

Journal Pre-proof

Cost-effectiveness of implementing objective diagnostic verification of asthma in the United States

Mohsen Yaghoubi, PhD, Amin Adibi, MSc, Zafar Zafari, PhD, J Mark FitzGerald, MD, Shawn D. Aaron, MD, Kate M. Johnson, MSc, Mohsen Sadatsafavi, MD, PhD



PII: S0091-6749(19)31634-3

DOI: <https://doi.org/10.1016/j.jaci.2019.11.038>

Reference: YMAI 14299

To appear in: *Journal of Allergy and Clinical Immunology*

Received Date: 25 July 2019

Revised Date: 31 October 2019

Accepted Date: 26 November 2019

Please cite this article as: Yaghoubi M, Adibi A, Zafari Z, FitzGerald JM, Aaron SD, Johnson KM, Sadatsafavi M, Cost-effectiveness of implementing objective diagnostic verification of asthma in the United States, *Journal of Allergy and Clinical Immunology* (2020), doi: <https://doi.org/10.1016/j.jaci.2019.11.038>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2019 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology.

Cost-effectiveness of implementing objective diagnostic verification of asthma in the United States

Mohsen Yaghoubi, PhD¹; Amin Adibi, MSc¹; Zafar Zafari, PhD²; J Mark FitzGerald, MD³; Shawn D. Aaron, MD⁴; Kate M. Johnson, MSc¹; Mohsen Sadatsafavi, MD, PhD^{1,3}

Affiliations:

1. Respiratory Evaluation Sciences Program, Collaboration for Outcomes Research and Evaluation, Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, Canada
2. Pharmaceutical Health Services Research at University of Maryland School of Pharmacy, Baltimore, Maryland, United States
3. Institute for Heart and Lung Health, Department of Medicine, University of British Columbia, Vancouver, Canada
4. The Ottawa Hospital Research Institute, University of Ottawa, Ottawa, Canada

Corresponding Author:

Mohsen Sadatsafavi, MD, PhD
Associate Professor, Faculty of Pharmaceutical Sciences
Associate, Division of Respiratory Medicine
University of British Columbia
msafavi@mail.ubc.ca
<http://resp.core.ubc.ca/team/msafavi>

Authors' contribution: MS and JMF conceived the study question. MY developed the analytic plan, performed the literature review, and conducted the analyses. MS, SH and BF supervised the study progress and provided regular feedback. AA and ZZ contributed to the study design and KJ performed part of the statistical analyses. MY wrote the first draft of the manuscript. All authors critically revised the manuscript and approved the final copy.

Sources of support: This study was funded by an independent research contract by MethaPharm Inc. (Brantford, Ontario, Canada). The sponsor is aware of the content of the submitted material but neither played any role nor exerted any influence in the design of the study, conduct of the research, or reporting of the results.

Conflict of Interest statement: The authors declare no relevant conflicts of interest.

Abstract

Background

Asthma diagnosis in the community is often made without objective testing.

Objective

The aim of this study was to evaluate the cost-effectiveness of implementing a stepwise objective diagnostic verification algorithm among patients with community-diagnosed asthma in the United States (US).

Methods

We developed a probabilistic time-in-state cohort model that compared a stepwise asthma verification algorithm based on spirometry and methacholine challenge test against the current standard of care over 20 years. Model input parameters were informed from the literature and with original data analyses when required. The target population was US adults (≥ 15 y/o) with physician-diagnosed asthma. The final outcomes were costs (in 2018 \$) and quality-adjusted life years (QALYs), discounted at 3% annually. Deterministic and probabilistic analyses were undertaken to examine the effect of alternative assumptions and uncertainty in model parameters on the results.

Results

In a simulated cohort of 10,000 adults with diagnosed asthma, the stepwise algorithm resulted in the removal of diagnosis in 3,366. This was projected to be associated with savings of \$36.26 million in direct costs and a gain of 4,049.28 QALYs over 20 years. Extrapolating these results to the US population indicated an undiscounted potential savings of \$56.48 billion over 20 years. Results were robust against alternative assumptions and plausible changes in values of input parameters.

Conclusion

Implementation of a simple diagnostic testing algorithm to verify asthma diagnosis might result in substantial savings and improvement in patients' quality of life.

Key Messages

- Compared with current standards of practice, the implementation of an asthma verification algorithm among US adults with diagnosed asthma can be associated with reduction in costs and gain in quality of life.
- There is substantial room for improving patient care and outcomes through promoting objective asthma diagnosis.

Capsule summary

Asthma ‘overdiagnosis’ is common among US adults. An objective, stepwise verification algorithm for re-evaluation of asthma diagnosis can result in substantial savings in costs and improvements in quality of life.

Key words: Asthma, Cost-effectiveness analysis, Diagnosis, Medical test.

Abbreviations

ACT: Asthma Control Test
FEV₁: Forced Expiratory Volume
GBD: Global Burden of Disease
GINA: Global Initiative for Asthma
ICER: Incremental Cost Effectiveness Ratio
ICS: Inhaled Corticosteroids
LTRA: Leukotriene receptor antagonist therapy
MCT: Methacholine Challenge Test (Bronchoprovocation Test)
OR: Odds Ratio
PC20: The concentration of methacholine needed to produce a 20% fall in FEV₁
QALY: Quality Adjusted Life Year
US: United States

Introduction

Asthma is a common chronic respiratory disease, globally and in the United States (US)¹. According to the US Centers for Disease Control and Prevention, asthma prevalence continues to rise; the age-standardized prevalence increased by 1.5% per year since 2001, reaching 8.4% in 2010². There are approximately 11 million patients with physician-diagnosed asthma in the US³, and total costs of asthma in the US was estimated to be \$81.9 billion in 2013⁴. The annual incremental direct medical costs of adult asthma were reported to be \$3,266 per patient per year (in 2016 \$)⁴.

Evidence-based guidelines recommend that the diagnosis of asthma be made based on objective testing for reversible airflow obstruction or variability in lung function⁵. In some patients spirometry testing may be inconclusive; such patients may require provocative testing to document the presence of airway hyper-responsiveness. In reality, for many Americans, the diagnosis of asthma is made on clinical grounds alone^{6,7}. This approach can be inaccurate and can result in labelling individuals with asthma who otherwise have occasional respiratory symptoms without airflow obstruction. In addition, many asthma patients experience spontaneous clinical remission⁸. While the underlying inflammatory process can remain active, such patients may not experience symptoms of asthma for long periods of time even if they discontinue their therapies⁹⁻¹¹. Due to these factors, a significant proportion of asthma patients in the community might be inappropriately treated. In a multicenter, population-based prospective Canadian cohort study, Aaron et al followed 613 participants who reported a physician diagnosis of asthma within the previous five years and applied an objective algorithm to verify the existing asthma diagnosis. They found that more than 30% of participants could have their current diagnosis of asthma ruled out and safely discontinue their medications¹⁰.

Extrapolating these figures to the US indicates that there are potentially more than 3 million adults with an over-diagnosis of asthma. As such, the economic burden of over-diagnosed asthma warrants attention. Medication costs are the largest component of the direct economic burden of asthma, contributing to over half of the disease-related costs⁴. Patients with misdiagnosed asthma will incur these costs without gaining benefit, and are subject to harm due to the adverse effects of therapy as well as the lost opportunity to appropriately treat other health conditions that might be responsible for their symptoms.

In this context, a pressing public health question is whether a secondary verification of asthma diagnosis can be considered an efficient use of healthcare resources. A previous study on the economic impact of asthma screening strategies was limited to assessing asthma-related cost savings from implementing a secondary screening program in Canada¹². This study did not evaluate the effects on health outcomes, such as asthma control and quality of life.

The purpose of the current study was to evaluate the cost-effectiveness of objective diagnostic testing for asthma among previously diagnosed adults in the US. We calculated the incremental average costs and quality-adjusted life years (QALYs) associated with the implementation of objective diagnostic testing. We extrapolated the results to the entire US adult asthma population to evaluate the population-level impact of implementing such a strategy.

Methods

In reporting on the study's methodology and results we followed the Consolidated Health Economic Evaluation Reporting Standards¹³. The target population for this cost-effectiveness analysis was US adults (≥ 15 y/o) with self-reported physician-diagnosed asthma. The diagnostic verification was assumed to be conducted during routine outpatient encounters (e.g., during a scheduled follow-up visit). The main outcomes of the analysis were the incremental costs and QALYs associated with the use of diagnostic verification, compared with the current standard of care (*status quo*: no further verification of diagnosed asthma). We adopted a third-party payer's perspective (e.g., a Health Maintenance Organization) in the main analysis, and a societal perspective in a secondary analysis. The time horizon was 20 years, and costs and QALYs were discounted at the rate of 3% based on recommendations of the US Panel on Cost Effectiveness in Health and Medicine¹⁴.

The intervention

The comparator, the *status quo*, was the continuation of asthma management without any further evaluation of diagnosis. The intervention was defined as a two-stage diagnostic verification algorithm, as illustrated in **Figure 1**. In accordance with care standards set by the Global Initiative for Asthma (GINA)¹⁵, the first step is spirometry with reversibility testing before and after inhaled

bronchodilation. Asthma is verified in this step if the forced expiratory volume in the first second of expiration (FEV₁) improves by at least 12% and by 200 millilitres¹⁵. Those who do not exhibit reversible airflow obstruction undergo a single methacholine challenge test (MCT) at a second visit. Individuals whose FEV₁ decreases by 20% or more after breathing up to 8 mg/ml of methacholine (in a stepwise fashion based on doubling the methacholine dose) are considered to have their asthma confirmed. Individuals whose MCT is negative are considered to have their asthma ruled out and it was assumed that their asthma-related medications could be tapered off. The use of one MCT, as opposed to up to three MCTs implemented in the research context, was considered to be the most realistic scenario for clinical practice.

Modeling approach

We constructed a decision tree to model the diagnostic steps, and a time-in-state model to follow individuals at terminal branches of the tree over the analysis' time horizon in annual cycles. The model stratified US adult (≥ 15 years old) with diagnosed asthma into age (with 5-year intervals) and sex groups. A schematic illustration of the decision tree, with point estimates of branch probabilities, is provided in **Figure 2**. The major input parameters for the model are provided in **Table 1**.

The proportion of individuals at each branch of the decision tree was directly taken from the population-based study by Aaron et al¹⁰. In the *status quo* scenario, 33% of individuals were assumed not to have asthma. These are the individuals who responded negatively to spirometry and three subsequent MCTs in the above-mentioned study. Given that there will be no verification of diagnosis, these individuals remained 'over-diagnosed' throughout the time horizon of the study (and as such continued to be treated for asthma) under the *status quo* strategy.

In the diagnostic verification scenario, 15% of patients will have their asthma confirmed through a positive spirometry; of the remaining, 48% will have their asthma confirmed through a positive MCT. A diagnosis of asthma in individuals with a negative spirometry and a negative MCT will be considered to have been ruled out and these individuals will be advised to taper their medications. In the study by Aaron et al, in 10% of such individuals the asthma diagnosis was later confirmed with a positive second or third MCT, after tapering of controller medications (**Table 1** – section 1.1). This figure is similar to the study by Luks et al¹⁶(9%) and reflects imperfect sensitivity of MCT especially when the

patient is receiving asthma medications^{16,17}. Given that only one MCT is modeled in the diagnostic verification scenario in the present study, such individuals constitute the ‘false negative’ subgroup (those in whom an asthma diagnosis was erroneously reversed), with the rest of individuals under this branch of the decision tree constituting the ‘true negative’ subgroup (**Figure 2**). Compared to their counterparts in the *status quo* scenario, individuals in the false negative asthma subgroup will cease their controller medication, and as such will generally have worse asthma control.

Modeling asthma status over time

At terminal branches of the decision tree, each of these sub-populations was linked to its corresponding time-in-state model. Such models simulated the transition of a sex- and age-stratified population across mutually exclusive health states. For individuals with either true asthma or misdiagnosed asthma (true positive and false negative subgroups in **Figure 2**), the model contained three states pertaining to the three levels of asthma control were assigned, in addition to a state representing death. The distribution of levels of asthma control within a given sex and age group was derived using calibration techniques from a recent study based on US National Health and Wellness Survey, as described in our previous work^{18,19} (see distribution of asthma control in **Online Repository Materials - Section A**). The levels of asthma control were defined based on the asthma control test (ACT). This test classifies a patient’s asthma status into “poorly controlled” (scores ≤ 15), “not well controlled” (score 16-19), and “well controlled” (score 20-25)²⁰. In addition to asthma control, we modeled asthma exacerbations for individuals with true asthma as an event that are likely to be affected by controller therapy (see modeling asthma exacerbation in **Online Repository Materials - Section B**). On the other hand, in the subgroup with true negative and false positive asthma, the model consisted of only two states of “alive” and “dead”. Aside from mortality due to severe exacerbations, the probability of transitioning to death for all populations was equal to the age- and sex-specific background mortality rates, derived from the US life tables²¹.

It is likely that the degree of airway reactivity is an independent determinant of asthma control. As such, the distribution of asthma control levels can be different among individuals whose asthma can be confirmed using spirometry, those whose asthma verification requires an MCT, and those who have asthma but do not display reversibility or have a positive MCT. To elucidate such potential

differences, we used data from the Economic Burden of Asthma (EBA) study²². This longitudinal study used population-based sampling and followed 622 adult individuals with physician-diagnosed asthma over one year. Asthma status was verified with one pre- and post-bronchodilator spirometry and one MCT (similar to the protocol evaluated in this study). Asthma control was verified during baseline and each of the three-monthly visits. Using these data, we constructed a generalized linear model (with multinomial distribution and cumulative logit link) to estimate the odds ratio (OR) of having controlled asthma compared with uncontrolled asthma, as well as having partially controlled asthma compared with uncontrolled asthma, among the three-mentioned groups. The exposure was asthma verification status (response to spirometry, response to MCT, no response to spirometry and MCT). The model was adjusted for sex, age at baseline, and whether the individual used any controller medication in the 12 months before the study began (see **Online Repository Materials-Section C** and **Table 1** – section 1.2 for distribution of asthma control).

Modeling asthma treatment

A major benefit of the objective diagnostic verification would be the removal of asthma therapies in patients who do not need them. We modeled the utilization and short-term effects of inhaled corticosteroids (ICS) and leukotriene receptor antagonists (LTRA), namely in terms of improving asthma control and reducing exacerbation rates. We assumed that 51% of diagnosed asthma patients are on maintenance ICS therapy at any given time²³, while an additional 5% are on LTRAs²⁴. The use of reliever (rescue) medication was not directly modeled as their costs are embedded within the costs assigned to each control level, and it was assumed their usage will not have any direct impact on asthma control. To model the association between the use of controller medications and asthma control, we used the indirect evidence on the effect of ICS or LTRA use and asthma exacerbations, as performed in our previous modeling study^{23,25,26}. We did not include the longer-term adverse events associated with controller medications, but in a sensitivity analysis modeled the increased risk of acute pneumonia as an adverse effect of ICS²⁷.

Costs

Details on the cost parameters are provided in **Table 1** – section 1.3. In the base case analysis, costs included the cost of stepwise asthma verification testing, controller medication costs, direct asthma-attributable costs across levels of control, and direct medical costs resulting from asthma exacerbations. The costs of spirometry testing and MCT were derived from American Thoracic Society Coding and Billing Quarterly²⁸ for hospital-based lung function testing. In the intervention scenario, we assumed that interpreting the results of spirometry and MCT will each require one additional physician visit. The costs of office-based physician visit were derived from the Medical Expenditure Panel Survey (MEPS) based on average expenses per visit, assuming the mixture of general practitioner and specialist visits as observed in the MEPS data²⁹. In a sensitivity analysis, we varied this costs across the entire range of speciality types to cover scenarios that are based on general practitioner or specialist management only. Annual per-person direct medical costs of asthma (including healthcare provider visits, emergency visits, hospitalizations, and medication use) across levels of control (not including exacerbation costs or costs of controller use, as they were explicitly modeled) were derived from our previous work¹⁹. Costs of exacerbations were obtained from the literature^{30,31}.

All costs were adjusted to 2018 USD (\$) using historical inflation rates³². In the base case analysis we excluded indirect costs based on the recommendation of the US Panel on Cost-Effectiveness in Health and Medicine¹⁴. In a scenario analysis, we adopted a societal perspective and included costs due to asthma-related productivity loss (indirect costs). Indirect costs due to sub-optimal asthma control were derived from multiple sources^{19,33,34}. These included costs due to total cessation of work as well as loss of work time. Indirect costs per level of control included loss of productivity due to exacerbations. We did not include in the base case analysis the costs of work-up required for alternative diagnoses when asthma diagnosis was reversed. However, in a sensitivity analysis, we considered the first-year costs of six common and major alternative diagnoses as reported by Aaron et al¹⁰. These costs were derived from a dedicated analysis of 2017 MEPS data (details are provided in **Online Repository Materials - section D**).

Health State Utility Values

The health state utility values (utilities) associated with asthma across levels of control were derived from a study conducted on 2011–2013 US National Health and Wellness Survey¹⁸. We assigned US-specific general population utilities to individuals whose asthma was ruled out³⁵. Utilities associated with different severities of exacerbation were derived from previous studies^{30,31,36} (**Table 1** – section 1.3).

Analysis

In the base case analysis, we ran the model separately in the intervention and *status quo* scenarios and estimated total discounted costs and QALYs over the 20-year time horizon. We standardized the results such that they pertain to the outcome of a hypothetical cohort of 10,000 representative individuals.

Deterministic sensitivity and scenario analyses were conducted to investigate the impact of key parameter values and assumptions on the base case results. In addition, we performed two threshold analyses, one on the prevalence of asthma overdiagnosis, and another on the first-year diagnostic and management costs of alternative diagnoses. These analyses identified the critical value of their respective parameters around which the overall findings on the cost-effectiveness of the intervention would change. To fully account for uncertainty in all parameters, probabilistic sensitivity analyses were conducted through Monte Carlo simulations. Uncertainty in each of the underlying parameters was characterized by assigning a probability distribution to the parameter, and the model was run 10,000 times; within each run a new random value from each distribution was drawn and results were recalculated. Cost-effectiveness was assessed by using willingness-to-pay (WTP) thresholds of \$50,000/QALY.

Furthermore, we extrapolated the result to the entire US asthma population, using the general methodology as described in our recent work estimating the burden of uncontrolled asthma in the US¹⁹. In summary, projections of US population by state were derived from the Census Bureau - Population Division³⁷. The prevalence of physician-diagnosed asthma stratified by age and sex was

obtained from the Global Burden of Disease studies³ (**Online Repository Materials - Section E, Tables E2 & E3**). The baseline year was 2019 and cumulative projections were made to 2038 (20 years).

Results

Table 2 provides the results of base case analysis for a cohort of 10,000 adults with physician-diagnosed asthma under the diagnostic verification versus *status quo* scenarios. In the diagnostic verification scenario, in 1,500 patients asthma diagnosis will be confirmed through spirometry alone. Among the 8,500 that will undergo a subsequent MCT, asthma diagnosis will be confirmed in 4,760. Asthma will be ruled out in the remaining 3,740 patients in whom spirometry and MCT will be negative. Among these, in 374 the asthma diagnosis will be erroneously reversed. The total costs of spirometry and MCT in the diagnostic verification scenario will be \$2,480,000 and \$3,774,000, respectively.

Total patient-years on asthma controller medications will be 62,906 in the diagnostic verification and 98,402 in the *status quo* scenario. Total savings in medication costs will be \$49.85 million. Under the diagnostic verification scenario, there will be an extra 3,314 patient-years with uncontrolled asthma compared with the *status quo*, and as a result there will be 1,595 more exacerbations. Combining these results, for the diagnostic verification scenario, total discounted costs and QALYs will be \$279.06 million and 105,324, respectively. The corresponding values for the *status quo* scenario will be \$315.32 million and 101,275. As such, the implementation of the objective asthma verification algorithm will be associated with \$36.26 million reduction in direct costs and a gain of 4,049 in QALYs, compared with the *status quo* over the next 20 years.

Sensitivity and scenario analyses

Figure 3 depicts change in incremental costs for different analyses. Diagnostic verification remained cost-saving in all one-way sensitivity analyses. **Table 3** presents the results of scenario analyses. Again, the overall conclusion remained the same when several alternative assumptions were explored. The threshold analysis indicated that when the proportion of falsely diagnosed to overall asthma was 6% or lower (compared with 33% in the main analysis), the diagnostic verification was no longer cost-

saving. As well, the first-year costs of major alternative diagnoses had to be at least 3 times higher than their original estimates for the diagnostic intervention not to be cost-saving. The inclusion of indirect costs only slightly reduced the difference in costs between the two strategies, and diagnostic intervention remained dominant. Results of the probabilistic sensitivity analysis are provided in **Figure 4**. In >99% of all simulations, the intervention remained dominant.

Extrapolating the results to the entire US population

In 2019, there will be 15.55 million adolescents and adults with asthma in the US; this value will increase by 13% by 2038. After the implementation of diagnostic verification algorithm, during the 2018–2038 period a diagnosis of asthma will be reversed in 70.29 million individuals. The total undiscounted cost saving in the intervention scenario versus *status quo* will be \$56.48 billion, and there will be a cumulative gain in QALYs of 6.14 million (see analysis by year for the entire US population in **Online Repository Materials-Section E and Table E3**).

Discussion

Our results indicate that the implementation of a stepwise diagnostic verification algorithm at point of care among US adults with a self-reported diagnosis of asthma might be associated with significant savings in costs and improvements in quality of life over twenty years. In the main analysis as well as the sensitivity and scenario analyses, this strategy was dominant against the strategy of continuing asthma management; i.e., it was associated with reduced costs and improvements in quality of life. Extrapolating these results to the entire US population suggested that over 20 years, there could be a saving of \$40.51 billion in direct asthma-related medical costs.

These results are despite the fact that our modeling approach was based on several conservative assumptions against diagnostic verification. For one, in patients whose asthma is ruled out, the possible causes of underlying symptoms are more likely to be verified. As such, it is likely that there will be benefits to patients and reductions in costs due to the proper management of the underlying disease. In the study by Aaron et al., more than 50% of patients whose asthma was ruled out were ultimately diagnosed with other conditions. The most common alternative diagnoses were allergic

rhinitis, gastro-esophageal reflux disease, anxiety disorders, acute bronchitis, Chronic Obstructive Pulmonary Disease, and Ischemic heart disease. To some extent, the overall efficiency of the asthma verification algorithms is influenced by the efficiency of management of these conditions. It is likely that the additional costs of diagnostic workup and disease management will be offset by better outcomes and increase in quality of life under proper treatment of such conditions. In a sensitivity analysis that explored this aspect, asthma verification test remained cost-saving by incorporating the first-year costs of diagnostic and management of the six most common alternative diagnoses (a finding that remained valid when the prevalence of such conditions were assumed to be up to three times higher than their original values).

Further, we assumed that in around 4 % of individuals asthma will be ruled out incorrectly due to the imperfect sensitivity of spirometry and a single MCT. In such individuals we assumed that controller medications will be discontinued and as result asthma control status will deteriorate. This results in reduced quality of life and a higher rate of exacerbations that will last throughout the time horizon of the study. However, in reality it is likely that the intensification of symptoms and occurrence of exacerbations upon treatment withdrawal will result in further assessments and a re-establishment of the diagnosis. When we modeled this aspect in a sensitivity analysis, the diagnostic intervention scenario was even more cost-saving.

We are aware of one previous economic evaluation of secondary verification of asthma³⁸. In the study by Pakhale et al, which was performed in the Canadian context, implementation of an asthma verification algorithm was associated with an average cost savings of \$35,141 per 100 screened individuals. The main source of cost saving was medication costs but the authors did not consider the impact of diagnostic verification and subsequent medication changes on asthma control, exacerbations, and quality of life.

The strengths of our study includes its reliance on hierarchy of evidence in estimating model parameters, considering multiple sources of evidence about the burden of uncontrolled asthma and the association between asthma control, treatment, resource use, and quality of life. Nuanced modeling of asthma control over time and how it is affected by diagnostic verification and changes in treatments further enhances the generalizability of our results compared with previous evidence. The

incorporation of uncertainty in model inputs and assumptions into the results should provide reassurance that the overall findings are not materially affected by uncertain evidence.

The limitations of our study should also be acknowledged. The main source of evidence on the rate of asthma overdiagnosis was a Canadian study¹⁰. We could not find any US-based study, but a recent systematic review on this topic reported that studies across different jurisdictions have consistently reported an overdiagnosis rate between 29%-34%³⁹. Our threshold analysis also indicated that overdiagnosis rate in the US should be implausibly low for the diagnostic verification not to be cost-saving. We assumed that diagnostic verification will take place in the context of routine clinical practice, as such our results do not pertain to alternative schemes such as a systematic screening program. As well, a strict adherence to the diagnostic verification algorithm might not be achieved in the real world. For example, if the spirometry fails to establish the diagnosis, the physician might decide on a trial of medication cessation and re-evaluation of symptom burden before embarking on the assessment of airway hyperresponsiveness. Such departures from the verification protocol will inevitably affect the cost-effectiveness of diagnostic verification. Furthermore, in extrapolating the results to the entire US, we assumed immediate uptake of the diagnostic verification algorithm while in reality there will be gradual adoption of such a program and imperfect implementation. We did not consider alternative diagnostic strategies such as using the measurement of exhaled nitric oxide as the data for such a diagnostic strategy is less robust. Finally, changes in risk factors as well as future innovations in asthma diagnosis and care can impact the efficiency of the proposed intervention.

There are several opportunities for future research in this area. We evaluated the implementation of objective diagnostic verification in patients with a previous diagnosis of asthma. Objective diagnostic testing might also be beneficial in individuals who are suspected of having asthma for the first time. The cost-effectiveness profile of objective testing for such a population may be different than for individuals with an existing diagnosis. Further, we did not investigate to what extent individual characteristics can be used to refine the population for whom diagnostic verification will be beneficial. For instance, performing a diagnostic workup only among patients whose asthma diagnoses were not initially made through objective verification might further improve its cost-effectiveness. We did not have access to a reliable source of evidence to infer the performance of

diagnostic verification across such subgroups. However, previous objective verification testing should not necessarily preclude an objective re-evaluation of asthma, due to potentially inaccurate recall of the initial diagnosis, as well as the fact that asthma may become clinically dormant for extended periods of time, justifying treatment cessation among individuals in whom reversible airway obstruction cannot be reproduced.

In summary, our results indicate that secondary diagnostic verification of asthma during routine clinical encounters among adults with a self-reported asthma diagnosis may be cost-saving and may improve quality of life of patients. The overall conclusions made in this study about the merits of such diagnostic verification remained robust against changes in assumptions and parameter values. Nevertheless, evidence on the performance of diagnostic verification largely comes from research settings, some of which from countries other than the US. As the 'real-world' adherence to, and performance of, stepwise diagnostic algorithms remain untested, future implementation of such algorithms should also be coupled with subsequent evaluations.

References

1. Nunes C, Pereira AM, Morais-Almeida M. Asthma costs and social impact. *Asthma research and practice*. 2017;3:1.
2. Moorman JE, Akinbami LJ, Bailey CM, Zahran HS, King ME, Johnson CA LX. National Surveillance of Asthma: United States, 2001–2010. Vol. 3, Vital Health Statistics. 2012.
3. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet*. 2017;390:1211–59.
4. Nurmagambetov T, Kuwahara R, Garbe P. The Economic Burden of Asthma in the United States, 2008–2013. *Annals of the American Thoracic Society*. 2018;15:348–56.
5. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2018.
6. Sokol KC, Sharma G, Lin Y-L, Goldblum RM. Choosing wisely: adherence by physicians to recommended use of spirometry in the diagnosis and management of adult asthma. *The American journal of medicine*. 2015;128:502–8.
7. O'Dowd LC, Fife D, Tenhave T, Panettieri RA. Attitudes of physicians toward objective measures of airway function in asthma. *The American Journal of Medicine*. 2003;114:391–6.
8. Asthma not found in high percentage of adults who were previously diagnosed [Internet]. ScienceDaily. [cited 2019 Mar 4]. Available from: <https://www.sciencedaily.com/releases/2017/01/170117140129.htm>
9. de Marco R, Locatelli F, Cerveri I, Bugiani M, Marinoni A, Giammanco G. Incidence and remission of asthma: A retrospective study on the natural history of asthma in Italy. *Journal of Allergy and Clinical Immunology*. 2002;110:228–35.
10. Aaron SD, Vandemheen KL, FitzGerald JM, Ainslie M, Gupta S, Lemièrre C, et al. Reevaluation of diagnosis in adults with physician-diagnosed asthma. *JAMA - Journal of the American Medical Association*. 2017;317:269–79.
11. Chen W, Marra CA, Lynd LD, FitzGerald JM, Zafari Z, Sadatsafavi M. The natural history of severe asthma and influences of early risk factors: a population-based cohort study. *Thorax*. 2016;71:267–75.
12. Pakhale S, Sumner A, Coyle D, Vandemheen K, Aaron S. (Correcting) misdiagnoses of asthma: a cost effectiveness analysis. *BMC Pulmonary Medicine*. 2011;11:27.

- 436 13. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated
437 Health Economic Evaluation Reporting Standards (CHEERS) statement. *BMJ*. 2013;346:f1049.
- 438 14. Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the Panel on
439 Cost-effectiveness in Health and Medicine. *JAMA*. 1996;276:1253–8.
- 440 15. Weiler JM, Brannan JD, Randolph CC, Hallstrand TS, Parsons J, Silvers W, et al. Exercise-induced
441 bronchoconstriction update-2016. *J Allergy Clin Immunol*. 2016;138:1292-1295.e36.
- 442 16. Luks VP, Vandemheen KL, Aaron SD. Confirmation of asthma in an Era of Overdiagnosis.
443 *European Respiratory Journal* [Internet]. 2010 [cited 2019 Oct 28]; Available from:
444 <https://erj.ersjournals.com/content/early/2010/01/14/09031936.00165109>
- 445 17. Sumino K, Sugar EA, Irvin CG, Kaminsky DA, Shade D, Wei CY, et al. Methacholine challenge test:
446 diagnostic characteristics in asthmatic patients receiving controller medications. *J Allergy Clin*
447 *Immunol*. 2012;130:69-75.e6.
- 448 18. Lee LK, Obi E, Paknis B, Kavati A, Chipps B. Asthma control and disease burden in patients with
449 asthma and allergic comorbidities. *J Asthma*. 2018;55:208–19.
- 450 19. The Projected Economic and Health Burden of Uncontrolled Asthma in the United States. -
451 PubMed - NCBI [Internet]. [cited 2019 Jun 7]. Available from:
452 <https://www.ncbi.nlm.nih.gov/pubmed/31166782>
- 453 20. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, et al. Development of the asthma
454 control test: a survey for assessing asthma control. *J Allergy Clin Immunol*. 2004;113:59–65.
- 455 21. Products - Life Tables - Homepage [Internet]. 2018 [cited 2019 Feb 22]. Available from:
456 https://www.cdc.gov/nchs/products/life_tables.htm
- 457 22. RESP [Internet]. [cited 2019 Mar 1]. Available from:
458 http://resp.core.ubc.ca/research/Specific_Projects/Project:EBA
- 459 23. Williams LK, Pladevall M, Xi H, Peterson EL, Joseph C, Lafata JE, et al. Relationship between
460 adherence to inhaled corticosteroids and poor outcomes among adults with asthma. *J Allergy*
461 *Clin Immunol*. 2004;114:1288–93.
- 462 24. Wu AC, Butler MG, Li L, Fung V, Kharbanda EO, Larkin EK, et al. Primary adherence to controller
463 medications for asthma is poor. *Ann Am Thorac Soc*. 2015;12:161–6.
- 464 25. Chauhan BF, Ducharme FM. Anti-leukotriene agents compared to inhaled corticosteroids in the
465 management of recurrent and/or chronic asthma in adults and children. *Cochrane Database Syst*
466 *Rev*. 2012;5:CD002314.

- 467 26. Zafari Z, Lynd LD, FitzGerald JM, Sadatsafavi M. Economic and health effect of full adherence to
468 controller therapy in adults with uncontrolled asthma: a simulation study. *J Allergy Clin Immunol.*
469 2014;134:908-915.e3.
- 470 27. Bansal V, Mangi MA, Johnson MM, Festic E. Inhaled corticosteroids and incident pneumonia in
471 patients with asthma: Systematic review and meta-analysis. *Acta Med Acad.* 2015;44:135–58.
- 472 28. American Thoracic Society - ATS Coding & Billing Quarterly [Internet]. [cited 2019 Jun 29].
473 Available from: <http://www.thoracic.org/about/newsroom/newsletters/coding-and-billing/>
- 474 29. STATISTICAL BRIEF #517: Expenses for Office-Based Physician Visits by Specialty and Insurance
475 Type, 2016 [Internet]. [cited 2019 Jul 1]. Available from:
476 https://meps.ahrq.gov/data_files/publications/st517/stat517.shtml
- 477 30. Zafari Z, Sadatsafavi M, Marra CA, Chen W, FitzGerald JM. Cost-Effectiveness of Bronchial
478 Thermoplasty, Omalizumab, and Standard Therapy for Moderate-to-Severe Allergic Asthma.
479 *PLoS ONE.* 2016;11:e0146003.
- 480 31. Campbell JD, Spackman DE, Sullivan SD. The costs and consequences of omalizumab in
481 uncontrolled asthma from a USA payer perspective. *Allergy.* 2010;65:1141–8.
- 482 32. US Inflation Calculator [Internet]. US Inflation Calculator. [cited 2018 Dec 11]. Available from:
483 <https://www.usinflationcalculator.com/>
- 484 33. Cisternas MG, Blanc PD, Yen IH, Katz PP, Earnest G, Eisner MD, et al. A comprehensive study of
485 the direct and indirect costs of adult asthma. *J Allergy Clin Immunol.* 2003;111:1212–8.
- 486 34. Kleinman NL, Yu H, Beren IA, Sato R. Work-related and health care cost burden of community-
487 acquired pneumonia in an employed population. *J Occup Environ Med.* 2013;55:1149–56.
- 488 35. Fryback DG, Dunham NC, Palta M, Hanmer J, Buechner J, Cherepanov D, et al. U.S. NORMS FOR
489 SIX GENERIC HEALTH-RELATED QUALITY-OF- LIFE INDEXES FROM THE NATIONAL HEALTH
490 MEASUREMENT STUDY. *Med Care.* 2007;45:1162–70.
- 491 36. Lloyd A, Price D, Brown R. The impact of asthma exacerbations on health-related quality of life in
492 moderate to severe asthma patients in the UK. *Prim Care Respir J.* 2007;16:22–7.
- 493 37. Bureau UC. Population Projections [Internet]. [cited 2018 Aug 7]. Available from:
494 <https://www.census.gov/programs-surveys/popproj.html>
- 495 38. Ng B, Sadatsafavi M, Safari A, Fitzgerald JM, Johnson KM. The costs of misdiagnosed asthma in a
496 longitudinal study of the general population. *BioRxiv.* 2018;409870.
- 497 39. Aaron SD, Boulet LP, Reddel HK, Gershon AS. Underdiagnosis and Overdiagnosis of Asthma. *Am J*
498 *Respir Crit Care Med.* 2018;198:1012–20.

- 499 40. Suruki RY, Daugherty JB, Boudiaf N, Albers FC. The frequency of asthma exacerbations and
500 healthcare utilization in patients with asthma from the UK and USA. *BMC Pulm Med.* 2017;17:74.
- 501 41. Torrego A, Solà I, Munoz AM, Roqué I Figuls M, Yepes-Nuñez JJ, Alonso-Coello P, et al. Bronchial
502 thermoplasty for moderate or severe persistent asthma in adults. *Cochrane Database Syst Rev.*
503 2014;CD009910.
- 504 42. Castro M, Rubin AS, Laviolette M, Fiterman J, De Andrade Lima M, Shah PL, et al. Effectiveness
505 and safety of bronchial thermoplasty in the treatment of severe asthma: a multicenter,
506 randomized, double-blind, sham-controlled clinical trial. *Am J Respir Crit Care Med.*
507 2010;181:116–24.
- 508 43. Park H, Adeyemi AO, Rascati KL. Direct Medical Costs and Utilization of Health Care Services to
509 Treat Pneumonia in the United States: An Analysis of the 2007–2011 Medical Expenditure Panel
510 Survey. *Clinical Therapeutics.* 2015;37:1466-1476.e1.
- 511 44. Medical Expenditure Panel Survey Home [Internet]. [cited 2019 Oct 10]. Available from:
512 <https://www.meps.ahrq.gov/mepsweb/>
- 513 45. Andrade LF, Saba G, Ricard J-D, Messika J, Gaillat J, Bonnin P, et al. Health related quality of life
514 in patients with community-acquired pneumococcal pneumonia in France. *Health Qual Life*
515 *Outcomes.* 2018;16:28.

527 Tables and figure legends

528 *Table 1) Input parameters*

529

Journal Pre-proof

Ite m	Parameters	Value	SD	Distribution	Source
1.1 Epidemiological parameters and proportions of the population in sub-models					
1	Background mortality in US across age and sex				U.S life table ²¹
2	Proportion of individuals with positive spirometry	0.15	-	beta (86, 527)	¹⁰
3	Proportion of individuals with positive MCT	0.56	-	beta (297, 230)	¹⁰
4	Proportion of individuals with negative MCT who have asthma	0.10	-	beta (38, 344)	¹⁰
5	Proportion of individuals with a current diagnosis of asthma who do not have asthma	0.33	-	beta (203, 410)	¹⁰
1.2 Distribution of asthma control and other risk factors					
1	Association between asthma control and age/sex Well-controlled (vs. very poorly controlled) age sex Not well-controlled (vs. very poorly controlled) age sex	1.09 0.74 0.99 1.10	1.23 1.32 1.28 1.47	Log Normal	¹⁹
2	Association between asthma control and asthma reassessment method (reference: asthma verifiable by one spirometry) OR for asthma that is verifiable by 1 MCT OR for asthma that cannot be verified by 1 MCT	2.31 2.36	0.44 0.45	Log Normal	Analysis of data from economic burden of asthma study (Online Repository Materials-Section C)
3	Mean annual exacerbation rate per patient year (Uncontrolled)	1.02	0.081	Normal	⁴⁰
4	Mean annual exacerbation rate per patient year (well-controlled and not-well controlled)	0.15	0.002	Normal	⁴⁰
5	Relative frequency of exacerbation by severity Mild Moderate Severe	0.48 0.19 0.30		Log Normal (-0.73,0.09) Log Normal (-1.64,0.12) Log Normal (-1.21,0.14)	^{30,41,42}
6	Proportion of patients on ICS	0.51			²³
7	Ratio of Proportion of patients on LTRAs to ICS	0.05			²⁴
8	Relative risk of exacerbation associated with 25% decrease in ICS use	1.26	0.18	Normal	²³
9	Risk ratio of exacerbation associated with LRTA use	1.51	0.20	Normal	²⁵
10	Risk of pneumonia with ICS* in asthma patients	0.22	-	beta (3,517, 12,286)	²⁷
11	Risk of pneumonia without ICS in asthma patients	0.13	-	beta (3,733, 24,480)	²⁷
12	Prevalence of major alternative diagnosis in ruled out population Coronary heart disease Allergic rhinitis Gastroesophageal reflux disease Anxiety Acute bronchitis Chronic Obstructive Pulmonary Disease	1.9% 25.3% 8.5% 3.8% 2.8% 1.9%	-	-	¹⁰
13	Pneumonia death rate per 100,000	15.10			(19)
14	Sever exacerbation death rate	Online Repository Materials-Section B - Table E1			Global Burden of Diseases ³
15	Hearth disease death rate per 100,000	164.13			Global Burden of Diseases (3)
16	COPD death rate per 100,000	52.12			Global Burden of Diseases (3)
1.3 Costs and utilities parameters					
1	Annual direct costs of well-controlled asthma	2,372	458	Normal	¹⁹
2	Annual direct costs of not-well controlled asthma	2,965	211	Normal	¹⁹

3	Annual direct costs of uncontrolled asthma	3,127	268	Normal	19
4	Annual direct costs of exacerbation by severity†				
	Mild	130		Gamma (100,0.77)	
	Moderate	594		Gamma (98.01,0.17)	30,31
	Severe	9900		Gamma (100.08,0.01)	
5	Direct costs of pneumonia	5,006	520	Normal	43
6	Annual costs of medications	1,938	214.8	Normal	4
7	Cost of spirometry (with reversibility)	248	-	Fixed	28
8	Cost of MCT	444	-	Fixed	28
9	Cost of office-based GP visit	265	66.3	Normal	29
10	Annual indirect costs of well-controlled asthma	2,666	-	-	33
11	Annual indirect costs of not-well controlled asthma	3,206	389	Normal	19
12	Annual indirect costs of uncontrolled asthma	3,608	496	Normal	19
13	Annual indirect costs of pneumonia	2,312	-	-	34
14	First-year costs of alternative diagnoses				
	Coronary heart disease	19,506	-	-	
	Allergic rhinitis	6,202			Medical Expenditure Panel Survey ⁴⁴
	Gastroesophageal reflux disease	14,797			(Online Repository Materials-Section D)
	Anxiety	9,917			
	Acute bronchitis	12,456			
	Chronic Obstructive Pulmonary Disease	22,520			
15	Utility of well-controlled asthma	0.70	0.04	Normal	18
16	Utility of not-well controlled asthma	0.66	0.05	Normal	18
17	Utility of uncontrolled asthma	0.61	0.05	Normal	18
18	Utility of exacerbation by severity*				
	Mild	0.57		beta (23.57,17.78)	
	Moderate	0.45		beta (17.59,22.39)	30,31,36
	Severe	0.33		beta (2.32,4.72)	
19	Utility of pneumonia in men	0.63	0.31	Normal	45
20	Utility of pneumonia in women	0.58	0.33	Normal	45
21	Mean utility of US adults				
	Male, 15-44 y/o	0.81	0.01	Normal	
	Male, 45-74 y/o	0.80	0.01	Normal	
	Male, 75-89 y/o	0.77	0.01	Normal	35
	Female, 15-44 y/o	0.80	0.01	Normal	
	Female, 45-74 y/o	0.77	0.01	Normal	
	Female, 75-89 y/o	0.75	0.01	Normal	

1.4 Extrapolation to the entire US population's parameters

1	US adult population size in 2018	266,861,858			37
2	Prevalence of asthma in US across age and sex	Online Repository Materials-Section E Table E2			3

530 ICS: Inhaled corticosteroids; MCT: Methacholine challenge test; GP: General practitioner; OR: Odds ratio

531 * We assumed mild exacerbations last on average one week, and moderate / severe exacerbations last on average two weeks, to model reduction in
532 quality of life

533

534

535

Table 2. Results of cost-effectiveness analysis

Item	Intervention	Status Quo	Incremental
Total patients	10,000	10,000	0
Number of patients confirmed asthma by spirometry	1,500	0	1,500
Number of patients confirmed asthma by MCT*	4,760	0	4,760
Number of erroneous rule-outs of asthma	374	0	374
Number of correct rule-outs of asthma	3,366	0	3,366
Total number of spirometry tests required	10,000	0	10,000
Total number of MCTs required	8,500	0	8,500
Total patient-years across the stratum	192,944	192,944	0
Controlled	79,404	83,511	-4,107
Partially controlled	23,821	23,028	792
Uncontrolled	27,490	24,176	3,314
Asthma ruled out	62,229	0	62,229
False positive asthma on medication	0	62,229	-62,229
Total number exacerbations by severity	33,736	32,141	1,595
Mild	16,694	15,905	789
Moderate	6,608	6,296	312
Severe	10,434	9,940	493
Number of patient-years on asthma medication	62,906	98,402	-35,495
Total cost of spirometry	\$2,480,000	0	\$2,480,000
Total cost of MCTs	\$3,774,000	0	\$3,774,000
Total cost of GP visit	\$4,902,500	0	\$4,902,500
Total cost of well-controlled asthma	\$144,570,236	\$152,046,117	-7,475,881
Total cost of not well-controlled asthma	\$54,192,213	\$52,388,430	1,803,783
Total cost of poorly controlled asthma	\$65,958,334	\$58,005,565	7,952,769
Cost of medication in false positive asthma	0	\$49,850,476	\$-49,850,476
Total cost of exacerbations	\$3,187,580	\$3,036,891	\$150,689
Mild	\$31,937	\$30,427	\$1,510
Moderate	\$115,525	\$110,063	\$5,461

Severe	\$3,040,119	\$2,896,401	\$143,718
Total costs	\$279,064,863	\$315,327,479	\$-36,262,616
Total QALYs	105,324.89	101,275.61	4,049.28
ICER	Dominant*		

MCT: methacholine challenge tests; **QALY:** Quality-Adjusted Life Years; **ICER:** Incremental Cost-Effectiveness Ratio

* The diagnostic verification scenario was associated with lower costs and higher QALYs

Table 3: Results of scenario analyses

Scenario	Incremental Costs	Incremental QALYs	ICER
Base case (reference analysis)	-\$36,262,616	4,049.28	Dominant
10-year time horizon	-\$17,207,755	2,428.53	Dominant
Including the increased risk of pneumonia due to ICS†	-\$47,159,461	4,555.81	Dominant
Including indirect costs‡	-\$31,007,290	4,049.28	Dominant
Incorrectly ruled out asthma patients will be gradually re-diagnosed§	-\$36,772,837	4,155.28	Dominant
Diagnostic verification implemented only among current ICS users	-\$56,802,929	4,049.28	Dominant
Including first-year costs of major alternative diagnoses#	-\$21,616,552	4,049.28	Dominant
First-year costs of major alternative diagnoses			
Twice the base case	-\$7,088,114	4,049.28	Dominant
Three times the base case	\$7,438,783	4,049.28	1,837.06
Proportion of asthma overdiagnosis (33% in the base case analysis)			
30%	-\$30,648,255	3,554.1	Dominant
25%	-\$23,134,398	2,893.3	Dominant
20%	-\$15,620,879	2,232.5	Dominant
15%	-\$8,107,695	1,571.8	Dominant
10%	-\$594,842	911.0	Dominant
6%	\$1,411,089	-628.0	Dominated

ICER: Incremental cost-effectiveness ratio

†In this scenario we investigated increased risk of pneumonia. The probabilities of pneumonia according to ICS exposure were obtained from a recent systematic review and meta-analysis (23). Pneumonia-related death rate, direct costs of pneumonia and utilities associated with pneumonia were derived from literature (37-39) see table 1.

‡In this scenario we adopted a societal perspective by including costs due to loss of productivity

§In this Scenario we assumed the Individuals whose asthma will be incorrectly ruled out will be re-diagnosed over time (50% re-diagnosis over 20 years) due to unresolved symptoms and exacerbations after treatment withdrawal;

||We modeled a general decline in ICS use (from 100% in year one to 60% in year 20) derived from previous reports (13).

#We selected six major alternative diagnoses in patients whose asthma were ruled out See text and Tablw1 for details. We estimated the mean annual cost of first-time diagnosis for above-mentioned diseases from the Medical Expenditure Panel Survey data for 2017.

570 **Figure 1:** Algorithm for stepwise asthma verification testing

571 **Figure 2:** Decision tree combined with open population time-in-state model. Model used for evaluating costs and health-
572 related outcomes of asthma verification national program compared to status quo.

573 **Figure 3:** Results of deterministic one-way sensitivity analyses

574 **Figure 4:** Cost-effectiveness plane for a cohort of 10,000 individuals

575
576

577
578

579

580

581

582

583

584

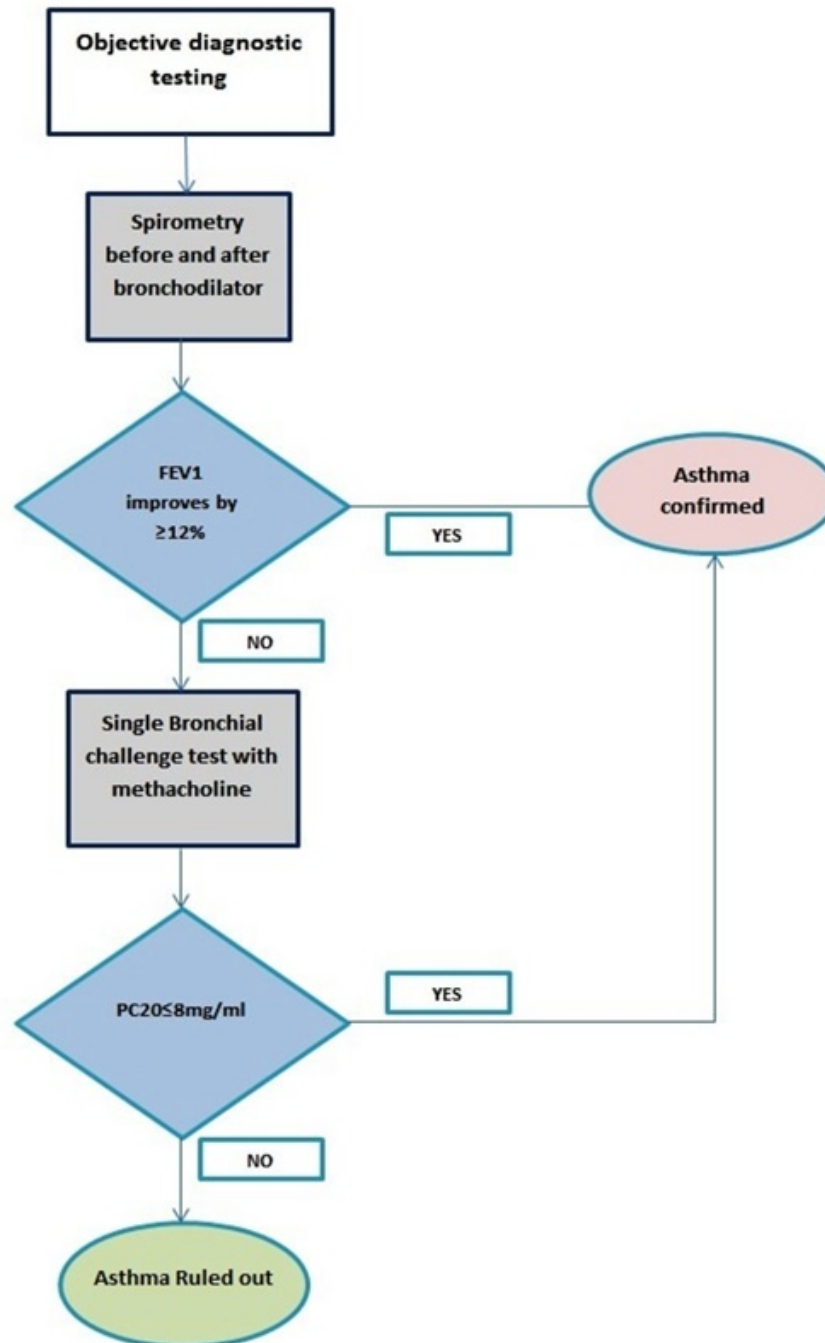
585

586

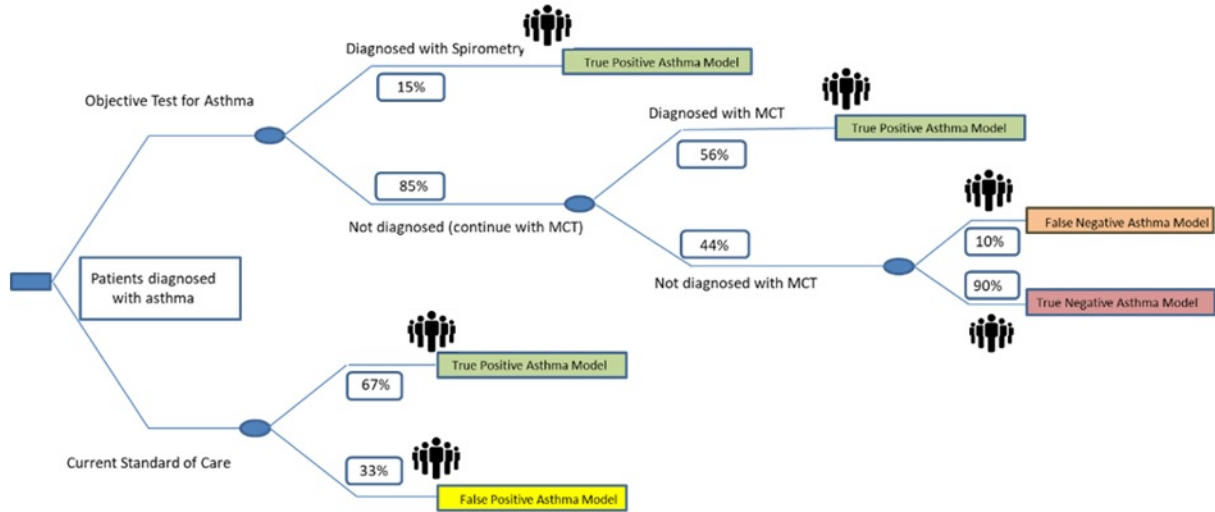
587

588

589



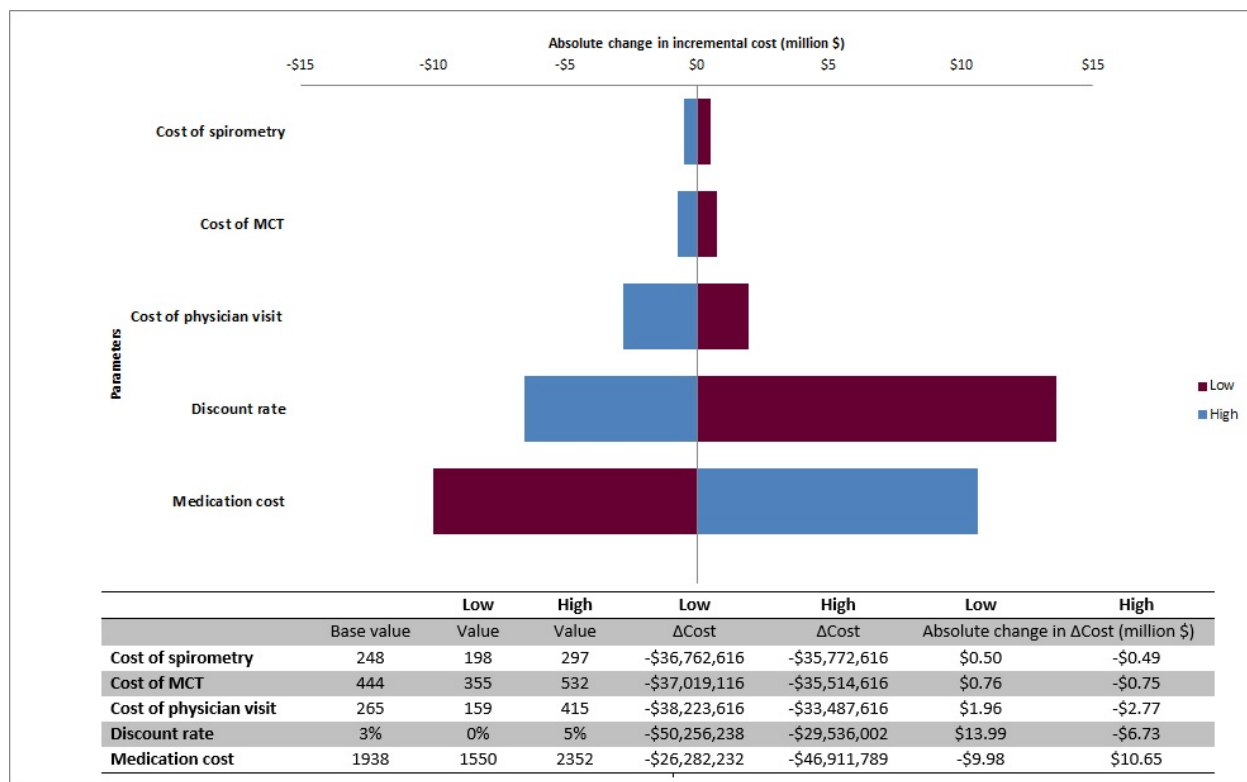
FEV₁: Forced expiratory volume at one second; PC20: methacholine provocative concentration causing a 20% drop in FEV₁



Numbers are point estimates of branch probabilities derived from Aaron et al (11).

All calculations are performed for individuals within sex and 5-year-age strata (not shown on this graph).

MCT: Methacholine Challenge Test (Bronchoprovocation Test)





Online Repository materials – Tables

Table E1: Asthma exacerbation death rate per 100,000 across age and sex

Death rate per 100,000	Value
Male (15-49)	0.65
Male (50-69)	1.16
Male (+70)	2.99
Female (15-49)	0.66
Female (50-69)	1.92
Female (+70)	6.08

Source: Institute for Health Metrics and Evaluation (IHME). GBD Compare, Seattle, WA: IHME, University of Washington, 2015. Available from <http://vizhub.healthdata.org/gbd-compare>

Table E2. Sex- and age-specific asthma prevalence in the United States (per 100,000)

Age	Sex	Value	Lower 95%CI bound	Upper 95%CI bound
15-19 years	Male	4327	4002.2	4678.3
20-24 years	Male	2896	2691.5	3136.8
25-29 years	Male	2702	2550.3	2893.2
30-34 years	Male	2881	2683.8	3106.7
35-39 years	Male	2977	2805.2	3145.6
40-44 years	Male	2992	2798.9	3197.6
45-49 years	Male	2936	2762.6	3101.8
50-54 years	Male	2905	2688.3	3109.5
55-59 years	Male	3158	2986.0	3337.7
60-64 years	Male	3540	3291.8	3786.1
65-69 years	Male	4033	3815.6	4276.9
70-74 years	Male	4411	4088.8	4758.1
75-79 years	Male	4333	4083.6	4577.2
80-84	Male	4115	3792.8	4413.1

85-89	Male	3983	3704.7	4260.6
90-94	Male	3887	3611.5	4194.2
95+ years	Male	3801	3380.0	4308.4
15-19 years	Female	5129	4798.6	5511.9
20-24 years	Female	4258	3967.1	4568.4
25-29 years	Female	4176	3946.4	4440.4
30-34 years	Female	4508	4227.4	4806.4
35-39 years	Female	4846	4603.4	5105.6
40-44 years	Female	5118	4828.3	5418.0
45-49 years	Female	5252	4987.5	5511.3
50-54 years	Female	5345	4998.2	5661.4
55-59 years	Female	5678	5403.0	5976.7
60-64 years	Female	6159	5764.7	6547.1
65-69 years	Female	6772	6442.3	7138.1
70-74 years	Female	7040	6565.3	7536.8
75-79 years	Female	6289	5950.4	6637.6
80-84	Female	5313	4907.4	5680.4
85-89	Female	4799	4463.4	5105.4
90-94	Female	4458	4170.1	4774.0
95+ years	Female	4181	3697.9	4748.6

Source: Institute for Health Metrics and Evaluation (IHME). GBD Compare, Seattle, WA: IHME, University of Washington, 2015. Available from <http://vizhub.healthdata.org/gbd-compare>

Table E3. The total undiscounted costs and QALYs of intervention group versus status quo (2018-2037)

	Total COST (Million \$)	TOTAL QALYs (Million)	Total COST (Million \$)	TOTAL QALYs (Million)
2018	\$33,560.84	8.20	\$24,467.70	7.89
2019	\$20,801.36	8.20	\$24,549.45	7.89
2020	\$20,932.24	8.21	\$24,638.37	7.90
2021	\$21,066.87	8.21	\$24,733.75	7.91
2022	\$21,205.35	8.22	\$24,835.15	7.92
2023	\$21,347.77	8.23	\$24,942.29	7.93
2024	\$21,494.22	8.25	\$25,055.00	7.95
2025	\$21,644.81	8.26	\$25,173.16	7.97
2026	\$21,799.63	8.28	\$25,296.74	7.99
2027	\$21,958.79	8.30	\$25,425.69	8.01
2028	\$22,122.39	8.32	\$25,560.04	8.03
2029	\$22,290.55	8.34	\$25,699.81	8.05
2030	\$22,463.38	8.37	\$25,845.03	8.08
2031	\$22,641.00	8.40	\$25,995.76	8.11
2032	\$22,823.53	8.42	\$26,152.07	8.14
2033	\$23,011.10	8.45	\$26,314.03	8.17
2034	\$23,202.37	8.49	\$26,481.73	8.21
2035	\$23,401.86	8.52	\$26,655.26	8.24
2036	\$23,605.32	8.56	\$26,834.73	8.28
2037	\$23,814.36	8.59	\$27,020.24	8.32
2038	\$24,004.36	8.63	\$27,221.24	8.36
Total	\$479,192	175.47	\$538,897	169.33

Journal Pre-proof

Online Repository materials

Mohsen Yaghoubi, Amin Adibi, Zafar Zafari, J Mark FitzGerald, Shawn D. Aaron, Kate M. Johnson, Mohsen Sadatsafavi

Section A: Distributions of asthma control levels across sex and age

The distribution of levels of asthma control within a given sex and age group was derived using calibration techniques from a recent study based on U.S. National Health and Wellness Survey (NHWS) by Lee et al (E1) which is explained in detail in our previous study (E2). Using model calibration, we estimated the coefficient of the following multinomial logit equations:

$$\text{Probability of not well-controlled} = \frac{\exp(\beta_0 + \beta_1 \cdot \text{age} + \beta_2 \cdot \text{sex})}{1 + \exp(\beta_0 + \beta_1 \cdot \text{age} + \beta_2 \cdot \text{sex}) + \exp(\beta_3 + \beta_4 \cdot \text{age} + \beta_5 \cdot \text{sex})}$$

$$\text{Probability of well-controlled} = \frac{\exp(\beta_3 + \beta_4 \cdot \text{age} + \beta_5 \cdot \text{sex})}{1 + \exp(\beta_0 + \beta_1 \cdot \text{age} + \beta_2 \cdot \text{sex}) + \exp(\beta_3 + \beta_4 \cdot \text{age} + \beta_5 \cdot \text{sex})}$$

Probability of very poorly controlled = 1 - (Probability of not well-controlled + Probability of well-controlled)

Section B: Modeling asthma exacerbations

For individuals with true asthma, we modeled asthma exacerbations associated with levels of asthma control. Asthma exacerbation rates across levels of control were derived from two retrospective cohort studies describing exacerbation frequency for patients with asthma in the US and UK (E3) (Table 1 in main text – section 1.2). Three levels of exacerbation severity were modeled (E4, E5). Exacerbations were classified as mild (increase in the intensity of symptoms, without patients seeking care), moderate (managed as an outpatient including an emergency department visit), or severe (managed in the inpatient setting). Asthma exacerbation death rate extracted from Global Burden of Disease study (E6) (Table E1).

<<Table E1>>

Section C: Distribution of asthma control in the true positive asthma in intervention arm

We used the longitudinal North Economic Burden of Asthma (EBA) study to estimate these parameters. Asthma control was based on the Global Initiative for Asthma (GINA) definition(E7). Although this definition of control is different than ACT, which is the basis of asthma control definition in the model, the clinical experts on our team deemed it acceptable to use GINA-based definition to examine the difference in the distribution of asthma control across different groups, while modeling the overall distribution of control according to ACT. A recent analysis of these data, based on an algorithm similar to the one used by Aaron et al., has demonstrated that in EBA, 24.9% of patients with a self-reported physician diagnosis of asthma do not have asthma(E8). Asthma status in this survey was verified with one pre- and post-bronchodilator spirometry and one MCT (like the protocol evaluated in this study). Asthma control was verified using ACT during baseline and each of the three-monthly visits. Using these data, we constructed a generalized linear model (multinomial distribution, cumulative logit link) to calculate the odds ratio (OR) of having controlled asthma compared with uncontrolled asthma, as well as partially controlled compared with uncontrolled asthma, among the following groups: patients whose asthma was diagnosed with spirometry, patients whose asthma was diagnosed with MCT, and patients whose asthma was erroneously ruled out. The model was adjusted for sex, age at baseline, and whether the individual used any ICS in the 12 months before the study began. We used generalized estimating equations to account for the clustering of observations within individuals.

Section D: Estimating costs of alternative diagnosis

In order to estimate costs of alternative diagnoses for patients whose asthma was ruled out, we calculated the mean annual costs of first-time diagnosis for selected disease from Medical Expenditure Panel Survey (MEPS). We considered patients who had a diagnosis of these conditions in 2017 (based on ICD-10 codes) and did not report the same condition in 2016 to calculate mean annual costs of first-time diagnosis. The following diseases were selected according to the corresponding ICD codes:

Chronic ischemic heart disease (ICD 10= I25)

Vasomotor and allergic rhinitis (ICD 10=J30)

Gastro Esophageal Reflux Disease (ICD 10=K21)

Phobic Anxiety Disorders (ICD 10=F40) / Other Anxiety Disorders (ICD 10=F41)

Acute Bronchitis (ICD 10=J20) / Unspecified Chronic Bronchitis (ICD 10=J42) / Bronchitis, Not Specified as Acute or Chronic (ICD 10=J40)

Chronic Obstructive Pulmonary Disease (ICD 10=J44)

Results are provided in the main text.

Section E: Analysis by year for the entire US population

Sex and age specific asthma prevalence in the United States (per 100,000) were derived from Global Burden of Disease study (E6) and provided in table (E2).

Table E3 provides the undiscounted costs and QALYs in the intervention and *status quo* groups (2018-2038). Undiscounted costs of intervention and *status quo* will total \$20.80 billion and \$24.54 billion, respectively, in 2019; these values will increase to \$21.95 billion and \$25.42 billion in 2027 and to \$24 billion and \$27.22 billion in 2038. Undiscounted QALYs of intervention and status quo scenarios in 2019 will total 8.20 million and 7.89 million, respectively; these values will increase to 8.30 million and 8.01million in 2027 and to 8.63 and 8.36 million in 2038.Total undiscounted incremental costs of spirometry and MCT for the entire US asthma adult population will be \$2.86 billion and \$4.35 billion, respectively.

<<Table E2>>

<<Table E3>>

References:

- E1. Lee LK, Obi E, Paknis B, Kavati A, Chipps B. Asthma control and disease burden in patients with asthma and allergic comorbidities. *J Asthma Off J Assoc Care Asthma*. 2018 Feb;55(2):208–19.
- E2. Yaghoubi M, Adibi A, Safari A, FitzGerald JM, Sadatsafavi M, Canadian Respiratory Research Network. The Projected Economic and Health Burden of Uncontrolled Asthma in the United States. *American journal of respiratory and critical care medicine*. 2019 Jun 5(ja).
- E3. Bansal V, Mangi MA, Johnson MM, Festic E. Inhaled corticosteroids and incident pneumonia in patients with asthma: Systematic review and meta-analysis. *Acta Med Acad*. 2015;44(2):135–58.
- E4. Williams LK, Pladevall M, Xi H, Peterson EL, Joseph C, Lafata JE, et al. Relationship between adherence to inhaled corticosteroids and poor outcomes among adults with asthma. *J Allergy Clin Immunol*. 2004 Dec;114(6):1288–93.
- E5. Zafari Z, Lynd LD, FitzGerald JM, Sadatsafavi M. Economic and health effect of full adherence to controller therapy in adults with uncontrolled asthma: a simulation study. *J Allergy Clin Immunol*. 2014 Oct;134(4):908-915.e3.
- E6. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet*. 2017;390:1211–59.
- E7. Global Initiative for Asthma (GINA). *Global Strategy for Asthma Management and Prevention*. 2018.
- E8. Ng B, Sadatsafavi M, Safari A, Fitzgerald JM, Johnson KM. The costs of misdiagnosed asthma in a longitudinal study of the general population. *BioRxiv*. 2018;409870