference standard included spirometry and methacholine challenge tests (reflecting standard practice in Ontario), and whether limitations were placed on the type of asthma included.

Pre-test Probability of Asthma

de Jong et al[50] estimated the pre-test probability of asthma in children to be 0.72 (Table 7). Louis et al[73] estimated the pre-test probability of asthma for the adult population to be 0.63 (Table 7). The pre-test probabilities were based on the same studies from which we obtained the diagnostic accuracy of FeNO testing and spirometry. In actual clinical practice, the pre-test probability of asthma likely varies significantly. Therefore, we used a wide range of possible values in our sensitivity analyses to explore the impacts of this parameter on the cost-effectiveness result.

Diagnostic Accuracy

SPIROMETRY

For children, we took the diagnostic accuracy of spirometry (FEV_1/FVC ratio) from the study published by de Jong et al[50] (included in the clinical review). The authors reported the sensitivity and specificity of spirometry at 0.46 and 0.93, respectively (Table 7). For adults, we took the diagnostic accuracy of spirometry (FEV_1/FVC ratio) from the study published by Louis et al.[73] The authors reported the sensitivity and specificity of spirometry at 0.54 and 0.79, respectively (Table 7). The 2 studies were included in the clinical review and the diagnostic accuracy of FeNO for children and adults was also taken from these studies for the reference case analyses.

BRONCHIAL PROVOCATION

For children, the diagnostic accuracy of bronchial provocation was taken from de Jong et al.[50] The authors reported the sensitivity and specificity of bronchial provocation at 0.83 and 0.72, respectively (Table 7). For adults, the diagnostic accuracy of bronchial provocation was taken from Louis et al.[73] The authors identified 3 studies reporting on the diagnostic accuracy of bronchial provocation. After reviewing the studies, we decided to take the sensitivity and specificity of bronchial provocation from

Porpodis et al.[128] The Porpodis authors reported the diagnostic accuracy of bronchial provocation at 0.63 and 0.86 respectively (Table 8).

FeNO Testing

For children, we obtained the diagnostic accuracy from de Jong et al.[50] The authors reported the sensitivity and specificity of FeNO testing (using a cut off value of 21 ppb) at 0.59 and 0.87, respectively (Table 7). For adults, we obtained the diagnostic accuracy from Louis et al.[73] The authors reported the sensitivity and specificity of spirometry at 0.32 and 0.83, respectively (Table 8).

The diagnostic accuracy of FeNO testing varied significantly across studies (see clinical evidence review, above). In a scenario analysis, we used the diagnostic accuracy of FeNO testing from Louis et al.[73] The authors identified 6 studies reporting the diagnostic accuracy of FeNO testing (using a cut off of 25 ppb). These studies were meta-analyzed to provide pooled estimates for the sensitivity and specificity of FeNO testing, which were 0.53 (95% CI: 0.33–0.72) and 0.72 (95% CI: 0.61–0.81; Table 8). We also explored the diagnostic accuracy of FeNO testing at the higher cut off of 50 ppb used by Schneider et al,[85] in which the sensitivity and specificity of FeNO testing was reported at 0.24 and 0.99, respectively.

Combined Test Accuracy

We calculated the sensitivity and specificity of FeNO testing and spirometry as a combined test (taken in the same visit). In this strategy, ruling in asthma required only that 1 test be positive (either FeNO or spirometry). This approach allowed us to capture the maximum number of patients with asthma. However, it would also reduce the specificity or increase the false negative diagnoses. We, therefore, calculated the sensitivity and specificity of FeNO testing and spirometry according to the following formula, in which the 2 tests are labelled A and B:

> *A or B*
> *If either test is positive, it was considered that the disease or condition was present*
> *Sensitivity:* $(A)_{sen} + (B)_{sen} - ([A])_{sen} \times [B]_{sen})$
> *Specificity:* $(A)_{spec} \times (B)_{spec}$

Based on these formulas, the sensitivity and specificity of the combined FeNO and spirometry was 0.85 (beta distribution: $\alpha = 70$; $\beta = 12$) and 0.53 (beta distribution: $\alpha = 49$; $\beta = 43$), respectively. Data is shown in Tables 7 and 8. The formulas assume A and B are independent of each other. However, when a patient receives 2 imperfect tests, the results might not be independent (i.e., they may have conditional dependence). Therefore, if a patient had a positive (or negative) result in one test, the likelihood of having the same result in another test may be increased. Ideally, it would be important to look at the conditional dependence between different tests used for diagnosing asthma. However, there is limited data available to support modelling. Therefore, we assumed that there was no conditional dependence between FeNO and the other tests (spirometry or bronchial provocation test), based on a prior economic evaluation conducted by NICE.[19]

Time to Resolution of Wrong Diagnoses

The time to resolve incorrect diagnoses was mostly based on expert opinion and published literature. For our reference case analysis, we assumed that a FN diagnosis would be resolved when an exacerbation occurred as a result of uncontrolled asthma, or within 5 years (60 months), whichever

comes first (i.e., the maximum time to resolve a false negative diagnosis is 5 years). According to Jayaram et al,[129] the rate of uncontrolled asthma was 1.02 exacerbations per patient-year. For the purpose of our analysis, we first calculated a monthly rate and then a monthly probability to fit the model parameter (Tables 7 and 8). We assumed that this rate applied to both children and adults.

Mortality/Life Expectancy

Asthma mortality in Ontario was about 0.55 per 100,000 population in 2018.[130] We used all-cause natural mortality from the Canadian life table to estimate the probability of dying and assumed that improved diagnostic accuracy has no impact on mortality.[131]

Table 7: Input Parameters – Asthma Diagnostic Model for Children

Model parameter	Mean	Distribution	Source
Pre-test probability of asthma	0.72	NA	de Jong et al, 2019[50]
Spirometry: sensitivity	0.46	Normal (mean of logit of sensitivity mean = –0.16; SE of logit of sensitivity = 0.24)	Oh et al, 2019[132]
Spirometry: specificity	0.93	Normal (mean of logit of sensitivity mean = 2.59; SE of logit of sensitivity = 0.85)	de Jong et al, 2019[50]
FeNO: sensitivity, 21 ppb	0.59	Normal (mean of logit of sensitivity mean = 0.36; SE of logit of sensitivity = 0.25)	de Jong et al, 2019[50]
FeNO: specificity, 21 ppb	0.87	Normal (mean of logit of sensitivity mean = 1.90; SE of logit of sensitivity = 0.59)	de Jong et al, 2019[50]
FeNO + spirometry: sensitivity (combined test)	0.78	A decision rule is applied following by the OR rule	Calculation
FeNO + spirometry: specificity (combined test)	0.81	A decision rule is applied following by the OR rule	Calculation
Bronchial provocation test: methacholine PC20 < 8 mg/ml – sensitivity	0.83	Normal (mean of logit of sensitivity mean = 1.58; SE of logit of sensitivity = 0.32)	de Jong et al, 2019[50]
Bronchial provocation test: methacholine PC20 < 8 mg/ml – specificity	0.72	Normal (mean of logit of sensitivity mean = 0.94; SE of logit of sensitivity = 0.45)	de Jong et al, 2019[50]
Probabilities under treated asthma (standard care)			
Monthly probability of exacerbations in treated asthmatics	0.0550	Beta	Calculation
Monthly probability of mild exacerbations in treated asthmatics	0.0122	Beta	Calculation
Monthly probability of severe exacerbations in treated asthmatics	0.0428	Beta	Calculation
• Monthly probability of hospitalization due to severe exacerbations in treated asthmatics	0.0039	Beta	Calculation
• Monthly probability of ED visits due to severe exacerbations in treated asthmatics	0.0244	Beta	Calculation
• Monthly probability of GP visits due to severe exacerbations in treated asthmatics	0.0145	Beta	Calculation

Model parameter	Mean	Distribution	Source
Untreated asthma			
Annual rate of exacerbations in untreated asthmatics (FNs)	1.02	Normal (1.02; 0.10)	Harnan et al, 2015[97] and Lloyd et al, 2007[133]
Monthly probability of exacerbations in untreated asthmatics (FNs)	0.08	Beta	Harnan et al, 2015[97]
Ratio for exacerbation of untreated/treated	1.48	Fixed	Calculation
Monthly probability of false positive diagnosis to be corrected between the 25th and 59th months	0.08	Fixed	Calculated

Abbreviations: ED, emergency department; FeNO, fractional exhaled nitric oxide; FN, false negative; GP, general practitioner; NA, not applicable; OR, odds ratio; SE, standard error.

Table 8: Input Parameters – Asthma Diagnostic Model for Adults

Model parameter	Mean	Distribution	Source
Pre-test probability of asthma	0.63	0.15–0.63 for one-way sensitivity analysis	Louis et al, 2023[73]
Spirometry – sensitivity	0.54	Normal (mean of logit of sensitivity = 0.1603; SE of logit of sensitivity = 0.2082)	Louis et al, 2023[73]
Spirometry – specificity	0.79	Normal (mean of logit of sensitivity = 1.3249; SE of logit of sensitivity = 0.3391)	Louis et al, 2023[73]
FeNO – sensitivity, 33 ppb	0.32	Normal (mean of logit of sensitivity = –0.7309; SE of logit of sensitivity = 0.2479)	Louis et al, 2023[73]
FeNO – specificity, 33 ppb	0.83	Normal (mean of logit of specificity = 1.5999; SE of logit of specificity = 0. 01576)	Louis et al, 2023[73]
FeNO + spirometry – sensitivity (combined test)	0.69	A decision rule is applied following by the OR rule	Calculation Reference
FeNO + spirometry – specificity (combined test)	0.66	A decision rule is applied following by the OR rule	Calculation
Bronchial provocation test: methacholine PC20 < 8 mg/ml – sensitivity	0.63	Beta (42; 25)	Porpodis et al, 2016[128]
Bronchial provocation test: methacholine PC20 < 8 mg/ml –specificity	0.86	Beta (18; 3)	Porpodis et al, 2016[128]
Probabilities under treated asthma (standard of care)			
Monthly probability of exacerbations in treated asthmatics	0.0334	Beta	Calculation

Model parameter	Mean	Distribution	Source
Monthly probability of mild exacerbations in treated asthmatics	0.0065	Beta	Calculation
Monthly probability of severe exacerbations in treated asthmatics	0.0269	Beta	Calculation
• Monthly probability of hospitalization due to severe exacerbations in treated asthmatics	0.0008	Beta	Calculation
• Monthly probability of ED visits to severe exacerbations in treated asthmatics	0.0012	Beta	Calculation
• Monthly probability of GP visits due to exacerbations in treated asthmatics	0.0249	Beta	Calculation
Probabilities under untreated asthma			
Annual rate of exacerbations in untreated asthmatics (FNs)	1.02	Normal (1.02; 0.10)	Harnan et al, 2015[97] and Lloyd et al, 2007[133]
Monthly probability of exacerbations in untreated asthmatics (FNs)	0.08	Beta	Calculation
Ratio for exacerbation of untreated/treated asthma	2.37	Fixed	Calculation
Monthly probability of false positive diagnosis to be corrected between 25th and 59th months	0.08	Fixed	Calculated

Abbreviations: ED, emergency department; FeNO, fractional exhaled nitric oxide; FN, false negative; GP, general practitioner; OR, odds ratio; SE, standard error.

Health State Utilities

We considered the patient's HRQoL in the model. A health state utility represents a person's preference for a certain health state or outcome, such as living with asthma. Utilities are often measured on a scale ranging from 0 (death) to 1 (full health). The HRQoLs for different health states are presented in Table 9. Different utility values were used for children and adults.

Non-Asthma Utility

We did a thorough search of the utilities associated with the non-asthma population and decided to use the utility value reported in Harnan et al.[97] The authors estimated that the health utility of people with no asthma was 0.96. This value was calculated based on a paper published by Ara and Brazier.[134] People who do not have underlying asthma, but present with symptoms suggestive of asthma, could have a wide range of other non-asthma conditions and it may be difficult to estimate their utility.

Utility Associated With Asthma

For adults, the utilities associated with asthma were taken from a recent systematic review and meta-analysis of HRQoL in adults with asthma by Oh et al.[132] The authors performed a meta-analysis for each utility instrument according to levels of asthma control and severity. The EQ-5D-3L was the most used instrument (24.5%) and the meta-analysis included 15 studies, for a total of 6,212 participants. The pooled utility value for adults with asthma from the EQ-5D-3L was 0.72 (95% CI: 0.63–0.80) for uncontrolled, 0.82 (95% CI: 0.75–0.88) for partly controlled, and 0.87 (95% CI: 0.84–0.90) for well-controlled asthma. For people who did not experience an exacerbation in our reference case, we used the pooled baseline utility score for adults with partially controlled asthma (0.87). For people with a false negative diagnosis, we applied the utility value of 0.72 for uncontrolled asthma.[132]

We used Health Utilities Index Mark 3 (HUI3) data from two recent cycles of the Canadian Health Measures Survey (i.e., 2016/17 and 2018/19), as reported by Molina et al,[135] to provide utility score norms for children with asthma aged 6 to 11 years and adolescents aged 12 to 17 years. The mean utility score was 0.93 (95% CI: 0.92–0.94) for children and 0.89 (95% CI: 0.86–0.92) for adolescents.

Impact of Misdiagnosis on Health-Related Quality of Life

We assumed that a misdiagnosis would have a negative impact on a person's HRQoL. We assumed that the utility of uncontrolled asthma would be applied for people with a false negative diagnosis and that people with a false positive diagnosis would experience a disutility. Sullivan et al[136] used regression models to estimate the marginal disutility associated with a variety of diseases and conditions, and the disutility of having asthma was estimated to be –0.0463. Uncertainty surrounding this disutility was modelled using the beta distribution (Table 9).

Impact of Exacerbations on Health-Related Quality of Life

Lloyd et al[133] reported health utility losses due to asthma exacerbation. For people experiencing hospitalized exacerbation, the utility loss after 4 weeks of observation was –0.2 and, for people experiencing non-hospitalized exacerbation, it was –0.1. We calculated the baseline utility according to the values for people with no exacerbation, non-hospitalized exacerbation, and hospitalized exacerbation. We further calculated the adjusted utility loss due to an exacerbation based on the

baseline utility of people with controlled asthma conditions (0.82) and the 4-week observation of utility loss due to an exacerbation. The adjusted value of the utility loss was used in our model for reference case analyses. In details, the adjusted utility decrement for a hospitalized exacerbation was estimated at –0.33 and the adjusted utility decrement of a non-hospitalized exacerbation was estimated at –0.12. We assumed that there was no utility loss for mild asthma exacerbation. This utility loss would apply in both children and adults. In a scenario analysis, we explored the utility loss that other published papers used to see the impact of utility loss due to exacerbation on the cost-effectiveness results (Table 9).

Table 9: Utilities Used in the Economic Model – Adults and Children

Health or treatment state	Utility or disutility[a]	Distribution[b]	Reference
Adults			
TN, non-asthma	0.96	Fixed	Harnan et al, 2015[97]
TP, patients correctly identified as having asthma	0.82	Beta (371.0; 45.0)	Oh et al, 2022[132]
FN, patients incorrectly identified as having no asthma (we use utility value of uncontrolled asthma)	0.72	Beta (2324.9; 174.1)	Oh et al, 2022[132]
FP, patients incorrectly identified as having asthma	0.91	Utility of TN–disutility of FP (0.96–0.05)	Calculated
Children			
TN, non-asthma	0.96	Fixed	Molina et al, 2023[135]
TP, patients correctly identified as having asthma (aged 6–11 year)	0.93	Beta (2,324.9; 174.1)	Molina et al, 2023[135]
TP, patients correctly identified as having asthma (aged 12–17 year)	0.89	Beta (371.0; 45.0)	Molina et al, 2023[135]
FN, patients incorrectly identified as having no asthma (we use utility value of uncontrolled asthma; aged 5–17 year)	0.72	Beta (2,324.9; 174.1)	Oh et al, 2022[132]
FP, patients incorrectly identified as having asthma (patient doesn't have asthma; aged6–11 year)	0.91	Utility of TN – disutility of FP (0.96–0.05)	Calculation
FP, patients incorrectly identified as having asthma (patient doesn't have asthma; aged 12–17 year)	0.91	Utility of TN – disutility of FP (0.96–0.05)	Calculation
Disutility from severe exacerbation			
Hospitalized exacerbation (adjusted): adults and children	–0.31	Normal (–0.31; –0.062)	Calculated using studies by Lloyd et al, 2007[133]; Harnan et al, 2015[97]

Health or treatment state	Utility or disutility[a]	Distribution[b]	Reference
Non-hospitalized exacerbation (adjusted): adults and children	–0.12	Normal (–0.12; –0.024)	Lloyd et al, 2007[133]; Harnan et al, 2015[97]
Duration of severe exacerbation (in years)	0.08	Gamma (α = 19.26, λ = 246.34)	Harnan et al, 2015[97]
Duration of non-severe exacerbation (in years)	0.01	Gamma (α = 82.9, λ = 8259	Harnan et al, 2015[97]

Abbreviations: FN, false negative; FP, false positive; TN, true negative; TP, true positive.

[a]Negative numbers indicate disutility.

[b]Beta distribution: parameter 1 = alpha, parameter 2 = beta.

Cost Parameters

Cost parameters were taken from various Canadian costing studies that published treatment costs related to asthma.[137-140] Resources used (i.e., physician, nurse, and technician time, etc.) were determined through expert consultation. Whenever data was not available in the literature, we consulted with experts to identify model parameters and data sources (Table 10). This component includes cost of diagnostic tests, asthma treatment, and costs to correct a misdiagnosis.

Cost of Spirometry

The cost of spirometry testing involves two components: (1) GP referral fee $37.95; fee code A007) and (2) costs of the procedure, including pre- and post-bronchodilator (pre-bronchodilator: fee code J304, $19.60 technical fee and $11.55 professional fee; post-bronchodilator: fee code J327, $2.97 technical fee and $6.90 professional fee). The total cost of spirometry would be $78.97 (Table 10).

Cost of FeNO Testing

As FeNO testing was assumed to be conducted in a specialized office/lab where spirometry would be done, we assumed in our reference case analysis that it would be conducted by a respirologist/specialist (a patient with suspected asthma would first be referred by a GP to a respirologist/specialist). Therefore, the cost of FeNO testing per patient would consist of the cost of the referral and the actual costs of performing the FeNO test.

Since in our analysis, FeNO testing would not be conducted as a stand-alone test, but as a combined test with spirometry, we excluded the GP fee and only accounted for the actual cost incurred by FeNO testing. The actual cost incurred consists of costs of material (i.e., consumables and the cost of a FeNO device) and the professional fees (including the cost of test interpretation). Currently, there is no OHIP fee code for FeNO testing. Based on consultation with the Ontario Ministry of Health, we used the fee code for simple spirometry testing as a proxy to estimate the physician fee component (J301: $9.85 for technical fee and $7.85 for professional fee; Ministry of Health, email communication, September 19, 2023).

To calculate the overhead cost of a FeNO device per patient, in the reference case analysis we applied the annual amortization cost of $560 divided by 100 patients, which is the testing capacity of a single health professional. This resulted in $5.60 per patient. For consumables, it is estimated that the cost per patient would depend on the capacity of testing per health care practitioner or laboratory. If in 1 year a

respirologist could conduct FeNO testing on 100 patients, the cost of consumables would be $21 per patient. If a respirologist were to conduct FeNO testing on 500 patients, the cost of consumables would be $13 per patient. For the reference case analysis, we conservatively assumed that in 1 year a health practitioner would conduct FeNO testing on 100 patients (McArthur Medical, email communication, October 7, 2022). For professional fees, we applied the billing code of J301 ($17.70). Please note that this service may be included in an existing insured service or may require its own fee code. Changes to the schedule of benefits are jointly negotiated between the Ministry of Health and the Ontario Medical Association. The total cost per FeNO test would be $44.30 (Table 10). In our scenario analysis, we used the consumable cost of $13 per person and a total cost per FeNO test of $31.82.

Cost of Bronchial Provocation Testing

A bronchial provocation test would also be conducted by a specialist. The cost was estimated to be $85.60 based on the OHIP fee code J333 ($48.25 and $ 37.35 for the technical and professional components, respectively, Table 10). We used methacholine as the medication for the challenge testing, which is common in Ontario. According to experts, the cost of methacholine is already included in the cost of the test (Dr. David Kaplan, email communication, June 5, 2023).

Cost of Resolving False Negative and False Positive Diagnoses

The costs related to false results consist of two components: cost of follow-up visits and cost of (unnecessary) treatment of asthma. Our reference case model assumed that the maximum time for resolving a false negative (FN) or false positive (FP) diagnosis would be about 5 years (60 months).

Aaron et al[141] estimated that roughly 33% of people who received an asthma test but did not have asthma were over-diagnosed with a FP result. This means that they received asthma treatment unnecessarily. The authors also showed that resource use for people with FN diagnoses included hospitalization, ED visits, asthma medications, and ICS use.[141]

We assumed that medication costs were the same for people with confirmed asthma as for people with a FP diagnosis. 90.8% of people with confirmed asthma, but only 72.7% of people with FPs took asthma medications.[141] The monthly cost of asthma medications for people with confirmed asthma was $26.63, so we estimated that the average monthly cost of asthma medications for patients with FPs would be roughly $21.05 ($26.63 × 72.7%/90.8%; Table 10). We assumed that people with FP diagnoses have 2 GP visits and 1 diagnostic test per year (Dr. Alan Kaplan, email communication, November 19, 2022). We assumed that spirometry would be the test used in all strategies for follow-up of FN and FP cases. Therefore, the yearly cost incurred before a FP diagnosis was resolved would be $369.52 (Table 10). In our reference case analysis, for modelling purposes, we assumed that a FP would not be corrected during the first 24 months. but all FP diagnoses would be corrected within 60 months. To calculate the proportion of FP diagnoses corrected each cycle and for simplicity, we assumed a constant rate of FP diagnoses being corrected per year. We then converted the yearly rate into the monthly rate (0.08; Tables 7 and 8).

For people with FNs, there was no treatment cost because of the misdiagnosis until an exacerbation occurred. However, because of the misdiagnosis, there would be an increase in GP visits and/or ED visits. According to expert opinion, a FN diagnosis would lead to 3 to 4 GP visits or 1 ER visit/specialist in a year (Dr. Alan Kaplan, telephone communications, November 19–20, 2022). For our reference case, we assumed that in 1 year, a person with a FN diagnosis would require 3 GP visits and 1 diagnostic test per year. We assumed that spirometry was used as the diagnostic test in all strategies. Therefore, the cost

incurred by a FN diagnosis would be $154.87 per year until resolved (Table 10). In our reference case analysis, we assumed that a FN would be resolved after 5 years unless there was an exacerbation.

Table 10: Costs in the Economic Asthma Diagnostic Model – Adults and Children

Costing variables	Unit cost, mean (SE) $	Distribution[a]	Reference
FeNO test	**44.3**		**Sum of consumable cost, overhead cost, plus physician fee**
Consumables (per patient)	21	$13 in scenario analysis	Consultation with manufacturers
Overhead (per patient)	5.6		Consultation with manufacturers (assuming device cost is $2,800 and lifetime of device is 5 year)
Physician fee	17.70	Fixed	Assume same as SOB (J301)
Spirometry test	78.97	Fixed	SOB (J301 and J304)
Bronchial provocation test	85.60	Fixed	SOB (J333)
Yearly cost before a FP diagnosis is corrected	369.52	Gamma (369.52; 92.38)	Calculation
Yearly cost before a FN diagnosis is corrected	154.87	Gamma (154.87; 38.72)	Calculation
GP visit	37.95	Fixed	SOB (A007)
Outpatient, TP diagnosis (over 3 mo)	52.68 (145.24)	Gamma	Sadatsafavi et al, 2016[142]
Asthma medication: TP diagnosis (over 3 mo)	79.89 (128.5)	Gamma	Sadatsafavi et al, 2016[142]

Abbreviations: FeNO, fractional exhaled nitric oxide; FN, false negative; FP, false positive; GP, general practitioner; SE, standard error; SOB, Ontario Schedule of Benefits.

[a]Strategy 2: FeNO testing combined with spirometry; Strategy 3: spirometry is the first test and FeNO testing is the second test if a patient tests negative with spirometry.

Internal Validation

Formal internal validation was conducted by the secondary health economist. This included testing the mathematical logic of the model and checking for errors and accuracy of parameter inputs and equations.

Analysis

We conducted a reference case analysis and sensitivity analyses. Our reference case analysis adhered to the Canadian Agency for Drugs and Technologies in Health (CADTH) guidelines[123] when appropriate. The reference case represents the analysis with the most likely set of input parameters and model assumptions relevant to Ontario. Our scenario and sensitivity analyses explored how the results would be affected by varying input parameters and model assumptions.

For the reference case analysis, we conducted a probabilistic analysis to capture uncertainty in model parameters. When possible, we specified distributions around input parameters using the mean and standard error. Selected cost parameters were characterized by gamma distributions, probabilities and

utilities were characterized by beta distributions, and relative risks were characterized by log-normal distributions. We ran a total of 5,000 simulations and calculated the expected values of costs and outcomes for each strategy. We presented the probability that each strategy was cost-effective over a range of willingness-to-pay values on a cost-effectiveness acceptability curve.

The results of the probabilistic analysis are also presented on a cost-effectiveness acceptability curve. We present uncertainty quantitatively as the probability that a treatment is cost-effective at WTP values from $0 to $100,000 per QALY.

Scenario Analyses

We conducted different scenario analyses to assess the impact of key assumptions on model results.

Scenario D1–2: Varying Pre-test Probability of Asthma

The pre-test probability of asthma may vary significantly across different clinical settings depending on many factors. For both child and adult models, we conduct scenario analyses using a wide range of values for the pre-test probability of asthma to explore its impacts on the cost-effectiveness results.

Scenario D3–4: Time to Resolution of a FP Diagnosis

The time needed to resolve a FP diagnosis is very uncertain and could vary from person to person. Therefore, we conducted multiple scenario analyses. In one scenario, we assumed that FP diagnoses would start to be resolved 6 months after the initial incorrect diagnosis, with all FP diagnoses resolved within 42 months (the duration of correction was 3 years). In another scenario, we assumed that FP diagnoses would start to be resolved 2 months after the initial incorrect diagnosis, with all FP diagnoses resolved in within 42 months (the duration of correction was 3.3 years), as opposed to the 5-year period we used in the reference case analysis.

Scenario D5–6: Cost of FeNO Testing

The cost of FeNO testing varies depending on the respirologist's capacity. For example, if a respirologist conducts 500 tests per year, the cost of consumables would be $13 per patient, for a total per-test cost of $31.82. But if the respirologist conducts only 100 tests per year, the per-test cost rises to $44.30. In Scenario D5–6, we explored the impact of the cost of FeNO testing on the cost-effectiveness results.

Scenario D7: Diagnostic Accuracy of FeNO

As indicated in the clinical review, the diagnostic accuracy of FeNO testing varied across studies depending on the cut offs, the population of interest (e.g., children, adults, smokers, patients with lung diseases, etc.), setting (primary vs. special care settings). Instead of taking the diagnostic accuracy of FeNO from another single study identified in the clinical review, we decided to use the diagnostic accuracy of FeNO from the most recently published paper by the European Respiratory Society to provide guidelines for the diagnosis of asthma in adults.[73] In this paper, the authors identified 6 studies that reported the diagnostic accuracy of FeNO (with a cut-off of 25 ppb). Table 11 shows the pooled estimates of sensitivity and specificity using meta-analyses of these 6 studies. The pooled sensitivity was 0.53 (95% CI: 0.33–0.72) and the pooled specificity was 0.72 (95% CI: 0.61–0.81). To account for uncertainty, we assign a normal distribution. The values are presented in Table 7.

Results

Asthma Diagnosis

Reference Case Analysis (Children)

Tables 11 and 12 present the results of the reference case analysis for children. We found that, over a 20-year time horizon, the sequential testing strategy was slightly more costly and more effective than standard testing, which translated to an ICER of $6,192 per QALY gained, and the combined testing strategy was slightly more costly and more effective than standard testing, which translated to an ICER of $8,972 per QALY gained. The sequential testing strategy was less costly and equally effective compared with the combined testing strategy. Therefore, sequential testing dominated the combined testing strategy (Table 11).

Table 12 shows the number of TP, FN, FP, and TN diagnoses detected by each diagnostic strategy per 1,000 patients. Compared with standard testing, sequential testing and combined testing strategies increased the number of TP and FP diagnoses, but reduced the number of TN and FN diagnoses.

Table 11: Reference Case Analysis Results for Children (Costs and QALY Per Patient)

Strategies[a]	Cost incurred per strategy[b] (95% CrI)	Number of QALYs (95% CrI)	Incremental costs (95% CrI)	Incremental QALYs (95% CrI)	Sequential ICER	ICER vs. standard testing
Standard testing	$6,784 ($3,338–$27,961)	15.6737 (15.3412 – 15.9705)	—	—	NA	NA
FeNO and spirometry sequential testing strategy	$6,820 ($3,401–$28,013)	15.6794 (15.3491 – 15.9754)	$35[c] (-$93 to $178)	0.0057[c] (-0.0017 to 0.0152)	$6,192	$6,192
FeNO and spirometry combined testing strategy	$6,835 ($3,417–$28,031)	15.6794 (15.3491 – 15.9754)	$16[d] ($12–$20)	0.0000[d]	Dominated by FeNO and spirometry sequential testing strategy[e]	$8,972

Abbreviations: CrI, credible interval; ICER, incremental cost-effectiveness ratio; FeNO, fractional exhaled nitric oxide; NA, not applicable; QALY, quality-adjusted life year.

[a]Strategies are ranked by cost from lowest to highest.

[b]All costs I 2022 CAD.

[c]Incremental cost and effect of sequential testing compared with standard testing.

[d]Incremental cost and effect combined testing compared with sequential testing.

[e]A dominated strategy was more costly and less expensive than the comparator.

Table 12: Reference Case Analysis Results for Children (Number of Diagnoses Per 1,000 Patients)

Strategies	True positives	False negatives	False positives	True negatives
Standard tests	652	68	99	181
FeNO and spirometry sequential testing strategy	692	28	125	155
FeNO and spirometry combined testing strategy	692	28	125	155

Abbreviations: FeNO, fractional exhaled nitric oxide.

Cost-Effectiveness Acceptability Curves (Children)

Figure 11 presents the cost-effectiveness acceptability curves, which represent the uncertainty around the estimated ICER generated in the probabilistic sensitivity analyses for standard testing, sequential testing, and combined testing for children. The results in Figure 11 show that when the willingness-to-pay (WTP) value is greater than $6,192 per QALY gained, the sequential testing strategy is the most cost-effective.

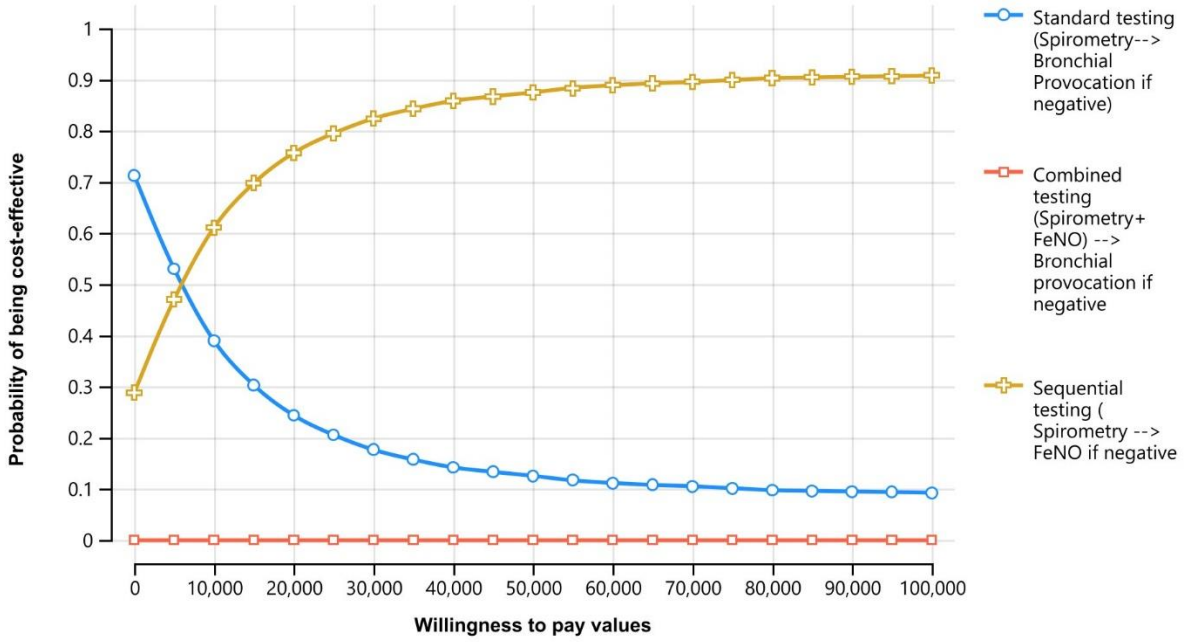


Figure 11: Cost-Effectiveness Acceptability Curve (Children)

Line graph showing the cost effectiveness acceptability curve in children. Standard testing has about a 70% chance of being cost effective at a WTP of $0, falling rapidly to about a 15% probabiltiy at a WTP of $35,000 and then leveling off through the end of the chart at a WTP of $100,000. Sequential testing has a 30% probability of being cost effective at a WTP of $0, increasing to 80% at a WTP of $25,000 and leveling off at about 90% probability at a WTP of $65,000. Combined testing has a 0% probability of being cost effective at any WTP value.

Scenario Analysis Results (Children)

Scenario D1: Varying Pre-test Probability of Asthma

The pre-test probability of asthma in children suspected of having asthma varies from 5% to 72% (Table 13). When the pre-test prevalence was approximately 58.6%, sequential testing was still more costly and more effective than standard testing. The ICER of sequential versus standard testing was $21,288 per QALY gained. Combined testing was always more costly than sequential testing, but equally effective. When the pre-test probability was lower than 45%, standard testing become the dominant strategy (less costly and more effective than both sequential and combined testing strategies).

Table 13: Scenario Analysis Results – Varying Pre-test Probability of Asthma in Children

Pre-test probability	Strategies	Costs[a]	QALYs	Incremental costs	Incremental QALYs	ICER
72% (reference case)	**Standard testing**	**$6,784**	**15.6737**	**—**	**—**	**NA**
	FeNO and spirometry sequential testing strategy	**$6,820**	**15.6794**	**$35**	**0.0057**	**$6,192**
	FeNO and spirometry combined testing strategy	**$6,835**	**15.6794**	**$16**	**0.0000**	**Dominated by sequential testing**
58.60%	Standard testing	$5,546	15.8577	—	—	NA
	FeNO and spirometry sequential testing strategy	$5,596	15.8601	$50	0.0024	$21,288
	FeNO and spirometry combined testing strategy	$5,609	15.8601	$13	0.0000	Dominated by sequential testing
45.20%	Standard testing	$4,409	16.0392	—	—	NA
	FeNO and spirometry sequential testing strategy	$4,477	16.0383	$68	–0.0009	Dominated by standard testing
	FeNO and spirometry combined testing strategy	$4,488	16.0383	$79	–0.0009	Dominated by standard testing
31.80%	Standard testing	$3,272	16.2206	—	—	NA
	FeNO and spirometry sequential testing strategy	$3,358	16.2164	$86	–0.0042	Dominated by standard testing
	FeNO and spirometry combined testing strategy	$3,367	16.2164	$94	–0.0042	Dominated by standard testing
18.40%	Standard testing	$2,136	16.4020	—	—	NA
	FeNO and spirometry sequential testing strategy	$2,239	16.3945	$103	–0.0075	Dominated by standard testing
	FeNO and spirometry combined testing strategy	$2,245	16.3945	$110	–0.0075	Dominated by standard testing
5%	Standard testing	$999	16.5835	—	—	NA
	FeNO and spirometry sequential testing strategy	$1,120	16.5727	$121	–0.0108	Dominated by standard testing
	FeNO and spirometry combined testing strategy	$1,124	16.5727	$125	–0.0108	Dominated by standard testing

Abbreviations: FeNO, fractional exhaled nitric oxide; ICER, incremental cost-effectiveness ratio; NA, not applicable; QALY, quality-adjusted life year.
[a]All costs in 2022 CAD.

Scenario D3: Time to Resolution of a False Positive Diagnosis

We assumed that a FP diagnosis would be corrected within 7 to 42 months of the initial diagnosis (the duration of correction is 3 years). The cost-effectiveness results showed that sequential testing was more costly, but also more effective. This translated into an ICER of $2,810 per QALY gained (Table 14). Combined testing was more costly but equally effective compared with sequential testing; thus, combined testing was dominated by sequential testing.

When we assumed that a FP diagnosis would be corrected within 2–42 months, sequential testing was more costly and more effective than standard testing. This translated into an ICER of $2,281 per QALY gained (Table 15). Combined testing was more costly but equally effective compared with sequential testing; thus, combined testing was dominated by sequential testing.

Table 14: Scenario Analysis – Change of Duration of False Positive Case Correction in Children, Results per Patient

Strategies[a]	Cost incurred per strategy[b]	Number of QALYs	Incremental costs	Incremental QALYs	Sequential ICER
Standard testing	$6,782	15.6803	—	—	NA
FeNO and spirometry sequential testing strategy	$6,802	15.6878	$21[c]	0.0073	$2,810
FeNO and spirometry combined testing strategy	$6,818	15.6878	$16[d]	0.0000	Dominated by sequential testing[e]

Abbreviations: FeNO, fractional exhaled nitric oxide; ICER, incremental cost-effectiveness ratio; NA, not applicable; QALY, quality-adjusted life year.

[a]Strategies are ranked by cost from lowest to highest.

[b]All costs in 2022 CAD.

[c]Incremental cost and effect of sequential testing compared with standard testing

[d]Incremental cost and effect of combined testing compared with sequential testing

[e]A dominated strategy is more costly and less effective than the comparator

Table 15: Scenario Analysis – Change of Duration of False Positive Case Correction in Children, Results Per Patient

Strategies[a]	Cost incurred per strategy[b]	Number of QALYs	Incremental costs	Incremental QALYs	Sequential ICER
Standard testing	$6,770	15.6814	—	—	NA
FeNO and spirometry sequential testing strategy	$6,788	15.6896	18[c]	0.0076	2,281
FeNO and spirometry combined testing strategy	$6,804	15.6896	15[d]	0.0000	Dominated by sequential testing[e]

Abbreviations: FeNO, fractional exhaled nitric oxide; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.
[a]Strategies are ranked by cost from lowest to highest.
[b]All costs in 2022 CAD.
[c]Incremental cost and effect of sequential testing compared with standard testing
[d] Incremental cost and effect of combined testing compared with sequential testing
[e]A dominated strategy is more costly and less effective than the comparator

Scenario D5: Cost of FeNO Testing

We assumed a FeNO test cost of $31.82. In this scenario, the cost-effectiveness results showed that sequential testing was more costly but also more effective, which translated into an ICER of $4,673 per QALY gained (Table 16). Combined testing was more costly but equally effective compared with sequential testing; thus, combined testing was dominated by sequential testing.

Table 16: Scenario Analysis – Change in the Cost of FeNO Testing in Children, Results per Patient

Strategies[a]	Cost incurred per strategy[b]	Number of QALYs	Incremental costs	Incremental QALYs	Sequential ICER
Standard testing	$6,835	15.6737	—	—	NA
FeNO and spirometry sequential testing strategy	$6,710	15.6794[c]	$26	0.0056	$4,673
FeNO and spirometry combined testing strategy	$6,721	15.6794[d]	$11	0.0000	Dominated by sequential testing[e]

Abbreviations: FeNO, fractional exhaled nitric oxide; ICER, incremental cost-effectiveness ratio; NA, not applicable; QALY, quality-adjusted life year.
[a]Strategies are ranked by cost from lowest to highest.
[b]All costs in 2022 CAD.
[c]Incremental cost and effect of sequential testing compared with standard testing
[d]Incremental cost and effect of combined testing compared with sequential testing
[e]A dominated strategy is more costly and less effective than the comparator

Reference Case Analysis (Adults)

Table 17 presents the results of the reference case analysis for adults. We found that, over a 20-year time horizon, both the sequential and combined testing strategies were dominated by standard testing (they were slightly more costly and less effective than standard testing).

Table 18 shows numbers of TP, FN, FP and TN diagnoses detected by each diagnostic strategy, per 1,000 patients. Compared with standard testing, the sequential and combined testing strategies increased the number of TP and FP diagnoses, but reduced the number of TN and FN diagnoses.

Table 17: Reference Case Analysis Results for Adults (Costs and QALYs per Patient)

Strategies[a]	Cost incurred per strategy[b] (95% CrI)	Number of QALYs (95% CrI)	Incremental costs (95% CrI)	Incremental QALYs (95% CrI)	Sequential ICER	ICER vs. standard testing
Standard testing	$5,400 ($2,155–$24,173)	14.9250 (14.2027–15.5576)	—	—	NA	NA
FeNO and Spirometry Sequential Testing Strategy	$5,465 ($2,207–$24,413)	14.9229 (14.1973–15.5608)	64[c] (–50 to 193)	–0.0021[c] (–0.0069 to 0.0038)	Dominated by standard testing[d]	Dominated by standard testing[d]
FeNO and Spirometry Combined Testing Strategy	$5,483 ($2,226–$24,431)	14.9229 (14.1973–15.5608)	83[e] (–30 to 211)	–0.0021[e] (–0.0069 to 0.0038)	Dominated by standard testing[d]	Dominated by standard testing[d]

Abbreviations: CrI, credible interval; FeNO, fractional exhaled nitric oxide; ICER, incremental cost-effectiveness ratio; NA, not applicable; QALY, quality-adjusted life year.

[a]Strategies are ranked by cost from lowest to highest.

[b]All costs in 2022 CAD.

[c]Incremental cost and effect of sequential testing compared with standard testing.

[d]A dominated strategy is more costly and less effective than the comparator.

[e]Incremental cost and effect of combined testing compared with standard testing because sequential testing is dominated by standard testing.

Table 18: Reference Case Analysis Results for Adults (Number of Diagnoses per 1,000 Patients)

Strategies	True Positives	False Negatives	False Positives	True Negatives
Standard testing	522	108	121	249
FeNO and spirometry sequential testing strategy	557	73	163	207
FeNO and spirometry combined testing strategy	557	73	163	207

Abbreviation: FeNO, fractional exhaled nitric oxide.

Figure 12 presents the cost-effectiveness acceptability curves, which represent the uncertainty around the estimated ICER generated in the probabilistic sensitivity analyses for standard testing, sequential testing, and combined testing for adults. Figure 11 showed that standard testing is always the most cost-effective strategy regardless of WTP values.

Cost-Effectiveness Acceptability Curves (Adults)

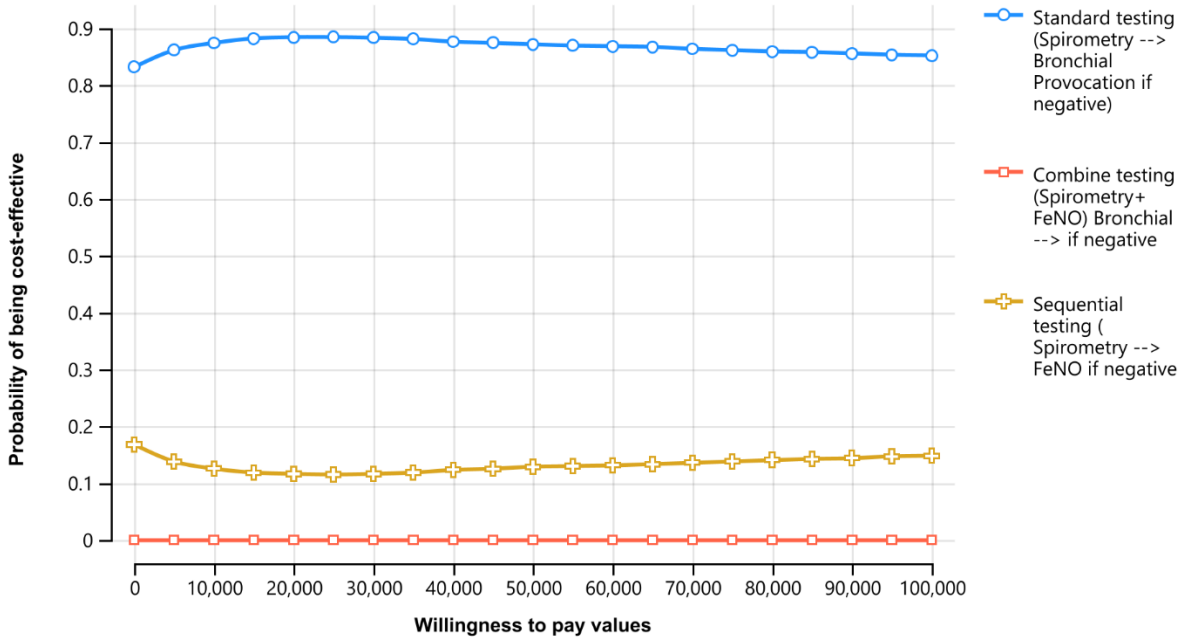


Figure 12: Cost-Effectiveness Acceptability Curve (Adults)

Line graph showing the cost effectiveness acceptability curve in adults. Standard testing has about an 83% chance of being cost effective at a WTP of $0, rising to about a 90% probabiltiy at a WTP of $10,000 before droping gradually back to about 86% at a WTP of $100,000. Sequential testing has about an 18% probability of being cost effective at a WTP of $0, dropping to 10% at at a WTP of $30,000 before increasing gradually to about 15% at a WTP of $100,000. Combined testing has a 0% probability of being cost effective at any WTP value.

Scenario Analysis Results (Adults)

Scenario D2: Varying Pre-test Probability of Asthma

In adults, when the pre-test prevalence was less than 0.80, standard testing was always less costly and more effective than sequential and combined testing strategies. When the pre-test prevalence was higher than 0.80, sequential testing was more costly, but generated slightly higher QALYs, which translates into an ICER of $30,727 per QALY gained (Table 19).

Table 19: Scenario Analysis Results: Varying Pre-test Probability of Asthma in Adults

Pre-test probability	Strategies	Cost incurred per strategy[a]	Number of QALYs	Incremental costs	Incremental QALYs	ICER[b]
0.15	Standard testing	$1,640	16.0331	—	—	NA
	FeNO and spirometry sequential testing strategy	$1,769	16.0207	$129	–0.0125	Dominated by Standard testing
	FeNO and spirometry combined testing strategy	$1,780	16.0207	$141	–0.0125	Dominated by Standard testing
0.31	Standard testing	$2,870	15.6597	—	—	NA
	FeNO and spirometry sequential testing strategy	$2,977	15.6507	$108	–0.0090	Dominated by Standard testing
	FeNO and spirometry combined testing strategy	$2,991	15.6507	$121	–0.0090	Dominated by Standard testing
0.48	Standard testing	$4,100	15.2862	—	—	NA
	FeNO and spirometry sequential testing strategy	$4,186	15.2807	$86	–0.0056	Dominated by Standard testing
	FeNO and spirometry combined testing strategy	$4.202	15.2807	$102	–0.0056	Dominated by Standard testing
0.63	Standard testing	$5,400	14.9251	—	—	NA
	FeNO and spirometry sequential testing strategy	$5,465	14.9229	$65	–0.0021	Dominated by standard testing
	FeNO and spirometry combined testing strategy	$5,483	14.9229	$83	–0.0021	Dominated by standard testing

Pre-test probability	Strategies	Cost incurred per strategy[a]	Number of QALYs	Incremental costs	Incremental QALYs	ICER[b]
0.8	Standard testing	$6,560	14.5393	—	—	NA
	FeNO and spirometry sequential testing strategy	$6,602	14.5407	$42	0.0014	$30,727
	FeNO and spirometry combined testing strategy	$6,623	14.5407	$21	0.0000	Dominated by sequential testing

Abbreviations: FeNO, fractional exhaled nitric oxide; ICER, incremental cost-effectiveness ratio; NA, not applicable; QALY, quality-adjusted life year.

[a]All costs in 2022 CAD.

[b]A dominated strategy is more costly and less effective than the comparator.

Scenario D4: Time to Resolution of a False Positive Diagnosis

We assumed that a FP diagnosis would be corrected within 7 to 42 months after the initial diagnosis (the duration of correction is 3 years). The cost-effectiveness results showed that sequential testing was more costly, but also more effective. This translated into an ICER of $70,000 per QALY gained (Table 20). Combined testing was more costly but equally effective compared with sequential testing; thus, combined testing was dominated by sequential testing.

When we assumed a FP diagnosis would be corrected within 2–42 months, sequential testing was more costly and more effective than standard testing. This translated into an ICER of $29,616 per QALY gained (Table 21). In other words, at a WTP higher than $29,700 per QALY, sequential testing is more cost-effective than standard testing.

Table 20: Scenario Analysis – Change of Duration of False Positive Case Correction in Adults

Strategies[a]	Cost incurred per strategy[b]	Number of QALYs	Incremental costs	Incremental QALYs	ICER
Standard testing	$5,393	14.9332	—	—	NA
FeNO and spirometry sequential testing strategy	$5,435	14.9338	$42[c]	0.0006[c]	$70,000
FeNO and spirometry combined testing strategy	$5,454	14.9338	$19[d]	0.0000[d]	Dominated by sequential testing[e]

Abbreviations: FeNO, fractional exhaled nitric oxide; ICER, incremental cost-effectiveness ratio; NA, not applicable; QALY, quality-adjusted life year.

[a]Strategies are ranked by cost from lowest to highest.

[b]All costs in 2022 CAD.

[c]Incremental cost and effect of sequential testing compared with standard testing.

[d]Incremental cost and effect of combined testing compared with sequential testing.

[e]A dominated strategy is more costly and less effective than the comparator.

Table 21: Scenario Analysis – Change of Duration of False Positive Case Correction in Adults, Results Per Patient

Strategies[a]	Cost incurred per strategy[b]	Number of QALYs	Incremental costs	Incremental QALYs	ICER
Standard testing	$5,379	14.9350	—	—	NA
FeNO and spirometry sequential testing strategy	$5,416	14.9363	$37[c]	0.0013[c]	$29,616
FeNO and spirometry combined testing strategy	$5,435	14.9363	$19[d]	0.0000[d]	Dominated by sequential testing[e]

Abbreviations: FeNO, fractional exhaled nitric oxide; ICER, incremental cost-effectiveness ratio; NA, not applicable; QALY, quality-adjusted life year.

[a]Strategies are ranked by cost from lowest to highest.

[b]All costs in 2022 CAD.

[c]Incremental cost and effect of sequential testing compared with standard testing.

[d]Incremental cost and effect of combined testing compared with sequential testing.

[e]A dominated strategy is more costly and less effective than the comparator.

Scenario D6: Cost of FeNO Testing

In this scenario, we assumed that the cost of a FeNO test would be reduced to $31.82. The cost-effectiveness results showed that sequential testing was more costly but also less effective than standard testing (Table 22). In other words, sequential testing was dominated by standard testing. Combined testing was more costly but also less effective than standard testing; thus combined testing was dominated by standard testing.

Table 22: Scenario Analysis – Change in the Cost of FeNO Testing in Adults, Results per Patient

Strategies[a]	Cost incurred per strategy[b]	Number of QALYs	Incremental costs	Incremental QALYs	ICER
Standard testing	$5,400	14.9250	—	—	NA
FeNO and spirometry sequential testing strategy	$5,457	14.9229	$57[c]	–0.0021[c]	Dominated by standard testing[d]
FeNO and spirometry combined testing strategy	$5,470	14.9229	$70[e]	–0.0021[e]	Dominated by standard testing[d]

Abbreviations: FeNO, fractional exhaled nitric oxide; ICER, incremental cost-effectiveness ratio; NA, not applicable; QALY, quality-adjusted life year.

[a]Strategies are ranked by cost from lowest to highest.

[b]All costs in 2022 CAD.

[c]Incremental cost and effect of sequential testing compared with standard testing.

[d]A dominated strategy is more costly and less effective than the comparator.

[e]Incremental cost and effect of combined testing compared with sequential testing.

Scenario D7: Alternative Source for FeNO Testing Accuracy

When we used an alternative source to estimate the diagnostic accuracy of FeNO (higher sensitivity and specificity values than those used in the reference case analysis: sensitivity = 0.53 and specificity = 0.72, vs. sensitivity = 0.32 and specificity = 0.83 in the reference case), the cost-effectiveness results did not change significantly. Standard testing remained less costly and more effective than both the sequential and combined testing strategies (Table 23A).

Scenario D8: Higher Cut-Off Value of 50 ppb

When we used a higher cut off value of 50 ppb for FeNO, in which the specificity of FeNO testing is almost 100% compared with the value used in reference case analysis (sensitivity = 0.24 and specificity = 0.99), sequential testing was highly likely cost-effective compared to standard testing at the commonly accepted willingness-to-pay of $50,000 and $100,000 per QALY (Table 23B).

Table 23A: Scenario Analysis Results – Alternative Source for FeNO Diagnostic Accuracy in Adults (Sensitivity = 0.53; Specificity = 0.72)

Strategies[a]	Cost incurred per strategy[b]	Number of QALYs	Incremental costs	Incremental QALYs	ICER
Standard testing	$5,459	14.9250	—	—	NA
FeNO and spirometry sequential testing strategy	$5,550	14.9213	$91[c]	–0.0037[c]	Dominated by standard testing[d]
FeNO and spirometry combined testing strategy	$5,569	14.9213	$109[e]	–0.0037[e]	Dominated by standard testing[d]

Abbreviations: FeNO, fractional exhaled nitric oxide; ICER, incremental cost-effectiveness ratio; NA, not applicable; QALY, quality-adjusted life year.

[a]Strategies are ranked by cost from lowest to highest.

[b]All costs in 2022 CAD.

[c]Incremental cost and effect of sequential testing compared with standard testing.

[d]A dominated strategy is more costly and less effective than the comparator.

[e]Incremental cost and effect of combined testing compared with standard testing.

Table 23B: Scenario Analysis Results – Alternative Source for FeNO Diagnostic Accuracy in Adults (Sensitivity = 0.24; Specificity = 0.99)

Strategies[a]	Cost incurred per strategy[b]	Number of QALYs	Incremental costs	Incremental QALYs	ICER
Standard testing	$5,459	14.9250	—	—	NA
FeNO and spirometry sequential testing strategy	$5,485	14.9274	$26[c]	0.0023	$11,278
FeNO and spirometry combined testing strategy	$5,504	14.9274	$19[d]	0	Dominated by sequential testing[e]

Abbreviations: FeNO, fractional exhaled nitric oxide; ICER, incremental cost-effectiveness ratio; NA, not applicable; QALY, quality-adjusted life year

[a]Strategies are ranked by cost from lowest to highest.

[b]All costs in 2022 CAD.

[c]Incremental cost and effect of sequential testing compared with standard testing.

[d]Incremental cost and effect of combined testing compared with sequential testing.

[e]A dominated strategy is more costly and less effective than the comparator.

Discussion

Our primary economic evaluation investigated the cost-effectiveness of 3 diagnostic strategies for children and adults suspected of asthma from the perspective of the Ontario Ministry of Health: (1) sequential testing (spirometry followed by FeNO if spirometry is negative, and then by bronchial provocation if FeNO is negative), (2) combined testing (spirometry and FeNO in the same visit, followed by bronchial provocation if either spirometry or FeNO is negative), and (3) standard testing (spirometry followed by bronchial provocation if spirometry is negative).

For children with suspected asthma, we found that both the sequential and combined testing strategies were more costly and more effective than standard testing (with ICERs of $6,192 and $8,972 respectively, per QALY gained). At willingness-to-pay values of $50,000 and $100,000 per QALY, the probability of the sequential testing strategy being cost-effective was 88% and 90%, respectively. The results were most sensitive to the pre-test probability of asthma, the time to resolve a false negative diagnosis, and the cost of FeNO testing. For example, when the pre-test probability was lower than 0.45, standard testing was less costly and more effective than both the sequential and the combined testing strategies (standard testing was a dominant strategy). However, when the pre-test prevalence was higher than 0.58, sequential testing was more costly and more effective than standard testing. At a willingness to pay threshold of more than $22,000 per QALY, sequential testing was more cost-effective than standard testing. The sooner a FP diagnosis is corrected, the more cost-effective sequential testing becomes. For our analysis, combined testing was always more costly than sequential testing while having similar health outcomes.

For adults with suspected asthma, the reference case analysis showed that standard testing was less costly and more effective than both the sequential and combined testing strategies (standard testing was a dominant strategy). We conducted extensive scenario analyses for the cost-effectiveness model for adults with suspected asthma to identify how the model's parameters could impact the cost-effectiveness results. The cost-effectiveness model was sensitive to the duration of correction of FP diagnoses. When the duration of correction was at least 7 months after an incorrect diagnosis and no more than 42 months, then, compared with standard testing, sequential testing was more costly but

also generated more effectiveness, with an ICER of $70,000 per QALY gained. When the minimum duration of correction was reduced to 2 months, and no more than 42 months, then, compared with standard testing, sequential testing was more costly but also generated more effectiveness, with an ICER of $29,616 per QALY gained. At higher cut off values (i.e., > 50 ppb), specificity of FeNO is almost 100%. At a WTP of $50,000 per QALY gained, sequential testing is highly likely to be cost-effective compared to standard testing. In this scenario, adding FeNO to standard testing would increase the sensitivity (i.e., capture more cases of asthma), but would not increase the specificity (i.e., would not reduce false negatives). Therefore, when the specificity of FeNO is close to 100%, sequential testing is highly likely to be cost-effective compared to standard testing.

For both children and adults with suspected asthma, the QALY difference between standard testing and sequential and combined testing was very small. This result is in line with the findings from other published economic studies.[110,116,120]

For adults with suspected asthma, our results were different from the 2 studies identified in our economic evidence review.[116,120] First, these studies investigated FeNO testing as a stand-alone test in comparison with existing standard diagnostic testing in the United Kingdom and Germany. Second, our model used a 20-year time horizon, while the models by Price et al[120] and Berg and Lindgren[116] used a 1-year time horizon. The diagnostic model used by Price and colleagues indicates that NIOX MINO was likely to be cost saving in comparison to other tests routinely used in the diagnosis of asthma. The diagnostic model used by Berg and Lindgren indicated that an asthma diagnosis based on FeNO measurement alone (exemplified with NIOX MINO) costs more per patient than standard diagnostic methods while offering improved accuracy. In the reference case, the findings from our model indicate that, for adults with suspected asthma, both the sequential testing strategy and the combined testing strategy are more costly than standard testing.

Our economic review identified only 1 study that focused on both children and adults.[97] Unlike our study, Harnan et al[97] investigated FeNO testing either as a stand-alone strategy or in combination with other tests used in the standard diagnosis of asthma in United Kingdom. They found that, in both children and adults, all strategies that included NIOX MINO or NIOX VERO were expected to be dominated as their marginal per-test cost was higher than the comparator, NObreath. Their model was also sensitive to the time to resolve misdiagnoses (i.e., false negatives and false positives).

Strengths and Limitations

Our analysis had several strengths. First, we developed separate cost-effectiveness models for both children and adults to capture the clinical practice in Canada. The models captured important clinical outcomes, including numbers of TPs, FNs, FPs, TNs, and QALYs. While most published models applied a 1-year time horizon, our models applied a 20-year time horizon to capture the long-term effects of asthma diagnoses. We also used the best available data from the literature and applied Canadian data where possible. We used Ontario-specific inputs for the cost of treating exacerbations for both children and adults.

Our model also had limitations. Since the clinical review did not conduct a meta-analysis on the diagnostic accuracy of FeNO testing, we opted to pick the diagnostic accuracy of FeNO from a single study.[73,132] This potentially affects the cost-effectiveness results of strategies that involve FeNO testing since the diagnostic accuracy of FeNO testing varies across studies using different cut-off values. To overcome this limitation, we conducted extensive scenario analyses using the sensitivity and specificity

of FeNO testing, which was meta-analyzed and recently published by the European guidelines on asthma.[21] We explored the impact of other model parameters such as pre-test prevalence and time to resolution of a false positive diagnosis. However, for adults with suspected asthma, the cost-effectiveness results did not change. Standard testing seems to be better than diagnostic testing that includes FeNO testing for adults with suspected asthma.

Another limitation was that our reference case analysis did not consider the conditional dependence between test results in our analysis due to the lack of data. If we had considered it, it is possible the cost-effectiveness results comparing the different diagnostic tests would change.

Conclusions

Diagnosing asthma in children using either a sequential strategy (spirometry testing first, with FeNO testing later if spirometry results are negative) or a combined strategy (spirometry and FeNO testing performed at the same time) is likely cost-effective compared with standard testing (ICERs of $6,192 and $8,972 for the sequential and combined testing strategies, respectively). To diagnose asthma in adults, neither the sequential nor the combined testing strategy is likely to be cost-effective (both are more costly and with fewer QALYs compared to standard testing). However, they may be cost-effective in adults when a higher FeNO testing diagnostic cut off value is applied (cost-effective at a higher cut-off value of > 50 parts per billion).

Budget Impact Analysis – Asthma Diagnosis

Research Question

What is the potential 5-year budget impact for the Ontario Ministry of Health of publicly funding fractional exhaled nitric oxide (FeNO) testing for diagnosis in people with suspected asthma?

Methods

Analytic Framework

We estimated the budget impact of publicly funding FeNO testing for the diagnosis of asthma using the cost difference between two scenarios: (1) current clinical practice without FeNO testing (the current scenario), and (2) the anticipated clinical practice with FeNO testing (the new scenario). We conducted separate budget impact analyses for children and adults. Figure 13 presents the schematic model of budget impact in the diagnosis of asthma.

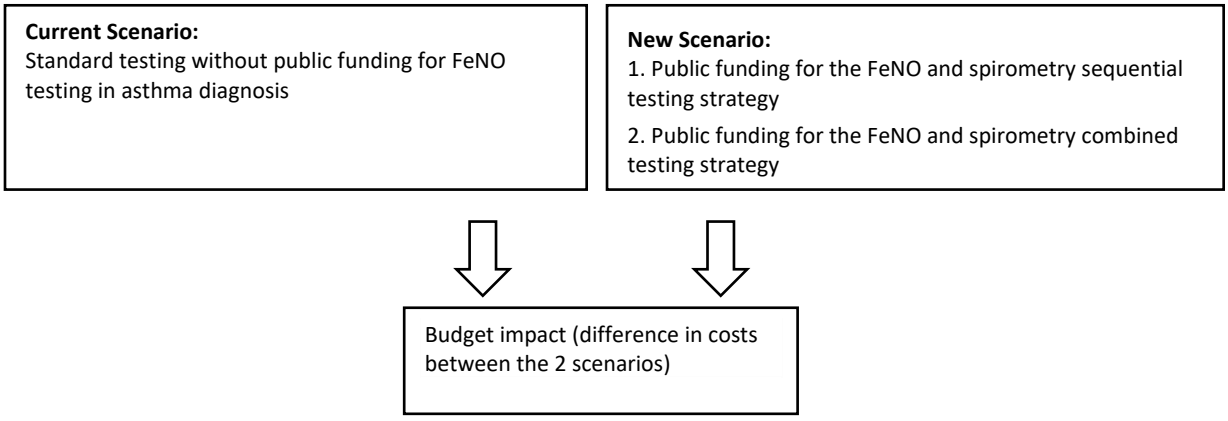


Figure 13: Schematic Model of Budget Impact in the Diagnosis of Asthma

Flow chart describing the model for the budget impact analysis. Based on the size of the population of interest, we created 2 scenarios: the current scenario, which would explore the distribution of treatment strategies, resource use, and total costs without public funding for FeNO testing; and the new scenario, which would explore the distribution of treatment strategies, resource use, and total costs with public funding for FeNO testing (i.e., sequential and combined testing strategies). The budget impact would represent the difference in costs between the two scenarios.

Note: Sequential testing strategy: FeNO testing is conducted if the result from spirometry is negative. Bronchial provocation would be conducted if the result of FeNO testing is negative.

Combined testing strategy: FeNO testing is conducted at the same time as spirometry. FeNO and spirometry can be done in 1 visit at either a specialist's office or in the laboratory. Bronchial provocation would be conducted if the result of either FeNO or spirometry is negative.

Key Assumptions

- FeNO testing was administered in the special care setting
- Our budget impact used the costs from the economic model; thus, all of the assumptions in the primary economic evaluations remained valid

Population of Interest

The populations of interest are children (5–17 years of age) and adults (≥ 18 years of age) with suspected asthma in Ontario. Below is the process of calculating the projected population of suspected asthma for the 5-year period 2023 to 2027.

Calculating Projected Age-Specific General Population in Ontario

The average increase in population in Ontario was about 1.5% per year between 2018 and 2022.[143] We assumed that this increase would remain the same for the next 5 years (2023–2027). The population categorized by aged groups is presented in Table A9 (Appendix 9).

Calculating Suspected Asthma Cases in Ontario

To estimate the prevalence of suspected asthma in Ontario, we focussed on new confirmed asthma cases per year. Using the projected age-specific incidence rate in Ontario between 2023 and 2027 (Appendix 9, Table A10) and the projected age-specific general population in Ontario between 2023 and 2027 (Appendix 9, Table A9), we calculated the projected new confirmed cases of asthma in Ontario between 2023 and 2027 (Table 24). Using estimated proportions of 72% and 63% between confirmed and suspected asthma (i.e., pre-test probability) for children and adults, respectively, and the projected new confirmed cases of asthma between 2023 and 2027 (Table 24), we estimated the suspected cases of asthma in Ontario between 2023 and 2027 (Table 25). Figure 14 shows steps to calculate suspected asthma cases.

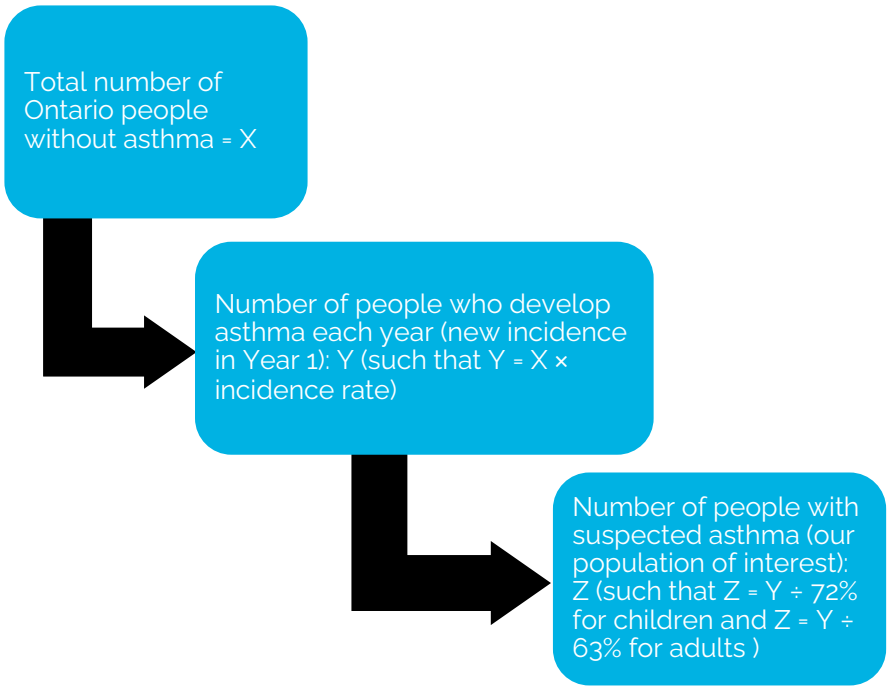


Figure 14: Process of Estimating the Size of Population of Interest for Suspected Asthma

Note: Using data from Statistics Canada.

Visual representation of the calculations for deriving the size of the population of interest for suspected asthma in Ontario. X = the total number people in Ontario without asthma; Y = the number of people who develop asthma each year, such that Y = X × incidence rate; and Z = the number of people with suspected asthma (the population of interest), such that Z = Y ÷ 72% for children and Z = Y ÷ 63% for adults (see Table 13)

Table 24: Projected Number of New Asthma Cases in Children and Adults in Ontario, 2023–2027 (Diagnostic Model)

Population	2023	2024	2025	2026	2027
Children (5–17 years of age)	8,153	7,942	7,736	7,535	7,339
Adults (≥ 18 years of age)	22,284	21,706	21,143	20,594	20,060
Total	**30,437**	**29,647**	**28,878**	**28,129**	**27,399**

Table 25: Projected Number of Children and Adults With Suspected Asthma in Ontario, 2023–2027

Population of Interest	2023	2024	2025	2026	2027
Children (5–17 years of age)	11,324	11,030	10,744	10,465	10,194
Adults (≥ 18 years of age)	35,371	34,454	33,560	32,689	31,841
Total	**46,695**	**45,484**	**44,304**	**43,154**	**42,035**

Current Scenario

We assumed that FeNO testing is not used in Ontario in the current scenario. We assumed spirometry and bronchial provocation tests are the most commonly used standard diagnostic tests.

New Scenario

We estimate the budget impact of funding FeNO testing according to the suggested diagnostic strategies in Ontario. In the absence of data on the potential uptake of FeNO testing in the next 5 years, we consider that FeNO testing is a relatively easily used test and assume the uptake rate of FeNO testing would increase 5% each year (from 5% in Year 1 to 25% in Year 5; Table 26). In a scenario analysis, we explore the extreme scenario, in which the FeNO testing uptake rate increases in 20% increments (from 20% in Year 1 to 100% in Year 5; Table 27). In this scenario, by Year 5, FeNO testing would be available for all patients with suspected asthma.

Table 26: Uptakes of FeNO Testing in Diagnosis of Asthma in Ontario – Reference Case

Uptake rates	Year 1	Year 2	Year 3	Year 4	Year 5
New scenario 1[a]					
FeNO and spirometry sequential testing strategy	5%	10%	15%	20%	25%
Standard testing	95%	90%	85%	80%	75%
New scenario 2[a]					
FeNO and spirometry combined testing strategy	5%	10%	15%	20%	25%
Standard testing	95%	90%	85%	80%	75%

Abbreviation: FeNO, fractional exhaled nitric oxide.

[a]New scenario 1: FeNO and spirometry sequential testing strategy; New scenario 2: FeNO and spirometry combined testing strategy.

Table 27: Uptakes of FeNO Testing in Diagnosis of Asthma in Ontario – Scenario Analysis

Uptake rates	Year 1	Year 2	Year 3	Year 4	Year 5
New scenario 1[a]					
FeNO and spirometry combined testing strategy	20%	40%	60%	80%	100%
Standard testing	80%	60%	40%	20%	0%
New scenario 2[a]					
FeNO and spirometry combined testing strategy	20%	40%	60%	80%	100%
Standard testing	80%	60%	40%	20%	0%

Abbreviation: FeNO, fractional exhaled nitric oxide.
[a]New scenario 1: FeNO and spirometry sequential testing strategy; New scenario 2: FeNO and spirometry combined testing strategy.

Resources and Costs

We included the cost of FeNO testing and standard testing, the cost incurred to correct misdiagnoses (e.g., cost of physician's visits and additional diagnostic testing) and the treatment cost of asthma (including the cost of exacerbations, if any). The annual costs incurred from diagnostic strategies for children and adults were taken from the diagnostic models in our Primary Economic Evaluation (see also Tables 28 and 29).

Table 28: Costs Incurred per Child by Asthma Diagnostic Strategy

Strategies	Cost incurred per strategy ($)[a]				
	Year 1	Year 2	Year 3	Year 4	Year 5
Standard testing					
Diagnostic tests	151.51	4.51	2.93	1.09	0.40
Asthma treatment	383.26	389.78	378.33	362.47	354.93
Total[b]	**534.77**	**394.29**	**381.26**	**363.56**	**355.33**
Sequential testing					
Diagnostic tests	146.09	5.04	3.43	1.26	0.46
FeNO test	28.76	0.00	0.00	0.00	0.00
Other tests	117.33	5.04	3.43	1.26	0.46
Asthma treatment	391.67	398.05	383.99	364.55	355.69
Total[b]	**537.76**	**403.09**	**387.42**	**365.81**	**356.14**
Combined testing					
Diagnostic tests	161.63	5.04	3.43	1.26	0.46
FeNO test	44.3	0	0	0	0
Other tests	117.33	5.04	3.43	1.26	0.46
Asthma treatment	391.67	398.05	383.99	364.55	355.69
Total[b]	**553.29**	**403.09**	**387.42**	**365.81**	**356.14**

Abbreviation: FeNO, fractional exhaled nitric oxide.

[a]All costs in 2022 CAD.

[b]Results may appear inexact due to rounding.

Table 29: Costs Incurred per Adult by Asthma Diagnostic Strategy

Strategies	Cost incurred per strategy ($)[a]				
	Year 1	Year 2	Year 3	Year 4	Year 5
Standard testing					
Diagnostic tests	136.61	6.28	4.02	1.47	0.53
Asthma treatment	303.19	317.24	304.62	284.77	275.06
Total[b]	**439.80**	**323.52**	**308.64**	**286.24**	**275.60**
Sequential testing					
Diagnostic tests	151.02	7.76	5.17	1.89	0.68
FeNO test	25.78	0.00	0.00	0.00	0.00
Other tests	125.24	7.76	5.17	1.89	0.68
Asthma treatment	320.16	332.35	314.66	288.43	276.39
Total[b]	**471.18**	**340.11**	**319.83**	**290.32**	**277.07**
Combined testing					
Diagnostic tests	169.53	7.76	5.17	1.89	0.68
FeNO test	44.30	0.00	0.00	0.00	0.00
Other tests	125.23	7.76	5.17	1.89	0.68
Asthma treatment	320.16	332.35	314.66	288.43	276.39
Total[b]	**489.69**	**340.11**	**319.83**	**290.32**	**277.07**

Abbreviation: FeNO, fractional exhaled nitric oxide.
[a]All costs in 2022 CAD.
[b]Results may appear inexact due to rounding.

Internal Validation

A secondary health economist conducted a formal internal validation. This process included checking for errors and ensuring the accuracy of parameter inputs and equations in the budget impact analysis.

Analysis

We conducted a reference case analysis and sensitivity analyses. Our reference case analysis represents the analysis with the most likely set of input parameters and model assumptions. Our sensitivity analyses explored how the results are affected by varying input parameters and model assumptions.

Results

Asthma Diagnosis

Reference Case Analysis (Children)

The reference case analysis showed that, for children with suspected asthma, sequential testing would incur an additional cost of $0.10 million over the next 5 years (Table 30) and combined testing would

incur an additional cost of $0.22 million over the next 5 years (Table 31). The 5-year cost of FeNO testing would be $0.23 and $0.35 million for sequential and combined testing, respectively.

Table 30: Budget Impact Analysis Results – Reference Case for Children (Sequential Testing Strategy)

Resource item	Year 1[a]	Year 2	Year 3	Year 4	Year 5	Total[b]
Current Scenario						
Standard testing	**6.06**	**10.36**	**14.41**	**18.16**	**21.71**	**70.69**
Diagnostic testing[c]	1.72	1.72	1.71	1.68	1.64	8.47
Asthma treatment[d]	4.34	8.64	12.70	16.48	20.07	62.23
New scenario 1: sequential testing						
Sequential testing	**0.30**	**0.82**	**1.53**	**2.41**	**3.44**	**8.51**
Diagnostic testing[e]	0.08	0.16	0.24	0.32	0.39	1.20
FeNO testing[f]	0.02	0.03	0.05	0.06	0.07	0.23
Other tests[g]	0.07	0.13	0.20	0.26	0.32	0.97
Asthma treatment[d]	0.22	0.66	1.29	2.09	3.05	7.31
Standard testing	**5.75**	**9.55**	**12.90**	**15.77**	**18.30**	**62.28**
Diagnostic testing[c]	1.63	1.55	1.46	1.35	1.24	7.23
Asthma treatment[d]	4.12	8.00	11.44	14.42	17.07	55.05
Budget impact of sequential testing	**0.002**	**0.01**	**0.02**	**0.03**	**0.04**	**0.10**
Cost of FeNO test	0.02	0.03	0.05	0.06	0.07	0.23

Abbreviation: FeNO, fractional exhaled nitric oxide.

[a]All costs in millions, 2022 CAD.

[b]Results may appear inexact due to rounding.

[c]Diagnostic tests in the current scenario include cost of spirometry and bronchial provocation testing.

[d]Asthma treatment includes costs of drugs, follow-up visits, and management of exacerbations, if any.

[e]Diagnostic tests in the new scenario include spirometry, FeNO, and bronchial provocation testing as described in the sequential testing strategy.

[f]FeNO testing includes the cost of FeNO device, consumables, and professional and technical cost incurred by the administering health professional.

[g]Other tests include the cost of spirometry and bronchial provocation testing.

Table 31: Budget Impact Analysis Results – Reference Case for Children (Combined Testing Strategy)

Resource item	Year 1[a]	Year 2	Year 3	Year 4	Year 5	Total[b]
Current scenario						
Standard testing	**6.06**	**10.36**	**14.41**	**18.16**	**21.71**	**70.69**
Diagnostic testing[c]	1.72	1.72	1.71	1.68	1.64	8.47
Asthma treatment[d]	4.34	8.64	12.70	16.48	20.07	62.23
New scenario 2: combined testing						
Combined testing	**0.31**	**0.84**	**1.56**	**2.44**	**3.48**	**8.63**
Diagnostic testing[e]	0.09	0.18	0.27	0.35	0.43	1.32
FeNO testing[f]	0.03	0.05	0.07	0.09	0.11	0.35
Other tests[g]	0.07	0.13	0.20	0.26	0.32	0.97
Asthma treatment[d]	0.22	0.66	1.29	2.09	3.05	7.31
Standard testing	**5.75**	**9.55**	**12.90**	**15.77**	**18.30**	**62.28**
Diagnostic testing[c]	1.63	1.55	1.46	1.35	1.24	7.23
Asthma treatment[d]	4.12	8.00	11.44	14.42	17.07	55.05
Budget impact of combined testing	**0.01**	**0.03**	**0.04**	**0.06**	**0.08**	**0.22**
Cost of FeNO testing	0.03	0.05	0.07	0.09	0.11	0.35

Abbreviation: FeNO, fractional exhaled nitric oxide.

[a]All costs in millions, 2022 CAD.

[b]Results may appear inexact due to rounding.

[c]Diagnostic testing in the current scenario includes cost of spirometry and bronchial provocation testing.

[d]Asthma treatment includes costs of drugs, follow-up visits, and management of exacerbations, if any.

[e]Diagnostic tests in the new scenario include spirometry, FeNO, and bronchial provocation testing as described in the sequential testing strategy.

[f]FeNO testing includes the cost of FeNO device, consumables, and professional and technical costs incurred by the administering health professional.

[g]Other tests include the cost of spirometry and bronchial provocation testing.

Scenario Analysis (Children)

In the scenario analysis in which the uptake of FeNO increased 20% per year, reaching 100% in Year 5, to fund sequential and combined testing for children would cost an additional $0.38 to $0.87 million, respectively, over the 5-year period. Funding sequential and combined testing for the following 5-year period (100% uptake) would cost an additional $0.81 and $1.64 million, respectively. When the cost of FeNO testing was reduced to $31.82, funding sequential and combined testing in children would require an additional $0.03 and $0.12 million, respectively, over Years 1 to 5 (Table 32 and Table 33).

Table 32: Budget Impact Analysis Results – Scenario Analysis for Children (Sequential Testing)

Resource item	Year 1[a]	Year 2	Year 3	Year 4	Year 5	Total[b]
Reference case						
Budget impact of sequential testing	0.002	0.01	0.02	0.03	0.04	0.10
Cost of FeNO testing	0.02	0.03	0.05	0.06	0.07	0.23
Faster uptake						
Budget impact of sequential testing	0.01	0.03	0.07	0.11	0.16	0.38
Cost of FeNO testing	0.07	0.13	0.19	0.24	0.29	0.91
Uptake of 100% per Year						
Budget impact of sequential testing	0.03	0.13	0.20	0.22	0.22	0.81
Cost of FeNO testing	0.33	0.32	0.31	0.30	0.29	0.91
Cost of FeNO = $31.82 per test						
Budget impact of sequential testing	-0.003	-0.001	0.005	0.01	0.02	0.03
Cost of FeNO testing	0.01	0.02	0.03	0.04	0.05	0.16

Abbreviation: FeNO, fractional exhaled nitric oxide.
[a]All costs in millions, 2022 CAD.
[b]Results may appear inexact due to rounding.

Table 33: Budget Impact Analysis Results – Scenario Analysis for Children (Combined Testing)

Resource item	Year 1[a]	Year 2	Year 3	Year 4	Year 5	Total[b]
Reference case						
Budget impact of combined testing	0.01	0.03	0.04	0.06	0.08	0.22
Cost of FeNO testing	0.03	0.05	0.07	0.09	0.11	0.35
Faster uptake						
Budget impact of combined testing	0.04	0.10	0.17	0.24	0.31	0.87
Cost of FeNO testing	0.10	0.20	0.29	0.37	0.45	1.40
Uptake of 100% per year						
Budget impact of combined testing	0.21	0.30	0.37	0.38	0.38	1.64
Cost of FeNO testing	0.50	0.49	0.48	0.46	0.45	2.38
Cost of FeNO = $31.82 per test						
Budget impact of combined testing	0.003	0.01	0.02	0.03	0.05	0.12
Cost of FeNO testing	0.02	0.04	0.05	0.07	0.08	0.25

Abbreviation: FeNO, fractional exhaled nitric oxide.
[a]All costs in millions, 2022 CAD.
[b]Results may appear inexact due to rounding.

Reference Case Analysis (Adults)

The reference case analysis showed that, for adults with suspected asthma, sequential testing would incur an additional cost of $1.19 million over the next 5 years (Table 34) and combined testing would incur an additional cost of $1.61 million over the next 5 years (Table 35). The 5-year cost of FeNO testing would be $0.64 and $1.14 million for sequential and combined testing, respectively.

Table 34: Budget Impact Analysis Results – Reference Case for Adults (Sequential Testing Strategy)

Resource item	Year 1[a]	Year 2	Year 3	Year 4	Year 5	Total[b]
Current scenario						
Standard testing	**15.56**	**26.60**	**36.82**	**45.99**	**54.55**	**179.51**
Diagnostic testing[c]	4.83	4.93	4.94	4.87	4.76	24.33
Asthma treatment[d]	10.72	21.67	31.88	41.13	49.79	155.18
New scenario 1: sequential testing						
Sequential testing	**0.83**	**2.22**	**4.11**	**6.41**	**9.07**	**22.65**
Diagnostic testing[e]	0.27	0.53	0.80	1.05	1.29	3.93
FeNO testing[f]	0.05	0.09	0.13	0.17	0.21	0.64
Other tests[g]	0.22	0.45	0.67	0.88	1.08	3.29
Asthma treatment[d]	0.57	1.69	3.31	5.36	7.79	18.72
Standard testing	**14.78**	**24.51**	**32.95**	**39.92**	**45.90**	**158.06**
Diagnostic testing[c]	4.59	4.45	4.23	3.93	3.60	20.79
Asthma treatment[d]	10.19	20.06	28.72	35.99	42.30	137.26
Budget impact of sequential testing[h]	**0.06**	**0.14**	**0.23**	**0.33**	**0.43**	**1.19**
Cost of FeNO testing	**0.05**	**0.09**	**0.13**	**0.17**	**0.21**	**0.64**

Abbreviation: FeNO, fractional exhaled nitric oxide.

[a]All costs in millions, 2022 CAD.

[b]Results may appear inexact due to rounding.

[c]Diagnostic test components in the current scenario includes cost of spirometry and bronchial provocation testing.

[d]Non-diagnostic test components include costs of asthma treatment such as drugs, follow-up visits, and exacerbation treatment, if any.

[e]Diagnostic test components include spirometry, FeNO, and bronchial provocation testing, as described in the sequential testing strategy.

[f]FeNO testing includes the cost of the FeNO device, consumables, and professional and technical costs incurred by the administering health professional.

[g]Other costs include the cost of spirometry and bronchial provocation testing.

[h]Budget impact = cost of new scenario – cost of current scenario.

Table 35: Budget Impact Analysis Results – Reference Case for Adults (Combined Testing Strategy)

Resource item	Year 1[a]	Year 2	Year 3	Year 4	Year 5	Total[b]
Current scenario						
Standard testing	**15.56**	**26.60**	**36.82**	**45.99**	**54.55**	**179.51**
Diagnostic testing[c]	4.83	4.93	4.94	4.87	4.76	24.33
Asthma treatment[d]	10.72	21.67	31.88	41.13	49.79	155.18
New scenario 2: combined testing						
Combined testing	**0.87**	**2.29**	**4.19**	**6.52**	**9.21**	**23.06**
Diagnostic testing[e]	0.30	0.61	0.89	1.17	1.43	4.40
FeNO testing[f]	0.08	0.17	0.22	0.29	0.35	1.11
Other tests[g]	0.22	0.44	0.67	0.88	1.08	3.29
Asthma treatment[d]	0.57	1.68	3.30	5.35	7.77	18.66
Standard testing	**14.78**	**24.51**	**32.95**	**39.92**	**45.90**	**158.06**
Diagnostic testing[c]	4.59	4.45	4.23	3.93	3.60	20.79
Asthma treatment[d]	10.19	20.06	28.72	35.99	42.30	137.26
Budget impact of combined testing	**0.09**	**0.20**	**0.31**	**0.44**	**0.57**	**1.61**
Cost of FeNO testing	**0.08**	**0.17**	**0.22**	**0.29**	**0.35**	**1.11**

Abbreviation: FeNO, fractional exhaled nitric oxide.

[a]All costs in millions, 2022 CAD.

[b]Results may appear inexact due to rounding.

[c]Diagnostic testing in the current scenario includes cost of spirometry and bronchial provocation testing.

[d]Asthma treatment includes cost of drugs, follow-up visits, and management of exacerbations, if any.

[e]Diagnostic testing in the new scenario includes spirometry, FeNO, and bronchial provocation testing, as described in the combined testing strategy.

[f]FeNO testing includes the cost of FeNO device, consumables, and professional and technical cost incurred by a health professional.

[g]Other tests include the cost of spirometry and bronchial provocation testing.

Scenario Analysis (Adults)

In the scenario analysis in which the uptake of FeNO increased 20% per year, reaching 100% in Year 5, to fund sequential and combined testing for adults would cost an additional $4.77 and $6.26 million, respectively, over the 5 year period. Funding sequential and combined testing for the following 5-year period (100% uptake) would cost an additional $9.02 and 12.13 million, respectively. When the cost of FeNO testing was reduced to $31.82, funding sequential and combined testing in adults would require an additional $1 and $1.34 million, respectively, over Years 1 to 5 (Tables 36 and 37).

Table 36: Budget Impact Analysis Results – Scenario Analysis for Adults (Sequential Testing)

Resource item	Year 1[a]	Year 2	Year 3	Year 4	Year 5	Total[b]
Reference case						
Budget impact of sequential testing	**0.06**	**0.14**	**0.23**	**0.33**	**0.43**	**1.19**
Cost of FeNO testing	**0.05**	**0.09**	**0.13**	**0.17**	**0.21**	**0.64**
Faster uptake						
Budget impact of sequential testing	0.22	0.55	0.94	1.34	1.72	4.77
Cost of FeNO testing	0.18	0.36	0.52	0.67	0.82	2.55
Uptake of 100% per Year						
Budget impact of sequential testing	1.11	1.67	2.02	2.11	2.11	9.02
Cost of FeNO testing	0.91	0.89	0.87	0.84	0.82	4.33
Cost of FeNO = $31.82 per test						
Budget impact of sequential testing	0.04	0.11	0.20	0.28	0.37	1.00
Cost of FeNO testing	0.03	0.06	0.09	0.12	0.15	0.46

Abbreviation: FeNO, fractional exhaled nitric oxide.

[a]All costs in millions, 2022 CAD.

[b]Results may appear inexact due to rounding.

Table 37: Budget Impact Analysis Results – Scenario Analysis for Adults (Combined Testing)

Resource item	Year 1[a]	Year 2	Year 3	Year 4	Year 5	Total[b]
Reference case						
Budget impact of combined testing	**0.09**	**0.20**	**0.31**	**0.44**	**0.57**	**1.61**
Cost of FeNO testing	**0.08**	**0.17**	**0.22**	**0.29**	**0.35**	**1.11**
Faster uptake						
Budget impact of combined testing	0.35	0.80	1.19	1.70	2.21	6.26
Cost of FeNO testing	0.31	0.61	0.89	1.16	1.41	4.38
Uptake of 100% per year						
Budget impact of combined testing	1.76	2.31	2.64	2.72	2.70	12.13
Cost of FeNO testing	1.57	1.53	1.49	1.45	1.41	7.44
Cost of FeNO = $31.82 per test						
Budget impact of combined testing	0.07	0.17	0.26	0.37	0.48	1.34
Cost of FeNO testing	0.06	0.12	0.16	0.21	0.25	0.80

Abbreviation: FeNO, fractional exhaled nitric oxide.

[a]All costs in millions, 2022 CAD.

[b]Results may appear inexact due to rounding.

Discussion

In our reference case analysis, we found that publicly funding sequential and combined testing for children with suspected asthma would incur an additional cost of $0.10 and $0.22 million, respectively, over the next 5 years. Publicly funding sequential and combined testing for adults with suspected asthma would incur an additional cost of $0.19 and $1.61 million, respectively, over the next 5 years.

We ran a scenario analysis in which the annual uptake of FeNO testing was steadily increased by 20% per year over 5 years. All patients with suspected asthma would be tested with FeNO in Year 5. For this scenario, funding sequential and combined testing in children with suspected asthma would incur an additional cost of $0.38 to $0.87 million, respectively, while funding for adults with suspected asthma would incur an additional cost of $4.77 and $6.26 million, respectively. Sequential testing seemed to be more cost-effective than combined testing, but combined testing seemed to be more feasible for implementation when both diagnostic tests could be done in 1 visit for a patient. Combined testing potentially saves travel time and cost and increases diagnostic test accuracy.

Strengths and Limitations

Our analysis had several strengths. Since our cost-effectiveness models treated children and adults separately, we were able to calculate the budget impact for each population separately. We used the yearly costs from our cost-effectiveness models, which consisted of the costs of diagnostic testing, the treatment costs for patients with asthma, treatment costs of exacerbations, if any, and follow up costs from misdiagnoses. Our budget impact explored different scenarios in which the uptake of FeNO testing was increased so that, after 5 years of implementation, all patients with suspected asthma would be tested with FeNO. We also explored a scenario in which the cost of FeNO testing was reduced based on the assumption that testing capacity would increase. None of the scenarios we explored led to cost savings for FeNO testing.

Our analysis also faced limitations. Given the lack of available uptake rates for FeNO testing from other settings, we made assumptions regarding how quickly FeNO testing may be adopted over the next 5 years. Our assumptions may not reflect the real landscape of FeNO testing implementation in Ontario. The diagnostic and treatment costs used in the budget impact were derived from the cost-effectiveness models, in which we also made assumptions to build our model parameters. Therefore, the results of our budget impact should be interpreted with caution.

Conclusions

We found that publicly funding FeNO testing with standard testing for asthma diagnosis in children would lead to a total additional cost of $0.1 to $0.22 million over the next 5 years (depending on the testing method adopted). The cost of FeNO testing alone would be $0.23 to $0.35 million over the next 5 years (depending on the testing method adopted).

Publicly funding FeNO testing with standard testing over the next 5 years for asthma diagnosis in adults would cost $1.19 to $1.61 million (depending on the testing method adopted). The cost of FeNO testing alone over the next 5 years would be $0.64 to $1.14 million (depending on the testing method adopted).

Primary Economic Evaluation – Asthma Management

Research Question

From the perspective of the Ontario Ministry of Health, what is the cost-effectiveness of FeNO testing with standard care compared with standard care alone to monitor and manage people with diagnosed asthma?

Methods

The information presented in this report follows the reporting standards set out by the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.[122] The content of this report is based on a previously developed economic project plan.

Type of Analysis

For the reference case, we conducted a probabilistic cost–utility analysis using QALYs as the effectiveness outcome. We also conducted a cost-effectiveness analysis using the number of exacerbations as the effectiveness outcome.

Population of Interest

For asthma management, the population of interest is individuals with clinician-diagnosed asthma (with or without objective testing) that is controlled or uncontrolled. We conduct separate analyses for children (aged 5–17 years) and adults (aged ≥ 18 years) because they are managed differently clinically and may respond differently to the intervention. They also have different baseline risks for exacerbation and different quality of life.

The starting age for the children model was 5 years old to reflect the eligible population. The starting age of the adult model was 40 years, based on the average age seen in the clinical trials in this population. We conducted scenario analysis using a starting age of 14 years for the children cohort based on the average age seen in the clinical trials in this population.

Subgroup Analysis

We did not conduct an equity-related subgroup analysis due to limitations in the data.

Perspective

We conducted this analysis from the perspective of the Ontario Ministry of Health.

Interventions and Comparators

Comparators

The comparator was standard care for asthma management. Asthma management in primary care typically involves a combination of education (including the development of an asthma action plan),

pharmacological intervention, and regular monitoring and assessment of asthma control through physical exams and testing. Referral to specialized care (e.g., respirologist, allergist, therapist, asthma educator) is considered in the case of asthma that is severe, difficult to diagnose, uncontrolled, or results in acute exacerbations or hospital admission.[13]

Based on their current level of asthma control, appropriate medications and devices are offered and treatment is escalated or de-escalated as needed. Asthma control indicators such as symptoms, lung function, and airway inflammation are assessed on a regular basis. Ontario Health's Quality Standards[13] suggest that validated symptom control questionnaires as well as spirometry be conducted at least annually to assess changes in control and predict likelihood of exacerbations. Some cases indicate more frequent assessments. For people with uncontrolled moderate to severe asthma who are in the care of specialists, inflammation should be assessed using sputum eosinophil levels. Experts in our clinical review noted that yearly spirometry measurements are not always accessible, resulting in a growing gap between current practice and recommended yearly testing. The wait time for a test, especially following the pandemic, can be 3 to 4 months.[13]

Interventions

We evaluate the addition of FeNO testing to standard care for asthma management. A FeNO test can be used to measure the level of NO in the lungs to help diagnose airway inflammation (generally as a rule-in test, using cut-off values in parts per billion [ppb]) and predict responsiveness to medication.[15,16]

For the reference case analysis, we assumed that FeNO testing for asthma management would be done during standard care physician visits. Treatment would be adjusted based on FeNO levels, as well as standard asthma control measures. People with uncontrolled or undiagnosed symptomatic asthma generally have FeNO levels above 30 ppb in adults and 25 ppb in children. Acceptable cut-offs vary between devices and administrators. There is insufficient evidence to recommend the number of tests or cut-off points that should be used to titrate doses of asthma medication. Generally, higher levels of FeNO (i.e., in excess of 30 or 25 ppb in adults and children, respectively) indicate airway inflammation that has been associated with lower lung function and increased risk for future asthma exacerbation.

Because FeNO is a rule-in test, it is recommended that the level of FeNO should be combined with other measures that are used to assess asthma control and that the level of FeNO should be interpreted within the context of pretest probability.[34] For simplicity, we assumed that all devices for FeNO testing have an equivalent effectiveness in dose titration for asthma management. See Table 38 for interventions, comparators, and outcomes evaluated.

Table 38: Interventions, Comparators, and Outcomes Evaluated in the Primary Economic Model

Decision problem	Patient population	Interventions	Comparator	Outcomes
Asthma management	Individuals diagnosed with asthma • Children (aged 5–17 year) • Adults (aged ≥ 18 year)	FeNO testing with standard care	Standard care	Total costs, QALYs, total number of exacerbations, incremental cost per QALY gained

Abbreviations: FeNO, fractional exhaled nitric oxide; QALY, quality adjusted life year.

Time Horizon and Discounting

We applied a 20-year time horizon in our reference case analysis, in alignment with the asthma diagnostic model. Since asthma is a chronic disease, a 20-year time horizon allows the long-term effects of FeNO testing on costs and clinical outcomes to be captured. For the children model, once a cohort member reached age 18, it was assumed that they would experience the same outcomes as adults.

We conducted a scenario analysis with a 1-year time horizon to reflect the availability of clinical evidence. We also explored different time horizons in scenario analyses (5 and 10 years). In accordance with CADTH guidelines,[125] we applied an annual discount rate of 1.5% to all outcomes (costs, QALYs, and exacerbations) incurred after the first year.

Model Structure

The asthma management model structure is identical to the Markov model for true positive diagnoses of the asthma diagnostic model (Figure 10). The management model is primarily concerned with outcomes associated with using FeNO levels to help control disease in people diagnosed with asthma. Asthma exacerbations, which are often due to poorly controlled asthma, may impact people's health-related quality of life (HRQoL). Exacerbations can also be costly to manage. Measuring FeNO levels may provide information to better control asthma and avoid the negative health consequences and costs associated with asthma exacerbations.

In the asthma management model, all patients start in the "Correctly treated asthma" health state and remain there until they die. Within this state, patients receive asthma treatment, and some may experience an exacerbation. If the asthma exacerbation is severe, it may require hospitalization. Otherwise, exacerbation would be managed in an emergency department, outpatient clinic, or at home. Exacerbations resulted in a reduction in quality of life and increased treatment costs. During the model time horizon, patients could also possibly die and enter the absorbing "Dead" health state (Figure 10). The Markov model has a monthly cycle length.

Main Assumptions

The main assumptions for the management model are as follows:

- All people entering the model are assumed to have diagnosed asthma (true positive diagnosis)
- Short-term impacts of FeNO testing on exacerbations and medication use seen in the clinical studies associated with FeNO testing are assumed to be maintained in the longer term
- The impacts of FeNO testing on exacerbations and medication use were assumed to occur only during the period in which FeNO testing is used (20-years in the reference case)
- Asthma exacerbations are associated with a short-term reduction in HRQoL
- Some people may experience asthma exacerbations requiring hospitalization or an emergency department visit. Other asthma exacerbations were assumed to be managed in a primary care setting
- Asthma mortality is assumed to be the same as age-specific mortality in the general population

- All devices for FeNO testing are assumed to have an equivalent effectiveness in dose titration for managing asthma
- Once a person in the children cohort reaches age 18, they experience the same outcomes as adults

Clinical Outcomes and Utility Parameters

We used several input parameters to populate the model:

- Baseline rate of exacerbation in people diagnosed with asthma
- Changes in risk of asthma exacerbation and medication use to account for treatment effects of FeNO testing
- Health state utilities (i.e., HRQoL)

For our reference case, we derived the baseline rate of asthma exacerbation and the effect of FeNO testing with standard care on clinical outcomes from the systematic review and meta-analysis by Khatri et al.[34]

Khatri et al[34] conducted a systematic review and meta-analysis of randomized controlled trials published between 2004 and 2019 to develop evidence-based clinical guidance on whether FeNO testing is indicated to optimize asthma treatment in patients with asthma in whom treatment is being considered. They conducted meta-analyses on several outcomes, aggregating data from randomized controlled trials (RCTs) conducted in adults and children. The majority of the studies had a 1-year time horizon and followed patients who were already being treated with a stable inhaled-corticosteroid (ICS) dose at study enrollment. The rate of asthma exacerbation, emergency department and unscheduled health care visits, and hospitalization for asthma were presented for the total population. We used the data from the subgroup analyses conducted for adults and children in our clinical evidence review for relative risk values for each model.

Baseline Rates of Asthma Exacerbations

The exacerbation rates for people under standard care (without FeNO testing) were derived from 3 RCTs included in the meta-analysis by Khatri et al.[34] The rates of exacerbations for children and adolescents was taken from an RCT reported by Szefler et al,[144] and the rates for adults from RCTs reported by Shaw et al[145] and Honkoop et al.[146]

The RCT by Szefler et al[144] was used to inform the exacerbation rates of children under standard care (see Table 39). Out of the studies focused on children in the systematic review by Khatri et al,[34] this study by Szefler and colleagues was the largest and best reflected current practice in Ontario. This study included people aged between 12 and 20 years, with symptoms of persistent asthma or uncontrolled disease. The trial was conducted in the United States, and participants were followed for 46 weeks. They reported that 43.6% of 270 patients in the control group experienced an exacerbation during the study period and that, in the control group, 22.7% of people had more than 1 unscheduled visit to an emergency department (ED) or clinic, and 4.1% of people were hospitalised at least once. We used these data to estimate the annual probability of exacerbations, unscheduled visits to the ED or clinic, and hospitalizations for the standard care comparator arm (0.49, 0.26, and 0.05, respectively).

An RCT reported by Shaw et al[145] was used to inform the rate of exacerbations in adults with asthma treated under standard care (Table 40). The study was conducted in the United Kingdom and included adults between the ages of 20 and 81 who were non-smokers, were compliant with their medications, and had not experienced a severe exacerbation within 4 weeks of the start of the study. Standard asthma management was based on the British Thoracic Society guidelines.[147] Over 12 months, the standard care group (n = 60) reported 26 exacerbations in 19 patients (annual exacerbation rate: 0.42; SD = 0.79). Shaw et al[145] did not report the proportion of exacerbations requiring hospitalisation or an ED visit, so this probability was taken from the RCT reported by Honkoop et al.[146]

Honkoop et al[146] was the only study focusing on adults that was included in the meta-analysis of hospitalization for asthma by Khatri et al.[34] The population included in this RCT were people aged 18–50 years with a diagnosis of asthma according to the Dutch national guidelines, who had had a prescription for ICSs for at least 3 months in the previous year, and were being managed in primary care. Participants were treated and followed up for 12 months. Honkoop and colleagues reported the mean severe exacerbation rate per strategy as the sum of courses of prednisone, hospitalizations, and emergency department visits. If a patient visited the hospital or emergency department and also received prednisone, the exacerbation was counted only once in the most severe category. In the group receiving standard care to achieve asthma control (n = 203), the mean severe exacerbation rate per patient per year was calculated as 0.29 (95% CI: 0.17–0.40). The authors reported 53 courses of prednisone administered and 3 visits to the emergency department, with 2 hospitalizations. We estimated the probability of ED visit and hospitalization for exacerbation for the standard care comparator arm to be 0.015 and 0.010, respectively, for the standard care arm. We assumed that the probabilities of exacerbation, ED and unscheduled health care visit, and hospitalization followed a beta distribution, while rates followed a gamma distribution.

Effect of FeNO Testing With Standard Care

For exacerbation, from Khatri et al,[34] the risk ratio (RR) for adults was based on 3 RCTs (RR: 0.77; 95% CI: 0.47–1.27), and for children on 6 RCTs (RR: 0.70; 95% CI: 0.51–0.96; see Tables 39 and 40). For hospitalizations, the relative risk in adults was based on 1 RCT (RR: 0.54; 95% CI: 0.05–5.91), and for children on 2 RCTs (RR: 0.82; 95% CI: 0.36–1.86). There were only 3 studies identified for ED and unscheduled health care visits, all conducted in children. For this outcome, the same relative risk was used for adults and children (RR: 0.67; 95% CI: 0.36–1.23).

We assumed that the relative risk values followed log-normal distributions. For the relative risk of hospitalizations in adults, assuming a log-normal distribution around the 95% CI changed the direction of the results. For this reason, we used a fixed value of 0.54 for the relative risk of hospitalizations in adults.

For our sensitivity analysis, we derived the effect of FeNO testing with standard care on asthma exacerbations from the systematic reviews and meta-analyses by Petsky et al,[95] which was also identified in the clinical evidence review. Petsky and colleagues' meta-analyses on the number of people experiencing asthma exacerbations in adults included 5 studies with a total of 1,005 participants, and found an odds ratio (OR) of 0.60 (95% CI: 0.43–0.84). They included 8 studies in children with 2,284 participants and found an OR of 0.58 (95% CI: 0.45–0.76).

Changes in Medication (Inhaled Corticosteroid) Use Over Time

We used the systematic review by Khatri et al[34] to base the effect of FeNO testing in the reference case. Khatri and colleagues found mixed results, with some evidence of increased ICS use reported in some studies and lower ICS use reported in others. However, a majority of the studies reported no difference in ICS use between groups. The authors did not conduct a pooled estimate due to differences in medications and doses reported in the RCTs. As such, we assumed no effect of FeNO testing with standard care on ICS in our model.

In our scenario analysis, we derived estimates of change in ICS use with and without FeNO testing, using a relative dose intensity (RDI) from Szefler et al[146] for children and from Honkoop et al[146] for adults. An RDI was calculated as the mean ICS use at final visit divided by the baseline ICS dosage for each study arm.

Mortality/Life Expectancy

As indicated in the Background, above, asthma mortality in Ontario was about 0.55 per 100,000 population in 2018.[130] For our modelling, under the 20-year time horizon, we assumed that mortality attributed to asthma is very small. Additionally, we found no evidence on the impact of FeNO testing on mortality. We used the Canadian life table to estimate the probability of dying[148] and applied it based on the ratio of males to females in the asthma cohort.[149]

Table 39: Clinical Inputs Used in the Asthma Management Model for Children

Model parameter	Mean[a]	Distribution[b]	Source
Exacerbation rate per person-year under standard care[c]			
Annual probability of exacerbation	0.49	Beta (133.07; 136.93)	Szefler et al[144]
Annual probability of severe exacerbation	0.47	Beta (128.19; 141.81)	Szefler et al[144]
Annual probability exacerbation requiring ED visit	0.26	Beta (69.3; 200.7)	Szefler et al[144]
Annual probability exacerbation requiring hospitalization	0.05	Beta (12.5; 257.5)	Szefler et al[144]
Rate ratio of exacerbation with addition of FeNO testing			
Rate ratio of exacerbation with FeNO testing	0.70	Log-normal (–0.36; 0.16)	CER; Khatri et al[34]
Rate ratio of ED or unscheduled visits with FeNO testing	0.67	Log-normal (–0.40; 0.31)	CER; Khatri et al[34]
Rate ratio of hospitalization with FeNO testing	0.82	Log-normal (–0.19; 0.42)	CER; Khatri et al[34]

Abbreviations: CER, clinical evidence review; ED, emergency department; FeNO, fractional exhaled nitric oxide; SE, standard error.

[a]Rate and probability over 12-month period.

[b]Log-normal distribution: parameter1 = mean, parameter2 = SE; beta distribution: parameter1 = alpha, parameter2 = beta.

[c]Mild/moderate exacerbations were calculated as the remaining cases (e.g., annual probability of exacerbation – annual probability of severe exacerbation).

[d]For the relative risk of hospitalizations in adults, assuming a log-normal distribution around the 95% CI changed the direction of the results. For this reason, we used a fixed value of 0.54 for the relative risk of hospitalizations in adults.

Table 40: Clinical Inputs Used in the Asthma Management Model for Adults

Model parameter	Mean[a]	Distribution[b]	Source
Exacerbation rate per person-year under standard care[c]			
Annual rate of exacerbation	0.42	Normal (0.42; 0.102)	Shaw et al[145]
Annual probability of severe exacerbation	0.29	Beta (58;145)	Honkoop et al[146]
Annual probability exacerbation requiring ED visit	0.015	Beta (3; 200)	Honkoop et al[146]
Annual probability exacerbation requiring hospitalization	0.010	Beta (2; 201)	Honkoop et al[146]
Rate ratio of exacerbation with addition of FeNO testing			
Rate ratio of exacerbation with FeNO testing	0.77	Log-normal (–0.26; 0.25)	CER; Khatri et al[34]
Rate ratio of ED or unscheduled visits with FeNO testing	0.67	Log-normal (–0.40; 0.31)	CER; Khatri et al[34]
Rate ratio of hospitalization with FeNO testing	0.54	Fixed	CER; Khatri et al[34]

Abbreviations: CER, clinical evidence review; ED, emergency department; FeNO, fractional exhaled nitric oxide; SE, standard error.
[a]Rate and probability over 12-month period.
[b]Log-normal distribution: parameter1 = mean, parameter2 = SE; beta distribution: parameter1 = alpha, parameter2 = beta.
[c]Mild/moderate exacerbations were calculated as the remaining cases (e.g., annual probability of exacerbation – annual probability of severe exacerbation).

Health State Utilities

A health state utility represents a person's preference for a certain health state or outcome, such as a diagnosis of asthma. Utilities are often measured on a scale ranging from 0 (dead) to 1 (full health). The HRQoL for different health states are presented in Table 41. Different utility values were used for children and adults.

Utility Associated With Asthma

For adults, utility associated with asthma was taken from a systematic review and meta-analysis by Oh et al[132] (Table 41). Meta-analyses were performed for each utility instrument according to health states based on the level of asthma control and severity. The EQ-5D-3L was the most used instrument (24.5%), and the meta-analysis included 15 studies with a total of 6,212 participants. The pooled EQ-5D-3L utility value for adults with asthma was 0.72 (95% CI: 0.63–0.80) for uncontrolled, 0.82 (95% CI: 0.75–0.88) for partly controlled, and 0.87 (95% CI: 0.84–0.90) for well-controlled asthma. In our reference case, for patients not experiencing an exacerbation, we took the pooled baseline utility score for adults with partially controlled asthma.

For children, we were unable to find EQ-5D utility values from Canada. Therefore, we used the Health Utilities Index Mark 3 (HUI3) data from two recent cycles of the Canadian Health Measures Survey (i.e., 2016–2017 and 2018–2019), as reported in Molina et al.[135] The authors used utility score norms for children (aged 6–11 years) and adolescents (aged 12–17 years) with asthma. For children, the mean utility score was 0.93 (95% CI: 0.92–0.94) and for adolescents, the mean utility score was 0.89 (95% CI: 0.86–0.92).

Impact of Exacerbations on Health-Related Quality of Life

As noted above, we derived the impact of asthma exacerbation on HRQoL from a prospective observational study conducted in adults with moderate to severe asthma in the United Kingdom.[133] The data has been used to inform estimates of utility decrement associated with asthma exacerbation in multiple published economic evaluations. For example, Lloyd et al[133] presented the change in HRQoL over the 1-month course of the study using the EQ-5D. This study was restricted to more severe patients to capture the effects of as many exacerbations as possible. We calculated the adjusted utility loss due to an exacerbation based on the baseline utility of patients and the 4-week observation of utility loss due to an exacerbation. The adjusted utility decrement for a hospitalized exacerbation was estimated at –0.33, and the adjusted utility decrement of a non-hospitalized exacerbation was estimated at –0.12. The authors did not include a disutility value for severe exacerbations requiring an ED visit, so we assumed the same utility decrement for patients who experienced a non-hospitalized exacerbation (Table 41).

We used the assumption of the NICE health technology assessment[97] that it would take an average of 4 days (~0.01 years) for people experiencing an exacerbation not resulting in hospitalization to recover to the baseline utility, while people experiencing a severe exacerbation resulting in hospitalization would require 4 weeks to recover (~0.08 years).

We did not find studies directly measuring health utilities in children with asthma exacerbation using a generic preference-based measure. This lack has been previously reported by Kua and Davis.[150] Therefore, we assumed that the disutility data for children would be similar to adults and we applied the same values for both populations.

Table 41: Utilities Used in the Economic Model

Health or treatment state	Utility or disutility (mean)	Distribution[a]	Model duration	Reference
Controlled asthma, non-exacerbation (children 6–11 y)	0.93 (HUI3)	Beta (2,324.9; 174.1)	20 years	Molina et al[135]
Controlled asthma, non-exacerbation (children 12–17 y)	0.89 (HUI3)	Beta (371.0; 45.0)	20 years	Molina et al[135]
Controlled asthma, non-exacerbation (adults > 18 y)	0.82 (EQ-5D)	Beta (371.0; 45.0)	20 years	Oh et al[132]
Disutility for exacerbation (children and adults)				
Non-hospital exacerbation: Mild/moderate exacerbation Severe exacerbation managed by GP Severe exacerbation managed in ED	–0.12	Normal (–0.12; –0.024)	0.01 years Gamma (α = 19.26, λ = 246.34)	Lloyd et al[133]; Harnan et al[97]
Severe exacerbation requiring inpatient hospitalization	–0.31	Normal (–0.31; –0.062)	0.08 years Gamma (α = 82.9, λ = 8,259	Lloyd et al[133]; Harnan et al[97]

Abbreviations: ED, emergency department; GP, general practitioner; HUI, health utility index.
[a]Beta distribution: parameter1 = alpha, parameter2 = beta; Gamma distribution: parameter 1 = alpha, parameter 2 = beta.

Cost Parameters

Cost parameters were obtained from Ontario sources, published literature, and clinical experts. The fees for professional visits were obtained from the Ontario Schedule of Benefits for Physician Services and Ontario Schedule of Benefits for Laboratory Services. All costs were reported in 2022 CAD. When 2022 CAD was not available, the Statistics Canada Consumer Price Index (CPI) was used to adjust the costs to 2022 CAD.

We considered the following costs in this model (see Table 42):

- FeNO testing, including costs related to the consumables and equipment, physician fees for conducting the test (technical and professional fees)
- Standard outpatient management of people with asthma
- Pharmacological management of asthma
- Costs related to managing exacerbations

Cost of FeNO Testing

We assumed that FeNO testing would be conducted during standard care visits to a person's physician; therefore, we exclude the consultation/visit fee and only include the additional cost of conducting a FeNO test. Currently there is no OHIP fee code for FeNO testing. Based on consultation with the Ontario Ministry of Health (MOH), we assumed that the technical and professional fees associated with FeNO testing would likely be similar to that associated with a simple spirometry volume time versus study (SOB J301, technical fee: $9.85, professional fee: $7.85). Please note that this service may be included in an existing insured service or may require its own fee code. Changes to the schedule of benefits are jointly negotiated between the Ministry of Health and the Ontario Medical Association.

The cost of consumable mouthpieces and the FeNO testing machine was dependent on the capacity of the practitioner or lab. In our reference case, we assumed that a primary care practitioner would conduct 500 FeNO tests per year, making the cost of consumables $13 per patient. For the overhead cost of a device for FeNO testing per patient, we applied the annual amortization cost of $560 divided by 500 tests resulting in an overhead cost of $1.12 per patient. As a result, we estimated that the total cost per FeNO test including device, consumables, and physician fees would be $31.82 (Table 32).

In a scenario analysis, we assumed a practitioner would conduct only 100 tests for asthma management per year. The total cost per FeNO testing in this scenario would be $44.30 ($5.60 for device overhead, $21 for consumable mouthpiece, and $17.70 for physician fees).

In the reference case, we assumed that in the first year after FeNO testing was introduced for asthma management, patients would undergo FeNO testing every 3 months to titrate medication dose and bring asthma under control. We assumed that, in the subsequent years, FeNO tests would be conducted only twice a year to monitor and maintain control of asthma.

Cost Associated With Management of Asthma

As indicated in the clinical section, above, asthma management in primary care involves a combination of education, action planning, pharmacological intervention, and regular assessment of asthma control. If the asthma worsens, a patient might experience an exacerbation, which might require rescue medications, urgent care, and/or hospitalization, depending on the severity. In the reference case analysis, we capture the cost of standard care of asthma control through outpatient management, including follow-up visits and testing, pharmacological intervention, and the cost of exacerbations.

The costs associated with outpatient asthma management were derived from a longitudinal study conducted in British Columbia on the economic burden of asthma.[151] This analysis included people aged 12 years and older with asthma who were recruited through random digit dialing. The use of health care resources was assessed at baseline and every 3 months up to 1 year for 517 individuals. To calculate the average cost of outpatient visits, the authors grouped all services performed (e.g., consultation or follow-up, physical exam, and spirometry testing) with the same date and physician identifier and summed their costs. The mean cost of outpatient visits for the per person was $42.40 (SD: $116.90) over 3 months.

Medication Costs

To determine medication costs for children covered under the provincial drug plan, we used a study by Miregwa et al,[152] who analysed prescription drug claims from the Canadian Institute for Health

Information's National Prescription Drug Utilization Information System, for people in Ontario younger than 25 years of age, from January 2016 to October 2019.[152] They found that the monthly rate of cost for asthma prescriptions per 1,000 people was $4,548.

For adults, the cost of asthma medications covered by the MOH was derived from a study of the patient level costs of asthma in people over 15 years of age in south central Ontario.[153] The annual cost of medications, covered from the MOH perspective, was $101.80 in 1995 CAD. The monthly cost per person was $14.64 in 2022 CAD.

Cost of Managing Exacerbations

We derived the cost of asthma hospitalization and the cost of ED visits for asthma from the most current data available from the Ontario Case Costing Initiative. Cases with the most responsible diagnosis of asthma (ICD-10 code J45.x) were included in the average cost of the ED or hospitalization event. Costs were derived separately for the children and adult models. The average cost of an ED visit for asthma was $319.04 and $285.63 and for inpatient hospitalization was $2,712.85 and $3,667.79 for children and adults, respectively. We also included the cost of a follow-up visit to a primary care provider (SOB A007 cost: $37.95) because, according to the Ontario Quality Standards for Asthma, people who have had an ED visit or been hospitalized for an asthma exacerbation have a follow-up assessment within 2 to 7 days after discharge.

We assumed that severe exacerbations that do not require hospitalization or an emergency department visit would require 2 GP visits ($37.95 each) plus one course of oral corticosteroids (OCS) (M. Newton, MD, email communication, July 7, 2023). Mild to moderate exacerbations were assumed to be managed at home, requiring 1 course of OCS and a follow-up visit to a primary care provider. The cost of OCS was assumed to be $9.88.[154] Mild to moderate exacerbations were assumed to be managed at home, requiring one course of OCS and a follow-up visit to a primary care provider.

Table 42: Costs Used in the Management Model

Variable	Unit cost, mean[a]	Range (one-way sensitivity analysis)	Distribution[b]	Reference
Cost of FeNO testing				
Total per FeNO test	$31.82	$31.82–$44.30	Fixed	Calculated assuming 500 tests annually
FeNO test consumables per patient	$13	$13–$21	Fixed	Consultation with manufacturers[c]
FeNO device per patient	$1.12	$1.12–$5.60	Fixed	Calculated assuming 500 tests annually
Total cost of FeNO device	$2800	—	Fixed	Consultation with manufacturers [c]
Lifetime use of FeNO device	5 years	—	Fixed	Consultation with manufacturers [c]
Technical and professional fees for FeNO testing	$17.7	—	Fixed	Assumption, SOB J301
Number of FeNO tests in first year	4	2–6	Fixed	Assumptions based on clinical studies

Variable	Unit cost, mean[a]	Range (one-way sensitivity analysis)	Distribution[b]	Reference
Number of FeNO tests in subsequent years	2	2–4	Fixed	Assumptions based on clinical studies
Cost of asthma-related management				
Outpatient asthma management (over 3 month)	$52.68	—	Gamma (52.68; 6.11)	Sadatsafavi et al, 2016[151]
Monthly asthma medication (children)	$4.55	—	Gamma (4.55; 1.14)	Miregwa et al, 2022[152]
Annual asthma medication (adult)	$175.71	—	Gamma (175.71; 43.93)	Ungar et al, 1998[153]
Cost of exacerbations				
Mild/moderate	$47.83	—	Gamma (47.83; 11.99)	SOB; Ismaila et al, 2019[154]
Severe, managed by in primary care	$85.78	—	Gamma (85.78; 21.45)	SOB; Ismaila et al, 2019[154]
Severe, managed in ED (children)	$319.04	—	Gamma (319.04; 2.69)	OCCI; SOB
Severe, managed in ED (adults)	$285.63	—	Gamma (285.63; 2.35)	OCCI; SOB
Severe, requiring inpatient hospitalization (children)	$2,712.85	—	Gamma (2,712.85; 248.24)	OCCI; SOB
Severe, requiring inpatient hospitalization (adults)	$3,667.79	—	Gamma (3,667.79; 230.63)	OCCI; SOB

Abbreviations: ED, emergency department; FeNO, fractional exhaled nitric oxide; OCCI, Ontario Case Costing Initiative; SOB, Ontario Schedule of Benefits.

[a]All costs in 2022 CAD.

[b]Standard errors were calculated from the standard deviations (SD/Vsample size) or 95% confidence intervals (upper limit – lower limit)/3.92) if reported in the literature, or using ¼ the mean when not reported.

[c]McAuthur Medical, email communication, October 7, 2022.

Internal Validation

Formal internal validation was conducted by the secondary health economist. This included testing the mathematical logic of the model and checking for errors and accuracy of parameter inputs and equations.

Equity Considerations

Economic evaluations inherently focus on horizontal equity (i.e., people with similar characteristics are treated in a similar way). Where possible, we conduct subgroup or scenario analyses to best address vertical equity (which allows for people with different characteristics to be treated differently according to their needs).

In our economic evaluation, the use of QALYs reflects horizontal equity because equal social value is assigned to each unit of health effect, regardless of the characteristics of the people who receive those effects or the condition being treated.

We were unable to conduct any other equity-related subgroup analysis because information on the effect of FeNO testing across different populations was not presented in the systematic reviews.

Analysis

Our reference case and sensitivity analyses adhered to the Canadian Agency for Drugs and Technologies in Health (CADTH) guidelines[125] when appropriate. The reference case represents the analysis with the most likely set of input parameters and model assumptions.

We calculated the reference case of this analysis by running 5,000 simulations (probabilistic analysis) that simultaneously captured the uncertainty in all parameters that were expected to vary. We set distributions for variables within the model. Tables 39–42 list the model variables and corresponding distributions. We calculated mean costs with credible intervals and mean QALYs with credible intervals for each intervention assessed. We also calculated the mean incremental costs with credible intervals, incremental QALYs with credible intervals, and ICERs for FeNO testing in addition to standard care versus standard care alone.

The results of the probabilistic analysis are presented in a cost-effectiveness acceptability curve. Although not used as definitive willingness-to-pay (WTP) thresholds, including graphical indications of the location of the results relative to guideposts of $50,000 and $100,000 per QALY facilitates interpretation of the findings and comparison with historical decisions. We also present uncertainty quantitatively as the probability that an intervention is cost-effective at previously mentioned WTP guideposts. This uncertainty is also presented qualitatively, in 1 of 5 categories defined by the Ontario Decision Framework[155]: highly likely to be cost-effective (80%–100% probability of being cost-effective), moderately likely to be cost-effective (60%–79% probability), uncertain if cost-effective (40%–59% probability), moderately likely to not be cost-effective (20%–39% probability), or highly likely not to be cost-effective (0%–19% probability).

Scenario Analyses

Table 43: Variables Varied in Scenario Analyses

Scenario	Parameter	Reference case	Scenario analysis
Short time horizon	Time horizon	20 years	1, 5, and 10 years
Start age, children model	Start age of child cohort	5 years old	14 years old
Testing costs	FeNO testing	$31.82 (including estimated consumable and machine costs assuming a capacity of 500 tests/year)	$44.30 (including estimated consumable and machine costs assuming a capacity of 100 tests/year)
	Annual number of FeNO tests	4 tests in first year and 2 tests/year in subsequent years	2 tests in first year and 1 test/year in subsequent years
	Annual number of FeNO tests	4 tests in first year and 2 tests/year in subsequent years	6 tests in first year and 4 tests/year in subsequent years
Impact of FeNO testing on exacerbation	Rate ratio/odds ratio of exacerbation	Khatri et al[34] meta-analysis used for impact of FeNO testing on number of people experiencing exacerbations	Petsky et al[95] meta-analysis used for impact of FeNO testing on number of people experiencing exacerbations
Impact of FeNO testing on ICS	Relative dose intensity of ICS	No difference from Khatri et al[34]	ICS use based on RCTs reported by Szefler et al[144]; and Honkoop et al[146] Children: RDI standard care: 0.76; RDI FeNO: 0.98 Adults: RDI standard care: 1.00; RDI FeNO: 0.91
Impact of exacerbation on utility	Exacerbation disutility	Assumed disutility of non-hospital exacerbations for ED exacerbations (ED disutility: –0.12)	Assume disutility of hospital exacerbations for ED exacerbations (ED disutility: –0.31)
Exacerbation rate	Baseline exacerbation rate for standard arm	Exacerbation rate based on clinical trials	Exacerbation rates of the standard group were doubled Exacerbation rates of the standard group were halved
Impact of FeNO testing on rate ratio for exacerbation	Rate ratio for exacerbation	Impacts of FeNO testing on exacerbation occur only during the period in which FeNO testing is used (FeNO testing for 20 years)	No impact of FeNO testing on exacerbation after 5 and 10 years (FeNO testing is continued for 20 years)
		Impacts of FeNO testing on exacerbation occur only during the period in which FeNO testing is used (FeNO testing for 20 years)	Sustained impact of FeNO testing on rate of exacerbation over 20 years (FeNO testing is discontinued after 10 years)

Abbreviations: ED, emergency department; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroids; RCT, randomized controlled trial; RDI, relative dose intensity.

Results

Asthma Management

Reference Case Analysis (Children)

Tables 44 and 45 present the results of the reference case analysis for children. The average total cost per child for standard care alone and for FeNO testing with standard care was $8,476.73 and $8,970.13, respectively. Compared to standard care alone, including FeNO testing led to increased costs of $1,165.11. This additional cost is partially offset by the fewer asthma exacerbations in the FeNO testing with standard care scenario. Overall, adding FeNO testing to the standard care for asthma management could increase the total cost by $493.40 per patient. The addition of FeNO testing did not lead to much improvement in QALYs (from –0.0095 to 0.0159), but it reduced the number of exacerbations (–0.19 to –4.24). The resulting ICERs were $103,893 per QALY gained, and $207 per exacerbation avoided.

Table 44: Reference Case Analysis Results – Children (Start Age: 5 Years Old)

Strategy	Average total costs[a]	Incremental cost[a,b,c]	Average total effects	Incremental effect[c,d,e]	ICER[c]
Standard care	$8,476.73 ($7,142.52 to $9,976.71)		15.2161 (14.7656 to 15.6215)		
FeNO testing with standard care	$8,970.13 ($7,395.13 to $11,128.45)	$493.40 (–$609.42 to $2,071.74)	15.2209 (14.7721 to 15.6269)	0.0047 (–0.0095 to 0.0159)	$103,893

Abbreviations: FeNO, fractional exhaled nitric oxide; ICER, incremental cost-effectiveness ratio.

[a]All costs in 2022 CAD.

[b]Incremental cost = average cost (strategy B) − average cost (strategy A).

[c]Negative costs indicate savings.

[d]Results may appear inexact due to rounding.

[e]Incremental effect = average effect (strategy B) − average effect (strategy A).

Table 45: Reference Case Analysis Results – Children (Start Age: 5 Years Old)

Findings	Standard care, mean (95% CI)[a]	FeNO testing with standard care, mean (95% CI)	Difference, mean (95% CI)
Average total cost	$8,476.73 ($7,142.52 to $9,976.71)	$8,970.13 ($7,395.13 to $11,128.45)	$493.40 ($474.23 to $512.58)
Additional FeNO testing cost	$0	$1,165.11	$1,165.11
Cost of all exacerbations	$3,236.47 ($2,382.92 to $4,322.26)	$2,564.76 ($1,460.59 to $4,550.88)	–$671.71 (–$1,774.53 to $906.63)
Average QALYs	15.2161 (14.7656 to 15.6215)	15.2209 (14.7721 to 15.6269)	0.0047 (–0.0095 to 0.0159)
Average exacerbations	9.13 (7.36 to 11.32)	6.74 (4.64 to 9.52)	–2.38 (–0.19 to –4.24)
ICER (cost per QALY gained)	—	—	$103,893
ICER (cost per exacerbation prevented)	—	—	$207

Abbreviations: CI, confidence interval; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.
[a]All costs in 2022 CAD.

Cost-Effectiveness Acceptability Curves (Children)

Figure 15 presents the cost-effectiveness acceptability curve for children, showing the probability of either treatment being cost-effective across a range of willingness-to-pay values. At the commonly reported willingness-to-pay value of $50,000 per QALY, standard care had the highest probability of being cost-effective (56.50%); however, at a willingness-to-pay value of $100,000 per QALY, FeNO testing with standard care had the highest probability of being cost-effective (54.78%).

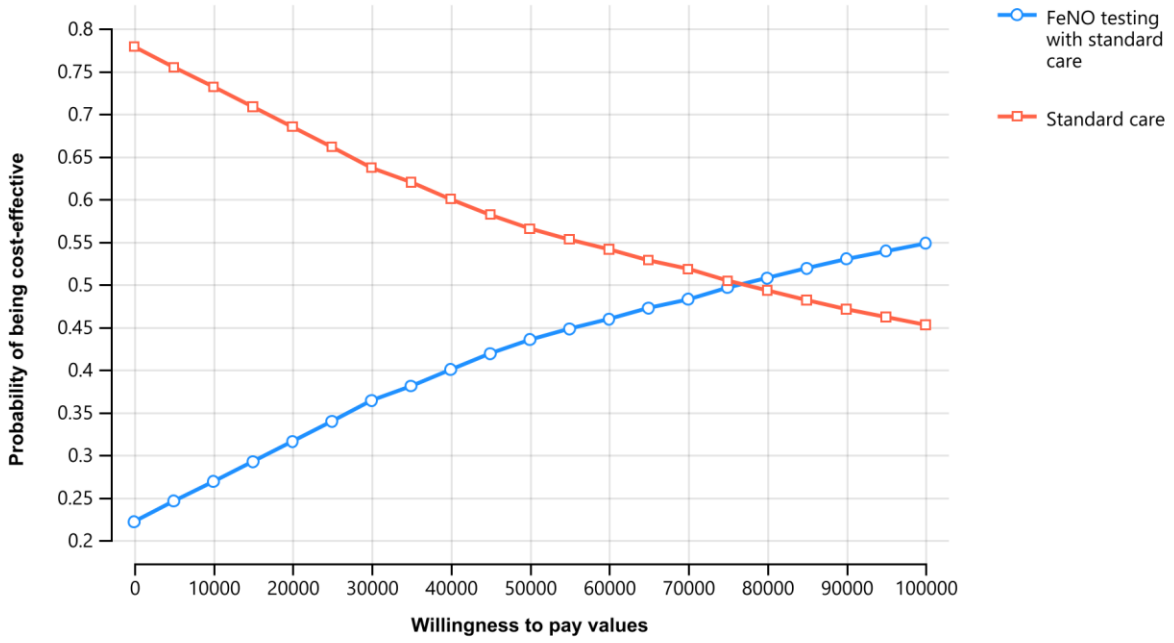


Figure 15: Cost-Effectiveness Acceptability Curve – Children Cohort

Line graph showing the cost effectiveness acceptability curve in children. Standard care has about a 78% chance of being cost effective at a WTP threshold of $0, reducing to about a 45% probability at a WTP of $100,000. FeNO testing with standard care has about a 22% probability of being cost effective at a WTP threshold of $0, rising to 55% at a WTP of $100,000. FeNO testing with standard care becomes more likely to be cost effective than standard care alone at a WTP of about $75,000.

Scenario Analysis (Children)

The results of the scenario analysis for children are shown in Table 46. FeNO testing with standard care was more costly and more effective, except when more frequent exacerbations were considered or we made strong assumptions favoring FeNO testing.

In scenarios M1, M3, and M5, we varied the time horizons to consider the cost-effectiveness over shorter periods. It was assumed that when they reach the age of 18, the people in the children cohort would start experiencing the same effects as the adult cohort. For the children cohort, in the reference case, the starting age was set at 5 years old.

Scenario M7 shows that, when an older start age (14 years) is considered, the ICER is higher and closer to the ICER seen in the adult cohort. This is likely due to the greater probability of severe exacerbation seen in children.

In scenarios M11 and M29, we assume the frequency of FeNO testing could be reduced while maintaining the same benefits of FeNO testing. When we assume the impacts of FeNO testing are sustained after FeNO testing is discontinued, FeNO testing with standard care is less costly and more effective than standard care alone.

In scenario M15, we consider the odds ratio for exacerbation when using FeNO testing (using the meta-analysis by Petsky et al)[95]. Over a 20-year time horizon, the ICER became smaller at $78,263 per QALY, although it was still uncertain if FeNO testing with standard care would be cost-effective at a WTP of $50,000 per QALY.

In scenario M21, we assume the baseline exacerbation rates are doubled. In this scenario, FeNO testing with standard care is less costly and more effective than standard care alone, with a 70.32% likelihood of being cost-effective at a WTP threshold of $50,000 per QALY (indicating that FeNO testing may be more beneficial for people who experience more frequent exacerbations). We see the opposite in scenario M23, where we assume the baseline exacerbation rates are halved. In this scenario, the addition of FeNO testing with standard care is highly likely to not be cost-effective.

In scenarios M25 and M27, we assume a reduction in the impact of FeNO testing on the rate of exacerbation after 5 and 10 years, respectively, while continuing to receive FeNO testing twice a year. In these scenarios, FeNO testing with standard care was highly likely to not be cost effective.

Table 46: Scenario Analysis Results – Children Model

Strategy	Average total costs[a]	Average total effects, QALYs	ICER ($/QALY)[b,c]	CE probability at WTP of $50,000/QALY (%)
Reference case				
Standard care	$8,476.73	15.2161	—	56.50
FeNO testing with standard care	$8,970.13	15.2209	$103,893	43.50
Time horizon				
M1: 1 year				
Standard care	$501.40	0.9217	—	81.60
FeNO testing with standard care	$582.58	0.9220	$271,103	18.60
M3: 5 years				
Standard care	$2,433.67	4.4736	—	46.50
FeNO testing with standard care	$2,586.87	4.4751	$105,410	53.50
M5: 10 years				
Standard care	$4,691.88	8.5209	—	49.58

Strategy	Average total costs[a]	Average total effects, QALYs	ICER ($/QALY)[b,c]	CE probability at WTP of $50,000/QALY (%)
FeNO testing with standard care	$4,926.19	8.5237	$83,626	50.42
Cohort start age				
M7: assuming starting age 14				
Standard care	$8,085.09	14.3972	—	87.86
FeNO testing with standard care	$8,744.59	14.4012	$162,441	12.14
FeNO testing costs				
M9: assuming lower testing capacity (100 tests per physician, total test cost $44.30)				
Standard care	$8,476.73	15.2161	—	78.36
FeNO testing with standard care	$9,427.10	15.2209	$200,113	21.64
M11: assuming 6 FeNO tests in first year and 4 tests annually in subsequent years				
Standard care	$8,476.73	15.2161	—	95.26
FeNO testing with standard care	$10,069.47	15.2209	$335,373	4.74
M13: assuming 2 FeNO tests in first year and 1 test annually in subsequent years				
Standard care	$8,476.73	15.2161	—	29.76
FeNO testing with standard care	$8,387.58	15.2209	Dominant	70.24
Alternate sources				
M15: impact of FeNO testing on number of people experiencing exacerbation (Petsky et al[95] meta-analysis)				
Standard care	$8,476.73	15.2161	—	51.56
FeNO testing with standard care	$8,914.14	15.2218	$77,946	48.44
M17: impact of FeNO testing on inhaled corticosteroids				
Standard care	$8,323.59	15.2161	—	59.54
FeNO testing with standard care	$8,872.52	15.2209	$115,585	40.46
Model assumptions				
M19: assuming hospitalized disutility for ED exacerbation (–0.31)				
Standard care	$8,476.73	15.2094	—	52.38
FeNO testing with standard care	$8,970.13	15.2161	$73,658	47.62
M21: assuming baseline exacerbation rates are doubled				
Standard care	$11,664.86	15.1894	—	29.68

Strategy	Average total costs[a]	Average total effects, QALYs	ICER ($/QALY)[b,c]	CE probability at WTP of $50,000/QALY (%)
FeNO testing with standard care	$11,462.76	15.1991	Dominant	70.32
M23: assuming baseline exacerbation rates are halved				
Standard care	$6,863.50	15.2255	—	94.68
FeNO testing with standard care	$7,681.66	15.2279	$332,413	5.32
Impact of FeNO testing on exacerbation				
M25: no impact of FeNO testing on exacerbation after 5 years (FeNO testing is continued for 20 years)				
Standard care	$8,476.73	15.2161	—	99.70
FeNO testing with standard care	$9,419.16	15.2176	$638,210	0.30
M27: no impact of FeNO testing on exacerbation after 10 years (FeNO testing is continued for 20 years)				
Standard care	$8,476.73	15.2161	—	80.30
FeNO testing with standard care	$9,216.04	15.2190	$261,837	19.70
M29: sustained impact of FeNO testing on exacerbation over 20 years (FeNO testing is discontinued after 10 years)				
Standard care	$8,476.73	15.2161	—	32.48
FeNO testing with standard care	$8,459.59	15.2209	Dominant	67.52

Abbreviations: CE, cost-effectiveness; ED, emergency department; FeNO, fractional exhaled nitric oxide; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; WTP, willingness-to-pay.

[a]All costs in 2022 CAD.

[b]Dominant ICER indicates less costly and more effective.

[c]Results may appear inexact due to rounding.

Reference Case Analysis (Adults)

The average total cost per adult was $7,782.96 for standard care and $8,516.80 for FeNO testing with standard care. Similar to children, the addition of FeNO testing led to increased costs associated with the test itself ($1,147.01). This increase was partially offset by reduced costs related to asthma exacerbation (–$962.12 to –$28.82). Overall, adding FeNO testing to the standard care for asthma management would increase the total cost by $184.89 to $1,118.19 per patient. Compared to standard care alone, FeNO testing with standard care led to similar QALYs (–0.0008 to 0.0091), but fewer exacerbations (–4.24 to 1.67). The resulting ICER was $200,135 per QALY gained and $408 per exacerbation avoided (Tables 47 and 48).

Table 47: Reference Case Analysis Results – Adults

Strategy	Average total cost[a]	Incremental cost[b,c,d]	Average total effects	Incremental effect[d,e]	ICER[d]
Standard care	$7,782.96 ($6,020.42 to $9,831.43)	—	14.0037 (12.8427 to 15.0167)	—	—
FeNO testing with standard care	$8,516.80 ($6,865.95 to $10,369.21)	$733.84 ($184.89 to $1,118.19)	14.0074 (12.8443 to 15.0202)	0.0037 (–0.0008 to 0.0091)	$200,135

Abbreviations: FeNO, fractional exhaled nitric oxide; ICER, incremental cost-effectiveness ratio.

[a]All costs in 2022 CAD.

[b]Incremental cost = average cost (strategy B) − average cost (strategy A).

[c]Negative costs indicate savings.

[d]Results may appear inexact due to rounding.

[e]Incremental effect = average effect (strategy B) − average effect (strategy A).

Table 48: Reference Case Analysis Results – Adults

Finding	Standard care, mean (95% CI)	FeNO testing with standard care, mean (95% CI)	Difference, mean (95% CI)
Average total cost	$7,782.96 ($6,020.42 to $9,831.43)	$8,516.80 ($6,865.95 to $10,369.21)	$733.84 ($184.89 to $1,118.19)
Additional FeNO testing cost	$0	$1,147.01	$1,147.01
Cost of all exacerbations	$1,208.57 (557.76 to $2,400.83)	$795.40 ($365.69 to $1,518.02)	–$413.17 (–$962.12 to –$28.82)
Average QALYs	14.0037 (12.8427 to 15.0167)	14.0074 (12.8443 to 15.0202)	0.0037 (–0.0008 to 0.0091)
Average exacerbations	7.09 (4.59 to 11.17)	5.56 (2.75 to 10.35)	1.53 (–4.24 to 1.67)
ICER (cost per QALY gained)	—	—	$200,135
ICER (cost per exacerbation prevented)	—	—	$480

Abbreviations: CI, confidence interval; FeNO, fractional exhaled nitric oxide; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

[a]All costs in 2022 CAD.

Cost-Effectiveness Acceptability Curves (Adults)

For adults, at commonly reported willingness-to-pay values of $50,000 and $100,000 per QALY, standard care alone had the highest probability of being cost-effective: 93.48% and 80.82%, respectively (see Figure 16). Based on these results, FeNO testing with standard care is unlikely to be cost-effective for adults.

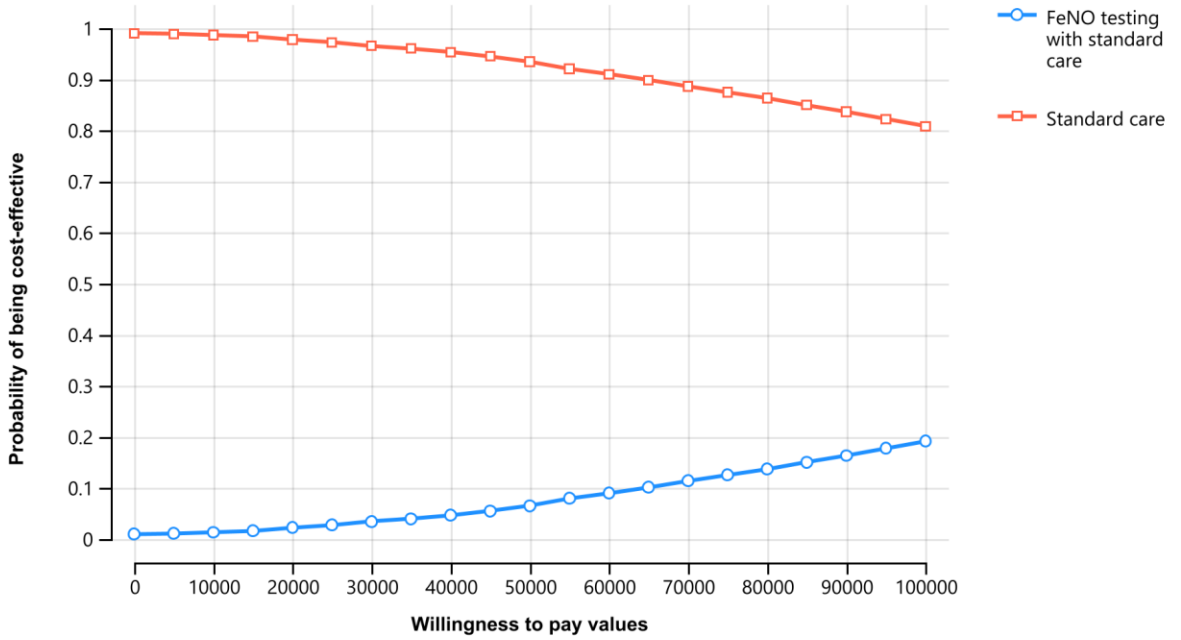


Figure 16: Cost-Effectiveness Acceptability Curve – Adult Cohort

Line graph showing the cost effectiveness acceptability curve in adults. Standard care has a near 100% chance of being cost effective at a WTP threshold of $0, reducing to about an 80% probability at a WTP of $100,000. FeNO testing with standard care has a near 0% probability of being cost effective at a WTP of $0, rising to 20% at a WTP of $100,000.

Scenario Analysis (Adults)

The results of the scenario analyses for adults are shown in Table 49. FeNO testing with standard care was more costly and more effective in all scenarios, and the probability of FeNO testing with standard care being cost-effective was unlikely to uncertain at a WTP threshold of $50,000 per QALY. Relative to the reference case, in scenarios M12 and M20, where we assume less frequent FeNO testing or an increased rate of exacerbation, the probability of cost-effectiveness of FeNO testing with standard care is uncertain.

The results were also sensitive to an increase in frequency of FeNO testing, as well as to assumptions around a reduction in the impact of FeNO testing on outcomes over the long-term. In scenario M10, increasing the frequency of FeNO testing to 6 in the first year, with 4 tests annually thereafter, and in scenarios M24 and M26, where we assume a reduction in the impact of FeNO testing on the rate of exacerbations after 5 and 10 years, FeNO testing with standard care was highly unlikely to be cost-effective.

When using alternate sources to examine the effect of FeNO testing on exacerbations (scenario M14) or on the use of inhaled corticosteroids (scenario M16), ICERs were lower relative to the reference case, although FeNO testing with standard care remained highly or moderately unlikely to be cost-effective.

In scenario M20, we assume the baseline exacerbation rates are doubled. In this scenario, FeNO testing with standard care provides a much more favorable ICER compared to the base case, although standard

care is still more likely to be cost-effective at a WTP threshold of $50,000 per QALY. Similarly, in scenario M22, when we assume the baseline exacerbation rates are halved, the addition of FeNO testing with standard care is highly likely to not be cost-effective.

Table 49: Scenario Analysis Results – Adult Model

Strategy	Average total cost[a]	Average total effects, QALYs	ICER ($/QALY)[b]	CE probability at WTP of $50,000/QALY (%)
Reference case				
Standard care	$7,782.96	14.0037	—	93.48
FeNO testing with standard care	$8,516.80	14.0074	$200,135	6.52
Time horizon				
M2: 1 year				
Standard care	$454.43	0.8177	—	99.9
FeNO testing with standard care	$556.57	0.8179	$477,126	0.10
M4: 5 years				
Standard care	$2,200.53	3.9594	—	96.70
FeNO testing with standard care	$2,455.17	3.9604	$245,637	3.30
M6: 10 years				
Standard care	$4,227.18	7.6059	—	94.92
FeNO testing with standard care	$4,655.80	7.6079	$215,229	5.08
FeNO testing costs				
M8: assuming lower testing capacity (100 tests per physician, total test cost $44.30)				
Standard care	$7,782.96	14.0037	—	99.14
FeNO testing with standard care	$8,966.66	14.0074	$322,824	0.86
M10: assuming 6 FeNO tests in first year and 4 tests annually in subsequent years				
Standard care	$7,782.96	14.0037	—	99.96
FeNO testing with standard care	$9,598.06	14.0074	$495,022	0.04
M12: assuming 2 FeNO tests in first year and 1 test annually in subsequent years				
Standard care	$7,782.96	14.0037	—	52.30
FeNO testing with standard care	$7,943.29	14.0074	$43,726	47.70

Strategy	Average total cost[a]	Average total effects, QALYs	ICER ($/QALY)[b]	CE probability at WTP of $50,000/QALY (%)
Alternate sources				
M14: impact of FeNO on number of people experiencing exacerbation (Petsky et al[95] meta-analysis)				
Standard care	$7,782.96	14.0037	—	88.68
FeNO testing with standard care	$8,423.34	14.0088	$125,525	11.32
M16: impact of FeNO testing on inhaled corticosteroids				
Standard care	$7,788.26	14.0037	—	77.46
FeNO testing with standard care	$8,252.42	14.0074	$126,588	22.54
Model assumptions				
M18: hospitalized disutility for ED exacerbation (–0.31)				
Standard care	$7,782.96	14.0032		93.10
FeNO testing with standard care	$8,516.80	14.0070	$192,489	6.90
M20: baseline exacerbation rates doubled				
Standard care	$8,969.35	13.9850		50.28
FeNO testing with standard care	$9,297.91	13.9921	$45,795	49.72
M22: baseline exacerbation rates halved				
Standard care	$7,166.72	13.9993		99.50
FeNO testing with standard care	$8,109.02	14.0011	$553,465	0.50
Impact of FeNO on exacerbation rates				
M24: no impact of FeNO testing on exacerbations after 5 years (FeNO testing is continued for 20 years)				
Standard care	$7,782.96	14.0037	—	100.00
FeNO testing with standard care	$8,811.29	14.0047	$976,343	0
M26: no impact of FeNO on exacerbations after 10 years (FeNO testing is continued for 20 years)				
Standard care	$7,782.96	14.0037	—	99.90
FeNO testing with standard care	$8,703.85	14.0057	$458,911	0.10
M28: sustained impact of FeNO on exacerbations over 20 years (FeNO testing is discontinued after 10 years)				
Standard care	$7,782.96	14.0037	—	61.74
FeNO testing with standard care	$8,020.56	14.0074	$64,799	38.26

Abbreviations: CE, cost-effectiveness; ED, emergency department; FeNO, fractional exhaled nitric oxide; ICER, incremental cost-effectiveness ratio; WTP, willingness-to-pay; QALY, quality adjusted life year.

[a]All costs in 2022 CAD.

Notes from Table 49 continued
[b]Dominant ICER indicates less costly and more effective.

Discussion

We conducted a primary economic evaluation to determine the cost-effectiveness of the addition of FeNO testing to standard care for people with diagnosed asthma in the Ontario setting. Our analysis suggested that the addition of FeNO testing for children and adults with diagnosed asthma may not be a favorable option for management from an economic perspective.

Our clinical evidence review reported Moderate- to Low-quality evidence (using GRADE[39]) on the benefits of FeNO testing with standard care. Likewise, our analysis found that FeNO testing with standard care was both more costly (the incremental costs were $493.40 and $733.84 for children and adults, respectively) and more effective in preventing exacerbation (–2.38 and –1.53 exacerbations, respectively), although we see similar differences in quality of life (0.0047 and 0.0037) compared to standard care over the 20-year time horizon. The 95% credible intervals around the increment QALYs for both children and adults was large, which is reflective of the uncertainty around the health care utilization parameter estimates. Further research is needed to better inform these parameters.

Our reference case results showed that, despite being associated with higher testing costs, the overall cost of FeNO testing with standard care was partially offset by the savings associated with preventing exacerbations. Each case of exacerbation was associated with substantial health care resource use.

We conducted a series of sensitivity and scenario analyses to examine uncertainty in model structure and parameters, including making assumptions about the benefits of FeNO testing for asthma management over the short- and long-term time horizons. The results from these sensitivity and scenario analyses were somewhat consistent with the reference case. For children, FeNO testing with standard care became more cost-effective over a 10-year time horizon, as children experience more severe exacerbations and a greater relative reduction in risk of exacerbation with FeNO testing. For adults, the results are sensitive to the cost and frequency of FeNO testing, as well as to the addition of alternate treatments such as inhaled corticosteroids.

Both models were very sensitive to assumptions regarding long-term benefits. In our reference case, we assume that the exacerbation rate reduction benefit will last as long as FeNO tests are given (i.e., the 20-year time horizon), which is a strong assumption considering data has been derived from clinical trials, most of which had 1-year time horizons. In scenarios M24/M25 and M26/M27, where the impact of FeNO testing on the rate of exacerbation is zero after years 5 and 10, respectively, we see FeNO testing with standard care is highly unlikely to be cost-effective. Scenarios M14/15 and M16/M17 examine different clinical inputs. When considering the annual probability of exacerbation, Petsky et al[95] found interventions that included FeNO testing substantially reduced the odds of exacerbation (odds ratio: 0.60 [95% CI: 0.43– to 0.84] for adults and 0.58 [95% CI: 0.45– to 0.76] for children) , when compared to standard care alone. When considering the effect of FeNO testing on use of inhaled corticosteroids, based on selected trials in children and adults, FeNO testing with standard care became more cost effective for adults and less cost-effective for children, relative to the reference case.

Equity Considerations

We were unable to conduct equity-related subgroup analyses due to the limitations of available data. Future studies are needed to provide data on equity-related subgroups and how access affects the use of FeNO testing in the Ontario context.

Strengths and Limitations

Our primary economic evaluation provides cost-effectiveness analyses of the addition of FeNO testing to help guide management of asthma. We obtained several key parameter inputs from local sources. For instance, we obtained the average cost of asthma-related hospitalization and emergency department visits from Ontario Case Costing.

Moreover, to ensure the quality of the evidence used, we derived key clinical parameters from our clinical review, which included an assessment of the quality of evidence. Our clinical review identified 1 recent systematic review and meta-analysis relevant to our research question. This review included a grouped meta-analysis for children and adults on the impact of FeNO testing on the number and frequency of asthma exacerbations, emergency department and unscheduled health care visits, and hospitalizations for asthma.[34] We also considered the results of meta-analyses by Petsky et al[95] on FeNO testing use in the management of asthma in children and adults in scenario analyses, which showed more favorable results towards FeNO testing.

An important limitation of our analyses is that the available evidence does not support a precise FeNO testing value that should initiate a change in decision-making regarding therapy for asthma. Because of the variability in the included studies, as well as the inherent phenotypic variability of asthma, it was the consensus of the committee that the available evidence did not provide enough data to recommend specific cut points associated with specific actions, such as starting or increasing the dose of an ICS. Additionally, a majority of the included studies followed patients for only 1 year, limiting the reliability of the data for modeling over a longer time horizon. There is limited long term evidence on the efficacy of FeNO testing.

Other limitations to our analysis should also be noted. Due to the unavailability of Ontario data, we determined the disutility associated with asthma from data in a UK study.[133] This study was limited to adults with severe asthma and reported disutility for hospitalized and non-hospitalized exacerbations. Due to the lack of information on types of non-hospital exacerbations, we assumed that all exacerbations not leading to an inpatient hospitalization, including those requiring an emergency department visit, would have the disutility of a non-hospital exacerbation.

Additionally, we did not explore potential consequences associated with asthma comorbidities, such as obesity and cardiovascular disease, or with asthma-related mortality or the impact of FeNO testing on outcomes such as lung function. Finally, we applied a public payer perspective in our analysis that does not consider indirect costs such as productivity loss and patients' out-of-pocket costs associated with uncontrolled asthma. Given these last two limitations, our results should be considered conservative.

Conclusions

It is uncertain if FeNO testing with standard care to monitor and manage children diagnosed with asthma is cost-effective at commonly used willingness-to-pay values of $50,000 and $100,000 per QALY gained (ICER of $103,893 per QALY). FeNO testing with standard care to monitor and manage adults

diagnosed with asthma is unlikely to be cost-effective at commonly used willingness-to-pay values of $50,000 and $100,000 per QALY gained (ICER of $200,135 per QALY).

Budget Impact Analysis – Asthma Management

Research Question

What is the potential 5-year budget impact for the Ontario Ministry of Health of publicly funding fractional exhaled nitric oxide (FeNO) testing with standard care to monitor and manage people diagnosed with asthma?

Methods

Analytic Framework

We estimated the budget impact of publicly funding FeNO testing for the management of asthma using the cost difference between two scenarios: (1) current clinical practice without public funding for FeNO testing (the current scenario), and (2) the anticipated clinical practice with public funding for FeNO testing (the new scenario). Figure 17 presents the model schematic.

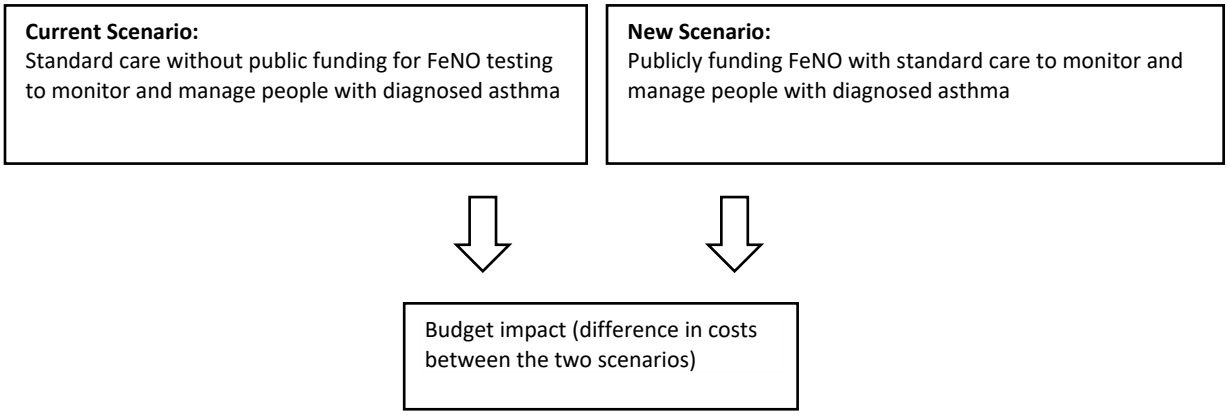


Figure 17: Schematic Model of Budget Impact in the Management of Asthma

Flow chart describing the model for the budget impact analysis. Based on the size of the population of interest, we created 2 scenarios: the current scenario, which would explore the distribution of treatment strategies, resource use, and total costs without public funding for FeNO testing; and the new scenario, which would explore the distribution of treatment strategies, resource use, and total costs with public funding for FeNO testing. The budget impact would represent the difference in costs between the two scenarios.

Key Assumptions

- We assumed no difference in the use of medication between FeNO testing with standard care and standard care alone. This assumption was based on our clinical review, which found little to no difference in inhaled corticosteroid (ICS) use between treatment strategies
- In the intervention arm, it was assumed that a person diagnosed with asthma would receive 4 FeNO tests in the first year and 2 FeNO tests in subsequent years (20-year time horizon)

Our budget impact used the costs from the economic model; thus, all of the assumptions in the primary economic evaluations remained valid.

Population of Interest

Our population of interest is people (aged ≥ 5 years) in Ontario who have been diagnosed with asthma. We estimated our population of interest using administrative and published data.

As mentioned in the diagnostic budget impact analysis, we estimated the age-specific general population in Ontario between 2023 and 2027 based on data from Statistics Canada.[156] We assumed that the average increase in the population in Ontario of around 1.5% per year between 2018 and 2022 would continue through 2027 (Appendix Table A9).

Following the same assumption, we used the asthma prevalence rates reported by The Ontario Asthma Surveillance Information System (OASIS)[157] from 2014 to 2019 to calculate an average change in prevalence in Ontario of 0.39% per year. Finally, we estimated the age-specific asthma prevalence in Ontario between 2023 and 2027 (Table 50). We then calculated the projected diagnosed cases of asthma in Ontario between 2023 and 2027 (Table 51), applying the asthma prevalence rate to the projected age-specific general population size. Assuming a uniform distribution of people aged 5 to 19 years, we calculated the size of the 5-to-17-year-old cohort.

Table 50: Projected Asthma Prevalence per 100 Population in Ontario, 2023–2027

Population of Interest (age in years)	2023	2024	2025	2026	2027
5–9	16.61	16.68	16.74	16.81	16.87
10–14	20.64	20.72	20.80	20.88	20.96
15–19	22.35	22.44	22.52	22.61	22.70
20–29	22.07	22.15	22.24	22.32	22.41
30–39	16.56	16.63	16.69	16.76	16.82
40–49	13.45	13.50	13.55	13.60	13.65
50–59	13.35	13.41	13.46	13.51	13.56
60–69	13.37	13.43	13.48	13.53	13.58
≥ 70	14.28	14.33	14.39	14.44	14.50

Table 51: Projected Population With Diagnosed Asthma in Ontario, 2023–2027

Population of Interest (age in years)	2023	2024	2025	2026	2027
Children (5–17)	425,210	433,046	441,027	449,155	457,433
Adults (≥ 18)	1,970,370	2,006,684	2,043,667	2,081,332	2,119,691
Total	**2,395,580**	**2,439,730**	**2,484,694**	**2,530,487**	**2,577,124**

Current Intervention Mix

At present, FeNO testing for asthma management is not publicly funded in Ontario. Therefore, we assumed that all patients in the current scenario were receiving standard care (without FeNO testing). We assumed the total cost incurred in this scenario would include the cost of standard care for asthma (e.g., standard follow up tests and medication) and the cost of exacerbations, if any.

Uptake of the New Intervention and New Intervention Mix

In the new scenario, all patients with diagnosed asthma would be eligible to receive FeNO testing with standard care for asthma management. A FeNO test would take place during a standard follow-up visit to a physician's office. The costs incurred in this scenario would include FeNO testing plus the usual costs of asthma management.

The uptake rates for Years 1–5 is expected to be 5% per year (i.e., 5% in Year 1, increasing to 25% in Year 5). The uptake rate is applied to the percentage of people who have not been treated with FeNO testing previously. Once a person is started on FeNO testing with standard care, we assume they remain under this treatment regimen. Tables 52–54 show the uptakes rates for FeNO testing with standard care.

Table 52: Uptake of FeNO Testing and Standard Care in Ontario

	Year 1	Year 2	Year 3	Year 4	Year 5
Current scenario					
Standard care	100%	100%	100%	100%	100%
New scenario					
FeNO testing with standard care	5%	10%	15%	20%	25%
Standard care	95%	90%	85%	80%	75%

We assumed that children who started receiving FeNO testing would age out of the children cohort and join the adult cohort, still receiving FeNO testing. Assuming a uniform distribution of ages from 5 to 17 years, we calculated 7.69% (1/13) of the children receiving FeNO testing would move to the adult cohort each year.

Table 53: Number of Children Receiving FeNO Testing With Standard Care Versus Standard Care Alone (Reference Case) in Ontario

	Year 1	Year 2	Year 3	Year 4	Year 5
Current scenario					
Standard care	425,210	433,046	441,027	449,156	457,434
New scenario[a,b]					
FeNO testing with standard care	21,260	60,967	113,990	185,264	268,923
Standard care	403,949	372,079	327,038	263,892	188,510

[a]The volume of interventions was calculated from the total population multiplied by the uptake rate of FeNO testing in the new scenario and assuming children join the adult cohort as they age out of the children cohort. For example, in the new scenario, the total number of people in Year 1 is 425,210 and the uptake rate of FeNO testing with standard care is 5%, so the number of people receiving FeNO testing with standard care in Year 1 is 21,260 (425,210 × 5%). The total volume in Year 2 is 433,046; assuming 21,260 children starting receiving FeNO testing with standard care in Year 1, and 7.69% of these children will leave the children cohort and join the adult cohort (21,260 x 7.69% = 1,635 children leaving cohort, 19,625 remain from Year 1), the total number of people receiving FeNO testing with standard care in Year 2 is 60,967 ([433,046 – 19,625] x 10% = 41,342 new children receiving FeNO with standard care in Year 2, plus the 16,626 children remaining from Year 1 = 60,967).
[b]Results may appear inexact due to rounding.

Table 54: Number of Adults Receiving FeNO With Standard Care Versus Standard Care Alone (Reference Case) in Ontario

	Year 1	Year 2	Year 3	Year 4	Year 5
Current scenario					
Standard care	1,970,370	2,006,684	2,043,667	2,081,332	2,119,691
New scenario[a,b]					
FeNO testing with standard care	98,518	290,807	557,968	870,920	1,197,575
Standard care	1,871,851	1,715,877	1,485,699	1,210,412	922,116

[a]The volume of interventions was calculated from the total population multiplied by the uptake rate of FeNO testing in the new scenario and assuming children join the adult cohort as they age out of the children cohort. For example, in the new scenario, the total volume in Year 1 is 1,970,370 and the uptake rate of FeNO testing with standard care is 5%, so the number of people receiving FeNO testing with standard care in Year 1 is 98,518 (1,970,370 × 5%). The total volume in Year 2 is 2,006,684; assuming 98,518 adults started receiving FeNO testing with standard care in Year 1, and 7.69% of the children receiving FeNO testing join the adult cohort (21,260 x 7.69% = 1,635, see Table 53), the total number of people receiving FeNO testing with standard care in Year 2 is 290,807 ([2,006,684 – 98,518 – 1,635] x 10% = 190,653 new adults receiving FeNO testing with standard care in Year 2 plus 98,518 adults from Year 1 and 1,635 people joining from the children cohort).
[b]Results may appear inexact due to rounding.

It is possible that access to FeNO testing may not be equitable, especially in areas where access to physicians or labs is limited. Uptake and costs may vary depending on how FeNO testing is implemented (funding for equipment and physician fees, and whether it is conducted in a primary or specialized setting). Due to a lack of available data, however, equity-related BIA scenarios were not conducted.

Resources and Costs

We included both health technology–associated (i.e., FeNO testing) and disease-associated resources and costs. We obtained the mean cost per patient from the deterministic analysis in our primary economic evaluation and separated costs associated with testing and with exacerbations. Table 55 contains the annual undiscounted per-patient costs for each intervention used in our budget impact model.

Table 55: Costs Incurred per Person, by Asthma Management Strategy

Strategies	Year 1[a]	Year 2	Year 3	Year 4	Year 5
Children					
Standard care	$504.78	$504.75	$504.71	$504.68	$504.65
FeNO testing with standard care	$572.82	$511.79	$509.11	$509.07	$509.04
Adults					
Standard care	$456.22	$455.69	$455.12	$454.50	$453.85
FeNO testing with standard care	$558.56	$497.02	$493.75	$493.09	$492.38

[a]All costs in 2022 CAD.

Internal Validation

A secondary health economist conducted a formal internal validation. This process included checking for errors and ensuring the accuracy of parameter inputs and equations in the budget impact analysis.

Analysis

We conducted a reference case analysis and scenario analyses. Our reference case analysis represents the analysis with the most likely set of input parameters and model assumptions. We calculate the required budget to publicly fund FeNO testing for management of asthma in people in Ontario and the budget impact as the cost difference between the new scenario (public funding for FeNO testing with standard care) and the current scenario (standard care with no public funding for FeNO testing).

In addition to the reference case, we also calculated the budget impact in several scenario analyses, including varying the parameters for uptake rate and the frequency of FeNO testing. In total, we conducted the following four scenario analyses:

- Uptake rate of FeNO testing was 100%
- Assuming less frequent FeNO testing
- Assuming more frequent FeNO testing
- Assuming a higher cost of FeNO testing

Results

Asthma Management

Reference Case Analysis (Children)

Table 56 summarizes the total costs associated with FeNO testing with standard care over the next 5 years for children. The annual budget impact ranged from an additional $1.45 million in Year 1 to $7.63 million in Year 5, and the total 5-year budget impact was an additional $22.37 million. When we accounted for only the direct costs of FeNO testing, the total 5-year budget impact was $60.86 million.

Table 56: Budget Impact Analysis Results – Children

	Budget impact (in millions)[a]					
Scenario	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total[b]**
Current scenario						
Standard care	$214.64	$218.58	$222.59	$226.68	$230.85	$1,113.34
Cost of FeNO testing	$0	$0	$0	$0	$0	$0
Cost of asthma exacerbations	$101.84	$103.71	$105.61	$107.55	%109.53	$528.25
Hospital exacerbations	$54.61	$55.62	$56.64	$57.68	$58.74	$283.29
ED exacerbations	$39.73	$40.46	$41.20	$41.96	$42.73	$206.08
Exacerbations managed in primary care	$7.50	$7.63	$7.77	$7.92	$8.06	$38.88
New scenario						
Standard care	$203.91	$187.81	$165.06	$133.18	$95.13	$785.08
Cost of FeNO testing	$0	$0	$0	$0	$0	$0
Cost of asthma exacerbations	$96.75	$89.11	$78.32	$63.19	$45.14	$372.50
Hospital exacerbations	$51.88	$47.79	$42.0	$33.89	$24.21	$199.76
ED exacerbations	$37.74	$34.76	$30.55	$24.65	$17.61	$145.32
Exacerbations managed in primary care	$7.12	$6.56	$5.76	$4.65	$3.32	$27.42
FeNO testing with standard care	$12.18	$33.73	$61.81	$99.56	$143.34	$350.62
Cost of FeNO testing	$2.71	$6.56	$11.03	$17.02	$23.54	$60.86
Cost of asthma exacerbations	$3.83	$10.99	$20.55	$33.39	$48.47	$117.24
Hospital exacerbations	$2.24	$6.42	$12.01	$19.51	$28.32	$68.50

Scenario	Budget impact (in millions)[a]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total[b]
ED exacerbations	$1.33	$3.82	$7.14	$11.60	$16.83	$40.71
Exacerbations managed in primary care	$0.26	$0.75	$1.41	$2.29	$3.32	$8.03
Budget impact	$1.45	$2.95	$4.28	$6.06	$7.63	$22.37
Cost of FeNO testing	$2.71	$6.56	$11.03	$17.02	$23.54	$60.86

Abbreviations: ED, emergency department; FeNO, fractional exhaled nitric oxide.

[a]In 2022 Canadian dollars.

[b]Results may appear inexact due to rounding. All costs were calculated using the mean cost from the Primary Economic Evaluation's deterministic results.

Sensitivity Analysis (Children)

The sensitivity analysis results for children are presented in Table 57. When we reduced the frequency of FeNO testing, the budget impact became negative, indicating a cost savings. When we raised uptake rates, the budget impact increased greatly.

Table 57: Budget Impact Analysis Results – Sensitivity Analysis (Children)

Scenario	Budget impact in millions[a]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total[b,c]
Reference case						
Budget impact	$1.45	$2.95	$4.28	$6.06	$7.63	$22.37
Cost of FeNO testing	$2.71	$6.56	$11.03	$17.02	$23.54	$60.86
100% uptake						
Budget impact	$28.93	$5.53	$4.67	$4.76	$4.85	$48.73
Cost of FeNO testing	$54.12	$31.18	$30.79	$31.36	$31.93	$179.37
Number of FeNO tests yearly, 2 initial, 1 subsequent						
Budget impact	$0.09	–$0.33	–$1.23	–$2.45	–$4.14	–$8.06
Cost of FeNO testing	$1.35	$3.28	$5.51	$8.51	$11.77	$30.43
Number of FeNO tests yearly, 6 initial, 4 subsequent						
Budget impact	$2.80	$6.83	$11.53	$17.85	$24.74	$63.76
Cost of FeNO testing	$4.06	$10.44	$18.28	$28.81	$40.65	$102.25
Higher cost of FeNO testing, $44.30						
Budget impact	$2.51	$5.53	$8.60	$12.74	$16.86	$46.24
Cost of FeNO testing	$3.77	$9.14	$15.35	$23.70	$32.77	$84.73

[a]All costs in 2022 CAD.

[b]Results may appear inexact due to rounding. All costs were calculated using the mean cost from the Primary Economic Evaluation's deterministic results.

[c]Negative costs indicate savings.

Reference Case (Adults)

The annual budget impact ranged from $10.08 million in Year 1 to $68.50 million in Year 5, and the total 5-year budget impact was $195.99 million (Table 58). When we accounted only for the direct costs of FeNO testing, the total 5-year budget impact was an additional $268.13 million.

Table 58: Budget Impact Analysis Results – Adults

	Budget impact (in millions)[a]					
Scenario	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total[b]**
Current scenario						
Standard care	$898.92	$914.44	$930.17	$946.11	$962.25	$4,651.89
Cost of FeNO testing	$0	$0	$0	$0	$0	$0
Cost of asthma exacerbations	$137.96	$140.34	$142.75	$145.20	$147.68	$713.92
Hospital exacerbations	$71.49	$72.72	$73.97	$75.24	$76.52	$369.95
ED exacerbations	$8.37	$8.51	$8.66	$8.81	$8.96	$43.31
Exacerbations managed in primary care	$58.10	$59.10	$60.12	$61.15	$62.19	$300.66
New scenario						
Standard care	$853.98	$781.90	$676.17	$550.14	$418.50	$3,280.69
Cost of FeNO testing	$0	$0	$0	$0	$0	$0
Cost of asthma exacerbations	$131.06	$120.0	$103.77	$84.43	$64.23	$503.48
Hospital exacerbations	$67.91	$62.18	$53.77	$43.75	$33.28	$260.90
ED exacerbations	$7.95	$7.28	$6.30	$5.12	$3.90	$30.55
Exacerbations managed in primary care	$55.19	$50.54	$43.70	$35.56	$27.05	$212.04
FeNO testing with standard care	$55.03	$156.27	$293.13	$450.51	$612.24	$1,567.19
Cost of FeNO testing	$12.53	$30.88	$52.66	$75.36	$96.70	$268.13
Cost of asthma exacerbations	$4.45	$13.12	$25.17	$39.26	$53.95	$135.95
Hospital exacerbations	$1.93	$5.70	$10.92	$17.04	$23.42	$59.0
ED exacerbations	$0.28	$0.83	$1.59	$2.48	$3.40	$8.57
Exacerbations managed in primary care	$2.24	$6.60	$12.66	$19.75	$27.14	$68.38

Scenario	Budget impact (in millions)[a]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total[b]
Budget impact	$10.08	$23.73	$39.13	$54.55	$68.50	$195.99
Cost of FeNO testing	$12.53	$30.88	$52.66	$75.36	$96.70	$268.13

Abbreviations: ED, emergency department; FeNO, fractional exhaled nitric oxide.

[a]In 2022 Canadian dollars.

[b]Results may appear inexact due to rounding. All costs were calculated using the mean cost from the Primary Economic Evaluation's deterministic results.

Sensitivity Analysis (Adults)

The sensitivity analysis results for adults are presented in Table 59. Similar to children, when we assume the frequency of FeNO testing is reduced, the budget impact greatly decreases. When we assume that if uptake rates were higher or the frequency of FeNO testing per person increases, the budget impact increases.

Table 59: Budget Impact Analysis Results – Sensitivity Analysis (Adults)

Scenario	Budget impact (in millions)[a]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total[b]
Reference case						
Budget impact	$10.08	$23.73	$39.13	$54.55	$68.50	$195.99
Cost of FeNO testing	$12.53	$30.88	$52.66	$75.36	$96.70	$268.13
100% uptake						
Budget impact	$201.64	$85.06	$81.11	$82.22	$83.24	$533.26
Cost of FeNO testing	$250.65	$134.92	$131.83	$133.82	$135.75	$786.97
Number of FeNO tests yearly, 2 initial, 1 subsequent						
Budget impact	$3.82	$8.29	$12.80	$16.87	$20.15	$61.92
Cost of FeNO testing	$6.27	$15.44	$26.33	$37.68	$48.35	$134.06
Number of FeNO tests yearly, 6 initial, 4 subsequent						
Budget impact	$16.35	$42.22	$74.59	$109.87	$144.52	$387.54
Cost of FeNO testing	$18.80	$49.37	$88.12	$130.68	$172.72	$459.68
Higher cost of FeNO testing, $44.30						
Budget impact	$15.0	$35.84	$59.78	$84.10	$106.42	$301.15
Cost of FeNO testing	$17.45	$42.99	$73.31	$104.92	$134.62	$373.29

Abbreviations: ED, emergency department; FeNO, fractional exhaled nitric oxide.

[a]In 2022 Canadian dollars.

[b]Results may appear inexact due to rounding. All costs were calculated using the mean cost from the Primary Economic Evaluation's deterministic results.

Discussion

We conducted a model-based budget impact analysis to examine the range of costs related to publicly funding FeNO testing with standard care for people with a diagnosis of asthma. For this population, we

based the cost and resource estimates on deterministic outputs from the models in our primary economic evaluation. Assuming the uptake of FeNO testing with standard care increased by 5% each year (i.e., 5% in Year 1, increasing to 25% in Year 5), publicly funding FeNO testing with standard care for children with asthma would lead to a budget increase of $1.45 million in Year 1 and $7.63 million in Year 5, for a total budget increase of $22.37 million over 5 years.

For adults with asthma, publicly funding FeNO testing with standard care would lead to a budget increase of $10.08 million in Year 1 and $68.50 million in Year 5, for a total budget increase of $195.99 million over 5 years. The cost increase was driven by the additional testing costs. Our budget impact analysis may be used to help estimate the resources needed to adopt eligibility criteria for FeNO testing with standard care for people with asthma.

We also reported the budget increase for the costs of FeNO tests alone to serve as guideposts for resource planning. According to our analysis, the unit cost for 1 FeNO test was estimated to be $31.82, and the budget impact per person over a 5-year period was $381.84, not considering the potential cost savings due to decreased need in exacerbation care.

We conducted sensitivity analyses to examine the robustness of our budget impact analysis. In the scenario of more frequent FeNO testing (6 tests in the first year, then 4 tests per year in subsequent years; compared with the reference case scenario of 4 tests in the first year and then 2 tests in each subsequent year), the total budget increase would be $63.76 million and $387.54 million for children and adults, respectively.

Strengths and Limitations

Our budget impact analysis had the following strengths. First, we used a model-based analysis that considered the costs of testing, standard care for asthma management, and exacerbations. Second, we conducted sensitivity analyses to examine the budget impact of FeNO testing alone. Our cost parameters were derived from Ontario and Canadian settings.

Our budget impact analysis was limited by some uncertainty. First, it was based on the economic model used in our primary economic evaluation, so it contains the same structural uncertainties. Second, our analysis contained uncertainties related to clinical and cost parameters, particularly clinical outcomes related to severe exacerbations, and the costs and impact of medications. To overcome this limitation, we reported the budget impact considering only FeNO testing costs.

Conclusions

We found that publicly funding FeNO testing with standard care to monitor and manage children with a diagnosis of asthma would lead to a total additional cost of $22.37 million over the next 5 years. The cost of FeNO testing alone in children (ignoring savings from reduced exacerbations) would be a total of $60.86 million over the next 5 years.

Publicly funding FeNO testing with standard care to monitor and manage adults with a diagnosis of asthma would lead to a total additional cost of $195.99 million over the next 5 years. The cost of FeNO testing alone in adults would be $268.13 million over the next 5 years.

Preferences and Values Evidence

Objective

The objective of this analysis was to explore the underlying values, needs, and priorities of those who have lived experience with asthma, as well as the preferences and perceptions of patients and their families and other caregivers.

Background

Exploring patient preferences and values provides a unique source of information about people's experiences of a health condition and the health technologies or interventions used to manage or treat that health condition. It includes the impact of the condition and its treatment on the person with the health condition, their family and other caregivers, and the person's personal environment. Engagement also provides insights into how a health condition is managed by the province's health system.

Information shared from lived experience can also identify gaps or limitations in published research (e.g., outcomes important to those with lived experience that are not reflected in the literature).[158-160] Additionally, lived experience can provide information and perspectives on the ethical and social values implications of health technologies or interventions.

Because the needs, preferences, priorities, and values of those with lived experience in Ontario are important to consider to understand the impact of the technology in people's lives, we may speak directly with people who live with a given health condition, including those with experience of the technology or intervention we are exploring.

Direct Patient Engagement

Methods

Partnership Plan

The partnership plan for this health technology assessment focused on consultation to examine the experiences of people with asthma and those of their families and other caregivers. We engaged people via phone interviews and one participant who provided an emailed response to the questions.

No relevant equity considerations were identified in this health technology assessment; as a result, we did not carry out specific engagement initiatives for distinct populations.

We used a qualitative interview, as this method of engagement allowed us to explore the meaning of central themes in the experiences of people with asthma, as well as those of their families and caregivers.[161] The sensitive nature of exploring people's experiences of a health condition and their quality of life are other factors that support our choice of an interview methodology.

Participant Outreach

We used an approach called purposive sampling,[162-165] which involves actively reaching out to people with direct experience of the health condition and health technology or intervention being reviewed. We approached a variety of partner organizations, including asthma clinics and education centres to spread the word about this engagement activity and to contact people with asthma, family members, and caregivers, including those with experience of FeNO testing.

Inclusion Criteria

We sought to speak with adults with lived experience with asthma or who were caregivers for someone with asthma who had or may have experience with FeNO testing. Participants did not have to have direct experience with FeNO testing to participate.

Exclusion Criteria

We did not set exclusion criteria for participants who otherwise met the inclusion criteria.

Participants

For this project, we engaged with a total of 12 people. 11 of those people participated via one on one interviews and 1 emailed their response to the questions. Eleven participants were diagnosed with asthma. Of the 11, 3 were also parents of children with asthma. One was a family member and caregiver to someone with asthma. None of the participants were aware if they had direct experience with FeNO testing since they were unable to distinguish between the different types of asthma tests.

Approach

At the beginning of the interview, we explained the role of our organization, the purpose of this health technology assessment, the risks of participation, and how participants' personal health information would be protected. We gave this information to participants both verbally and in a letter of information (Appendix 10). We then obtained participants' verbal consent before starting the interview. With participants' consent, we audio-recorded and then transcribed the interviews.

Interviews lasted approximately 45 to 60 minutes. The interview was loosely structured and consisted of a series of open-ended questions. Questions were based on a list developed by the Health Technology Assessment International Interest Group on Patient and Citizen Involvement in Health Technology Assessment.[166] Questions focused on the impact of asthma on the quality of life of people with asthma, their experiences with treatments to manage asthma, their experiences with the FeNO, and their perceptions of the benefits or limitations of FeNO testing. For family members and caregivers, questions focused on their perceptions of the impact of asthma and treatments on the quality of life of the person with asthma, as well as the impact of the person's health condition and treatments on the family members and caregivers themselves. See Appendix 11 for our interview guide.

Data Extraction and Analysis

We used a modified version of a grounded-theory methodology to analyze interview transcripts and the emailed response. The grounded-theory approach allowed us to organize and compare information on experiences across participants. This method consists of a repetitive process of obtaining, documenting,

and analyzing responses while simultaneously collecting, analyzing, and comparing information.[167,168] We used the qualitative data analysis software program NVivo[169] to identify and interpret patterns in the data. The patterns we identified allowed us to highlight the impact of asthma and treatments on the people with asthma, family members, and caregivers who we interviewed.

Results

Day to Day Experiences

Participants had varying degrees of asthma severity and there was a range of symptoms and burdens experienced. The symptoms described by participants included shortness of breath, coughing, chest tightness, and trouble breathing.

> *I'll start getting a really tight chest and shortness of breath. I'll experience that more acutely at night when I'm trying to sleep.*
>
> *I have always had problems with chronic cough, ever since childhood.*
>
> *I had a lot of breathing issues this year and, as you can tell, my voice goes all the time through the breathing issues.*

People with moderate to severe asthma commented on the lifestyle modifications they had to make, which had significant impacts on their day-to-day lives. Some spoke about avoiding strenuous activities such as participating in sports and other recreational activities.

> *I participated in certain sports that we were doing. I would just be winded and all red.*
>
> *I don't know how to swim, which is tied to being asthmatic. I kept getting sick whenever they took me in the chlorine pool as a kid.*

In more severe cases, participants had a difficult time with simple functions such as walking or using the stairs. This resulted in concerns over the inability to lead an active lifestyle and the impact of this on their overall health, especially for those with other chronic conditions.

> *I get breathless going upstairs…I'm going for very short walks, but I get quite breathless so it has changed my life.*
>
> *I think my body is less healthy because I can't be as active.*
>
> *I really rely on walking and that kind of exercise to keep my body healthy and when I can't do it, I end up getting extremely stiff and sore and then you're less likely to do it and it becomes a vicious cycle.*

A couple of participants spoke about the impact of asthma on employment. One person reflected on reducing the amount of traveling they had to do for work due to their asthma symptoms being triggered when flying. Another participant, who was a family member of someone with asthma, commented on their family member's experience working a job that was primarily based outdoors.

She has a highly stressful job. So she's being more careful about being outside as little as possible during the hot times…I consider myself really fortunate that I'm retired and I can control my environment.

The asthma got worse when I was working. I used to fly quite a bit and I actually started having asthma attacks on the airplanes.

The people we interviewed also spoke about the environmental impacts that trigger their asthma symptoms, such as seasonal changes, weather, and air quality. In these cases, people reported avoiding going outdoors. They also noted the increased air quality warnings and pollution over the years and concerns over the future impact on air quality in relation to their asthma symptoms.

This summer, the air quality was pretty terrible and I did end up staying indoors during those days, and I found that even just kind of going outside for a brief period of time, I'd have a coughing fit for the next hour.

As I age, the air seems to be getting worse…. The progression of my disease and my age and also the fact that the environment seems to be obviously getting worse.

Asthma symptoms were also triggered or exacerbated by respiratory illness such as the flu or COVID. In these cases, some participants reported that their symptoms, such as coughing, would linger even after they had recovered.

When I'm sick, there is a lot of coughing, kind of like uncontrollable coughing sometimes.

It's been weeks since I've been negative on COVID, but I still have that cough.

Mental Health

Some participants commented on how asthma has impacted their mental health. They spoke about their hypervigilance around their condition and symptoms. Parents of children with asthma also spoke about monitoring their children closely when they are in situations where their asthma symptoms may be exacerbated.

You have to be super, hyper aware of your condition... I mean that it can be deadly.

I get extremely stressed when he's sick. I'm constantly watching his breathing…. Even at night, I don't sleep.

People touched on the frustrations around their symptoms and the extent that it impacted their day-to-day lives. This hypervigilance and frustration led to increased anxiety and, in a few cases, depression and hopelessness. Participants spoke about how certain lifestyle modifications, such as limiting their participation in social activities, left them socially isolated.

It certainly does make anxiety higher when I have to avoid activities that other people can do. That makes you a little bit sad about your situation.

I am finding that I had aged like 10 years in the last year. I have had to change my lifestyle.... I get very short of breath when I talk. I can't talk and walk…. So yes, it has caused me to feel depressed and despondent and frustrated.

Asthma Diagnosis Journey

Participants were diagnosed at different points in their life. Some were diagnosed during childhood, while others when they were adults. There were a variety of different diagnosis journeys shared by participants. Some had a streamlined diagnosis process, where they were either diagnosed by a respirologist after submitting to various tests (though a few commented on the long wait time to see a respirologist and get access to testing) or were diagnosed by their GP through questions about their symptoms, without any asthma test being conducted.

I went to a respirologist for the first time and got diagnosed and got put on more of a chronic approach to the medication. I had to wait months for that appointment.

It would probably be more than 10 years that she managed it with short term puffers and stuff until she got the formal diagnosis.

I didn't have a respirologist for a number of years after that, but at the time, I was diagnosed as having asthma [and] given a puffer…, which is pretty much the only option.

Parents mentioned having difficulty getting their children diagnosed due to the child either being too young to be tested or being unable to follow the instructions during testing.

They started taking me to the ER for a number of visits from the time I was about 6 months old…. It wasn't until I was 2 years old that they had taken me for another ER visit and the doctor on staff that day was a pediatrician. He quickly diagnosed me as being asthmatic.

Everyone was frustrated. He wouldn't sit still, he wasn't listening. Testing him was tough.

She's too young to be tested, so we're just using the inhalers.

Those who were misdiagnosed as not having asthma expressed frustration over their symptoms being dismissed. In all these cases, an accurate asthma diagnosis took a long time.

I suffered for 10 years, [aged] between 30 and 40, without a diagnosis…. As soon as she heard my lungs, she said, "do you know you have asthma?"

I can't remember exactly the date, but it took at least 6 years to get diagnosed.

Some participants mentioned the difficulties they experienced when doing certain asthma tests, especially in cases where they were told to be off their medication prior to the tests.

The testing itself is awful because I can't breathe properly and they're trying to get me to do all sorts of breathing stuff.

Asthma Management Follow-Up

Several factors determined how participants managed their asthma, including asthma severity, type of treatment regimen, time of diagnosis, and the type of provider who was supporting them in managing their asthma. They emphasized the importance of being able to self-manage their asthma with the guidance of their care provider. Those who had been living with asthma for a longer period of time expressed confidence in managing their symptoms. Those who were newly diagnosed were still struggling with self-management between doctor appointments.

> *I gotta have a respirologist. For one thing, the fact that I see him twice a year. He will give you a change in your medication depending on the day that you are assessed.*
>
> *I remember there was a lot of attention on my asthma when I was younger…. There was an action plan developed…. I find it odd that there's just nothing once you enter adulthood.*
>
> *It took me 3 years to really get my head around it…. What changed my life was that education workshop.*
>
> *Two times that I had to go to the [emergency department] because it was so severe.*

All participants noted the importance of understanding asthma and increasing their knowledge of their own symptoms, the triggers and lifestyle modifications that can exacerbate or reduce their symptoms, and their familiarity with their medications.

> *I'm the one that needs to manage it everyday. I need to be able to know how to do that.*
>
> *The medication dosage hasn't changed. But there was some advice about how to take it and about some protective measures that I can take myself.*

People we spoke with reported a variety of experiences on the follow-up and management of their asthma in partnership with their care provider. A majority of patients value their follow-up and check-in appointments because they support their ability to self-management their asthma. Appointments with care providers are opportunities to make adjustments to their medication, as well as to raise any concerns regarding their asthma. Some participants have annual asthma testing, while others will get asked questions relating to their asthma symptoms.

> *I get asked a checklist of questions...annually.*
>
> *For many years, he would do the lung capacity test in office…every year.*
>
> *I definitely think having a respirologist gives me peace of mind…. I would have a routine appointment where he would just ask a couple of questions, do the lung capacity test, and make a change to my medication.*

Asthma Treatment

Due to the varying severity of asthma of the participants, treatments were personalized. Some participants take medications regularly, while others take it as needed (i.e., when their asthma

symptoms are triggered). All participants use inhalers as their main treatment method, with a minority also on oral medication.

Participants raised concerns around over and under treatment of their asthma. Some stated that they valued accuracy when assessing their required dosage and acknowledged that the dosage will change depending on a number of factors.

> *I really do not want to be overtreated, because I know the medications have side effects.*
>
> *When I get colds, there is a period in the winter where I'm very concerned about maybe not having enough medication for that period.*

Parents of children with asthma were especially concerned with overtreatment due to their concerns around the long term impact of corticosteroids on children. One parent whose child was too young to be tested questioned the accuracy of the medication dosage when there had been no objective testing of the child's condition.

> *I worry about the long term impact of steroids. How is it impacting him physically and mentally?*
>
> *She's too young to be tested, so we're just using the inhalers…. We don't know if she's being over or undertreated.*

One participant commented on the negative impact of inhalers on the environment and the importance of having accurate dosages.

> *I was horrified at how destructive the puffers are for our environment.*

We asked participants about their medication adherence. Some participants spoke about being very diligent and taking their medications as prescribed. Others reported being told to regularly take medication but, due to the mildness of their symptoms, they used their medication on an as-needed basis.

> *I used to use the puffers whenever I needed them.*
>
> *I take it pretty consistently [but I'm] not 100% adherent.*
>
> *Three times a day for your life is a bit tricky to manage. Absolutely. Consistency. Every single day. So I do my very best and honestly my symptoms are, I would say, managed fairly.*

FeNO Testing Perspectives

Participants were unaware of FeNO testing or if they had direct experience with it. This is due to patients not being familiar with the medical terminology around asthma testing and the similarity of the process of FeNO testing as compared with other asthma tests (FeNO, as with most asthma tests, involves blowing into a tube), which made it difficult for patients to differentiate between the different types of tests.

When FeNO testing was described to participants, they did speak to their perception of the value of FeNO testing. They perceived FeNO testing as improving accuracy and addressing their concerns with over or under treatment of asthma. A few commented on the value of having an objective testing method while they wait to see a specialist.

> *I think it's important to have the most accurate diagnosis…. Just having that surety of information for the physician to be able to help her or him address health concerns and to be able to both diagnose and to adjust medications accordingly.*
>
> *So if the respirologist thinks I should do it then I'll do it.*
>
> *It would just be a good thing to kind of benchmark my asthma at this point in time.*
>
> *I would love to see this come to fruition. I would be thrilled if she had that option in her office to test me every time I go.*

FeNO Testing Barriers

One of the main barriers to FeNO testing is the lack of awareness. None of the participants were aware if they had had FeNO testing. Additionally, participants expressed that a majority of asthma testing involved a similar process, which made it difficult to understand what testing they experienced.

> *I had never heard of FeNO.*
>
> *I went back to my patient portals and I couldn't determine if I'd had this (FeNO testing).*
>
> *I've done tests where I blow into a tube, but I couldn't tell you what they are called.*

FeNO testing has limited availability across Ontario, which made it difficult for participants to access it. Additionally there was variability in the care plans for the participants which led to different experiences and processes for the diagnostic pathway.

> *I wasn't offered it…. I don't know if they have that option.*
>
> *Where can I access this? Is there a list of places? Do I have to call around and ask for this?*
>
> *Having a gold standard of how we diagnose asthma – you must have this to get this – if there is a standard of care. That would help.*

Discussion

Direct engagement with participants diagnosed with asthma of varying degrees of severity allowed for exploration of the impact of asthma, people's care journey for getting diagnosed, and asthma management across the severity spectrum. This range of experiences highlighted the variations in care and the inconsistencies in care pathways that patients with asthma experience.

Participants spoke of the perceived positive impact of FeNO testing and identified the value of its ability to assist with their self-management of asthma with the guidance of their care provider. They felt that FeNO testing would improve diagnostic accuracy, provide an objective test while waiting to see a

specialist, and address their concerns about over and under treatment of their asthma. They reported that they would appreciate increased accuracy in their medication dosages. Parents shared their concerns of the difficulties in getting an asthma diagnosis for their children, as well as concerns over the long-term impact of corticosteroids on their children.

In terms of limitations, there was low representation from Northern Ontario and parents of children with asthma. Due to a majority of participants not being familiar with the medical terminology around asthma testing as well as the similarity of different tests, it is unclear whether participants had direct experience with FeNO testing.

Conclusion

While symptoms varied from mild to severe, all participants spoke about the impact of asthma on their quality of life and mental health. Participants were unaware if they had experience with FeNO testing due to the similarities with various types of testing for asthma and because they are unaware of the testing terminology. Participants valued the potential for FeNO testing as an opportunity to obtain further information that could aid in the diagnosis and management of asthma. These perceived benefits were also reported by participants who were also caregivers to children with asthma.

Conclusions of the Health Technology Assessment

Clinical Conclusions

Asthma Diagnosis

Studies on the use of FeNO testing compared to a reference standard test for the diagnosis of asthma reported widely ranging (~30%–90%) sensitivities in children and adults. This variability in sensitivities may be due to the inclusion of studies with varying cut-offs, asthma sub-populations, FeNO device brands, reference standards, or clinical settings. The same studies reported consistently high (~70%–100%) diagnostic specificities in children and adults, supporting its use as an additional test to help rule-in a diagnosis of asthma.

Asthma Management

Asthma monitoring and management including FeNO testing likely decreases the number of patients experiencing exacerbations and reduces the use of oral corticosteroids in children with asthma. It will also likely decrease the number of patients experiencing exacerbations and the exacerbation rate in adults with asthma, and likely result in a small improvement in lung function in a mixed population of children and adults with diagnosed asthma. Little to no difference was reported in asthma symptom control scores, inhaled corticosteroid use, ED visits, hospitalizations due to asthma, days missed from school or work, frequency of symptom-free days, or asthma-related quality of life across the population groups.

Economic Conclusions

Asthma Diagnosis

We found that using FeNO testing in addition to standard testing in asthma diagnosis is cost-effective compared to standard testing in children, and in adults when a higher FeNO cut-off is applied. We estimated that publicly funding FeNO testing over the next 5 years for asthma diagnosis would cost $0.10 million and $0.22 million for children, and $1.19 million and $1.61 million for adults (depending on the testing method adopted).

Asthma Management

We found that including FeNO testing in the monitoring and management of asthma would be more costly and have a minimal impact on health-related quality of life in both children and adults. We estimate that publicly funding FeNO testing for asthma management over the next 5 years would cost about $22.37 million for children and $196 million for adults.

Patient Preferences and Values

We spoke with people with asthma and caregivers of people with asthma. Participants were unaware if they had experience with FeNO testing due to the similarities with other asthma testing processes. Participants valued the perceived opportunity offered by FeNO testing to obtain further information that could aid in the diagnosis and management of asthma.

Abbreviations

ACQ: Asthma Control Questionnaire

ACT: Asthma Control Test

CADTH: Canadian Agency for Drugs and Technologies in Health

CI: confidence interval

FeNO: fractional exhaled nitric oxide

FEV_1: forced expiratory volume in 1 second

FN: false negative

FP: false positive

GP: general practitioner

GRADE: Grading of Recommendations Assessment, Development, and Evaluation

HRQoL: health-related quality of life

HTA: health technology assessment

ICER: incremental cost-effectiveness ratio

ICS: inhaled corticosteroid

MD: mean difference

NICE: National Institute for Health and Care Excellence

NR: not reported

OCS: oral corticosteroid

OHIP: Ontario Health Insurance Plan

OR: odds ratio

ppb: parts per billion

QALY: quality-adjusted life-year

QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies tool, version 2

RCT: randomized controlled trial

ROBIS: Risk of Bias Assessment Tool for Systematic Reviews

RR: relative risk

SD: standard deviation

SMD: standard mean difference

TN: true negative

TP: true positive

WTP: willingness to pay

Glossary

Adverse event: An adverse event is an unexpected medical problem that happens during treatment for a health condition. Adverse events may be caused by something other than the treatment.

Base case: In economic evaluations, the base case is the "best guess" scenario, including any assumptions, considered most likely to be accurate. In health technology assessments conducted by Ontario Health, the reference case is used as the base case.

Budget impact analysis: A budget impact analysis estimates the financial impact of adopting a new health care intervention on the current budget (i.e., the affordability of the new intervention). It is based on predictions of how changes in the intervention mix will impact the level of health care spending for a specific population. Budget impact analyses are typically conducted for a short-term period (e.g., 5 years). The budget impact, sometimes referred to as the net budget impact, is the estimated cost difference between the current scenario (i.e., the anticipated amount of spending for a specific population without using the new intervention) and the new scenario (i.e., the anticipated amount of spending for a specific population following the introduction of the new intervention).

Corticosteroids Corticosteroids, often referred to as steroids, are an anti-inflammatory medicine. They are prescribed for a wide range of conditions, but are mainly used to reduce inflammation and suppress the immune system. Corticosteroids are prescribed in two forms: oral, which are taken in pill form, and inhaled, which are administered in spray form through either the mouth or nasal passages.

Cost–benefit analysis: A cost–benefit analysis is a type of economic evaluation that expresses the effects of a health care intervention in terms of a monetary value so that these effects can be compared with costs. Results can be reported either as a ratio of costs to benefits or as a simple sum that represents the net benefit (or net loss) of one intervention over another. The monetary valuation of the different intervention effects is based on either prices that are revealed by markets or an individual or societal willingness-to-pay value.

Cost-effective: A health care intervention is considered cost-effective when it provides additional benefits, compared with relevant alternatives, at an additional cost that is acceptable to a decision-maker based on the maximum willingness-to-pay value.

Cost-effectiveness acceptability curve: In economic evaluations, a cost-effectiveness acceptability curve is a graphical representation of the results of a probabilistic analysis. It illustrates the probability of health care interventions being cost-effective over a range of willingness-to-pay values. Willingness-to-pay values are plotted on the horizontal axis of the graph, and the probability of the intervention of interest and its comparator(s) being cost-effective at corresponding willingness-to-pay values is plotted on the vertical axis.

Cost-effectiveness analysis: Used broadly, "cost-effectiveness analysis" may refer to an economic evaluation used to compare the benefits of two or more health care interventions with their costs. It may encompass several types of analysis (e.g., cost-effectiveness analysis, cost–utility analysis). Used more specifically, "cost-effectiveness analysis" may refer to a type of economic evaluation in which the main outcome measure is the incremental cost per natural unit of health (e.g., life-year, symptom-free day) gained.

Cost-minimization analysis: In economic evaluations, a cost-minimization analysis compares the costs of two or more health care interventions. It is used when the intervention of interest and its relevant alternative(s) are determined to be equally effective.

Cost–utility analysis: A cost–utility analysis is a type of economic evaluation used to compare the benefits of two or more health care interventions with their costs. The benefits are measured using quality-adjusted life-years, which capture both the quality and quantity of life. In a cost–utility analysis, the main outcome measure is the incremental cost per quality-adjusted life-year gained.

Decision tree: A decision tree is a type of economic model used to assess the costs and benefits of two or more alternative health care interventions. Each intervention may be associated with different outcomes, which are represented by distinct branches in the tree. Each outcome may have a different probability of occurring and may lead to different costs and benefits.

Diagnostic test accuracy: The degree to which a test, owing to its technical properties and ability to reliably detect the phenomenon it is used to measure (its accuracy), can be used to make a diagnosis.

Discounting: Discounting is a method used in economic evaluations to adjust for the differential timing of the costs incurred and the benefits generated by a health care intervention over time. Discounting reflects the concept of positive time preference, whereby future costs and benefits are reduced to reflect their present value. The health technology assessments conducted by Ontario Health use an annual discount rate of 1.5% for both future costs and future benefits.

Disutility: A disutility is a decrease in utility (i.e., a decrease in preference for a particular health outcome) typically resulting from a particular health condition (e.g., experiencing a symptom or complication).

Dominant: A health care intervention is considered dominant when it is more effective and less costly than its comparator(s).

EQ-5D: The EQ-5D is a generic health-related quality-of-life classification system widely used in clinical studies. In economic evaluations, it is used as an indirect method of obtaining health state preferences (i.e., utility values). The EQ-5D questionnaire consists of five questions relating to different domains of quality of life: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. For each domain, there are three response options: no problems, some problems, or severe problems. A newer instrument, the EQ-5D-5L, includes five response options for each domain. A scoring table is used to convert EQ-5D scores to utility values.

Equity: Unlike the notion of equality, equity is not about treating everyone the same way.[170] It denotes fairness and justice in process and in results. Equitable outcomes often require differential treatment and resource redistribution to achieve a level playing field among all individuals and communities. This requires recognizing and addressing barriers to opportunities for all to thrive in our society.

Exacerbation: a flare up or worsening of symptoms, usually sudden, that may lead to a need for emergency treatment.

Health-related quality of life: Health-related quality of life is a measure of the impact of a health care intervention on a person's health. It includes the dimensions of physiology, function, social life, cognition, emotions, sleep and rest, energy and vitality, health perception, and general life satisfaction.

Health state: A health state is a particular status of health (e.g., sick, well, dead). A health state is associated with some amount of benefit and may be associated with specific costs. Benefit is captured through individual or societal preferences for the time spent in each health state and is expressed in quality-adjusted weights called utility values. In a Markov model, a finite number of mutually exclusive health states are used to represent discrete states of health.

Health Utilities Index Mark 3 (HUI3): The HUI3 is a generic health-related quality-of-life classification system widely used in clinical studies. In economic evaluations, it is used as an indirect method of obtaining health state preferences (i.e., utility values). The HUI3 was developed in Canada and is used in major Canadian population health surveys. The HUI3 comprises eight attributes: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain and discomfort. Each attribute is associated with five or six defined functional levels, thus producing a total of 972,000 unique health states. A predefined scoring formula is used to convert HUI3 scores to utility values.

Horizontal equity: Horizontal equity requires that people with like characteristics (of ethical relevance) be treated the same.

Incremental cost: The incremental cost is the additional cost, typically per person, of a health care intervention versus a comparator.

Incremental cost-effectiveness ratio (ICER): The incremental cost-effectiveness ratio (ICER) is a summary measure that indicates, for a given health care intervention, how much more a health care consumer must pay to get an additional unit of benefit relative to an alternative intervention. It is obtained by dividing the incremental cost by the incremental effectiveness. Incremental cost-effectiveness ratios are typically presented as the cost per life-year gained or the cost per quality-adjusted life-year gained.

Markov model: A Markov model is a type of decision-analytic model used in economic evaluations to estimate the costs and health outcomes (e.g., quality-adjusted life-years gained) associated with using a particular health care intervention. Markov models are useful for clinical problems that involve events of interest that may recur over time (e.g., stroke). A Markov model consists of mutually exclusive, exhaustive health states. Patients remain in a given health state for a certain period of time before moving to another health state based on transition probabilities. The health states and events modelled may be associated with specific costs and health outcomes.

Ministry of Health perspective: The perspective adopted in economic evaluations determines the types of costs and health benefits to include. Ontario Health develops health technology assessment reports from the perspective of the Ontario Ministry of Health. This perspective includes all costs and health benefits attributable to the Ministry of Health, such as treatment costs (e.g., drugs, administration, monitoring, hospital stays) and costs associated with managing adverse events caused by treatments. This perspective does not include out-of-pocket costs incurred by patients related to obtaining care (e.g., transportation) or loss of productivity (e.g., absenteeism).

Monte Carlo simulation: Monte Carlo simulation is an economic modelling method that derives parameter values from distributions rather than fixed values. The model is run several times, and in each iteration, parameter values are drawn from specified distributions. This method is used in microsimulation models and probabilistic analysis.

One-way sensitivity analysis: A one-way sensitivity analysis is used to explore uncertainty in the results of an economic evaluation. It is done by varying one model input (i.e., a parameter) at a time between its minimum and maximum values to observe the potential impact on the cost-effectiveness of the health care intervention of interest.

Probabilistic analysis: A probabilistic analysis (also known as a probabilistic sensitivity analysis) is used in economic models to explore uncertainty in several parameters simultaneously and is done using Monte Carlo simulation. Model inputs are defined as a distribution of possible values. In each iteration, model inputs are obtained by randomly sampling from each distribution, and a single estimate of cost and effectiveness is generated. This process is repeated many times (e.g., 10,000 times) to estimate the number of times (i.e., the probability) that the health care intervention of interest is cost-effective.

Quality-adjusted life-year (QALY): The quality-adjusted life-year (QALY) is a generic health outcome measure commonly used in cost–utility analyses to reflect the quantity and quality of life-years lived. The life-years lived are adjusted for quality of life using individual or societal preferences (i.e., utility values) for being in a particular health state. One year of perfect health is represented by one quality-adjusted life-year.

Reference case: The reference case is a preferred set of methods and principles that provide the guidelines for economic evaluations. Its purpose is to standardize the approach of conducting and reporting economic evaluations, so that results can be compared across studies.

Scenario analysis: A scenario analysis is used to explore uncertainty in the results of an economic evaluation. It is done by observing the potential impact of different scenarios on the cost-effectiveness of a health care intervention. Scenario analyses include varying structural assumptions from the reference case.

Sensitivity: The ability of a diagnostic test to correctly identify people who have the condition being tested for. It is calculated as the number of true positive identifications divided by the sum total of true positives plus false negatives (so that 1 would represent perfect sensitivity and 0 would be complete failure of sensitivity). See Specificity for related term.

Sensitivity analysis: Every economic evaluation contains some degree of uncertainty, and results can vary depending on the values taken by key parameters and the assumptions made. Sensitivity analysis allows these factors to be varied and shows the impact of these variations on the results of the evaluation. There are various types of sensitivity analysis, including deterministic, probabilistic, and scenario.

Specificity: The ability of a diagnostic test to correctly identify people who do not have the condition being tested for. It is calculated as the number of true negative identifications divided by the sum total of true negatives plus false positives (so that 1 would represent perfect specificity and 0 would be complete failure of specificity). See sensitivity for related term.

Time horizon: In economic evaluations, the time horizon is the time frame over which costs and benefits are examined and calculated. The relevant time horizon is chosen based on the nature of the disease and health care intervention being assessed, as well as the purpose of the analysis. For instance, a lifetime horizon would be chosen to capture the long-term health and cost consequences over a patient's lifetime.

Uptake rate: In instances where two technologies are being compared, the uptake rate is the rate at which a new technology is adopted. When a new technology is adopted, it may be used in addition to an existing technology, or it may replace an existing technology.

Utility: A utility is a value that represents a person's preference for various health states. Typically, utility values are anchored at 0 (death) and 1 (perfect health). In some scoring systems, a negative utility value indicates a state of health valued as being worse than death. Utility values can be aggregated over time to derive quality-adjusted life-years, a common outcome measure in economic evaluations.

Vertical equity: Vertical equity allows for people with different characteristics (of ethical relevance) to be treated differently.

Willingness-to-pay value: A willingness-to-pay value is the monetary value a health care consumer is willing to pay for added health benefits. When conducting a cost–utility analysis, the willingness-to-pay value represents the cost a consumer is willing to pay for an additional quality-adjusted life-year. If the incremental cost-effectiveness ratio is less than the willingness-to-pay value, the health care intervention of interest is considered cost-effective. If the incremental cost-effectiveness ratio is more than the willingness-to-pay value, the intervention is considered not to be cost-effective.

Appendices

Appendix 1: Literature Search Strategies

Clinical Evidence Search

Search Date: October 06, 2022

Databases searched: Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, NHS Economic Evaluation Database, and EBSCO Cumulative Index to Nursing and Allied Health Literature

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <September 2022>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to October 5, 2022>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2022 Week 39>, Ovid MEDLINE(R) ALL <1946 to October 05, 2022>

Search Strategy:

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1 exp Asthma/ (429191)
2 asthma*.ti,ab,kf. (458629)
3 Respiratory Hypersensitivity/ (15978)
4 Bronchial Hyperreactivity/ (19018)
5 ((bronch* or respirat* or airway* or lung*) adj2 (hypersensitiv* or hyper-sensitiv* or hyperreactiv* or reactiv* or hyperrespons* or hyper-respons* or allerg* or Insufficienc*)).ti,ab,kf. (101347)
6 Bronchial Spasm/ (26285)
7 Bronchoconstriction/ (7298)
8 (bronchspas* or bronchoconstrict* or (bronch* adj2 (spas* or constrict*))).ti,ab,kf. (25261)
9 Cough/di, et (9558)
10 (chronic cough* or wheez*).ti,ab,kf. (55181)
11 or/1-10 (647230)
12 Fractional Exhaled Nitric Oxide Testing/ (106)
13 Nitric Oxide/ and (Breath Tests/ or Biomarkers/ or Respiratory Function Tests/) (10899)
14 ((fraction* adj3 (oxide* or nitric* or nitrogen*)) or (exhal* adj3 nitric* oxide*) or FeNO or fe no or eno or fraction* no or exhal* no).ti,ab,kf. (24705)
15 (((airway* or breath* or exhal* or expir* or pulmonary or lung* or respirat*) adj2 (oxide* or nitric* or nitrogen*)) and (analy#er* or test* or assess* or biomarker* or biological marker* or predict* or measurement* or score* or threshold* or cut-off* or ppb or parts per billion or monitor* or manag* or treatment* or chemiluminescence* or sensor* or device* or desktop* or portable* or handheld* or point-of-care)).ti,ab,kf. (15992)
16 (niox* or NObreath* or vivatmo* or ecomedics*).ti,ab,kf. (1450)
17 or/12-16 (34628)

18 11 and 17 (15130)
19 18 use medall (4654)
20 exp Animals/ not Humans/ (16057517)
21 19 not 20 (4570)
22 Case Reports/ or Comment.pt. or Editorial.pt. or (Letter not (Letter and Randomized Controlled Trial)).pt. or Congress.pt. (6168190)
23 21 not 22 (4299)
24 limit 23 to english language [Limit not valid in CDSR; records were retained] (4050)
25 limit 24 to yr="2010 -Current" (2849)
26 18 use cctr (1728)
27 Case Reports/ or (Letter not (Letter and Randomized Controlled Trial)).pt. or (Comment or Editorial or Congresses or Conference Abstract or Conference Proceeding or Journal: Conference Abstract).pt. (10861767)
28 26 not 27 (1393)
29 18 use coch,cleed (12)
30 28 or 29 (1405)
31 limit 30 to english language [Limit not valid in CDSR; records were retained] (1387)
32 limit 31 to yr="2010 -Current" (857)
33 25 or 32 (3706)
34 exp asthma/ (429191)
35 asthma*.tw,kw,kf. (460578)
36 respiratory tract allergy/ (10526)
37 bronchus hyperreactivity/ (12533)
38 ((bronch* or respirat* or airway* or lung*) adj2 (hypersensitiv* or hyper-sensitiv* or hyperreactiv* or reactiv* or hyperrespons* or hyper-respons* or allerg* or Insufficienc*)).tw,kw,kf. (105599)
39 bronchospasm/ (29523)
40 (bronchspas* or bronchoconstrict* or (bronch* adj2 (spas* or constrict*))).tw,kw,kf. (25533)
41 exp coughing/di, et [Diagnosis, Etiology] (6208)
42 (chronic cough* or wheez*).tw,kw,kf. (55812)
43 or/34-42 (647471)
44 fractional exhaled nitric oxide test/ (106)
45 nitric oxide analyzer/ (588)
46 fractional exhaled nitric oxide/ (3505)
47 nitric oxide breathanalyzer/ (42)
48 nitric oxide/ and (breath analysis/ or diagnostic breathalyzer/ or biological marker/ or lung function test/) (9722)
49 ((fraction* adj3 (oxide* or nitric* or nitrogen*)) or (exhal* adj3 nitric* oxide*) or FeNO or fe no or eno or fraction* no or exhal* no).tw,kw,kf,dv. (24886)
50 (((airway* or breath* or exhal* or expir* or pulmonary or lung* or respirat*) adj2 (oxide* or nitric* or nitrogen*)) and (analy#er* or test* or assess* or biomarker* or biological marker* or predict* or measurement* or score* or threshold* or cut-off* or ppb or parts per billion or

monitor* or manag* or treatment* or chemiluminescence* or sensor* or device* or desktop* or portable* or handheld* or point-of-care)).tw,kw,kf,dv. (17191)
51 (niox* or NObreath* or vivatmo* or ecomedics*).tw,kw,kf,dv. (1665)
52 or/44-51 (36693)
53 43 and 52 (15913)
54 53 use emez (9529)
55 (exp animal/ or nonhuman/) not exp human/ (11556200)
56 54 not 55 (9289)
57 Case Report/ or Comment/ or Editorial/ or (letter.pt. not (letter.pt. and randomized controlled trial/)) or conference abstract.pt. or conference review.pt. (12805196)
58 56 not 57 (5348)
59 limit 58 to english language [Limit not valid in CDSR; records were retained] (4969)
60 limit 59 to yr="2010 -Current" (3548)
61 33 or 60 (7254)
62 61 use medall (2849)
63 61 use emez (3548)
64 61 use coch (5)
65 61 use cctr (852)
66 61 use cleed (0)
67 limit 61 to yr="2010 - 2017" (3989)
68 remove duplicates from 67 (2253)
69 limit 61 to yr="2018 -Current" (3265)
70 remove duplicates from 69 (1997)
71 68 or 70 (4250)

CINAHL – Clinical

#	Query	Results
S1	(MH "Asthma+")	38,310
S2	asthma*	50,306
S3	(MH "Respiratory Hypersensitivity")	838
S4	((bronch* or respirat* or airway* or lung*) N2 (hypersensitiv* or hyper-sensitiv* or hyperreactiv* or reactiv* or hyperrespons* or hyper-respons* or allerg* or insufficienc*))	5,355
S5	(MH "Bronchial Spasm")	602
S6	(MH "Bronchoconstriction")	503
S7	(bronchspas* or bronchoconstrict* or (bronch* N2 (spas* or constrict*)))	1,852
S8	(MH "Cough/DI/ET")	2,372
S9	(chronic cough* or wheez*)	5,265
S10	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9	57,652
S11	(MH "Fractional Exhaled Nitric Oxide Testing")	40
S12	(MH "Nitric Oxide") AND (MH "Breath Tests" or MH "Biological Markers" or MH "Respiratory Function Tests")	984

S13 ((fraction* N3 (oxide* or nitric* or nitrogen*)) or (exhal* N3 nitric* oxide*) or FeNO or fe no or eno or fraction* no or exhal* no) 4,300
S14 (((airway* or breath* or exhal* or expir* or pulmonary or lung* or respirat*) N2 (oxide* or nitric* or nitrogen*)) AND (analy#er* or test* or assess* or biomarker* or biological marker* or predict* or measurement* or score* or threshold* or cut-off* or ppb or parts per billion or monitor* or manag* or treatment* or chemiluminescence* or sensor* or device* or desktop* or portable* or handheld* or point-of-care)) 1,362
S15 (niox* or NObreath* or vivatmo* or ecomedics*) 36
S16 S11 OR S12 OR S13 OR S14 OR S15 5,102
S17 S10 AND S16 1,002
S18 PT (Case Study or Commentary or Editorial or Letter or Proceedings) 1,353,415
S19 s17 not s18 914
S20 Narrow by Language - English 904
S21 Limiters - Published Date: 20100101-20221231 636

Economic Evidence Search

Search date: October 3, 2022

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <August 2022>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to September 28, 2022>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2022 Week 39>, Ovid MEDLINE(R) ALL <1946 to September 30, 2022>

Search Strategy:
---
1 exp Asthma/ (429200)
2 asthma*.ti,ab,kf. (458582)
3 Respiratory Hypersensitivity/ (15978)
4 Bronchial Hyperreactivity/ (19018)
5 ((bronch* or respirat* or airway* or lung*) adj2 (hypersensitiv* or hyper-sensitiv* or hyperreactiv* or reactiv* or hyperrespons* or hyper-respons* or allerg* or Insufficienc*)).ti,ab,kf. (101337)
6 Bronchial Spasm/ (26286)
7 Bronchoconstriction/ (7298)
8 (bronchspas* or bronchoconstrict* or (bronch* adj2 (spas* or constrict*))).ti,ab,kf. (25262)
9 Cough/di, et (9558)
10 (chronic cough* or wheez*).ti,ab,kf. (55169)
11 or/1-10 (647157)
12 Fractional Exhaled Nitric Oxide Testing/ (107)
13 Nitric Oxide/ and (Breath Tests/ or Biomarkers/ or Respiratory Function Tests/) (10897)
14 ((fraction* adj3 (oxide* or nitric* or nitrogen*)) or (exhal* adj3 nitric* oxide*) or feno or fe no or eno or fraction* no or exhal* no).ti,ab,kf. (24699)
15 (((airway* or breath* or exhal* or expir* or pulmonary or lung* or respirat*) adj2 (oxide* or nitric* or nitrogen*)) and (analy#er* or test* or assess* or biomarker* or biological marker*

or predict* or measurement* or score* or threshold* or cut-off* or ppb or parts per billion or monitor* or manag* or treatment* or chemiluminescence* or sensor* or device* or desktop* or portable* or handheld* or point-of-care)).ti,ab,kf. (15992)
16 (niox* or NObreath* or vivatmo* or ecomedics*).ti,ab,kf. (1450)
17 or/12-16 (34621)
18 11 and 17 (15123)
19 economics/ (263977)
20 economics, medical/ or economics, pharmaceutical/ or exp economics, hospital/ or economics, nursing/ or economics, dental/ (1003818)
21 economics.fs. (467254)
22 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).ti,ab,kf. (1192247)
23 exp "costs and cost analysis"/ (664887)
24 (cost or costs or costing or costly).ti. (318679)
25 cost effective*.ti,ab,kf. (425504)
26 (cost* adj2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog* or increment*)).ab,kf. (294939)
27 models, economic/ (15471)
28 markov chains/ or monte carlo method/ (102327)
29 (decision adj1 (tree* or analy* or model*)).ti,ab,kf. (61500)
30 (markov or markow or monte carlo).ti,ab,kf. (169495)
31 quality-adjusted life years/ (52306)
32 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).ti,ab,kf. (104207)
33 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).ti,ab,kf. (177337)
34 or/19-33 (3200892)
35 18 and 34 (449)
36 35 use medall,cctr (169)
37 18 use coch,cleed (12)
38 36 or 37 (181)
39 limit 38 to english language [Limit not valid in CDSR; records were retained] (178)
40 exp asthma/ (429200)
41 asthma*.tw,kw,kf. (460529)
42 respiratory tract allergy/ (10526)
43 bronchus hyperreactivity/ (12533)
44 ((bronch* or respirat* or airway* or lung*) adj2 (hypersensitiv* or hyper-sensitiv* or hyperreactiv* or reactiv* or hyperrespons* or hyper-respons* or allerg* or Insufficienc*)).tw,kw,kf. (105591)
45 bronchospasm/ (29524)
46 (bronchspas* or bronchoconstrict* or (bronch* adj2 (spas* or constrict*))).tw,kw,kf. (25534)
47 exp coughing/di, et [Diagnosis, Etiology] (6208)
48 (chronic cough* or wheez*).tw,kw,kf. (55800)

49 or/40-48 (647400)
50 fractional exhaled nitric oxide test/ (107)
51 nitric oxide analyzer/ (588)
52 fractional exhaled nitric oxide/ (3506)
53 nitric oxide breathanalyzer/ (42)
54 nitric oxide/ and (breath analysis/ or diagnostic breathalyzer/ or biological marker/ or lung function test/) (9719)
55 ((fraction* adj3 (oxide* or nitric* or nitrogen*)) or (exhal* adj3 nitric* oxide*) or feno or fe no or eno or fraction* no or exhal* no).tw,kw,kf,dv. (24878)
56 (((airway* or breath* or exhal* or expir* or pulmonary or lung* or respirat*) adj2 (oxide* or nitric* or nitrogen*)) and (analy#er* or test* or assess* or biomarker* or biological marker* or predict* or measurement* or score* or threshold* or cut-off* or ppb or parts per billion or monitor* or manag* or treatment* or chemiluminescence* or sensor* or device* or desktop* or portable* or handheld* or point-of-care)).tw,kw,kf,dv. (17188)
57 (niox* or NObreath* or vivatmo* or ecomedics*).tw,kw,kf,dv. (1665)
58 or/50-57 (36684)
59 49 and 58 (15905)
60 Economics/ (263977)
61 Health Economics/ or Pharmacoeconomics/ or Drug Cost/ or Drug Formulary/ (143825)
62 Economic Aspect/ or exp Economic Evaluation/ (531677)
63 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw,kw,kf. (1212621)
64 exp "Cost"/ (664887)
65 (cost or costs or costing or costly).ti. (318679)
66 cost effective*.tw,kw,kf. (434518)
67 (cost* adj2 (util* or efficac* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog* or increment*)).ab,kw,kf. (305024)
68 Monte Carlo Method/ (79632)
69 (decision adj1 (tree* or analy* or model*)).tw,kw,kf. (64914)
70 (markov or markow or monte carlo).tw,kw,kf. (172969)
71 Quality-Adjusted Life Years/ (52306)
72 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw,kw,kf. (107525)
73 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw,kw,kf. (198317)
74 or/60-73 (2743671)
75 59 and 74 (519)
76 75 use emez (290)
77 Case Report/ or Comment/ or Editorial/ or (letter.pt. not (letter.pt. and randomized controlled trial/)) or conference abstract.pt. or conference review.pt. (12804229)
78 76 not 77 (182)
79 limit 78 to english language [Limit not valid in CDSR; records were retained] (179)
80 39 or 79 (357)

81 80 use medall (110)
82 80 use emez (179)
83 80 use coch (10)
84 80 use cctr (56)
85 80 use cleed (2)
86 remove duplicates from 80 (246)

Grey Literature Search

Performed on: Oct 5- 17, 2022

Websites searched:
Alberta Health Evidence Reviews, BC Health Technology Assessments, Canadian Agency for Drugs and Technologies in Health (CADTH), Institut national d'excellence en santé et en services sociaux (INESSS), Institute of Health Economics (IHE), University Of Calgary Health Technology Assessment Unit, Ontario Health Technology Assessment Committee (OHTAC), McGill University Health Centre Health Technology Assessment Unit, Centre Hospitalier de l'Universite de Quebec-Universite Laval, Contextualized Health Research Synthesis Program of Newfoundland (CHRSP), Health Canada Medical Device Database, International HTA Database (INAHTA), Agency for Healthcare Research and Quality (AHRQ) Evidence based Practice Centers, Centers for Medicare & Medicaid Services Technology Assessments, Veterans Affairs Health Services Research and Development, Institute for Clinical and Economic Review, Oregon Health Authority Health Evidence Review Commission, Washington State Health Care Authority Health Technology Reviews, National Institute for Health and Care Excellence (NICE), National Health Service England (NHS), Healthcare Improvement Scotland, Health Technology Wales, Ireland Health Information and Quality Authority Health Technology Assessments, Australian Government Medical Services Advisory Committee, Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S), Health Council of Australian Governments Health Technologies, Italian National Agency for Regional Health Services, Belgian Health Care Knowledge Centre, Ludwig Boltzmann Institute for Health Technology Assessment, Swedish Agency for Health Technology Assessment and Assessment of Social Services, Ministry of Health Malaysia Health Technology Assessment Section, Tuft's Cost-Effectiveness Analysis Registry, PROSPERO, EUnetHTA, ClinicalTrials.gov

Keywords used: asthma, FeNO, fe no, eno, nitric oxide, fractional oxide, fractional nitric, fractional nitrogen, niox, NObreath, vivatmo, ecomedics

Clinical results (included in PRISMA): 15
Economic results (included in PRISMA): 30
Ongoing HTAs (PROSPERO/EUnetHTA): 17
Ongoing clinical trials: 84

Appendix 2: Additional Information on Studies Included in Systematic Reviews – Diagnosis

Table A1 lists the 110 primary studies included by the authors of the 15 reviews identified in this health technology assessment. The reviews are numbered and correspond to the marked table columns as follows: (1) Gaillard et al[31] (5 studies), (2) Tang et al[103] (8 studies), (3) Zhao et al[104] (20 studies), (4) Zhang et al[105] (12 studies), (5) Wang et al[106] (43 studies), (6) Karrasch et al[25] (27 studies), (7) NICE[19] (9 studies), (8) Guo et al[108] (25 studies), (9) Zhong et al[109] (14 studies), (10) Harnan et al[110] (28 studies) (11) Li et al[111] (19 studies), (12) Louis et al[21] (21 studies), (13) Sano et al[112] (13 studies), (14) Harnan et al[113] (35 studies), (15) Song et al[114] (13 studies).

Table A1: Overlap of Primary Studies Included in Relevant Reviews Identified in the Literature

Author, year (primary studies)[a]	No. of reviews that include the primary study	Includes studies in children only (columns 1–3)			Includes studies in children and adults (columns 4–11)								Includes studies in adults only (columns 12–15)			
Review[b]		(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)
Cordeiro, 2011	9					1	1	1	1		1	1	1	1	1	
Sivan Y, 2009	9	1	1	1		1	1	1	1		1	1				
Woo S, 2012	9	1	1	1		1	1	1	1		1	1				
Fukuhara, 2011	8					1	1	1			1	1	1	1	1	
Heffler, 2006	8					1	1	1		1	1	1	1		1	
Sato S, 2008	8				1	1	1	1	1		1	`			1	1
Schneider A, 2013	8					1	1		1		1	1	1	1	1	
Arora, 2006	7					1	1			1	1	1	1		1	
Fortuna, 2007	7					1	1				1	1	1	1	1	
Pedrosa M, 2010	7						1		1		1	1	1	1	1	
Smith AD, 2004	7					1	1		1	1	1			1	1	
Schleich FN, 2012	6					1	1				1		1	1	1	
Schneider A, 2009	6					1			1		1	1		1	1	
Pizzimenti, 2009	6				1	1	1				1				1	1
Zhang YM, 2011	6				1		1		1		1				1	1
Berkman, 2005	5					1			1	1		1		1		
Jerzynska J, 2014	5		1	1		1			1			1				
Katsoulis, 2013	5					1	1				1		1		1	
Kostikas 2008	5					1	1		1				1	1		
Kowal K, 2009	5						1	1	1				1			1
Malinovschi, 2012	5					1	1		1			1	1			
Sachs-Olsen C, 2010	5		1	1		1	1					1				
Wang Y, 2015	5			1	1		1						1	1		
Dupont, 2003	4					1			1	1				1		
Voutilainen M, 2013	4						1	1				1	1			

Author, year (primary studies)[a]	No. of reviews that include the primary study	Includes studies in children only (columns 1–3)			Includes studies in children and adults (columns 4–11)								Includes studies in adults only (columns 12–15)			
Chatkin, 1999	3							1		1						1
Grzelewski T, 2014	3	1		1		1										
Smith AD, 2005	3						1				1				1	
Yao T, 2011	3		1	1		1										
El Halawani SM, 2003	3						1				1				1	
Florentin, 2014	3					1	1					1				
Zhu H, 2015	3		1	1	1											
Bommarito, 2008	2					1						1				
de la Barra SL, 2011	2										1				1	
Deykin, 2002	2					1				1						
Matsunaga, 2011	2					1						1				
Miedinger, 2007	2					1				1						
Tilemann L, 2011	2						1						1			
An SH, 2015	2		1	1												
Backer, 2014	2					1									1	
Bobolea ID, 2012	2										1				1	
Brannan JD, 2013	2										1				1	
Chancafe-Morgan J, 2013	2										1				1	
Giovannini M, 2014	2						1								1	
Hahn PY, 2007	2										1				1	
Hsu JY, 2013	2										1				1	
Linkosalo L, 2012	2						1				1					
Liu, 2011	2			1						1						
Malmberg LP, 2003	2									1		1				
Martin, 2016	2					1							1			
Mathew S, 2011	2										1				1	
Perez Tarazona S, 2011	2		1			1										
Prieto L, 2009	2										1				1	
Ramser M, 2008	2					1					1					
Ren XB, 2009	2								1	1						
Yang YJ, 2013	2								1	1						
Ye L, 2010	2								1							1
Yi, 2016	2				1											1
Asano, 2016	1				1											
Berlyne, 2006	1					1										
de Jong CCM, 2019	1	1														
He L, 2018	1												1			

Author, year (primary studies)[a]	No. of reviews that include the primary study	Includes studies in children only (columns 1–3)			Includes studies in children and adults (columns 4–11)								Includes studies in adults only (columns 12–15)			
Ishizuka, 2011	1				1											
Kanemitsu, 2016	1				1											
Menzies, 2007	1				1											
Miedinger, 2010	1				1											
Nekoee H, 2020	1												1			
Schneider A, 2014	1				1											
Thomas PS, 2005	1				1											
Tomita, 2013	1													1		
Travers J, 2007	1				1											
Avital, 2001	1				1											
Biju Thomas, 2016	1			1												
Boon, 2014	1			1												
Brouwer AFJ, 2010	1	1														
Ceng J, 2011	1							1								
Chai J, 2010	1								1							
Chen, 2017	1				1											
Cirillo I, 2013	1												1			
Fang, 2017	1				1											
Franklin, 2003	1								1							
Glowacka, 2013	1			1												
Henriksen, 2000	1				1											
Inoue, 2016	1			1												
Ji XM, 2013	1							1								
Jiang XB, 2012	1							1								
Johnson B, 2021	1												1			
Kaplan AG, 2019	1												1			
Karrasch S, 2017	1												1			
Korevaar DA, 2015	1												1			
Lemiere, 2010	1				1											
Lin G, 2013	1															1
Mahut, 2009	1			1												
Maniscalco, 2015	1				1											
Munnik, 2010	1				1											
Nayak, 2013	1				1											
Ni J, 2014	1															1
Oh MJ, 2008	1															1
Qiu JP, 2012	1															1
Raj, 2014/2016	1			1												
Sastre, 2013	1														1	

Author, year (primary studies)[a]	No. of reviews that include the primary study	Includes studies in children only (columns 1–3)	Includes studies in children and adults (columns 4–11)	Includes studies in adults only (columns 12–15)
Schimoda, 2013	1		1	
Seo, 2018	1	1		
Shen X, 2015	1			1
Singer, 2013	1	1		
Visitsunthorn 2016	1	1		
Xu YL, 2014	1		1	
Yao HJ, 2013	1		1	
Zetterquist, 2008	1	1		
Zhu N, 2014	1			1

[a]The 46 studies included in our review are highlighted in light blue.

[b]The primary studies included by the authors of the reviews identified in this health technology assessment are numbered in row 1 and correspond to the marked table columns as follows: (1) Gaillard et al[31] (5 studies), (2) Tang et al[103] (8 studies), (3) Zhao et al[104] (20 studies), (4) Zhang et al[105] (12 studies), (5) Wang et al[106] (43 studies), (6) Karrasch et al[25] (27 studies), (7) NICE[19] (9 studies), (8) Guo et al[108] (25 studies), (9) Zhong et al[109] (14 studies), (10) Harnan et al[110] (28 studies) (11) Li et al[111] (19 studies), (12) Louis et al[21] (21 studies), (13) Sano et al[112] (13 studies), (14) Harnan et al[113] (35 studies), (15) Song et al[114] (13 studies).

Appendix 3: Additional Information on Included Systematic Reviews – Management

Table A2: Distribution of Outcomes Reported Across Systematic Reviews With Meta-analyses[a]

Author, Year	Asthma/ symptom control	Lung function measures	Airway inflamm-ation tests	Use of inhaled cortico-steroids	Exacerbations	Use of oral cortico-steroids	ED/ unscheduled hospitalizations	Symptom-free days	Time off work/ school	Quality of Life measures
Children										
Khatri et al, 2021[34]	Asthma control test	Change in FEV_1	*Blood eosinophils*	*Change in ICS use*	Number of patients + frequency of exacerbations	Number of patients using OCS	Number + frequency of visits	*Frequency of days*	*Frequency of days missed*	*Pediatric asthma* *Caregivers quality of life questionnaire*
Wang et al, 2020[93]	Rate of symptom control + asthma severity score	—	—	Change in ICS daily dosage	No. of patients with ≥ 1 exacerbation + frequency of exacerbations	—	—	—	—	Pediatric asthma–related Quality of life questionnaire
Petsky et al, 2018[95]	Asthma control test	*FEV_1 + AHR*	—	ICS dose at final visit	No. of patients with > 1 exacerbation + exacerbation rate	—	—	—	—	Asthma-related quality of life score
Lu et al, 2015[94]	—	Change in FEV_1	—	Change in ICS dose from baseline to final visit	No. of patients with ≥ 1 exacerbation	—	—	—	—	—
Adults										
Khatri et al, 2021[34]	Asthma control questionnaire	Change in FEV_1	*Blood eosinophils*	*Change in ICS use*	No. of patients + frequency of exacerbations	Number of patients using OCS	Number + frequency of visits	*Frequency of days*	*Frequency of days missed*	*Asthma* *Quality of life questionnaire*
Petsky et al, 2018[95]	Asthma control test	*FEV_1 + AHR*	—	ICS dose at final visit	No. of patients with > 1 exacerbation +	—	—	—	—	Asthma-related quality of life score

Author, Year	Asthma/ symptom control	Lung function measures	Airway inflamm-ation tests	Use of inhaled cortico-steroids	Exacerbations	Use of oral cortico-steroids	ED/ unscheduled hospitalizations	Symptom-free days	Time off work/ school	Quality of Life measures
					exacerbation rate					
Essat et al, 2016[98]	—	—	—	Mean inhaled corticosteroid use	Major/severe exacerbation rate Composite outcome of any exacerbation or failure rate	Number of exacerbations resulting in the use of OCS	Health care utilization	—	—	Asthma-related quality of life score

Abbreviations: AHR, airway hyper-responsiveness; ED, emergency department; FEV_1, forced expiratory volume (in one second); ICS, inhaled corticosteroids; OCS, oral corticosteroids.

[a]Italicized outcomes were collected in the review, but meta-analysis not possible/not done. —, not applicable (outcome not included in review)

Appendix 4: Summary Characteristics Table of All Identified Diagnostic Accuracy Studies (n = 73)

Table A3: Summary Characteristics of Included Diagnostic Accuracy Studies

	Number of studies			
	Children	Mixed	Adults	Total
	21	**12**	**40**	**73**
Countries of conduct				
China	4	1	5	**10**
Germany	1	0	7	**8**
Japan	0	1	6	**7**
Poland	4	0	1	**5**
Belgium	0	2	2	**4**
New Zealand	0	2	2	**4**
Switzerland	2	0	2	**4**
Korea	3	0	0	**3**
United Kingdom	1	0	2	**3**
Canada	0	0	2	**2**
Denmark	0	1	1	**2**
Greece	0	0	2	**2**
Israel	1	0	1	**2**
Italy	0	1	1	**2**
Spain	0	1	1	**2**
United States	0	0	3	**3**
Australia	1	0	0	**1**
Finland	0	1	0	**1**
India	0	1	0	**1**
Iran	0	0	1	**1**
Netherlands	0	1	0	**1**
Norway	1	0	0	**1**
Portugal	1	0	0	**1**
Taiwan	1	0	0	**1**
Turkey	1	0	1	**2**
Clinical settings				
Specialists (clinic, university/hospital, outpatient)	14	11	33	**58**
Primary care	1	1	2	**4**

	Number of studies			
	Children	**Mixed**	**Adults**	**Total**
Other (population-based cohort/database, medical record review)	6	0	5	**11**
Sample size ranges				
0–100	2	4	10	**16**
101–250	10	5	13	**28**
251–500	5	2	11	**18**
501–1,000	1	1	6	**8**
> 1,000	3	0	0	**3**
Types of asthma				
Any asthma (not limited)	14	9	36	**59**
Cough-variant asthma	2	0	3	**5**
Bronchial asthma	1	2	1	**4**
Asthma with rhinitis	1	1	0	**2**
Atopic asthma	1	0	0	**1**
Chest tightness variant asthma (CTVA)	1	0	0	**1**
Chronic cough	1	0	0	**1**
FeNO device brands				
NIOX MINO	12	2	16	**30**
NIOX (non-specific)	1	5	6	**12**
NIOX VERO	0	0	2	**2**
Sievers 240/280	2	0	7	**9**
CLD88	3	1	0	**4**
NObreath	1	0	1	**2**
CLD 700	0	1	0	**1**
PGM-1860	1	0	0	**1**
SIR N-6008	0	0	1	**1**
Sunvou-CA2122	0	0	1	**1**
NA623N	0	1	0	**1**
Nano Coulomb	0	1	0	**1**
LR 2000	0	0	1	**1**
Unclear/not reported	1	1	5	**7**
Optimal FeNO cut-off values reported by study authors (ppb)				
Low (< 20 child, < 25 adult)	6	5	13	**24**
Mid (20–35 child, 25–45 adult)	15	6	22	**43**

	Number of studies			
	Children	**Mixed**	**Adults**	**Total**
High (> 35 child, > 45 adult)	0	1	5	**6**
Reference standards				
Spirometry with reversibility + bronchoprovocation (methacholine)	1	3	10	**14**
Other reference standard combinations	2	1	8	**11**
Spirometry with reversibility + bronchoprovocation (other)	3	2	3	**8**
Self-reported asthma diagnosis/ symptoms/ medication use	3	1	2	**6**
Spirometry with reversibility	3	1	2	**6**
Spirometry + bronchoprovocation (methacholine)	1	1	3	**5**
Spirometry + bronchoprovocation (other)	1	2	2	**5**
WBP (with spirometry +/– reversibility) + bronchoprovocation	0	0	5	**5**
Spirometry alone	3	0	1	**4**
FeNO sensitivities				
0%–50%	8	2	15	**25**
51%–60%	2	1	5	**8**
61%–70%	4	0	6	**10**
71%–80%	2	6	5	**13**
81%–90%	4	3	8	**15**
91%–100%	1	0	1	**2**
FeNO specificities				
0%–50%	0	0	2	**2**
51%–60%	1	1	3	**5**
61%–70%	3	2	4	**9**
71%–80%	2	3	8	**13**
81%–90%	8	3	16	**27**
91%–100%	7	3	7	**17**

Abbreviations: FeNO, fractional exhaled nitric oxide; WBP, whole body plethysmography .

Appendix 5: Findings From All Identified Diagnostic Accuracy Studies (n = 73)

Table A4: Findings From All Identified Diagnostic Accuracy Studies

	Population				Intervention		Comparator	Outcomes			
Author, Year (country of conduct)	Age (year)	Clinical setting	Prevalence of asthma (% with asthma out of sample)	Type of asthma (if reported)	FeNO device	Optimal cut-off (ppb)	Reference standard	Sensitivity (%)	Specificity (%)	Positive predictive value	Negative predictive value
Children (21)											
Thomas et al, 2005[171]	Mean: 14.7 ± 2.3	Secondary school recruitment	Unclear		Unclear	7	Self-reported asthma symptoms	47.0	93.0	63.0	69.0
Feng et al, 2022[91]	Range: 6–13	Clinic: pulmonary (outpatient hospital)	12%	CTVA	NIOX MINO	15	Spirometry + bronchoprovocation	75.0	74.0	29.0	96.0
Sachs-Olsen et al, 2010[172]	Mean: 10.9 (healthy) Mean: 11.1 (allergic sensitization only) Mean: 10.8 (allergic asthma in remission) Mean: 10.7 (non-allergic asthma in remission) Mean: 10.7 (allergic asthma) Mean: 10.8 (non-allergic asthma)	Unclear	9%	Allergic asthma subgroups	CLD 88 + DENOX 88	15.6	Self-reported asthma diagnosis + symptoms or medication use	35.0	94.0	50.0	90.0
Grzelewski et al, 2014[173]	Range: 6–18	Clinic: outpatient	60%		Sievers 280	15.8	Spirometry with reversibility	38.0	62.0	31.0	72.0
Jang et al, 2020[174]	Range: 5–18	Clinic: asthma	**21%**	Asthma (subgroup with rhinitis also reported)	NIOX MINO	16.5	Spirometry with reversibility + bronchoprovocation	66.7	64.1	62.9	60.0
Sivan et al, 2009[175]	Range: 5–18	Clinic: outpatient (hospital)	71%		CLD88 (EcoMedics)	19	Spirometry with reversibility + bronchoprovocation	86.0	89.0	92.0	80.0
Eom et al, 2020[49]	Range: 8–16	Clinic: hospital (outpatient)	69%		NIOX MINO	19.6	Spirometry alone	64.0	83.0	90.0	50.0
de Jong et al, 2019[50]	Range: 6–16	Clinic: outpatient	72%		NIOX MINO	21	Spirometry with reversibility + bronchoprovocation	59.0	87.0	92.0	45.0
Woo et al, 2012[51]	Range: 8–16	Clinic: outpatient (hospital)	68%		NIOX MINO	22	Spirometry + bronchoprovocation	56.9	87.2	90.5	48.6

	Population				Intervention		Comparator	Outcomes			
Author, Year (country of conduct)	Age (year)	Clinical setting	Prevalence of asthma (% with asthma out of sample)	Type of asthma (if reported)	FeNO device	Optimal cut-off (ppb)	Reference standard	Sensitivity (%)	Specificity (%)	Positive predictive value	Negative predictive value
Jerzynska et al, 2014[52]	Range: 6–18	Clinic: outpatient	60%		Sievers 280	23	Spirometry with reversibility	90.0	52.0	25.0	97.0
Murray et al, 2017[53]	Range: 13–16	Primary care	6%		NIOX	24	Spirometry with reversibility	63.0	73.0	29.0	92.0
Baranski and Schlünssen, 2022[54]	Range: 6–9	Primary school recruitment	8%		NIOX MINO	24	NR	32.4	98.5	14.4	93.1
Yildiz et al, 2018[55]	Range: 6–17	Clinic: pediatric immunology and allergy	30%	Chronic cough patients	NIOX MINO	24	Spirometry + IgE + skin prick	78	92	81.0	91.0
Zho et al, 2018[56]	Mean: 7 Range: 6–14	Hospital: tertiary care	20%	Cough-variant asthma (vs. NCVA or chronic cough)	NIOX MINO	25	Spirometry with reversibility + bronchoprovocation	84.0	97.1	97.5	81.4
de Jong et al, 2020[57]	Range: 5–17	Clinic: pulmonary (outpatient)	69%		NIOX MINO + CLD88	25	Spirometry + bronchoprovocation	46.0	88.0	90.0	42.0
Kesler et al, 2019[58]	Mean: 9.7 Range: 5–17	Specialist practice: pneumologists + allergists	35%	Atopic asthma (non-atopic subgroup also reported)	NIOX MINO	25	Spirometry + bronchoprovocation	31.0	84.0	72.0	48.0
Zhu et al, 2019[60]	Mean: 8.03 in CVA Mean: 8.61 in nCVA	Clinic: pediatric respiratory and inpatient	42%	Cough-variant asthma	NIOX MINO	25.5	Spirometry alone	82.2	90	91.8	85.7
Baranski and Zejda, 2022[54]	Mean: 7.49 Range: 6–10	Primary school recruitment	5%		NIOX MINO	25	Spirometry alone	27.2	88.9	12.3	95.9
Yao et al, 2011[176]	Mean: 10.3 Range: 5–18	Public school recruitment	4%		CLD88	28	Self-reported asthma diagnosis, symptoms or medication use	64.3	69.9	8.8	97.7
Li et al, 2019[62]	Mean: 5.08 (75) Mean: 5.13 (50)	Hospital	60%	Bronchial asthma	PGM-1860	32	Spirometry	90.7	100.0	NR	NR
Silva et al, 2019[63]	Mean: 9 Range: 7–12	Primary school recruitment	10.5%		NObreath	35	Self-reported asthma diagnosis + symptoms + spirometry with reversibility	11.6	98.6	52.4	89.1
Mixed population (12)											
Dupont et al, 2003[177]	Range: 12–75	Clinic - asthma (outpatient)	67%		CLD 700	13	Reported asthma diagnosis	85.0	80.0	89.5	89.5

	Population				Intervention		Comparator	Outcomes			
Author, Year (country of conduct)	Age (year)	Clinical setting	Prevalence of asthma (% with asthma out of sample)	Type of asthma (if reported)	FeNO device	Optimal cut-off (ppb)	Reference standard	Sensitivity (%)	Specificity (%)	Positive predictive value	Negative predictive value
Malinovschi et al, 2012[178]	Range: 14–44	Outpatient	34%		NIOX MINO	15	Spirometry with reversibility +/– bronchoprovocation +/– medication use	77.8	63.5	60.0	80.0
Cordeiro et al, 2011[179]	Range: 7–87	Clinic: asthma	37%		CLD88 (EcoMedics)	19	Spirometry + bronchoprovocation	86.0	89.0	92.0	80.0
Kumar et al, 2017[180]	Mean: 26.7	Clinic: outpatient	41%	Bronchial asthma (subgroup of asthma + rhinitis also reported)	NIOX	19.45	Spirometry with reversibility	71.2	81.8	96.8	30.0
Smith et al, 2004[181]	Range: 9–72	Hospital: pulmonary function lab	36%		NR	20	Spirometry with reversibility + bronchoprovocation	88.0	79.0	70.0	92.0
Voutilainen et al, 2013[42]	Range: 14–31	Clinic: asthma + allergy	48%		NIOX	30	Spirometry + bronchoprovocation	43.0	89.0	68.0	75.0
Schleich et al, 2012[43]	NR	Hospital	47%		NIOX	34	Spirometry with reversibility + bronchoprovocation	35.0	95.0	88.0	62.0
Heffler et al, 2006[44]	Range: 11–75	Clinic: allergy (outpatient)	38%	Asthma in rhinitis patients	NIOX	36	Spirometry with reversibility + bronchoprovocation	77.8	60.0	54.0	81.8
Fukuhara et al, 2011[45]	Range: 17–81	Clinic: pulmonary (outpatient) hospital	69%	Called bronchial asthma (also known as asthma)	NA623N	40	Spirometry with reversibility + bronchoprovocation + sputum eosinophilia	78.6	89.5	NR	NR
de la Barra et al, 2011[46]	NR	Primary care/outpatient	37%		NIOX	40	Spirometry with reversibility + bronchoprovocation	75.0	70.0	42.9	90.3
Pedrosa et al, 2010[47]	Range: 14–68	Hospital	30%		NIOX MINO	40	Spirometry with reversibility + bronchoprovocation	74.3	72.5	54.2	86.6
Wang et al, 2015[48]	Range: 13–82 (for bronchoprovocation population)	Clinic: hospital (outpatient)	31%		Nano Coulomb	64	Spirometry + bronchoprovocation	52.0	94.4	80.2	72.8

	Population				Intervention		Comparator	Outcomes			
Author, Year (country of conduct)	Age (year)	Clinical setting	Prevalence of asthma (% with asthma out of sample)	Type of asthma (if reported)	FeNO device	Optimal cut-off (ppb)	Reference standard	Sensitivity (%)	Specificity (%)	Positive predictive value	Negative predictive value
Adults (41)											
Berkman et al, 2005[182]	Mean: 21.9 (asthma) Mean: 29.3 (non-asthma)	Clinic: pulmonary (outpatient)	47%		LR 2000	7	Self-reported asthma symptoms or spirometry with reversibility	82.5	89.9	89.1	85.4
Deykin et al, 2002[183]	Mean: 29.6 (asthma) Mean: 27.3 (non-asthma)	Outpatient	55%		Sievers 280	10.4	Spirometry with reversibility + bronchoprovocation	79.4	71.4	76.5	74.7
Menzies et al, 2007[184]	Mean: 48.5 (asthma) Mean: 35.6 (non-asthma)	Unclear	72%		NIOX	13	Spirometry alone	83.2	27.0	NR	NR
Kalkan et al, 2021[185]	Range: 18–65	Clinic: medical record review	37%	Asthma with bronchial hyperactivity	NIOX MINO	14	Spirometry + bronchoprovocation	63.1	62.5	50.0	74.1
Arora et al, 2006[186]	Range: 7–38	Clinic: allergy	80%		NIOX	17	Spirometry + bronchoprovocation	63.0	59.0	86.0	28.2
Berlyne et al, 2006[187]	Mean: 36 (healthy nonatopic) Mean: 37 (healthy atopic) Mean: 33 (asthma-no steroids) Mean: 46 (asthma-steroids) Mean: 44 (eosinophilic bronchitis without asthma)	Clinic: chest and allergy	NR	Atopic, eosinophilic bronchitis subgroups	Sievers 240	17.1	Spirometry with reversibility + bronchoprovocation	81.0	90.0	NR	NR
Bommarito et al, 2008[188]	Mean: 43.3	General population/outpatient ?	12%		Sievers	18.7	Self-reported asthma diagnosis + symptoms	69.2	71.0	24.0	95.0
Kostikas et al, 2008[189]	Mean: 21.4 (control) Mean: 21.6 (asthma) Mean: 21.5 (allergic rhinitis) Mean: 22.1 (nonspecific symptoms)	University hospital	29%	Allergic rhinitis subgroup	NIOX MINO	19	Spirometry with reversibility + bronchoprovocation	52.4	85.3	NR	NR

	Population				Intervention		Comparator	Outcomes			
Author, Year (country of conduct)	Age (year)	Clinical setting	Prevalence of asthma (% with asthma out of sample)	Type of asthma (if reported)	FeNO device	Optimal cut-off (ppb)	Reference standard	Sensitivity (%)	Specificity (%)	Positive predictive value	Negative predictive value
Travers J, 2007[190]	Range: 26–76	Outpatient?	27%		NIOX	20	Self-reported asthma diagnosis + symptoms + medication use or spirometry with reversibility	49.0	61.0	NR	NR
Matsunaga et al, 2011[92]	Mean: 39.4 (control) Mean: 41.5 (asthma)	Clinic: outpatient	39%		NIOX MINO	22	Spirometry with reversibility + bronchoprovocation	90.8	83.9	NR	NR
Kanemitsu et al, 2016[191]	Mean: 48.4 (CVA) Mean: 48.1 (non-CVA)	Clinic: asthma + chronic cough	64%		Sievers 280 (NOA280)	22	Bronchoprovocation	57.0	61.0	72.0	44.0
Fortuna, 2007[192]	Range: 18–68	Clinic: respiratory medicine (outpatient)	44%		SIR N-6008	23	Spirometry with reversibility + bronchoprovocation	77.0	64.0	62.0	78.0
He et al, 2018[193]	Range: 18–72	Clinic: respiratory (outpatient)	66%		NIOX MINO	23.5	Spirometry with reversibility + bronchoprovocation + responsive to treatment	79.9	54.7	77.9	58.1
Chen et al, 2021[194]	Range: 16–79	University: hospital	38%	Cough-variant asthma (vs. NCVA or chronic cough)	NIOX MINO	24.5	Spirometry with reversibility or bronchoprovocation	69.6	72.9	61.3	79.6
Feng-Jia et al, 2018[64]	Mean: 40.75 Range: 18–75	University:-hospital	38%	Cough-variant asthma (vs. NCVA or chronic cough)	NIOX MINO	25	Spirometry + bronchoprovocation	81.3	84.0	NR	NR
Jeppegaard et al, 2018[65]	Range: 15–63	Clinic: respiratory (outpatient)	76%		NIOX MINO	25	Spirometry with reversibility + bronchoprovocation	70.0	72.0	45.0	88.0
Schneider et al, 2013[66]	Range: 23–60	Specialists - pneumologist	39%		NIOX MINO	25	WBP with spirometry + bronchoprovocation	49.0	75.0	56.0	69.0
Schneider et al , 2014[67]	Mean: 41.9 (asthma) Mean: 45.5 (non-asthma)	Specialists: pneumologist	28%		NR	26	WBP with spirometry with reversibility + bronchoprovocation	47.0	73.1	39.8	78.4
Asano et al, 2016[68]	Mean: 51.7 (cough-predominant asthma)	Clinic: asthma	73%	Cough-variant asthma	NR	29.2	Spirometry with reversibility + bronchoprovocation	60.0	89.3	NR	NR

Author, Year (country of conduct)	Population				Intervention		Comparator	Outcomes			
	Age (year)	Clinical setting	Prevalence of asthma (% with asthma out of sample)	Type of asthma (if reported)	FeNO device	Optimal cut-off (ppb)	Reference standard	Sensitivity (%)	Specificity (%)	Positive predictive value	Negative predictive value
	Mean: 48.2 (cough variant asthma) Mean: 43.6 (NAC)										
Chatkin et al, 1999[69]	Mean: 38 (control) Mean: 47 (CC non-asthma) Mean: 41 (CC asthma) Mean: 38 (wheezing asthma)	Clinic: asthma (outpatient)	21%	Chronic cough subgroups	Sievers 280	30	Spirometry with reversibility + bronchoprovocation	75.0	87.0	60.0	93.0
Schneider et al, 2022[70]	Mean: 44.3	Specialists: pneumologist	52%		NIOX VERO	30	WBP with spirometry + bronchoprovocation	44.0	91.0	85.0	60.0
Schneider et al, 2015[71]	Mean: 42	Specialist care	39%		NIOX MINO	31	WBP with spirometry with reversibility + bronchoprovocation	38.3	83.3	NR	NR
Katsoulis et al, 2013[72]	Range: 22 to 37	Clinic: outpatient	43%		NIOX MINO	32	Spirometry with reversibility + bronchoprovocation	47.0	85.0	NR	NR
Louis et al, 2023[73]	Mean: 51	Clinic: asthma (secondary care centre)	63%		NIOX	33	Spirometry with reversibility + bronchoprovocation	32.0	83.0	NR	NR
Kellerer et al, 2021[74]	Mean: 43.3	Specialist practice: pneumologists	39%		NIOX MINO	35	Spirometry with reversibility or WBP + bronchoprovocation	32.5	83.2	34.2	82.2
Tomita et al, 2013[75]	Range: 18–88	Clinic: outpatient (hospital)	65%		NR	35	Spirometry with reversibility + bronchoprovocation	53.0	59.0	NR	NR
Nekoee et al, 2020[76]	Mean: 51	Clinic: asthma	50%		NR	36	Spirometry with reversibility + bronchoprovocation	30.0	85.0	66.0	55.0
Miedinger et al, 2010[77]	Range: 18–19	Swiss armed forces	18%		NIOX MINO	36.5	Self-reported asthma diagnosis + symptoms + medication use + bronchoprovocation	36.0	84.0	33.0	86.0
Ishizuka et al, 2011[78]	Range: 18–24	University: outpatient	8%		Sievers 280	38	Self-reported asthma diagnosis + symptoms	86.8	74.0	NR	NR
Sato et al, 2008[79]	Range: 20–78	Hospital: pulmonary medicine	68%		Unclear	38.8	Spirometry with reversibility +	79.2	91.3	NR	NR

Author, Year (country of conduct)	Population				Intervention		Comparator	Outcomes			
	Age (year)	Clinical setting	Prevalence of asthma (% with asthma out of sample)	Type of asthma (if reported)	FeNO device	Optimal cut-off (ppb)	Reference standard	Sensitivity (%)	Specificity (%)	Positive predictive value	Negative predictive value
							bronchoprovocation + sputum eosinophilia				
Nickels et al, 2016[80]	Mean: 54.4	Tertiary care center: Mayo PFT laboratory database	16%		NIOX MINO	39	Spirometry + bronchoprovocation	17.9	79.3	14.0	83.6
Fard et al, 2022[81]	Mean: 34.5 Range: 18–77	Clinic: hospital + occupational medicine	80%		NObreath	39.5	Spirometry + bronchoprovocation	48.6	94.0	97.0	30.0
Kowal et al, 2009[82]	Range: 18–45	Clinic: asthma	33%		Sievers 280 (NOA280)	40	Spirometry with reversibility	88.3	82.6	NR	NR
Drake et al, 2021[83]	Mean: 34.7 Range: 16–61	Clinic: research (from primary care)	60%		NIOX VERO	40	Spirometry with reversibility + bronchoprovocation + serum eosinophil count + peak flow	56.0	88.0	87.0	57.0
Hou et al, 2021[84]	Range: 18–80	Clinic: outpatient (pulmonary)	52%		NIOX MINO	43	Spirometry + bronchoprovocation	61.2	84.1	80.5	67.0
Schneider et al, 2009[85]	Mean: 38.7 (asthma) Mean: 55.7 (COPD) Mean: 63.5 (Overlap) Mean: 42.8 (No OAD)	Primary care	47%		NIOX MINO	46	WBP with spirometry with reversibility or bronchoprovocation	32.0	93.0	80.0	61.0
Tilemann et al, 2011[86]	Mean: 38 (asthma) Mean: 56.8 (COPD) Mean: 57.9 (partial reversibility) Mean: 42.3 (no OAD)	Hospital: lung function	41%		NIOX MINO	46	Spirometry with reversibility	29.0	92.0	71.0	65.0
Smith et al, 2005[87]	Range: 12–75	Hospital: pulmonary function lab (PFT)	52%		NIOX	47	Spirometry with reversibility + bronchoprovocation	82.0	91.0	82.0	91.0
Miedinger et al, 2007[88]	Range: 23–64	Clinic: outpatient	14%		NIOX	47	Spirometry + bronchoprovocation	42.0	96.0	66.0	91.0
Wang et al, 2021[89]	Mean: 44.51 (CVA) Mean: 58.8 (TA)	Clinic: hospital (outpatient)	50%	Cough-variant asthma	Sunvou-CA2122	48.5	Spirometry + bronchoprovocation	90.4	42.2	NR	NR

Abbreviations: CC, chronic cough; COPD, chronic obstructive pulmonary disease, CTVA, chest tightness variant asthma; CVA, cough-variant asthma; NAC, non-asthmatic cough; NCVA, non cough-variant asthma; No-OAD, no obstructive airway disease; NR, not reported; PFT, pulmonary function test; ppb, parts per billion; TA, typical asthma; WBP, whole body plethysmography.

Appendix 6: Critical Appraisal of Clinical Evidence

Table A5: Risk of Bias Among Diagnostic Accuracy Studies (QUADAS-2 Tool)

	Risk of bias[a]				Applicability concerns		
Author, year	Patient selection[b]	Index test[c]	Reference standard[d]	Flow and timing[e]	Patient selection[f]	Index test[g]	Reference standard[h]
Children							
Eom SY, 2020[49]	Low	Low	High	Low	Low	Low	Unclear
de Jong CCM, 2019[50]	Low	High	Low	Low	Low	Low	Low
Woo S, 2012[51]	Low	Low	Low	Low	Low	Low	Low
Jerzynska J, 2014[52]	High	High	High	Low	High	Unclear	Unclear
Baranski & Schlünssen, 2022[54]	High	Low	High	Unclear	High	Low	High
Murray C, 2017[53]	High	Low	High	Low	High	Low	Unclear
Yildiz, 2018[55]	High	High	Unclear	Unclear	High	Low	Unclear
Baranski & Zejda, 2022[54]	Low	Low	High	Low	Low	Low	Unclear
de Jong CCM, 2020[57]	Low	High	Low	Low	Low	Low	Low
Kesler A, 2019[58]	Low	Low	Low	Low	Low	Low	Low
Zhou J, 2018[56]	Unclear	High	Low	Low	High	Low	Low
Zhu H, 2019[60]	High	High	High	Unclear	High	Low	Unclear
Yao T, 2011[176]	Low	High	High	Low	Low	Unclear	Unclear
Li X, 2019[62]	High	High	Unclear	Unclear	High	Unclear	High
Silva D, 2019[63]	High	High	High	Unclear	High	Unclear	Unclear
Mixed							
Voutilainen M, 2013[42]	High	High	Low	Unclear	High	Low	Low
Schleich FN, 2012[43]	Unclear	High	Low	Low	Low	Unclear	Low
Heffler, 2006[44]	High	High	Low	Low	High	Low	Low
de la Barra SL, 2011[46]	Unclear	High	Low	Unclear	Low	Low	Low
Fukuhara, 2011[45]	Unclear	Low	Low	Low	Low	Unclear	Low
Pedrosa M, 2010[47]	Low	High	Low	Low	Low	Low	Low
Wang Y, 2015[48]	Low	High	Low	Unclear	Low	Unclear	Low
Adults							
Feng-Jia C, 2018[64]	High	High	Low	Low	High	Low	Low
Jeppegaard M, 2018[65]	Low	Low	Low	Unclear	Low	Unclear	Low
Schneider A, 2013[66]	Low	Unclear	Low	Low	Low	Low	Low
Schneider A, 2014[67]	Low	High	Low	Unclear	Low	High	Low

Author, year	Risk of bias[a]				Applicability concerns		
	Patient selection[b]	Index test[c]	Reference standard[d]	Flow and timing[e]	Patient selection[f]	Index test[g]	Reference standard[h]
Asano, 2017[68]	High	High	Low	Low	High	Unclear	Low
Chatkin, 1999[69]	High	High	Low	Low	High	Unclear	Low
Schneider A, 2022[70]	Low	Low	Low	Unclear	Low	Low	Low
Schneider A, 2015[71]	Low	High	Unclear	Low	Low	Low	Low
Katsoulis, 2013[72]	Unclear	High	Low	Unclear	Low	Unclear	Low
Louis, 2023[73]	Unclear	High	Low	Low	Low	Low	Low
Kellerer K, 2021[74]	Low	Unclear	Low	Low	Low	Low	Low
Tomita, 2013[75]	Unclear	Low	Low	Low	Low	High	Low
Nekoee H, 2020[76]	Unclear	High	Low	Low	High	High	Low
Miedinger, 2010[77]	High	High	Low	Low	High	Low	Low
Ishizuka, 2011[78]	High	High	Unclear	High	High	Unclear	High
Sato S, 2008[79]	Unclear	High	Low	Low	High	High	Low
Nickels, 2016[80]	High	Unclear	Unclear	Unclear	High	Low	Low
Fard MB, 2022[81]	Low	High	Low	Low	Low	Unclear	Low
Drake, 2021[83]	Unclear	High	Low	Unclear	High	Low	Low
Kowal K, 2009[82]	High	High	Low	Low	High	Unclear	Low
Hou L, 2021[84]	Unclear	High	Low	Low	Unclear	Low	Low
Schneider A, 2009[85]	Unclear	Unclear	Low	Low	Low	Low	Low
Tilemann L, 2011[86]	Low	High	Low	Low	Low	Low	Low
Miedinger, 2007[88]	High	High	Low	Low	High	Low	Low
Smith AD, 2005[87]	Low	High	Low	Unclear	Unclear	Low	Low
Wang Y, 2021[89]	High	High	Low	Low	Unclear	Unclear	Low

Abbreviation: QUADAS, Quality Assessment of Diagnostic Accuracy Studies.

[a]Possible risk-of-bias levels: low, high, unclear.

[b]Patient selection is an unclear risk if recruitment of consecutive random sample is not mentioned; patient selection is a high risk if recruitment of consecutive random sample is not mentioned and a case-control group is used or exclusions to the population are based on type of asthma (e.g., cough variant asthma).

[c]Index test is an unclear risk if there is no mention of blinding; index test is a high risk if there is no mention of blinding and the optimal cut-off is not specified beforehand.

[d]Reference standard is an unclear risk of bias if reference standard is not clearly reported; reference standard is a high risk of bias if it is spirometry alone or there is no mention of the reference standard.

[e]Flow and timing are an unclear risk of bias if the interval and timing of the reference standard or the guideline followed is not mentioned or it is unclear whether all patients were followed.

[f]Applicability of patient selection is an unclear concern if recruitment and blinding not discussed; applicability of patient selection is a high concern if only specific sub-populations (CVA, allergic, chronic cough) of patients are recruited.

[g]Applicability of index test is an unclear concern if FeNO brand is not NIOX, as used in Ontario; applicability of index test is a high concern if the device brand is not reported.

[h]Applicability of reference tests are an unclear concern if the reference test is not spirometry + bronchoprovocation, as used in Ontario; applicability of reference tests is a high concern if the reference test is not clearly reported.

Table A6: Risk of Bias[a] Among All Identified Systematic Reviews (ROBIS Tool)

Author, year (country-affiliation)	Phase 2				Phase 3
	Study eligibility criteria	Identification and selection of studies	Data collection and study appraisal	Synthesis and findings	Risk of bias in the review
Khatri SB, 2021[34] (US ATS)	Low	Low[b]	Low	Low	Low
Wang X, 2020[93] (China)	Low	Low[c]	Unclear[c]	Low	Low
Petsky HL, 2018[95] (Australia)	Low	Low	Low	Low	Low
Harnan SE, 2015[97] (UK NHS)	Low	Low	Unclear[c]	Unclear[d]	Unclear
Wang Z, 2017[96] (US AHRQ)	Low	Low	Low	Unclear[d]	Low
Lu M, 2015[94] (China)	Low	Low[b]	High[e]	Low	High
Gomersal T, 2016[99] (UK NICE/NHS)	Low	Low	Unclear[c]	Unclear[d]	Unclear
Essat M, 2016[98] (UK NICE/NHS)	Low	Low	Unclear[c]	Unclear[d]	Unclear

Abbreviations: RCT, randomized controlled trial; ROBIS, Risk of Bias in Systematic Reviews.

[a]Possible risk-of-bias levels: low, high, unclear.

[b]Limited to published RCTs; however, the other reviews (except for Wang Z, 2017) only found RCTs without study design limits, so the impact of this limitation on overall risk of bias is presumed low.

[c]Quality appraisal on individual studies, but not on summary of evidence by outcome.

[d]Narrative synthesis (no pooling).

[e]No quality appraisal.

Table A7: GRADE Evidence Profile for Diagnostic Accuracy Studies

Outcome	Number of studies (N)	Risk of bias[a]	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
Diagnostic accuracy for asthma in children								
Sensitivity Cut-off 20–35 ppb	15	Serious limitations (−1)	Serious limitations (−1)[b]	No serious limitations	Serious limitations (−1)[c]	Undetected	None	⨁ Very low
Specificity Cut-off 20–35 ppb	15	Serious limitations (−1)	No serious limitations	No serious limitations	Serious limitations (−1)[c]	Undetected	None	⨁⨁ Low
Diagnostic accuracy for asthma in adults								
Sensitivity Cut-off 25–45 ppb	21	Serious limitations (−1)	Serious limitations (−1)[b]	No serious limitations	Serious limitations (−1)[c]	Undetected	None	⨁ Very low
Specificity Cut-off 25–45 ppb	21	Serious limitations (−1)	No serious limitations	No serious limitations	Serious limitations (−1)[c]	Undetected	None	⨁⨁ Low
Sensitivity Cut-off > 45 ppb	5	Serious limitations (−1)	Serious limitations (−1)[b]	No serious limitations	Serious limitations (−1)[c]	Undetected	None	⨁ Very low
Specificity Cut-off > 45 ppb	5	Serious limitations (−1)	No serious limitations	No serious limitations	Serious limitations (−1)[c]	Undetected	None	⨁⨁ Low
Diagnostic accuracy for asthma in mixed studies								
Sensitivity Cut-off > 30 ppb	7	Serious limitations (−1)	Serious limitations (−1)[b]	No serious limitations	Serious limitations (−1)[c]	Undetected	None	⨁ Very low
Specificity Cut-off > 30 ppb	7	Serious limitations (−1)	No serious limitations	No serious limitations	Serious limitations (−1)[c]	Undetected	None	⨁⨁ Low

Abbreviation: ppb, parts per billion.

[a]See Table A5 for reasons for risk of bias concerns across the studies (no mention of blinding, unreasonable exclusions, optimal cut-off not specified before but identified after, use of different index device brands, using different reference test combinations).

[b]Significant variability in values seen across studies.

[c]Confidence intervals not reported in most cases, and very wide when reported.

Appendix 7: Selected Excluded Studies

For transparency, we provide a list of studies that were included in some of the systematic reviews that we identified that readers might have expected to see but that did not meet the inclusion criteria, along with the primary reason for exclusion.

Citation	Primary reason for exclusion
An SH, Tian WQ, Li JY. Utility of fractional exhaled nitric oxide in children with asthma. Zhongguo Dang Dai Er Ke Za Zhi. 2015;17(8):134–7.	Not population of interest (includes children < 5 year)
Avital A, Uwyyed K, Berkman N, et al. Exhaled nitric oxide and asthma in young children. Pediatr Pulmonol. 2001 Oct;32(4):308–13.	Not population of interest (includes children < 5 year)
Backer V, Sverrild A, Porsbjerg C. FeNO and AHR mannitol in patients referred to an out-of-hospital asthma clinic: a real-life study. J Asthma. 2014 May;51(4):411-6.	No outcomes of interest
Thomas B, Chay OM, Allen JC Jr, Chiang AS, Pugalenthi A, Goh A, et al. Concordance between bronchial hyperresponsiveness, fractional exhaled nitric oxide, and asthma control in children. Pediatr Pulmonol. 2016 Oct;51(10):100–9.	No outcomes of interest
Bobolea ID, Barranco P, Lopez-Carrasco V, Calderon O, Guillen D, Quirce S. Is methacholine challenge sufficient to rule out bronchial hyperresponsiveness in patients with suspected asthma? J Allergy Clin Immunol. 2012;129(Suppl. 1):AB3.	Not FeNO
Boon M, Meyts I, Proesmans M, Vermeulen FL, Jorissen M, De Boeck K. Diagnostic accuracy of nitric oxide measurements to detect primary ciliary dyskinesia. Eur J Clin Invest. 2014 May;44(5):477–85.	Not target condition
Brannan JD, Adoni H, Daw L, Huang HC, Hurwitz M, Figurski D. Fraction exhaled NO in patients referred to pulmonary function laboratory (PFLAB) for mannitol challenge. Respirology. 2013;18:43.	Conference abstract
Brouwer A.F.J., Visser C.A.N., Duiverman E.J., Roorda R.J., Brand PLP. Is home spirometry useful in diagnosing asthma in children with nonspecific respiratory symptoms? Pediatr Pulmonol. 2010 April 2010;45(4):326–32.	Not FeNO
Ceng J, Jin XY. The diagnostic value of fractional exhaled nitricoxide test in patients with cough variant asthma. J Intern Med Concepts Prac. 2011;6:125–7.	Unable to locate
Chai J, Jiang P, Qian X. The value of exhaled nitric oxide in diagnosis of bronchial asthma. Zhong Guo Hu Xi Yu Jian Hu Za Zhi. 2010;04:81-4.	Unable to locate
Chancafe-Morgan J, Ramos-Quispe Y, Gomez-García R, Vargas-Espinal J, Puente-Maestú L. Validity of the fractional exhaled nitric oxide (FeNO) for identification of bronchial	Conference abstract

Citation	Primary reason for exclusion
hyperresponsiveness in a pulmonary function laboratory. Eur Respir J. 2013;42(Suppl. 57):P1273.	
Chen. 2017.	Unable to locate
Cirillo I, Ricciardolo FL, Medusei G, et al. Exhaled nitric oxide may predict bronchial hyperreactivity in patients with allergic rhinitis. Int Arch Allergy Immunol. 2013;160: 322–8.	Not target condition
El Halawani SM, Ly NT, Mahon RT, et al. Exhaled nitric oxide as a predictor of exercise-induced bronchoconstriction. Chest. 2003;124:639–43.	Not target condition
Fang S, Chen SY, He X, Shen QX, Fan HZ, Wu XP, et al. Evaluating the efficacy of fractional exhaled nitric oxide and impulse oscillometry in screening out cough variant asthma from patients with subacute cough. Zhonghua Yi Xue Za Zhi. 2017;97:2338–43.	Not available in English
Florentin A, Acouetey DS, Remen T, et al. Exhaled nitric oxide and screening for occupational asthma in two at-risk sectors: bakery and hairdressing. Int J Tuberc Lung Dis. 2014 Jun;18(6):744–50.	Not population of interest (occupational exposure)
Franklin PJ, Turner SW, Le Souef PN, Stick SM. Exhaled nitric oxide and asthma: complex interactions between atopy, airway responsiveness, and symptoms in a community population of children. Thorax. 2003;58:1048–52.	No outcomes of interest
Giovannini M, Valli M, Ribuffo V, et al. Relationship between methacholine challenge testing and exhaled nitric oxide in adult patients with suspected bronchial asthma. Eur Ann Allergy Clin Immunol. 2014;46:109–13.	No outcomes of interest
Glowacka E, Jedynak-Wasowicz U, Sanak M, Lis G. Exhaled eicosanoid profiles in children with atopic asthma and healthy controls. Pediatr Pulmonol. 2013;48: 324-35.	Not target condition
Hahn PY, Morgenthaler TI, Lim KG. Use of exhaled nitric oxide in predicting response to inhaled corticosteroids for chronic cough. Mayo Clin Proc. 2007;82:1350–5.	No outcomes of interest
Henriksen AH, Lingaas-Holmen T, Sue-Chu M, et al. Combined use of exhaled nitric oxide and airway hyperresponsiveness in characterizing asthma in a large population survey. Eur Respir J. 2000 May;15(5):849–55.	Not FeNO alone
Hsu JY, Wang CY, Cheng YW, Chou MC. Optimal value of fractional exhaled nitric oxide in inhaled corticosteroid treatment for patients with chronic cough of unknown cause. J Chin Med Assoc. 2013;76:15–19.	No outcomes of interest
Inoue T, Akashi K, Watanabe M, Ikeda Y, Ashi-zuka S, Motoki T, et al. Periostin as a biomarker for the diagnosis of pediatric asthma. Pediatr Allergy Immunol. 2016;27:521–6.	Not FeNO

Citation	Primary reason for exclusion
Ji XM, Wang KX, Chen JP, Zhou X, Wang DY, Zheng CH. Clinical significance of fractional exhaled nitric oxide test in children with chronic cough. China Modern Doctor. 2013;51:39–41.	Unable to locate
Jiang XB, Huang M, Yin KS, Zhu Y. Diagnostic value of fractional exhaled nitric oxide in non-typical bronchial asthma. Chin J Postgrad Med. 2012;35:17–19.	Unable to locate
Johnson B, Steenbruggen I, Graham BL, et al. Improving spirometry testing by understanding patient preferences. ERJ Open Res. 2021;7(1):712–2020.	Not FeNO
Kaplan AG. Chronic cough in adults: make the diagnosis and make a difference. Pulm Ther. 2019;5: 11–21.	Not relevant study design
Karrasch S, Linde K, Rücker G, et al. Accuracy of FeNO for diagnosing asthma: a systematic review. Thorax. 2017;72:109–16.	Systematic review, already considered
Korevaar DA, Westerhof GA, Wang J, et al. Diagnostic accuracy of minimally invasive markers for detection of airway eosinophilia in asthma: a systematic review and meta-analysis. Lancet Respir Med. 2015;3:290–300.	Systematic review, already considered
Lemiere C, D'Alpaos V, Chaboillez S, et al. Investigation of occupational asthma: sputum cell counts or exhaled nitric oxide? Chest. 2010 Mar;137(3):617–22.	Not population of interest (occupational exposure)
Lin G. The clinical diagnosis value of exhaled nitric oxide test in chronic cough. Chin Modern Med. 2013;20:42-5.	Unable to locate
Linkosalo L, Lehtimäki L, Holm K, et al. Relation of bronchial and alveolar nitric oxide to exercise-induced bronchoconstriction in atopic children and adolescents. Pediatr Allergy Immunol. 2012;23:360–6.	Not target condition
Liu N, Zhao D, Wu M. Exhaled nitric oxide measurement in diagnosis of bronchial asthma in children. Nan Jing Da Xue Xue Bao: Zi Ran Ke Xue edition. 2011;4:553-6.	Unable to locate
Mahut B, Peiffer C, Thibaudon M, Chevalier-Bidaud B, Defrance-Hutinet MF, Trinquart L, et al. What does a single exhaled nitric oxide measurement tell us in asthmatic children? J Asthma. 2009;46: 810–4.	No outcomes of interest
Malmberg LP, Pelkonen AS, Haahtela T, Turpeinen M. Exhaled nitric oxide rather than lung function distinguishes preschool children with probable asthma. Thorax. 2003;58:494–9.	Population (children < 5 years)
Maniscalco M, Faraone S, Sofia M, Molino A, Vatrella A, Zedda A. Extended analysis of exhaled and nasal nitric oxide for the evaluation of chronic cough. Respir Med. 2015;109:970–4.	Not target condition
Martin MJ, Wilson E, Gerrard-Tarpey W, et al. The utility of exhaled nitric oxide in patients with suspected asthma. Thorax. 2016 Jun;71(6):562–4.	Letter

Citation	Primary reason for exclusion
Mathew S, Cliff I, Agarwal S, Lim A, Allen M, Mustfa N. Relationship between exhaled nitric oxide and methacholine challenge test in suspected asthma. Am J Respir Crit Care Med. 2011;183. Available at: http://ajrccm.atsjournals.org/cgi/reprint/183/1_MeetingAbstracts/A5554?sid = 0209d9f3-c74d-409d-8e6e-81ebe76d2328.	Conference abstract
Munnik P, van der Lee I, Fijn J, et al. Comparison of FeNO and histamine hyperresponsiveness in diagnosing asthma in new referrals. Respir Med. 2010 Jun;104(6):801–7.	No outcomes of interest
Nayak, UB, Morakhia NV, Scharya VK, Srinivas L. A study of fraction of exhaled nitric oxide levels as a diagnostic marker in patients with bronchial asthma. Journal, Indian Academy of Clinical Medicine. 2013;14(2):123-7.	Unable to locate
Ni J, Cheng Q, Feng Y, Cao B, Cheng L, Wan H. Exhaled nitric oxide combined with relevant factors in the diagnosis of cough variant asthma. J Diagn Concepts Pract. 2014;13:606–9.	Unable to locate
Oh MJ, Lee JY, Lee BJ, Choi DC. Exhaled nitric oxide measurement is useful for the exclusion of nonasthmatic eosinophilic bronchitis in patients with chronic cough. Chest. 2008;134:990–5.	Not target condition
Pérez Tarazona S, Martínez Camacho RM, Alfonso Diego J, Escolano Serrano S, Talens Gandía J. Diagnostic value of exhaled nitric oxide measurement in mild asthma. An Pediatr (Barc). 2011;75(5):320–8.	Not available in English
Pizzimenti S, Heffler E, Piccioni P, Bugiani M, Migliore E, Guida G, et al. Usefulness of exhaled nitric oxide (FeNO) measured by a portable analyzer to diagnose cough variant asthma in a clinical setting of chronic cough. Allergy. 2009;64:395.	Conference abstract
Prieto L, Ferrer A, Ponce S, Palop J, Marin J. Exhaled nitric oxide measurement is not useful for predicting the response to inhaled corticosteroids in subjects with chronic cough. Chest. 2009;136:816–22.	No outcomes of interest
Qiu JP, Jin XY, Shen HY. Application of fractional exhaled nitric oxide and impulse oscillometry in patients with chronic cough. Int J Respir. 2012;32:1297-300.	Unable to locate
Raj D, Lodha R, Mukherjee A, Sethi T, Agrawal A, Kabra SK. Fractional exhaled nitric oxide in children with acute exacerbation of asthma. Indian Pediatr. 2014 Feb;51(2):105–11.	No outcomes of interest
Ramser M, Hammer J, Amacher A, et al. The value of exhaled nitric oxide in predicting bronchial hyperresponsiveness in children. J Asthma. 2008 Apr;45(3):191–5.	No outcomes of interest

Citation	Primary reason for exclusion
Ren XB, Liu CT, Huang YF, Zhu T. The diagnostic value of the fractional exhaled nitric oxide for asthma. Chin J Respir Crit Care Methods. 2009;8:322–6.	Unable to locate
Sastre J, Costa C, del Garcia Potro M, Aguado E, Mahillo I, Fernandez-Nieto M. Changes in exhaled nitric oxide after inhalation challenge with occupational agents. J Investig Allergol Clin Immunol. 2013; 23:421–7.	Not population of interest (occupational exposure)
Shimoda T, Obase Y, Kishikawa R, Iwanaga T, Miyatake A, Kasayama S. The fractional exhaled nitric oxide and serum high sensitivity C-reactive protein levels in cough variant asthma and typical bronchial asthma. Allergol Int. 2013;62:251–7.	No outcomes of interest
Seo Yeon Y, Yoon Hee K, Min Kwang B, Hyung Jung K, Chul Min A, Seong Han K, et al. Repeated fractional exhaled nitric oxide measurements is not essential for asthma screening. J Investig Allergol Clin Immunol. 2017.	Unable to locate
Shen X, Chen C, Zhou N, Huang J, Xiuqin Z. Feasibility study of fractional exhaled nitric oxide in the diagnosis of cough variant asthma. Int J Respir 2015; 35:329-32.	Unable to locate
Singer F, Luchsinger I, Inci D, Knauer N, Latzin P, Wildhaber JH, et al. Exhaled nitric oxide in symptomatic children at preschool age predicts later asthma. Allergy. 2013 Apr;68(4):531–8.	Not population of interest (includes children < 5 years)
Visitsunthorn N, Mahawichit N, Maneechotesuwan K. Association between levels of fractional exhaled nitric oxide and asthma exacerbations in Thai children. Respirology. 2017 Jan;22(1):71–7.	No outcomes of interest
Xu YL, Ma XT, Yang ZG. Fractional exhaled nitric oxide in the diagnosis of bronchial asthma. Henan Med Res. 2014;23:23–5.	Unable to locate
Yang YJ, Zheng XW, Yang GL. Study on the diagnostic value of fractional exhaled nitric oxide in bronchial asthma. Ningxia Med J. 2013;35:835–7.	Unable to locate
Yao HJ, Zhang RM, Li ZK. Fractional exhaled nitric oxide in diagnosis of bronchial asthma. Int J Respir. 2013;33:508–12. Abstract available at: https://www.oriprobe.com/journals/gwyx-hxxt/2013_7.html	Unable to locate full article
Ye L, Gong Y, Tong YY, Jin ML. The etiological diagnosis value of fractional exhaled nitric oxide test in patients with chronic cough. J Clin Intern Med 2010;27:601–602.	Unable to locate
Yi F, Chen R, Luo W, Xu D, Han L, Liu B, et al. Validity of fractional exhaled nitric oxide in diagnosis of corticosteroid-responsive cough. Chest. 2016;149:1042–51.	Not target condition

Citation	Primary reason for exclusion
Zetterquist W, Marteus H, Hedlin G, Alving K. Increased exhaled nitrite in children with allergic asthma is not related to nitric oxide formation. Clin Respir J. 2008;2:166–74.	No outcomes of interest
Zhang YM, Lin JT, Su N, et al. Values of fractional exhaled nitric oxide in the diagnosis of chronic cough. Chung Hua I Hsueh Tsa Chih. 2011;91:1254–8.	Not available in English
Zhu H, Yu X, Hao C, Wang Y, Yang X, Lu Y, et al. The diagnostic value of the fractional exhaled nitric oxide for cough variant asthma in children. Zhonghua Jie He He Hu Xi Za Zhi. 38(5):352–5.	Not available in English
Zhu N, He J, Chen XD. Diagnostic value of fractional exhaled nitric oxide in the diagnosis of cough variant asthma. J Clin Pulm Med. 2014;19:1628–31.	Not available in English

Appendix 8: Results of Applicability Checklist for Studies Included in the Economic Literature Review

Table A8. Assessment of the Applicability of Studies Evaluating the Cost-Effectiveness of FeNO

Author, year, country	Is the study population similar to the question?	Are the interventions similar to the question?	Is the health care system studied sufficiently similar to Ontario?	Were the perspectives clearly stated? If yes, what were they?	Are all direct effects included? Are all other effects included where they are material?	Are all future costs and outcomes discounted? If yes, at what rate?	Is the value of health effects expressed in terms of quality-adjusted life-years?	Are costs and outcomes from other sectors fully and appropriately measured and valued?	Overall judgment[a]
Berg et al, 2008,[116] Germany	Yes	Yes	Partially	Yes, health care payer		No	Partially	No	Partially applicable
Brooks et al, 2018,[117] United States	Yes	Yes	Partially	Yes, health care payer	No	NA	Yes	No	Partially applicable
Buendia et al, 2021,[118] Colombia	Yes	Yes	No	Yes, societal	No	NA	Yes	Partially	Partially applicable
Darba et al, 2021,[119] Sweden	Yes	Yes	Partially	Yes, health care payer	No	NA	No	No	Not applicable
Harnan et al, 2015,[110] United Kingdom	Yes	Yes	Partially	Yes, UK health care payer	Yes	Yes, 3.5%	Yes	No	Partially applicable
Price et al, 2009,[120] United Kingdom	Yes	Yes	Partially	Yes, health care payer	No	No	Partially	No	Partially applicable
Sabatelli et al, 2017,[121] Spain	Yes	Yes	No	Yes, health care payer	No	Yes	Yes	Partially	Partially applicable

Note: Response options for all items were "yes," "partially," "no," "unclear," and "NA" (not applicable).

[a]Overall judgment may be "directly applicable," "partially applicable," or "not applicable."

Appendix 9: Input Parameters for Budget Impact Analysis

Size of the General Population, by Age

We obtained the current size of the Ontario general population by age group from Statistics Canada. The average increase in population was around 1.5% per year between 2018 and 2022,[156] and we conservatively assumed that this increase would remain the same for the next 5 years (2023–2027). The projected population size by aged group is presented in Table A9.

Table A9: Projected General Population by Age Groups in Ontario, 2023–2027

Population of Interest	2023[a]	2024[a]	2025[a]	2026[a]	2027[a]
5–9	780,217	791,540	803,026	814,680	826,502
10–14	815,560	827,395	839,402	851,583	863,941
15–19	862,128	874,639	887,332	900,208	913,272
20–29	2,214,916	2,247,058	2,279,667	2,312,748	2,346,311
30–39	2,177,100	2,208,693	2,240,745	2,273,262	2,306,251
40–49	1,900,912	1,928,498	1,956,483	1,984,875	2,013,679
50–59	2,018,884	2,048,182	2,077,905	2,108,059	2,138,650
60–69	1,887,285	1,914,673	1,942,458	1,970,647	1,999,244
70+	1,946,657	1,974,907	2,003,566	2,032,641	2,062,138
Total	**14,603,659**	**14,815,584**	**15,030,584**	**15,248,704**	**15,469,989**

[a]Results may appear inexact due to rounding.

Asthma Incidence and Prevalence

Asthma incidence was estimated to reduce by 3.99 per 1,000 Ontario population per year between 2014 and 2018.[130] We assumed that, with the impact of asthma diagnosis and management measures, this reduction will continue at the same rate for all age groups over the time horizon of our models. The projected asthma incidence rate between 2023 and 2027, stratified by age-specific groups, is presented Table A10.

Asthma prevalence was estimated to increase by 3.90 per 1,000 Ontario population per year between 2014 and 2018.[130] This number suggests that more people are living with asthma for longer. In our reference case analysis, we assumed the increase in asthma prevalence would continue at the same rate for the next few years for all age groups. The projected asthma prevalence between 2023 and 2027 stratified by age-specific groups is presented Table 50.

Table A10: Projected Asthma Incidence per 1,000 Ontario Population

Population	2023	2024	2025	2026	2027
5–9 years	5.87	5.63	5.41	5.19	4.99
10–14 years	3.29	3.16	3.03	2.91	2.79
15–19 years	1.73	1.66	1.59	1.53	1.47
20–29 years	1.35	1.29	1.24	1.19	1.14
30–39 years	1.56	1.50	1.44	1.38	1.32
40–49 years	1.64	1.57	1.51	1.45	1.39
50–59 years	1.75	1.68	1.61	1.55	1.48
60–69 years	2.16	2.08	1.99	1.91	1.84
≥ 70 year	2.36	2.26	2.17	2.09	2.00

Appendix 10: Letter of Information

LETTER OF INFORMATION

Ontario Health

Ontario Health is conducting a review of **Fractional Exhaled Nitric Oxide (FeNO) testing for the diagnosis and the management of asthma in both adults and children.** The purpose is to better understand how this technique can be publicly funded in Ontario.
An important part of this review involves gathering perspectives of patients and caregivers of those who have been diagnosed and/or managed with asthma and who may or may not have used FeNO testing.

WHAT DO YOU NEED FROM ME

- ✓ Willingness to share your story
- ✓ 30-40 minutes of your time for a phone interview
- ✓ Permission to audio- (not video-) record the interview

What Your Participation Involves

If you agree to share your experiences, you will be asked to have an interview with Ontario Health (OH) staff. OH staff will contact interested participants by collecting contact information (i.e., email address and/or phone number) to set up an interview. The interview will last about 30-40 minutes. It will be held over the telephone. With your permission, the interview will be audio-taped. The interviewer will ask you questions about you or your loved one's condition and your perspectives about asthma diagnosis and treatment options in Ontario. Participation is voluntary. You may refuse to participate, refuse to answer any questions or withdraw before or at any point during your interview. Withdrawal will in no way affect the care you receive.

Confidentiality

All information you share will be kept confidential and your privacy will be protected except as required by law. The results of this review will be published, however no identifying information will be released or published. Any records containing information from your interview will be stored securely until project completion. After completion of the project, the records will be destroyed. If you are sending us personal information by email, please be aware that electronic communication is not always secure and can be vulnerable to interception.

Ontario Health is designated an "institution" by the *Freedom of Information and Protection of Privacy Act* (FIPPA) and is collecting your personal information pursuant to FIPPA and the *Connecting Care Act, 2019* to support the Health Technology Assessment Program. If you have any questions regarding Ontario Health's collection and use of personal information for the purposes of this program, please contact Team Lead, Jigna Mistry noted below.

Risks to participation

There are no known physical risks to participating. Some participants may experience discomfort or anxiety after speaking about their experience.

If you are interested, please contact us:

Jigna Mistry
Team Lead, Clinical Institutes and Quality Programs
Tel: 1-647-953-0598
Email: Jigna.Mistry@ontariohealth.ca

Appendix 11: Interview Guide

FeNO Interview Guide

Lived- Experience
Health care journey involving development of symptoms up to diagnosis
-symptoms, triggers
-understanding and control over symptoms
-avoidance of activities that may trigger
-mental health

Diagnosis
Diagnosis process

Terminology around testing*

Experience getting testing
- off medication testing
Information
Access/barriers?
Impact of FeNO (if applicable)

Asthma
Treatments/management
Monitoring asthma
- How often to follow-up
  - Value in follow-up
- primary care vs respirologist
- checklist questions vs FENO testing

Medication adherence
- Barriers to treatment
- Concerns of over/under treatment

Cost of medication
Ongoing information
Impact of FeNO (if applicable)

FeNO
Awareness of FeNO testing
Potential Impact of FeNO testing
Any equity/ethical concerns? (theoretically)

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We are an agency created by the Government of Ontario to connect, coordinate, and modernize our province's health care system. We work with partners, providers, and patients to make the health system more efficient so everyone in Ontario has an opportunity for better health and well-being.

Equity, Inclusion, Diversity and Anti-Racism

Ontario Health is committed to advancing equity, inclusion and diversity and addressing racism in the health care system. As part of this work, Ontario Health has developed an Equity, Inclusion, Diversity and Anti-Racism Framework, which builds on existing legislated commitments and relationships and recognizes the need for an intersectional approach.

Unlike the notion of equality, equity is not about sameness of treatment. It denotes fairness and justice in process and in results. Equitable outcomes often require differential treatment and resource redistribution to achieve a level playing field among all individuals and communities. This requires recognizing and addressing barriers to opportunities for all to thrive in our society.

For more information about Ontario Health, visit OntarioHealth.ca.

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