MATHEMATICAL DECISION-ANALTIC MODELLING TO EVALUATE ECONOMIC AND HEALTH CHALLENGES IN ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

by

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Abstract

Background: Reducing the burden associated with asthma and chronic obstructive pulmonary disease (COPD) requires addressing challenging care gaps. Mathematical decision-analytic models are among the best tools to address such challenges.

Objectives: My overall aim in this thesis was to identify cost-effective treatments in asthma, and to quantify the value of personalizing treatments in COPD. These goals led to four specific objectives: 1) To inform the economic and health impact of improving adherence to the standard controller medications in asthma; 2) To assess the cost-effectiveness step-up treatment options for severe asthma patients; 3) To build a framework for individualized prediction of lung function in COPD; and 4) To quantify the value of personalizing COPD treatments.

Methods: Cohort-based models were used to quantify the benefit of improving adherence to controller medications and evaluating the cost-effectiveness of treatments for severe asthma. Mixed-effects regression with external validation was undertaken to project lung function decline up to 11 years for COPD. Microsimulation was used to fully incorporate disease heterogeneity to evaluate the return on investment from individualizing treatments in COPD. All modeling studies were based on careful evidence synthesis and original data analyses whenever required.

Results: Improving adherence to controller medications in asthma results in a gain of 0.13 quality-adjusted life years (QALYs) at the incremental cost of $3,187 per patient over 10 years. Even with full adherence, 23% of patients would remain uncontrolled. For this group, the addition of bronchial thermoplasty was associated with an incremental cost-effectiveness ratio of $78,700/QALY. Clinical variables explain 88% of variability in lung function decline. The efforts towards individualizing treatments based on patients' clinical traits would be associated with an additional $1,265 net benefit per person.

Conclusion: The analyses in this thesis demonstrate the value of mathematical simulation models in evaluating the outcomes of policies and scenarios. It is unlikely that any empirical research per se would be able to provide the insight generated in this thesis regarding the identified care gaps. Mathematical models can not only be used to evaluate the outcomes associated with specific interventions, but also to objectively document the return on investment in personalized medicine.

Preface

My PhD thesis research addressed both care and methodological gaps in asthma and COPD using decision-analytic models. Overall my thesis consists of four original studies and one systematic review. In all five studies, I was responsible for the study design, evidence synthesis, model development, statistical data analysis, simulations, and writing the manuscripts. My supervisors, Drs. Mohsen Sadatsafavi, Stirling Bryan (and Carlo Marra who supervised the first two years of my PhD), as well as my PhD committee members, Drs. Donald Sin, Larry Lynd, and Jacek Kopec, provided me with their comments, thoughts, and advice along the way.

I have submitted five manuscripts as a result of this thesis (i.e., Chapters 2, 3, 4, 5, and 6) to peer-reviewed journals.

Chapter 1: Introduction. Zafar Zafari was responsible for writing the introduction to explain the overall scheme of this thesis, screening the articles from the updated literature search in asthma, and extracting and reporting the relevant data. Drs. Mohsen Sadatsafavi and Stirling Bryan contributed to the revision of this chapter. Mimi Doyle-Waters helped with the systematic search for asthma models in MEDLINE and EMBASE data bases.

Chapter 2: Systematic review of epidemiological and decision-analytic models of COPD. Zafar Zafari was responsible for performing a comprehensive systematic search for decision-analytic models in COPD, screening the articles, extracting the relevant data, and writing this chapter. Drs. Mohsen Sadatsafavi and Stirling Bryan contributed to the screening, interpretation of the results, and revision of this chapter. Mimi Doyle-Waters helped with the search strategy in MEDLINE and EMBASE. A version of this chapter has been accepted for publication in Value in Health.

Chapter 3: Economic and humanistic impact of improving adherence in asthma. Zafar Zafari was responsible for literature search, evidence synthesis, model development and computer programming, and writing of the manuscript. Dr. Mohsen Sadatsafavi contributed to the study design, helped with evidence synthesis and interpretation of the results, and revised the manuscript. Drs. J Mark Fitzgerald and Larry Lynd contributed to the clinical interpretation of the study and revision of the manuscript. A version of this chapter has been published in the *Journal of Allergy and Clinical Immunology* (JACI). 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 (JACI), 2014.

Chapter 4: Cost-effectiveness of treatments for severe uncontrolled asthma. Zafar Zafari led on study design, main analysis, mathematical modeling and Web Application development of this work, and wrote the manuscript. Dr. Mohsen Sadatsafavi provided methodological insight and revised the manuscript. Drs. Carlo Marra and J Mark

Fitzgerald, and Wenjia Chen provided clinical insight and helped with revision of the manuscript. A version of this chapter has been published in PLOS ONE. Zafari Z, Sadatsafavi M, Marra C, Chen W, Fitzgerald JM, "Cost-effectiveness of bronchial thermoplasty, omalizumab, and standard therapy for moderate-to-severe allergic asthma", PLOS ONE, 2016.

Chapter 5: Towards developing a microsimulation model of COPD: A framework for individualized prediction of lung function decline in COPD. Zafar Zafari developed the study idea, designed the experiments, performed all the statistical analyses, developed the Web Application, and wrote the manuscript of this study. Dr. Mohsen Sadatsafavi developed the idea, supervised the data analyses, provided technical support, and revised the manuscript. Dr. Don Sin helped with developing the study idea and data collection, provided clinical insight, and revised the manuscript. Drs. Stirling Bryan, Bruce McManus, and Raymond Ng provided methodological insight, helped with interpretation of the results and revision of the manuscript. Dr. Zsuszanna Hollander helped with data provision and managed regular meeting among the research team. Mr. Rahman Khakban provided methodological insights and helped with interpretation of the results. Dr. S.F. Paul Man assisted in obtaining data and provided intellectual input. Drs. Donald Tashkin, Robert Wise, John Connett, Stephen Lam, Martin Tammemagi, Dirkje S. Postma, Claes-Göran Löfdahl, and Judith Vonk helped with data collection, provided intellectual input to the study, and critically revised the manuscript. A version

of this chapter has been accepted and is soon to be published in the Canadian Medical Association Journal (CMAJ).

Chapter 6: Quantifying the value of personalizing medicine in COPD. Zafar Zafari developed the study idea, designed the study, developed a micro-simulation model, performed all the mathematical/statistical programming, and wrote the manuscript. Drs. Mohsen Sadatsafavi and Stirling Bryan provided methodological insight, and helped with revision of the manuscript. Dr. Don Sin helped with data provision, provided clinical insight, and revised the manuscript. A version of this chapter was accepted for an oral presentation in iHEA 2015, Milan, Italy.

Chapter 7: Conclusion. Zafar Zafari was responsible for discussing the results of this thesis in the final chapter. Drs. Mohsen Sadatsafavi and Stirling Bryan reviewed and gave comments on this chapter.

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Acknowledgements

Dedication

My PhD thesis is a fruit of many years of effort that have been made by my beloveds. I, gratefully, dedicate this thesis to the first teachers of my life, my parents, Jafar Zafari and Zohreh Feizi, for first, opening my eyes to this world, and second, their unconditional love, kindness, support, encouragement, and endless patience. I also dedicate this thesis to my wonderful partner-in-crime, Elaheh Aghaarabi, who supported me throughout my PhD. This thesis would not have been possible without their love.

Chapter 1: Introduction

1.1 Overall Objective

In this thesis I have identified three major gaps in care and potential areas in which patient outcomes can be improved in asthma and COPD. In order to evaluate the health and cost consequences of different strategies to close these gaps, I have used mathematical decision-analytic modeling.

1.2 Asthma and Chronic Obstructive Pulmonary Disease

1.2.1 Epidemiology of Asthma and COPD

Asthma is a chronic disease of the lungs characterized by reversible obstruction of the airways and symptoms such as shortness of breath, coughing, and wheezing (1). Almost 7% (2.4 million) of Canadians who are over 12 years old are diagnosed with asthma (2). The innate level of activity of asthma (degree of airway obstruction, symptoms), referred to as severity, is different among individuals. Asthma severity is typically categorized as mild, moderate, or severe (3). On the other hand, the clinical management of asthma is based on the concept of 'control'. According to the Global Initiative for Asthma (GINA) (3), asthma control refers to the clinical status of the disease for an individual and can be classified as controlled, partially controlled, and uncontrolled. Both asthma severity and clinical control are dynamic states and can vary over time.

COPD is a progressive disease of the airways, which is characterized by sputum production, chronic cough, and periods of intensified disease activity called exacerbations (4). According to Statistics Canada, 4% of Canadians between 35 and 79 years old have self-reported COPD (5). COPD is among the top 4 causes of death in Canada (6), and will be among the top diseases in terms of its overall burden in the coming years (7). Smoking is a major risk factor for COPD, but other factors such as environmental and occupational exposure can also affect the incidence of COPD (8).

1.2.2   Economic and Humanistic Burden of Asthma and COPD

Both asthma and COPD are major sources of economic and humanistic burden. When considered nationally, the total costs of COPD-related hospitalizations were estimated to be $1.5 billion per year in Canada (9), and the average annual indirect costs were estimated to be approximately $1,000 per patient (10). Exacerbations account for between 40-70% of all medical costs in COPD (11).

Asthma imposes a substantial economic burden to the society as well, in terms of both the direct and indirect costs (1). In 1990, Weiss et al. carried out a study on adults in the United States to quantify this burden (12), which was estimated as $1.195 billion (USD). In Canada, total asthma-related direct costs were estimated to be $315.9 million between 2002 and 2007 in British Columbia (BC) (13).

COPD and asthma exert a substantial toll on the quality of life of the affected individuals as well. Different studies have suggested that COPD and asthma are associated with a

significant reduction in quality of life. For instance, Marco daCosta et al. have shown lower health state utility values (HSUV) for COPD versus non-COPD patients after adjusting for co-morbidities (0.71 vs. 0.75) (14), and McTaggart-Cowan et al. (15) and Lavoie et al. (16) showed lower quality of life for more severe cases of asthma compared with less severe cases as well as non-asthma cases.

1.2.3   Management of Asthma and COPD

The general goals in the management of COPD and asthma are to prevent disease progression over time, improve quality of life of the patient, and avoid exacerbations. Achieving such goals requires a systematic approach and an appropriate combination of pharmacologic and non-pharmacologic management strategies. Patient education plays an important role, which has been shown to be associated with significant improvement in disease progression in both diseases (6,17). In addition, smoking cessation and self-management are shown to be effective in improving the outcomes in both diseases (6,18,19).

For asthma, the target of modern management is to achieve and maintain clinical control (3). Compared to uncontrolled (or partially controlled) asthma, controlled asthma is associated with better quality of life, lower rate of adverse outcomes such as hospitalization or death, and lower consumption of health care resources (20). While lifestyle changes such as avoidance of environmental exposures are important in this context, all patients, except those with the mildest form of the disease, ultimately

require pharmacological controller therapy (3). Controller therapies are those that, due to their anti-inflammatory effect, have a long-standing impact on the course of the disease in terms of improvements in symptoms and reduction in the risk of adverse outcomes. This is unlike reliever therapies which are associated with short-acting improvement in asthma symptoms but do not change the underlying inflammation. Inhaled corticosteroids (ICS) are the main class of asthma controller therapies. Leukotriene receptor antagonists (LTRAs) are another class of controller therapies that are mainly used in milder forms of asthma or in addition to ICS when monotherapy with ICS does not result in asthma control (3).

For COPD, on the other hand, pharmacotherapies have been shown to reduce the rate of exacerbations. Nevertheless, their role on modification of lung function decline has not yet well established. Prevention of subsequent decline in lung function once COPD is diagnosed remains a crucial factor in controlling the burden of COPD (21). COPD is a very heterogeneous disease (22), and mitigating future lung function decline requires a deep understanding of such heterogeneity and its determinants.

1.3   Decision-Analytic Modeling

1.3.1   The Role of Decision-Analytic Models in Addressing Policies

Decisions are being made at multiple levels of our health care system including clinical decision making at the bedside, best practice recommendations by clinical guideline developers, and decisions regarding the adoption of health technologies into health

markets made by policy makers. Predicting the outcomes of different policies and decisions is substantially important in health care. Epidemiological projections such as estimating the future prevalence of a disease are of tremendous importance for policy making and planning. In addition, economic evaluations that predict the future health and economic consequences of competing interventions, programs, and policies (health technologies) are important in informing the decision on health technology adoption. Such epidemiological projections or cost-effectiveness analyses usually require evidence from multiple resources, long-term predictions beyond the available data, and the need for translating evidence on intermediate outcomes to policy-relevant messages. Addressing these challenges typically requires computer modeling and disease simulation. Given such challenges in health care decision making, decision-analytic modeling is considered as an 'unavoidable fact of life' (23).

Models provide a unified framework for comparison of different interventions that are informed from different studies and trials (24). Most often, to address a clinical or health policy questions there are disparate approaches such as clinical trials, most of which are very expensive and time consuming.

A major role of such simulation models is to answer 'what if' scenarios to inform different policies. In answering such questions, the analyst also often performs a variety of sensitivity analyses to investigate the robustness of results against different input parameters or structural assumptions about the way the model represents reality.

Constructing and validating a decision-analytic model is a complex process, and generally, there are many challenges involved in this process, from the evidence synthesis stage to processing model outputs. Most often, there are multiple sources of evidence for different model inputs. Ruling out the irrelevant information as well as giving the correct weight to different studies and pooling the evidence to inform the final model inputs requires good understanding of the principles of evidence synthesis as well as knowledge of statistics. In addition, choosing the right modeling framework based on the context of the study subject, basing the model on sound underlying assumptions, realistically modeling the impact of health technologies on the natural history of the disease, and choosing reasonable analysis parameters such a relevant time horizon or discount rate plays a key role in any model development (25). It is implausible to reach full agreement among different model developers on these challenges and underlying assumptions, and the analyst might decide to perform various alternatives and sensitivity analyses to satisfy different concerns and opinions.

1.3.2   Different Analytical Frameworks for Decision-Analytic Modeling

From an analytical perspective, decision-analytic models are classified based on different perspectives. (26). Published model taxonomies do not fully agree with each other, reflecting the degree of subjectivity involved in such categorization. Below I will review such classifications to the extent that they relate to the methodology employed in this thesis.

There are several important considerations in a model that need to be carefully discussed before its development such as the relevant time horizon, discount rate for the future costs and health benefits, study perspective, and willingness-to-pay.

1.3.2.1   Cohort-based Models

Cohort-based models follow a closed cohort of patients with similar characteristics, which typically transition between different health states over the time horizon of the study (27). Monte Carlo simulation is among the best statistical tools to account for the variation in such characteristics for different cohorts. Different commonly used cohort-based models in health care are further discussed in the following section.

1.3.2.1.1   Markov Models

Markov models are among the most popular mathematical modeling techniques used in health care (26). Discrete-time Markov models are commonly used for disease modeling through which a patient can transition from a state into another at discrete time intervals. The underlying assumption of Markov models is that the future state of an individual only depends on its current state and not its previous ones. Typically, Markov models are cohort-based models, and simulate an infinitely large cohort of individuals. In addition, calculations based on Markov models mostly come with a shorter computation time. Nevertheless, it is often difficult to incorporate between-individual variability (i.e., heterogeneity) in such models, which exists in almost all situations.

1.3.2.1.2   Decision Trees

A decision tree is a modeling technique in which all possible sequence of events that relate to the outcomes of interest and the impact of an intervention are explicitly modeled (26). The paths that individuals can take are represented by nodes and branches, with changes in paths modeled by chance or decision nodes. Individuals take different paths either due to chance (at chance nodes) or because of an explicit decision (at decision nodes; e.g., to treat or not to treat). These models are, conceptually, close to Markov models with the distinction that time does not play any role in them and transitions across the sequence of events occur instantaneously. The implementation of such models are relatively easy with low computational burden; however, the fact that time cannot be accounted for in these models is a shortcoming that precludes using them in reflecting the trajectory of many decisions or projections whose outcomes materializes over long time (26). A decision tree is typically a cohort-based model in which the sequence of events for an infinitely large population is simultaneously evaluated. However, it is also possible to run a decision tree as an individual-based model.

1.3.2.1.3   System Dynamics Models

System dynamics is another approach used for cohort-based modeling, where the transition across a set of discrete health states are informed by differential equations (26). The time is often modeled continuously. Like other cohort-based modeling, System

Dynamics models are not ideal frameworks for reflecting between-individual variation in heterogeneous diseases.

1.3.2.1.4   Time-in-state Models

Time-in-state modeling is similar to Markov models in the sense that it consists of a set of mutually exclusive health states that each accommodates a proportion of the population at each time interval. Unlike Markov models, time-in-state models are not obliged to respect the Markovian assumption, and there are no transition probabilities for these models. Instead, the proportion of the population in each disease state is directly estimated as a function of the global time in the model. Like other cohort-based models, time-in-state models are suitable frameworks for addressing population-based policies and not for evaluations that require accurate modeling of the between-individual variation.

1.3.2.2   Individual-Level Models

In individual level models, an individual patient with his/her specific clinical characteristics is followed over time. The popular individual-level modeling approaches include discrete-event simulation and individual level sampling, which are discussed below.

1.3.2.2.1   Discrete-Event Simulation

Discrete-event simulation is a technique whereby the disease trajectory of an individual is modeled as a series of events over time (26). There are two important components for a discrete-event simulation, states and events. The occurrence of an event would normally lead to a change in the disease state. Interactions between individuals in such models can potentially be accommodated (26). DES models are very popular for situations where there is a need for modeling between-individual variation. This is because variables representing heterogeneity can easily be added to the actor. In Markov models, on the other hand, a disease states needs to be created for all unique combination of variables representing heterogeneity. This requires categorizing continuous variables into a few levels with associated approximation, and inevitably creating a model with many disease states. Interaction of multiple variables of this type will be practically impossible to be considered in Markov models given the multitude of disease states required. Discrete-event simulations, on the other hand, can fully capture heterogeneity by adding the required variables to actors (simulated individuals). Nevertheless, calculations based on discrete-event simulation models usually require higher computational demand, especially when it comes to a probabilistic analysis (26).

1.3.2.2.2   Individual Sampling Models

Individual sampling models are conceptually similar to discrete-event simulations with the distinction that there assumes to be no interaction between individuals in these models (26).

1.3.3 Overview of Decision-Analytic Models in Asthma and COPD

Creating a decision-analytic model can be critically informed by the work previously done in the field. In my comprehensive search for existing decision-analytic models of asthma and COPD, I found a very recent systematic review of asthma models, published in 2014 (28). Thereby, I have updated this review (to January 2016). The details of the search strategy are found in the supplementary material-Appendix A. My updated search for asthma resulted in only four additional publications that had used a decision-analytic or epidemiologic model of asthma for cost-effectiveness or epidemiological projection. I have provided the summary of the models from my search along with the ones from the previous published systematic review in Table 1.1. On the other hand, for COPD, I performed a comprehensive systematic review of the literature, which required a dedicated reporting. Thereby, the details of the systematic review of COPD models are presented in the next chapter.

Table 1-1 Summary of cost-effectiveness models for severe asthma

Authors	Country	Treatments	Identifying the optimal treatment strategy for severe uncontrolled asthma
Results from a recent systematic review			
Gerzeli et al. (29)	Italy	ICS/LABA (12eclomethasone/formoterol) vs ICS/LABA (fluticasone propionate/salmeterol)	No
Dewilde et al. (30)	Sweden	Omalizumab vs standard therapy	No
Brown et al. (31)	Canada	Omalizumab vs standard therapy	No
Wu et al. (32)	USA	Omalizumab vs standard therapy	No
Campbell et al. (33)	USA	Omalizumab vs standard therapy	No
Van Nooten et al. (34)	Netherlands	Omalizumab vs standard therapy	No
Willson et al. (35)	UK	Tiotropium vs standard therapy	No
Results from my updated search			
Morishima et al. (36)	Japan	Omalizumab vs standard therapy	No
Zein et al. (37)	US	BT vs standard therapy	No
Cangelosi et al. (38)	US	BT vs standard therapy	No
Rodriguez-Martinez et al. (39)	Columbia	Daily vs intermittent ICS	No

LABA: long-acting beta-agonists, ICS: inhaled corticosteroids, BT: bronchial thermoplasty.

Out of 11 mathematical models of asthma found in the literature, six evaluated the cost-effectiveness of omalizumab versus standard therapy (i.e., ICS+LABA), two compared the bronchial thermoplasty (BT) versus standard therapy, one compared two different ICS+LABA combinations with each other, one analyzed the cost-effectiveness of tiotropium versus standard therapy, and one evaluated the cost-effectiveness of daily use of ICS versus its intermittent use. All of the models were cohort-based Markov models.

Although, there have been asthma models that have evaluated the cost-effectiveness of treatments, whether or not being fully adherent to the standard asthma controller medications for severe uncontrolled asthma is cost-effective (chapter 3) has not yet been addressed. In addition, the most cost-effective step up therapy for those asthma patients who still remain uncontrolled despite full adherence to the standard controller medications is another issue that needs to be addressed (chapter 4).

For COPD, I found forty nine mathematical models (details provided in Chapter 2). Like asthma, most of the developed models were cohort based. However, the variety of model types adopted for COPD was more pronounced compared to that of asthma. Among forty nine models, forty one studies used Markov models, two studies used a decision-tree, one used time-in-state modeling approach, two used system dynamics, two employed individual sampling approach, and one used discrete-event simulation. The details of this systematic review are presented in the next chapter.

1.4   Overview of Thesis Objectives

1.4.1   Overview of Decision-analytic Models

In this thesis, I have identified important care gaps in asthma and COPD, selected based on consultation with expert respiratory clinicians at the University of British Columbia. Addressing these care gaps will inevitably require a comprehensive evidence-synthesis and outcome prediction approach, necessitating the use of modeling techniques. Accordingly, I have developed state-of-the-art decision-analytic models in evaluating these care gaps. In particular, I have developed, calibrated, and applied two different asthma models to evaluate the return on investment in improving adherence to asthma treatments, and evaluating cost-effectiveness of treatments for severe asthma. I have developed a decision-analytic model of COPD to quantify the monetary and health value of moving from population-based disease management to personalized medicine.

The asthma models required creation of models with specification of a few disease states that could capture the relevant aspect of the disease (asthma control and exacerbations). Disease heterogeneity was not considered to be a critical factor. As such, cohort-based Markov modeling was used to achieve the research objectives. For the COPD model, on the other hand, given the research objective, extensive characterization of disease heterogeneity was required. As such, the use of microsimulation modeling was inevitable. In the process, I faced a new gap in terms of lack of evidence on heterogeneity in lung function decline as the central pathology of

COPD. To address this, I developed a statistical framework for individualized prediction of lung function decline in COPD based on the patients' clinical traits.

Through these studies, not only did I provide critical new insights about the merits of different strategies for narrowing the identified care gaps, but also I demonstrated the value of using mathematical decision-analytic models in addressing specific or broad policy questions in health care. Evaluating such questions by other means (such as conducting clinical trials) would be infeasible due to the prohibitive costs of empirical studies that would need to collect all the relevant outcomes in a very large sample over a long time.

1.4.2   Care Gaps and Priorities in Asthma and COPD

For asthma, there are effective treatments that can bring the disease under control in the majority of patients (40). Despite the availability of effective and inexpensive controller treatments, many individuals with asthma are not receiving evidence-based, optimal treatments, resulting in substantial care gaps and indicating the potential for economic and humanistic gains through improving adherence (41). There is a strong association between poor outcomes and non-adherence to controller therapies in asthma. For instance, Williams et al. demonstrated that each 25% increase in adherence results in 1.26 fold decrease in asthma exacerbations requiring oral corticosteroids (42), and studies of controller therapies in asthma have shown that regular inhaled corticosteroids (ICS) use decreases asthma related death and exacerbations by up to

80% (43–46). At the population level, a recent study in the US has shown that full adherence to controller therapies can avoid up to one million asthma hospitalizations and four million emergency department visits annually (47). Therefore, it is postulated that the burden of asthma could be significantly reduced by improving adherence (48). Quantifying the health and economic consequences of improvement in adherence can be very informative for policy makers (care gap no. 1).

A minority of patients with severe asthma remain uncontrolled despite full adherence to standard controller medications (40). This minority group, compared with typical asthma patients, experience a disproportionate level of disease burden (49). Novel pharmaceutical and non-pharmaceutical therapies have recently become available with promising clinical results. Omalizumab is a monoclonal antibody for severe allergic patients with high level of IgE, which reduces the rate of exacerbations and hospitalizations (50). Bronchial thermoplasty (BT) is a radio-frequency technique to the peripheral sub-segmental airways, which is recently approved by the Food and Drug Administration (51). Bronchial thermoplasty involves three bronchoscopy procedures for treatment of the sequentially segmental airways (51). The combination therapy of BT and standard therapy has been shown to be effective in reducing the rate of exacerbations (52,53). To date, no study has evaluated the cost-effectiveness of all these treatment options, leaving patients, care providers, and policy makers uncertain about the efficient treatment of severe asthma (care gap no. 2).

It is well known that COPD is a very heterogeneous disease in many aspects. Importantly, the rate of lung function decline measured by the forced expiratory volume in 1 second (FEV_1), which is the cornerstone of disease pathology in COPD, is substantially different across individuals (54). Traditionally, most attention in COPD care has been given to the population based decisions. Heterogeneity in COPD means that the cost-effectiveness of treatments in patients can well be a function of their individual characteristics. Moving from a population-based disease management approach to an individualized one (personalized medicine) can result in significant gain in health and potentially saving in costs. Unfortunately, the research paradigm in COPD has also adopted the same population-based lens, resulting in the paucity of evidence and studies in quantifying the level of heterogeneity and its implications for disease managements (55–57). There is a great window of opportunity for individualizing care and basing treatment decisions upon patients' individualized clinical traits in COPD (55–57). An important step forward can be evaluating, at a broad level, the potential return on investment in making such a transition from population-based to personalized treatments. There is, to date, very scarce information on the additional value that can be gained by personalizing care in COPD (care gap no. 3).

1.4.3   Thesis Themes

Throughout my thesis, I aimed at narrowing three care gaps in asthma and COPD (mentioned in the previous section) using the power of mathematical decision-analytic modeling. Similar to many other issues in health, addressing policy questions towards

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closing these gaps is very difficult or almost impossible by other means such as conducting empirical studies that would single-handedly provide all the evidence that is needed. This is because of the requirement for information on many different parameters and the need for a very long follow-up in order to inform meaningful predictions.

In addition, as part of my model development work to address the care gap in COPD, I faced an evidential gap in terms of quantifying heterogeneity in lung function decline in COPD. Accordingly, I built a statistical framework for individualized prediction of lung function decline in COPD using 11-year data from a landmark, large COPD study. The ability to predict the future rate of lung function decline and properly quantify uncertainty around it would was not only a necessary step in quantifying the value of personalizing care in COPD, but also is also a valuable scientific study on its own. For example, funders and investors can use such a framework to conduct more efficient COPD clinical trials with smaller sample size through recruitment of patients with a greater likelihood of rapid lung function decline.

In chapter 2, I performed a comprehensive systematic review of COPD mathematical models to synthesize the evidence on the methods that have been already adopted by other investigators in the field, which will provide critical insights for my COPD model. For asthma, on the other hand, I found a very recent systematic review. Thereby, I only updated this review, results of which can be found in this chapter (section 1.3.3)

In chapter 3, I quantified the cost and health consequences of improving adherence to controller medications in asthma. Using evidence from the literature, I developed and calibrated a Markov model to investigate the simultaneous impact of partially or completely improving adherence to asthma medications compared with *status que* level of adherence (addressing the 1st care gap).

In Chapter 4, I developed a Markov model of asthma to determine the optimal step-up therapy for those severe asthma patients who are still symptomatic after full adherence to the standard controller medications (addressing the 2nd care gap). Since reducing the number of exacerbations and hospitalizations is the key target for treating these asthma patients, unlike my model in chapter 2 which was built around disease control states, my asthma model in this chapter is built upon exacerbation states.

In Chapter 5, I report on my research in quantifying heterogeneity in lung function decline in COPD. For this work, I have used a random effects regression model to quantify heterogeneity and its determinants for early-stage COPD. Based on the results of this regression, I have developed a framework for individualized, probabilistic prediction of lung function decline in COPD patients (addressing the methodological gap in COPD). As part of knowledge translation for this chapter, I have built an online Web application that makes the prediction tool available to stakeholders.

In Chapter 6, using the framework that I have built in chapter 5, I built a micro-simulation model of COPD to quantify the value personalizing medicine in this disease (addressing the 3rd care gap).

Finally, in Chapter 7, I conclude this body of work by summarizing the findings and highlighting the advantages of using the developed mathematical simulation frameworks to address these specific care gaps in asthma and COPD, and describing the potential applications in other similar contexts. I also identify the future research priorities that can build on the contributions made by the work conducted in this thesis.

Chapter 2: Systematic Review of Epidemiological and Decision-analytic Models of COPD

2.1 Introduction

The development and validation of a disease model is typically a highly complex process, requiring several fundamental assumptions, relating to, for example, natural history, impact of the health technologies on natural history, choice of model structure, relevant time horizon for the analysis, and the outcomes of interest (25). Evidence synthesis for many parameters of the model is typically the next step. While it is unlikely to have a general consensus among the investigators along the process, exploring and understanding the different decisions that investigators have made in the course of developing a disease model can inform and make more comprehensive the process of subsequent model development.

COPD is currently estimated to be the fourth most common cause of death worldwide, but studies project that it will become the third cause of death globally by 2030 (58). The significant economic and humanistic burden of COPD has caused many treatments and management strategies to emerge for prevention, diagnosis, and management of the disease (59,60). The interest in the projection of the future burden of COPD and the requirement for economic evaluations of existing and emerging technologies has resulted in multiple COPD models. Understanding the general characteristics of such models, including the target population, model structure, and type of the question

answered, can provide future investigators with a systematic and broad view of the COPD modeling landscape.

In addition to the general features of the models, characterizing the COPD-specific assumptions made in such models can support future model development and decision analysis in terms of comprehensiveness. COPD is a remarkably heterogeneous disease (22), which suggests the benefit of interventions can differ among different subgroups of individuals. In addition, the devastating impact of comorbid conditions in COPD is well recognized (61). One other potentially important factor is how the effect of pharmacological treatments is modeled, as clinical trials have evaluated the impact of pharmacotherapy both in terms of change in the rate of lung function decline and change in the incidence of exacerbations. Finally, there are alternative choices for modeling COPD progression; some studies modeled disease progression directly through continuum of lung function while others did it indirectly by translating lung function decline into discrete clinical states defined by Global initiative for Obstructive Lung Disease (GOLD grades) (62).

The aim of this chapter was to synthesize the state of science in the field by systematically exploring the characteristics of COPD models. Our review considered adherence to the best practice modeling guidelines as well as the assumptions made in COPD models relating to specific aspects of the disease. We were interested in finding the areas of similarity as well as differences across published COPD models, in search of opportunities for potential improvement in decision-analytic modeling in COPD.

2.2 Methods

A systematic review was undertaken, based on the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (63). We performed a search in MEDLINE and EMBASE (completed on August 24, 2015) limited to English language. Additionally, we performed manual searches on the reference lists of the included articles and consulted with experts for relevant publications. Details of the literature search are provided in the Supplementary Material-Appendix A.

The inclusion criteria were studies that used a formal mathematical modeling approach either to project the future burden of COPD or undertake a cost-effectiveness analysis of alternative interventions. Only studies with a primary focus on COPD were considered; therefore, publications considering COPD as an event or a complication of another condition were excluded.

Study selection was carried out in two phases, title and abstract screening, and full text analysis. A customized checklist was created to summarize key parameters of all simulation models. Key information from the reviewed articles was extracted and categorized according to the following three groups: adherence to guidelines, model lineage (i.e., further development of a previously published model), and COPD assumptions.

General characteristics and adherence to reporting guidelines: We summarized the general characteristics of the models using a modified checklist that was initially based on a previously published study (64). It included the target jurisdiction (country), authors, year of publication, type of model, intervention, type of population (static population that is the evolution of a fixed cohort, and dynamic (or open) population that incorporates arrival of new individuals during the study period), time horizon, cycle length (if applicable), perspective of the evaluation (e.g., third party or societal), discount rate, how effect measure was modeled (if applicable), and whether or not indirect costs were included.

Two researchers (including myself) evaluated the adherence of models to the health economic modeling report guidelines: the Consolidated Health Economic Evaluation Reporting Standards (CHEERS)(25).

Exploration of COPD-specific assumptions: We explored the COPD-specific elements of each model with a focus on the areas of active research in COPD, which were defined by the expert clinician of our team. The first criterion considered was COPD progression. This could either be modeled in terms of transition through severity stages (e.g., GOLD grade) or through continuous changes in lung function metrics (e.g., forced expiratory volume in 1 second (FEV_1)). While GOLD grades are mainly based on cut-offs of FEV_1, a fixed transition rate across GOLD grades does not necessarily correspond to a fixed rate of FEV_1 decline. The second component was the impact of pharmacotherapy, in terms of assumptions about the impact of treatment on lung function or exacerbation rate. Given

that exacerbation is a function of COPD severity (lung function), modeling treatment effect on lung function indirectly affects exacerbation rates. However, many studies have reported the direct impact of pharmacotherapy on exacerbation rates, which might not necessarily be mediated through lung function. Further, the assumptions regarding heterogeneity in natural history of COPD were investigated. Studies were assessed in terms of whether they incorporated heterogeneity in model calculations, and whether they reported results across subgroups. Finally, we determined whether or not COPD co-morbidities were considered explicitly in the model.

2.3   Results

The search resulted in 4,054 references, excluding duplicates. 3,911 citations were excluded during title and abstract screening, resulting in 143 articles for full text analysis. The agreement between reviewers in the screening process was very good (kappa statistic 0.89) (65). After full text review, 49 publications met the inclusion criteria (Figure 2.1) (63).

Figure 2-1 Preferred reporting items for systematic reviews and meta-analysis (PRISMA) flow diagram

Identification		
	Records identified through database searching (n =4,919) Medline: 1,882 Embase: 3,037	Additional records identified through manual search and expert consultation (n = 11)

Records before duplicates removed (n = 4,930) → Duplicates (n = 876)

Screening

Records screened (n = 4,054) → Records excluded (n = 3,911)

Eligibility

Full-text articles assessed for eligibility (n = 143) → Full-text articles excluded, with reasons (n = 94)

No simulation included: 46
COPD not the main focus: 42
Review/editorial: 6

Included

Studies included in qualitative synthesis (n = 49)

Summary of general characteristics of models and their adherence to CHEERS: Table

2.1 presents the summary of the 49 models. A wide range of simulation modeling

approaches has been applied: 41 studies were Markov models (MM) (66–106), 2 were

decision trees (DT) (107,108), 1 used a time-in-state model (TSM) (109), 2 employed an

individual sampling modeling (ISM) approach (110,111), 1 was a discrete-event

simulation (DES) (112), and 2 were system dynamics (SD) models (113,114).

The majority (n=40) of models were developed for the purpose of economic evaluation,

either of alterative COPD treatments or of a COPD management program (66–75,77–

81,83–87,90–92,95–105,107–109,111,113,114). Two models were developed to project

the future burden of COPD (93,94); 5 represented a case study for methodological work

(76,82,88,89,106); and 2 were developed as a generic modeling framework (*multi-

purpose* and not an *ad hoc* model) (110,112). Seven models (69,86,93,94,102,113,114)

were open population (dynamic) models.

Table 2-1 Summary of the simulation models in COPD

Authors Country Year	Type of model	Intervention	Dynamic	Time horizon	Cycle length	Perspective	discounting	Effect measure	Indirect costs
Borg et al (66) - **Sweden - 2004**	**Markov**	**2 hypothetical interventions: (1) improving FEV1 decline, (B) reducing exacerbation**	**No**	**30 years**	**1 year**	**Societal**	**3%**	**QALYs**	**No**
Lock et al (67) - Spain - 2011	Markov	Varenicline vs placebo	No	Life time	1 year	Healthcare system	3%	QALYs	No
Price et al (68) – **Germany - 2011**	**Markov**	**Indacaterol (LABA) vs tiotropium and salmeterol**	**No**	**3 years**	**3 months**	**Health service**	**3%**	**QALYs**	**No**
Ariza et al (69) – Columbia - 2012	Markov	Indacaterol vs salmeterol/fluticasone, formoterol/budesonide, and tiotropium	Yes	5 years	3 months	Health care payer	5%	QALYs	No
Price et al (70) – UK - 2013	Markov	Indacaterol (LABA) vs tiotropium and salmeterol	No	3 years	3 months	National Health Service (NHS)	3.50%	QALYs	No
Spencer et al (71) – **Canada - 2005**	**Markov**	**ICS+LABA (salmeterol/fluticasone propionate) vs placebo**	**No**	**life time**	**3 months**	**Healthcare payer**	**5%**	**QALYs**	**No**
Sun et al (72) – US - 2011	Markov	Roflumilast/tiotropium vs tiotropium monotherapy	No	5 years	3 months	Payer	3%	QALYs	No

Authors Country Year	Type of model	Intervention	Dynamic	Time horizon	Cycle length	Perspective	discounting	Effect measure	Indirect costs
Hertel et al (73) – UK - 2012	Markov	Various combinations of Roflumilast, LAMA, LABA, and ICS	No	life time	1 month	National Health Service (NHS)	3.5%	QALYs	No
Samyshkin et al (74) – Switzerland - 2013	Markov	Roflumilast, an oral, selective phosphodiesterase-4-inhibitor+LAMA vs Roflu+LABA/ICS, Roflu+LAMA+LABA/ICS vs no Roflu	No	life time	1 month	Payer	2.50%	QALYs	No
Samyshkin et al (75) – UK - 2014	Markov	Adding selective phosphodiesterase-4 inhibitor, roflumilast, to LABA vs LABA	No	life time	1 month	Payer	3.50%	QALYs	No
Vemer et al (76) – Netherlands - 2014	Markov	Comparing methods of heterogeneity on cost-effectiveness analysis	No	20 years	1 month	Societal	costs 4%, health outcomes at 1.5%	QALYs	Yes
Oostenbrink et al (77) - Netherlands and Canada - 2005	**Markov**	**Tiotropium vs ipratropium, and LABA**	**No**	**1 year**	**1 month (except 1st cycle 8 days)**	**Healthcare**	**NA***	**QALYs**	**No**
Maniadakis et al (78) – Greece - 2006	Markov	Tiotropium vs salmeterol	No	1 year	1 month (except 1st cycle 8 days)	National Health System (NHS)	NA*	QALYs	No
van Molken et al (79) – Spain - 2007	Markov	Tiotropium vs ipratropium, and salmeterol	No	5 years	1 month (except 1st cycle 8 days)	National Health System (NHS)	6%	QALYs	No
Oostenbrink et al (80) – Netherlands - 2008	Markov	Tiotropium vs salmeterol, and ipratropium	No	5 years	1 month	Healthcare	4% for costs and 1.5% for utilities	QALYs	No
Gani et al (81) – UK - 2010	Markov	Tiotropium vs salmeterol or ipratropium	No	1 year	1 month (except 1st cycle 8 days and 2nd cycle 22 days)	National Health Service (NHS)	NA*	QALYs	No
Oppe et al (82) - Not mentioned - 2011	Markov	Different methods of data synthesis on cost-effectiveness analysis	No	5 years	1 month (except 1st cycle 8 days)	Not mentioned	Not mentioned	QALYs	No
Hettle et al (83) - UK and Belgium - 2012	Markov	Adding tiotropium to usual care vs usual care alone	No	4 years	1 month	Healthcare payer	UK: 3.5%. Belguim: cost at 3% and benefit at 1.5%.	QALYs	No
Hoogendoorn et al (84) – Netherlands - 2012	Markov	Tiotroipum vs salmeterol	No	5 years	1 month	Both healthcare and societal	cost 4%, effects 1.5%	QALYs	Yes
Hoogendoorn et al (85) – Germany - 2013	Markov	Tiotropium vs salmeterol	Yes	5 years	1 month	Both statutory health insurance and the societal	3%	QALYs	Yes
Hoogendoorn et al. (86) – Netherlands - 2005	**Markov**	**Minimal smoking cessation counselling, and intensive counselling plus bupropion**	**Yes**	**25 years**	**1 year**	**Representative national registries**	**4%**	**QALYs**	**No**
van Boven et al (87) – Belgium - 2014	Markov	PHARMACOP-intervention (for improving adherence)	No	1 year	3 months	Healthcare payer	Costs at 3.0% and effects at 1.5%	QALYs	No
Zafari et al (88) – Canada - 2014	Markov	Impact of network vs pair-wise meta-analysis on the value of information	No	10 years	1 year	Not mentioned	3%	QALYs	Yes
Thorlund et al (89) – US - 2014	Markov	Impact of network vs pair-wise meta-analysis on cost-effectiveness analysis	No	10 years	1 year	Third-party payer	3%	QALYs	Yes
Sin et al (90) – Canada - 2004	**Markov**	**Inhaled corticosteroids**	**No**	**3 years**	**3 months**	**Societal**	**5%**	**QALYs**	**Yes**
Earnshaw et al (91) – US - 2008	Markov	Fluticasone propionate/salmeterol, salmeterol, fluticasone propionate, and no maintenance treatment	No	Life time	1 year	Third-party payer	3%	QALYs	No

Authors Country Year	Type of model	Intervention	Dynamic	Time horizon	Cycle length	Perspective	discounting	Effect measure	Indirect costs
Chuck et al (92) – Canada - 2008	Markov	ICS+LABA vs LABA only	No	3 years and life time	3 months	Health systems	3% and 5%	QALYs	No
Buist et al (93) - China, Turkey, Austria, Poland, South Africa, Iceland, Norway, Germany, US, Canada, and Philippines - 2005	Markov	Online interactive model for current and future economic burden of COPD	Yes	5, 10, or 20 years	1 year	Not mentioned	3%	NA	Yes
Nielsen et al (94) - Iceland and Norway - 2009	Markov	Present and future economic burden of COPD	Yes	10 and 20 years	1 year	Societal	3%	NA	No
Atsou et al (95) – France - 2011	Markov	Smoking cessation	No	Life time	1 year	Societal	3.50%	QALYs	Yes
Oba et al (96) – US - 2009	Markov	Long-term oxygen therapy (LTOT)	No	5 years	3 months	Third-party payer	3%	QALYs	No
Oba et al (97) – US - 2009	Markov	SFC, salmeterol, fluticasone, and placebo	No	3 years	3 months	Third-party payer	3%	QALY	No
Liu et al (98) – US - 2013	Markov	Home-based COPD management programs	No	Life time	6 weeks	Public insurer	3.50%	QALYs	No
Zaniolo et al (99) – Italy - 2012	Markov	Adding tiotropium bromide RC vs RC	No	Life time	1 year	National Health Service	3.50%	QALYs	No
Jubran et al (100) – US - 1993	Markov	Theophylline (T) and ipratropium bromide (IB)	No	1 year	1 month	Third-party payer	NA[*]	complication-free therapy-months	No
Chandra et al (101) – Canada - 2012	Markov	Smoking cessation programs	No	Life time	1 year	Publicly funded health care system	5%	QALYs	No
Hoogendoorn et al (102) – Netherlands - 2011	Markov	ICS+LABA, Counselling for smoking cessation, ICS+LABA+counselling for smoking cessation, and pulmonary rehabilitation	Yes	Life time	1 year	Not mentioned	Costs at 4% and health outcomes at 1.5%	QALYs	No
Naik et al (103) – US - 2010	Markov	Tiotropium, salmeterol, and no treatment	No	1 year	6 months	Third-party payer	NA[*]	Exacerbation avoided	No
Menn et al (104) – Germany - 2012	Markov	Smoking cessation vs usual care	No	10, 40, and 60 years	3 months	Societal	3%	QALYs	Yes
Dal Negro et al (105) – Italy - 2007	Markov	Salmeterol/fluticasone, formoterol/budesonide, salmeterol alone, fluticasone alone, and control	No	1, 5, 10 years, and life time	1 year	1)Patient, 2)National Health Service, and 3) societal	No	Symptom-free day and exacerbation avoided	Yes
Menn et al (106) - Not mentioned - 2009	Markov	Hypothetical smoking cessation	No	60 years	3 months	Not mentioned	No	QALYs	No
Van der Palen et al (107) – Netherlands - 2006	Decision tree	Fluticasone propionate vs withdrawal fluticasone propionate (ICS)	No	6 months	NA	Healthcare payer	NA[*]	Cost per exacerbation or hospital admission prevented	No
Neyt et al (108) – Belgium - 2010	Decision tree	Tiotropium vs no tiotropium	No	1 year	NA	Health care payer	NA[*]	QALYs	No
Karabis et al (109) – US - 2014	Time-in-state model	Aclidinium vs tiotropium	No	5 years	1 month	Third-party payer	3%	QALYs	No
Asukai et al (110) - UK - 2013	Individual sampling model	Develop and validate a COPD model to inform policies	No	Lifetime but can be chosen by user	Flexible and defined by user	Healthcare payer	Flexible and defined by user	Flexible with producing different health outcomes such as QALYs or number of exacerbation	No
Price et al (111) – Sweden - 2014	Individual sampling model	IND/GLY, IND+GLY, and SFC	No	Life time	6 months	Societal	3%	QALYs	Yes

Authors Country Year	Type of model	Intervention	Dynamic	Time horizon	Cycle length	Perspective	discounting	Effect measure	Indirect costs
Bilge et al (112) – Turkey - 2006	Discrete-event simulation	Impact of COPD in the future	Not mentioned	15 to 20 years	1 week	Individual's view point or system	Not mentioned	Not mentioned	Not mentioned
Najafzadeh et al (113) – Canada - 2012	System Dynamics	Screening test for COPD, predictive test for exacerbation, and new drugs to avoid progression into more severe COPD	Yes	25 years	Continuous	Societal	3%	QALYs	Yes
Stanciole et al (114) - sub-Saharan, Africa, and South East Asia- 2012	System Dynamics	Low dose ICS vs ICS+LABA, and influenza vaccine	Yes	Life time	Continuous	No	3%	Cost per DALY averted	No

QALYs: quality-adjusted life years, LABA: long-acting beta-agonists, LAMA: long-acting muscarinic antagonists, ICS: inhaled corticosteroids, Roflu: roflumilast, Tio: tiotropium. SFC: salmeterol-fluticasone propionate combination. DALY: disability adjusted life years. COPD: chronic obstructive pulmonary disease. RC: routine care, IND: Indacaterol, GLY: glycopyrronium. Bold: Original models are bolded, and their follower models are listed below them.
*: Time horizon was less than a year.

Table 2.2 represents the results of the assessment of adherence to CHEERS guideline(25). Studies generally did well in following the reporting guideline (even though several papers did not explicitly state adherence to CHEERS or any other guidelines). However, the report of some items was commonly neglected, such as details of the analytical methods (only 34 papers explicitly described the analytical methods), reporting probabilistic distributions along with their parameters (only 25 papers comprehensively mentioned deterministic and probabilistic distributions of parameters), and evaluating heterogeneity through subgroup-specific results (8 papers reported the results per subgroups).

Table 2-2 Evaluation of the simulation models based on Consolidated Health Economic Evaluation Reporting Standards

Legend: ■ = black · ▨ = gray · ▒ = light/hatched · □ = white

Authors	Study perspective	Choice of health outcomes	Measurement of effectiveness	Valuation of outcomes	Estimating resources and costs	Currency and price date	Assumptions	Analytic methods	Study parameters	Incremental outcomes	Characterizing uncertainty	Characterizing heterogeneity
Borg et al (66)	■	■	■	■	■	■	■	■	▒	■	▒	▨
Lock et al (67)	■	■	■	■	■	■	■	■	■	■	■	▒
Price et al (68)	■	■	■	■	■	■	■	▨	▒	■	■	▒
Ariza et al (69)	■	■	■	■	■	■	■	■	▒	■	■	▒
Price et al (70)	■	■	■	■	■	■	■	▨	■	■	■	▒
Spencer et al (71)	■	■	■	■	■	■	■	■	▒	■	■	▒
Sun et al (72)	■	■	■	■	■	▨	■	■	■	■	■	▒
Hertel et al (73)	■	■	■	■	■	■	■	■	▒	■	■	▒
Samyshkin et al (74)	■	■	■	▨	■	■	■	■	■	■	■	■
Samyshkin et al (75)	■	■	■	▨	■	▨	■	■	▒	■	▒	▨
Vemer et al (76)	■	■	■	■	■	■	■	▨	■	■	■	■
Oostenbrink et al (77)	■	■	■	■	■	■	■	■	■	■	■	▒
Maniadakis et al (78)	■	■	■	■	■	■	■	▨	▒	■	■	▒
van Molken et al (79)	■	■	■	■	■	■	■	■	▒	■	■	▒
Oostenbrink et al (80)	■	■	■	■	▨	■	■	▨	▒	■	■	□
Gani et al (81)	■	■	■	■	■	■	■	■	■	■	■	▒
Oppe et al (82)	▨	■	▨	▨	▨	▨	■	■	■	■	■	□
Hettle et al (83)	■	■	■	■	■	■	■	■	■	■	■	▒
Hoogendoorn et al (84)	■	■	▨	▨	■	■	■	▨	▒	■	■	▒
Hoogendoorn et al (85)	■	■	▨	▨	■	■	■	▨	▒	■	■	■
Hoogendoorn et al.	■	■	▨	▨	■	■	■	■	■	■	▒	■
van Boven et al (87)	■	■	■	■	■	■	■	■	■	■	■	▨
Zafari et al (88)	▨	■	■	▨	■	■	■	■	■	■	■	□
Thorlund et al (89)	■	■	■	▨	■	■	■	■	■	■	■	□
Sin et al (90)	■	■	■	▨	▨	▨	■	■	▒	■	▒	▒
Earnshaw et al (91)	■	■	■	▨	■	■	■	■	■	■	■	▨
Chuck et al (92)	■	■	■	■	■	■	■	■	▒	■	■	▒
Buist et al (93)	▨	□	□	□	■	▨	■	■	■	□	▒	■
Nielsen et al (94)	■	□	□	□	■	■	■	■	■	□	▒	■
Atsou et al (95)	■	■	■	▨	■	■	■	■	▒	■	▒	■
Oba et al (96)	■	■	■	▨	▨	■	■	▨	▒	■	■	▨
Oba et al (97)	■	■	■	■	■	■	■	■	▒	■	■	▨
Liu et al (98)	■	■	■	▨	■	■	■	■	■	■	■	▒
Zaniolo et al (99)	■	■	▨	■	■	▨	■	▨	▒	■	■	▒
Jubran et al (100)	■	■	■	■	▨	▨	■	▨	■	■	▒	▨

Authors	Study perspective	Choice of health outcomes	Measurement of effectiveness	Valuation of outcomes	Estimating resources and costs	Currency and price date	Assumptions	Analytic methods	Study parameters	Incremental outcomes	Characterizing uncertainty	Characterizing heterogeneity
Chandra et al (101)	yes	yes	yes	yes	yes	no	yes	yes	partial	yes	yes	no
Hoogendoorn et al	no	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	partial
Naik et al (103)	yes	yes	yes	no	yes	yes	yes	no	partial	yes	partial	no
Menn et al (104)	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Dal Negro et al (105)	yes	yes	yes	no	yes	no	yes	no	yes	yes	partial	no
Menn et al (106)	no	yes	no	no	no	no	yes	no	no	yes	yes	
Van der Palen et al	yes	yes	yes	yes	no	yes	no	yes	partial	yes	yes	yes
Neyt et al (108)	yes	yes	yes	yes	yes	no	yes	yes	yes	yes	yes	partial
Karabis et al (109)	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	no
Asukai et al (110)	yes	yes	no	yes	no	no	yes	yes	yes	yes		
Price et al (111)	yes	yes	yes	no	yes	yes	yes	yes	partial	yes	yes	no
Bilge et al (112)	yes	no	no	no	no	no	yes	no	no			
Najafzadeh et al (113)	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	partial	yes
Stanciole et al (114)	no	yes	yes	no	no	yes	yes	no	partial	yes	yes	no

(Black=yes, grey= no, shaded no colour=partially, no color=not applicable or not mentioned)

Review of models with regard to COPD-specific features: In terms of modeling COPD progression, 41 studies modeled transition across GOLD grades (66–97,99,101,102,104–106,109,113,114), whereas only 2 modeled progression through FEV$_1$ decline(110,111). Four Markov models used exacerbation status in defining model states (98,100,107,108), and one study modeled COPD through states defined by the maintenance therapy usage. One study did not clearly mention how the authors modeled the disease progression (112).

For the most part, treatment effect was modeled as a direct reduction in exacerbation rate without any impact on lung function (73,74,85,87–92,97–99,103,105,107,108).

However, several other studies modeled the impact of treatment in improving lung function either without (67,86,95,96,104,106,109) or with a simultaneous impact on reducing the rate of exacerbations (66,68–72,74,76–79,81–84,101,102,110,111,113). The impact on lung function, however, was mostly modeled through a one-time jump in lung function at the beginning of therapy. One study modeled treatment effect through direct reduction in disease mortality and disability (114). In 3 studies it was not clearly mentioned how the effect of treatments was modeled (80,100,112).

Most studies incorporated at least some aspects of disease heterogeneity into their main analysis through subgroup-level stratification. The most popular subgroup variables were baseline disease severity, sex, and age. However, only 8 studies clearly reported results of subgroup-specific analyses (75,76,85,86,94,95,104,113).

Only two models, those by Lock et al (67) and Zaniolo et al (99), explicitly incorporated the impact of co-morbidities. The former evaluated the cost-effectiveness of smoking cessation, and the latter the cost-effectiveness of tiotropium bromide. Both authors acknowledged the importance of comorbid conditions in the context of their evaluation. Some other models indirectly considered the impact of comorbidity. Price et al (111) mentioned co-morbidity as a predictor for calculating utility values. In Bilge et al (112), comorbidity was mentioned to be "a variable in the model"; however, the exact nature and impact of such variable was not discussed explicitly.

2.4   Discussion

We performed a systematic review of simulation models of COPD that have been used for burden of disease projections or economic evaluation of interventions and programs for COPD. Our systematic review identified 49 models. There are some general similarities among the studies. For example, most of the studies (n=43) used a Markov modeling approach. Modeling the progression of COPD based on transition across established clinical grades was a common feature. However, there was greater heterogeneity in modeling the specific aspects of COPD including assumptions of treatment effects and disease progression. Generally models did well in complying with the standard modeling reporting guidelines.

There were some limitations in this study. First, only English articles were included in our search. Second, model development is a very complex process containing many elements ranging from evidence synthesis to deciding on underlying assumptions to identify the relevant outcomes. As such, there has been a certain level of subjectivity in our assessment of published models. A more comprehensive assessment of models would involve access to the models' code and requesting additional details from the authors. Running identical scenarios on different models as well as enabling or disabling some of the model features would provide critical insight into the impact of different assumptions on the variability in the reported results.

Several models included some aspects of heterogeneity in the natural history of COPD, mainly through stratification of analysis on patient characteristics. However, given the extent of heterogeneity in the natural history of COPD, and that only a fraction of such heterogeneity can be explained by observable traits (115,116), my conclusion is that, for the most part, heterogeneity was not fully accounted for. In cohort models (e.g., Markov model), even if the outcome of interest is cost-effectiveness for the whole clinical population, violation of the homogeneity principle can cause bias in the estimated outcomes (117). Cohort models should be stratified on subgroups such that each subgroup can be considered a homogenous population. If the creation of many subgroups is required to account for heterogeneity, then cohort models can become unwieldy. In such instances, the use of microsimulation (individual-level modeling) is recommended (26). In addition to this technical requirement, we think there are other reasons to encourage the use of microsimulation. Individual-level modeling has the capacity to provide results that can guide decision making for individual patients based on his/her clinical traits. Individual-level models provide an ideal framework for modeling heterogeneity that is not accounted for by observable traits (e.g., through assigning random-effect terms to simulated individuals). However, it is important to note that implementing such individual-level modeling would, generally, come with more complexity and a longer development time.

In conclusion, many COPD models have been developed, generally with similar structural elements. However, modeling practice in COPD is in need of improvement to

more fully acknowledge the highly heterogeneous nature of the disease. This critical aspect has not been adequately addressed in the vast majority of the published COPD models. Accounting for such extensive heterogeneity would be very difficult through cohort-based models, as so many sub-groups should be created. Thereby, micro-simulation models seem to be a more valid tool for fully reflecting heterogeneity in this context. Therefore, there is a significant window of opportunity to quantify such heterogeneity, and quantify the value of personalizing medicine that capitalizes on the significant between-individual variation in COPD to maximize the efficient of disease management strategies.

Chapter 3: Economic and Health Impact of Improving Adherence in Asthma

3.1 Introduction

The current and future public health burden of asthma is a complex function of several factors including the characteristics of individuals with asthma, the current level of asthma control, the innate level of disease activity, as well as practice patterns, the availability of health care resources, and changes in the population (e.g., population growth and aging).

The main objective of asthma management is to achieve clinical control and prevent the future risk of exacerbations (118). My overall goal in this thesis has been to identify the most cost-effective treatment strategy in asthma to bring the disease under control. Despite the availability of effective treatments in achieving asthma control (119), in practice there remains a high prevalence of poorly controlled asthma due to sub-optimal adherence to the current standard therapy (e.g., ICS+LABA) (120,121). This signifies a care gap and potential for improvements in asthma control and reduction in the burden of disease. In this chapter, I investigated whether or not improving adherence to the asthma standard therapy is cost-effective.

3.2   Methods

A decision-analytic model of asthma was created to estimate the outcomes associated with two contrasting scenarios with regard to asthma management in the US: the *status quo* scenario which represents the current state of asthma controller therapy, and a *full-adherence* scenario based on providing regular controller treatment to all adults (19 years or older) with uncontrolled asthma at baseline. Although modern guidelines recommend controller therapy for all but the mildest asthma, regardless of the current control status, we thought potential programs in improving adherence would most likely start with patients with uncontrolled asthma. The outcomes associated with such a *full-adherence* scenario can be seen as an upper limit of the return on investment of programs that improve adherence. We also used the same analytical framework to perform a scenario analysis in which the cost-effectiveness of a hypothetical intervention as a function of its operational cost and the resulting change in adherence was quantified.

The outcomes of the model were the direct asthma-related medical costs, quality-adjusted life years (QALYs), and number of exacerbations, all measured over a 10-year time horizon among the cohort of prevalent uncontrolled asthma cases in the US. The figure of merit in this analysis was the incremental cost-effectiveness ratio (ICER), with QALY as the effectiveness outcome, for the *full-adherence* scenario relative to the *status quo* scenario, as well as for the hypothetical intervention relative to the *status quo*

scenario. Cost-effectiveness was assessed using willingness-to-pay (WTP) thresholds of $50,000/QALY and $100,000/QALY.

The Model: I created a Markov model of asthma with 1 week cycle length in which individuals with asthma transition between three levels of control (controlled, partially controlled, and uncontrolled) as defined by the Global Initiative for Asthma (GINA) (122), and separate states representing asthma exacerbation and death over a 10-year time horizon. Figure 3.1 provides an illustration of the asthma model. The model was created in the statistical programming environment R version 2.15.2 (123).

Figure 3-1 Schematic illustration of the asthma Markov model
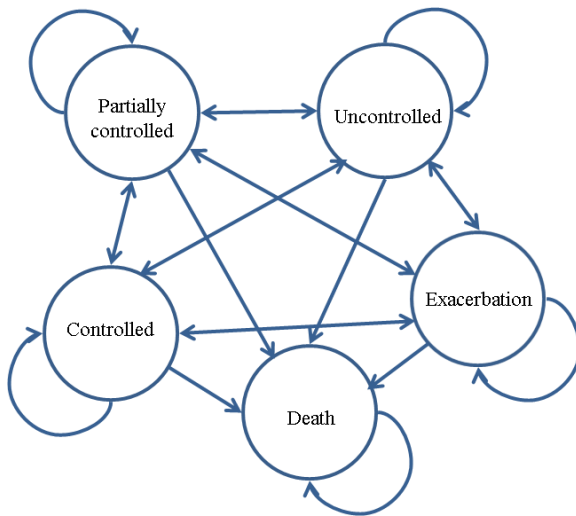
Subgroups: The cost-effectiveness of treatment strategies can be different across different subgroups in a population. Modeling the natural history of the disease and the impact of treatment within subgroups increases the accuracy of a decision analysis. In

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addition, if such subgroups can be determined at the time of providing the treatment, then the overall efficiency of the program can be improved through a targeted implementation of the subgroup-specific cost-effective strategies. In this context, age at baseline and the baseline level of controller therapy are two important variables that could conceivably affect the outcomes, which could also be easily ascertained at the implementation stage.

To model the effect of age at baseline, I stratified the population into three age groups (18-35, 36-64, and >64) (124). In addition, individuals with uncontrolled asthma at baseline can be receiving different intensities of controller therapies. The course of asthma and responsiveness to controller therapy is presumably different between an individual who is uncontrolled despite high doses of controller therapy, versus an individual who is uncontrolled but is not receiving any controller medication. To recognize the variation in the baseline level of controller therapy, I classified individuals at baseline into three strata, in accordance with the definition used in the landmark Gaining Optimal Asthma Control (GOAL) study (119). Stratum I consisted of individuals with uncontrolled asthma who are not using any controller medications; stratum II consisted of individuals with uncontrolled asthma who receive low dose controller therapy (beclomethasone-equivalent daily dose of up to 500mcg); and stratum III consisted of individuals who are uncontrolled despite medium or high doses of controller therapy (beclomethasone-equivalent daily dose of 500-1,000mcg). The proportion of patients who do not receive any controller medication despite having

uncontrolled asthma (stratum I) in the US is reported to be 40% (124). The relative proportion of individuals in strata II and III was inferred from another study that reported adherence rates to ICS in uncontrolled asthma patients (48).

Consistent with the step-up approach in asthma therapy as recommended by the GINA guideline (122), for patients in strata I and II the controller therapy was chosen to be higher doses of ICS, whereas for patients in stratum III who are already receiving high dose ICS, combination of ICS and long-acting beta agonists (LABA) was chosen as the treatment.

Model Parameters: Table 3.1 presents the parameters used to populate the model. Some model parameters were estimated through combining sources of evidence and performing model calibration.

Table 3-1 Model parameters

Parameter (Reference)	Baseline value	Probability distribution
Age distribution in Asthmatic population [*] (124)		
18-35	33%	
36-64	52%	Dir(6988.7, 11012.6, 3176.7)
>64	15%	
Prevalence of uncontrolled asthma [†] (124)		
18-35	71.3%	beta(5040, 2033)
36-64	75.8%	beta(8388, 2677)
>64	80.1%	beta(2435, 605)
Distribution of patients in strata [‡] (48,124)		
Stratum I	40%	
Stratum II	35%	Dir(17396.4, 15134.9, 10959.7)
Stratum III	25%	
Back ground mortality rates (125)	<See the relevant tables in the reference>	None

Parameter (Reference)	Baseline value	Probability distribution
Annual asthma mortality rate-age adjusted (126)	0.000011	None
Relative risk of exacerbation per 25% increase in Cumulative medication gap (48)	1.26	lognormal(0.23, 0.14)
Direct Costs (127,128) Treatment costs for *full-adherence* scenario (Weekly $US)[§]		
Stratum I	$9.94	gamma (3083.7, 310.2)
Stratum II	$11.18	gamma (3900.3, 348.9)
Stratum III	$18.4	gamma (10566.5, 574.3)
Other (maintenance) costs (Weekly $US)		
Controlled	$0.04	gamma (0.004, 0.112)
Partially controlled	$0.32	gamma (0.328, 1.024)
Uncontrolled	$2.21	gamma (15.631, 7.073)
Exacerbation	$64.49	gamma (33.039, 0.512)
Indirect costs (for sensitivity analysis) (129)		
Controlled	$159	gamma (0.1651, 0.0010)
Partially controlled	$179	gamma (0.1651, 0.0010)+gamma (0.1634, 0.0079)
Uncontrolled	$301	gamma (0.1651, 0.0010)+gamma (5.9329, 0.0419)
Exacerbation[||] (130)	$827	gamma (0.1651, 0.0010)+gamma (16, 0.0239)
Health state Utility Values (127)		
Controlled	0.946	beta(398.4, 22.7)
Partially controlled	0.9	beta(668.5, 74.3)
Uncontrolled	0.842	beta(924.9, 173.6)
Exacerbation	0.729	beta(851.5, 316.5)

All costs are adjusted to 2011 USA dollars. Dir(a, y, z): *dirichlet* distribution with concentration parameters a, y, and z. N(x, y): normal distribution with mean x and standard deviation y. lognormal(x,y): log normal distribution with mean x and standard deviation y for the log-transformed values. gamma (x, y): gamma distribution with shape parameter x and rate parameter y. beta(x, y): beta distribution with shape1(alpha) parameter x, and shape2 (beta) parameter y.

*: The probability distribution was estimated based on the population sample size (21,178) of adults with asthma (124).

†: The probability distribution was estimated based on the population size of adults with uncontrolled asthma across different age groups (9).

‡: We assumed distribution of uncontrolled asthmatics across age groups remains the same in all strata. Details are provided in the online Supplementary Material (Appendix I).

§: For strata I and II the controller therapy was considered to be ICS, whereas for stratum III the controller therapy was ICS+LABA.

||: When modeling productivity loss in exacerbation state, it was assumed that no patient goes to work.

Transition Probabilities: A critical set of model parameters is the transition probabilities across the model states for a given level of adherence to controller medications. For the *full-adherence* scenario, we used the stratum-specific weekly transition probabilities from the corresponding arm of the GOAL study (131). Because GOAL did not include a placebo arm, it does not provide evidence on the transition probabilities when individuals do not take controller medication, or take it irregularly. Unfortunately, no placebo-based randomized controlled trial (RCT) has reported transition between levels of asthma control. In general, asthma control as defined by modern guidelines has rarely been an outcome of previous RCTs. Nevertheless, many placebo-controlled RCTs have reported on asthma exacerbation rates which are related to the level of control (48,132–137). I used the reported association between rate of exacerbation and control status, as well as the relation between adherence to controlled medication (quantified as the proportion of days covered [PDC] with the controller medication) and exacerbation rates, to indirectly estimate the transition probabilities (48,132–137).

Model Costs: Details on the cost parameters are provided in Table 3.1. Costs in the base case analysis included the cost of controller treatment itself, costs incurred while experiencing exacerbation, and the 'maintenance' costs of asthma management within each level of control (not including the controller treatment costs). In the main analysis I followed the recommendation of the US Panel on Cost-Effectiveness in Health and Medicine (138) and excluded productivity costs from the reference case analysis. All the costs were adjusted to 2011 US dollars.

Health state utility values (HSUVs): HSUVs associated with each level of control were derived from Briggs et al (127), and are shown in Table 3.1. It was assumed that taking controller therapy does not directly affect HSUVs, and the impact of taking controller medication is mediated solely through changes in control levels and risk of exacerbation.

Analysis: In the main analysis, I ran the model simultaneously (to have the same characteristics for both arms) for the *status quo* and *full-adherence* scenarios and estimated the total (discounted) costs, number of exacerbations, and QALYs over a 10-year time horizon. The permutations of the two subgroup-defining variables create nine subgroups. I separately ran the model for all subgroups and evaluated whether the cost-effective scenario varies across subgroups. The outcomes for the whole population were the weighted-sum of the subgroup-specific outcomes with weights being the relative prevalence of the subgroup in the target population. I reported the expected value and variation of model outcomes, and calculated the incremental cost-effectiveness ratio (ICER) for the *full-adherence* versus the *status quo* scenarios. Costs and QALYs were discounted at the rate of 3%, while exacerbation rates were not discounted. All the analyses were done in statistical program R 3.1.0 (139).

In addition to the comparison between the *full-adherence* and *status quo* scenarios, I performed a scenario analysis in which the cost-effectiveness of a hypothetical intervention with a given cost (modeled as annual program costs) and efficacy (in terms of the relative improvement in adherence compared with the *status quo* scenario) was

evaluated. Results of the scenario analysis are presented as a 'cost-effectiveness map' highlighting the combination of program cost and efficacy values that will render such a hypothetical scenario cost-effective.

Probabilistic analysis was performed by assigning probability distribution to model parameters (reflecting uncertainty in their values) and using Monte Carlo simulation with 5,000 iterations to generate a random sample of model outcomes. In assigning probability distribution to model parameters, I relied on the reported measures of sampling uncertainty (e.g., standard error and confidence intervals); whenever such measures were not available, expert opinion was used to assign a plausible distribution to the parameter of interest. The output of the probabilistic analysis was used to construct credible intervals (CI) around point estimates of the model outcomes, and create the cost-effectiveness plane and cost-effectiveness acceptability curve (CEAC).

I performed a series of sensitivity analyses. These included incorporation of productivity loss in the analysis, varying the unit costs, investigating different parametric forms for relation between adherence and asthma control, as well as varying parameters such as baseline age, time horizon, and discount rate.

3.3 Results

Figure 3.2 depicts the changes in the level of control among asthma patients who are uncontrolled at baseline over 10 years under the *status quo* and *full-adherence*

strategies. At the end of the 10 years in *status quo* scenario, 62% of person-weeks belonging to the population who were still alive were controlled or partially controlled, whereas the corresponding value for the *full-adherence* scenario was 74%. Over the course of 10 years, the *full-adherence* scenario reduced the number of weeks with uncontrolled asthma by 31%, and the number of exacerbations by 40%.

Figure 3-2 Changes in levels of control over 10 years: (A) status quo scenario; (B) full-adherence scenario

(A)
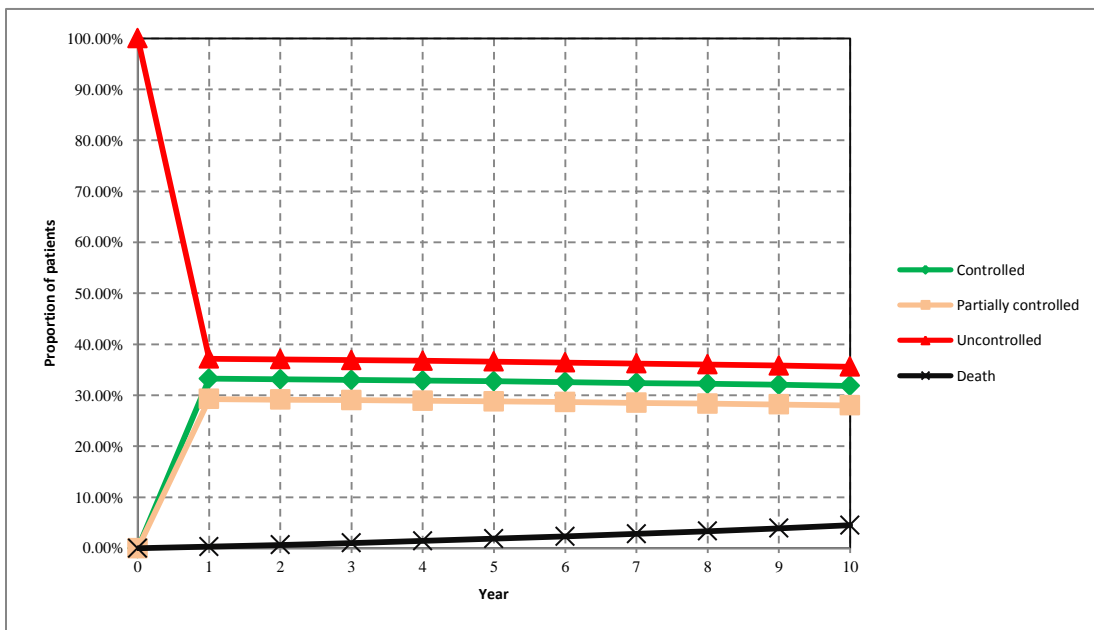
(B)
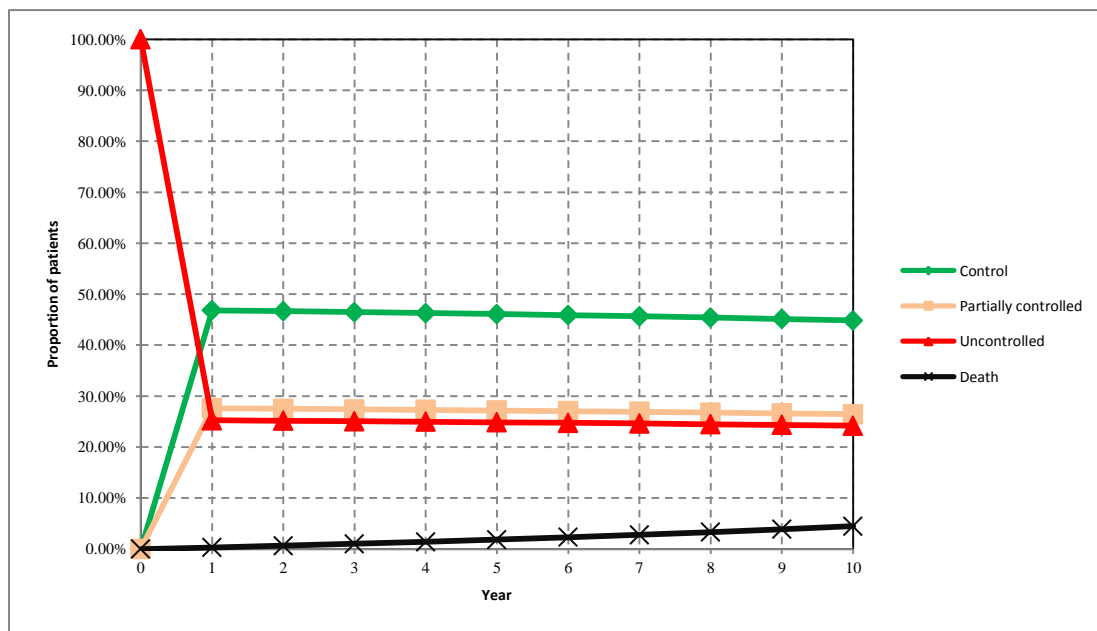
Exacerbation state was incorporated in the uncontrolled state in this figure.

Table 3.2 represents the outcomes for the overall population for both scenarios. For the *status quo* scenario, total costs, exacerbations, and QALYs were calculated as $2,786, 5.20, and 7.55, respectively, over 10 years. The corresponding values for the *full-adherence* scenario were $5,973, 2.94, and 7.68. In other words, the *full-adherence* scenario was associated with $3,187 more costs, 2.26 fewer exacerbations, and 0.13 more QALYs compared to the *status quo* scenario. The overall ICER was therefore $24,515/QALY. Subgroup-specific ICERs varied from $20,591/QALY (age group 36-64, stratum II) to $36,620/QALY (age group >64, stratum III). As such, for both WTP thresholds of $50,000/QALY and $100,000/QALY, the *full-adherence* scenario remained cost-effective across all subgroups.

Table 3-2 Outcomes associated with scenarios

Outcome parameter (10 years)	Scenario	
	Status quo (95% CI)	Full-adherence (95% CI)
Cost	$2,786 (2,476-3,246)	$5,973 (5,765-6,274)
Quality adjusted life years (QALY)	7.55 (7.40-7.69)	7.68 (7.56-7.79)
Number of exacerbation	5.20 (2.38-9.82)	2.94 (1.57-4.79)
Incremental cost per one QALY gained (ICER)	Reference	$24,515/QALY

CI: credible interval, QALY: quality-adjusted life year, ICER: Incremental cost-effectiveness ratio.

Deterministic and probabilistic analyses: Figure 3.3 depicts the results of one-way sensitivity analyses. Treatment cost had a substantial impact on the ICER. Nevertheless, even when the costs were increased by 25%, the ICER was still below $50,000/QALY. The ICER surpassed the WTP thresholds of $50,000/QALY and $100,000/QALY when unit cost of treatment increased by 80% and 250%, respectively. When indirect costs were included, the *full-adherence* scenario becomes dominant (cost-saving and more effective) compared with the *status quo* scenario. With regard to the relation between adherence and asthma control, the *full-adherence* strategy remained cost-effective at WTP of $50,000/QALY as long as each 25% increase in PDC reduces the exacerbation rate by at least 1.1-fold. Other scenarios such as changing baseline age, relative prevalence of uncontrolled asthma across age groups, time horizon, and discount rate did not have significant impact on the ICER.

Figure 3-3 Results of one-way sensitivity analyses

ICER for a QALY gained
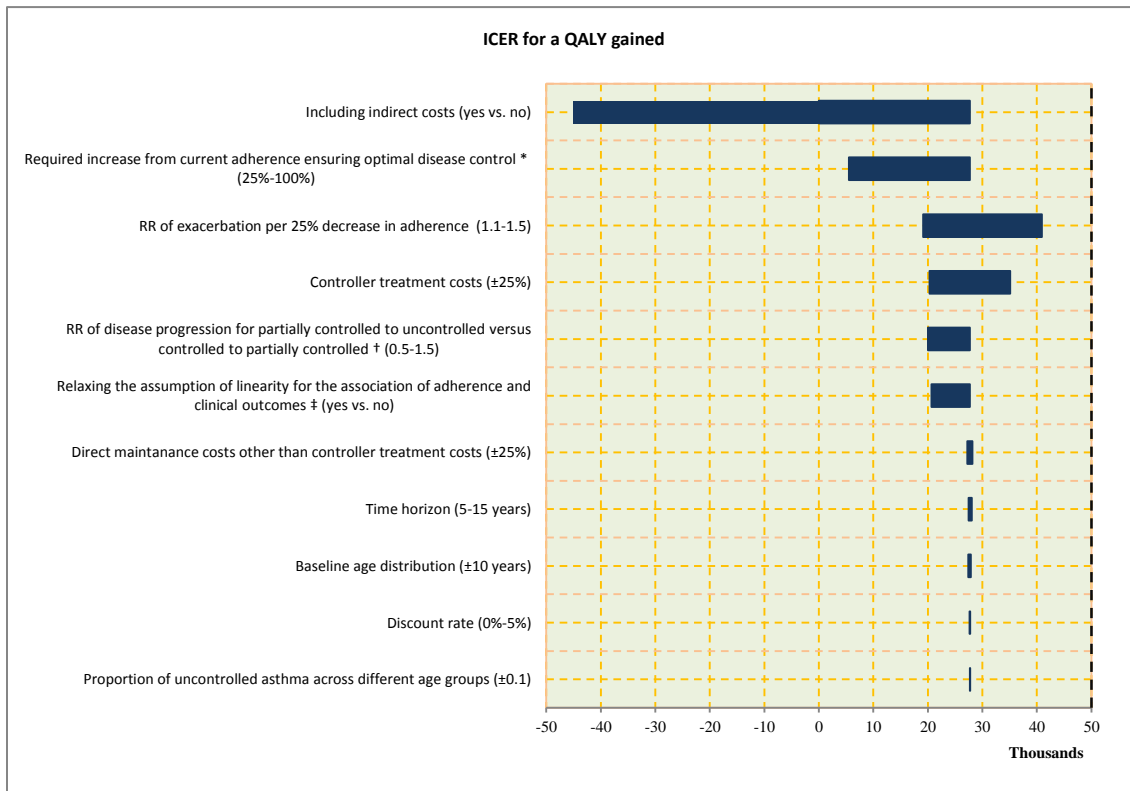
ICER: incremental cost-effectiveness ratio, QALY: quality-adjusted life years, RR: relative risk.

*: In this sensitivity analysis we assume that partial-adherence can have the same effect as full-adherence in achieving asthma control. For instance, lower bound of this sensitivity analysis means 25% increase in current adherence levels is as good as full adherence.

†: Effects the transition probabilities.

‡: Effects the transition probabilities.

Figure 3.4 shows the results of the probabilistic analysis. In the cost-effectiveness plane (Figure 3.4A), the entire uncertainty of cost-effectiveness pairs falls into the north-east quadrant, indicating that despite uncertainty in model parameters, the *full-adherence* scenario is always more costly but also more effective than the *status quo* scenario. The CEAC is provided in Figure 3.4B. At the WTP value of $50,000/QALY, the probability of

the *full-adherence* scenario being cost-effective was 0.9; this value increased to 0.99 at
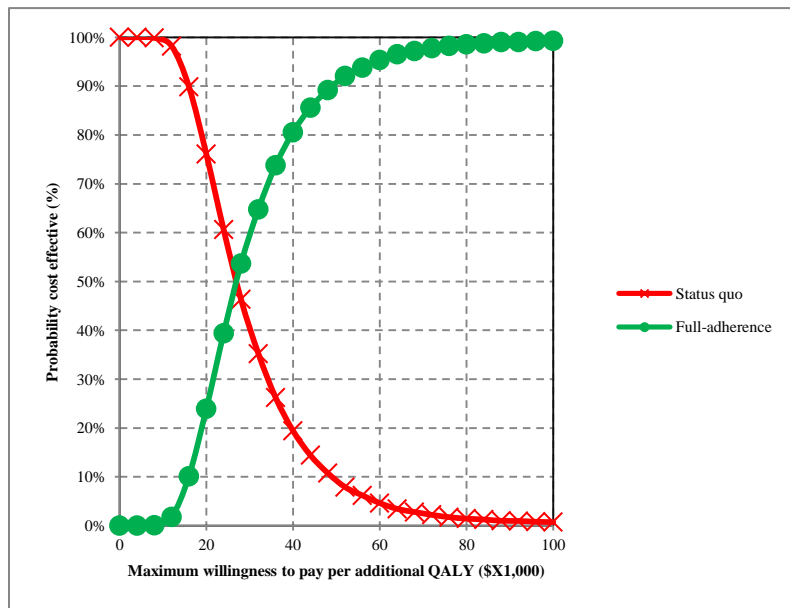
the WTP value of $100,000/QALY.

Figure 3-4 (A) Cost effectiveness plane; (B) Cost effectiveness acceptability curve (CEAC)

(A)
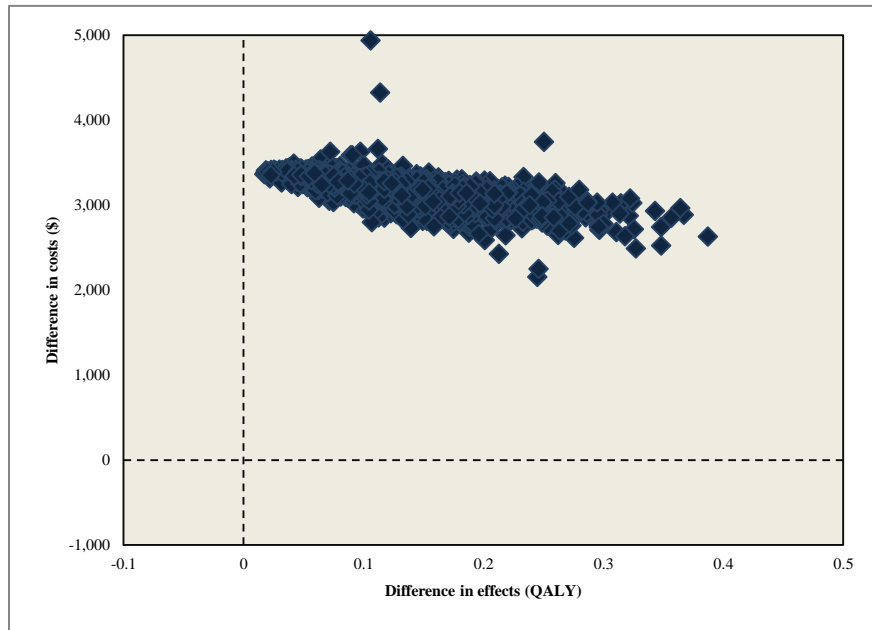
(B)

QALY: quality-adjusted life years.

Scenario analysis: Figure 3.5 represents the results of the scenario analysis in which the cost-effectiveness of a hypothetical program aimed at improving adherence is provided as a function of the program's costs (dollar/year) and efficacy (% improvement in adherence or % decrease in non-adherence). The shaded areas represent the cost-effective region. At WTP of $50,000/QALY, each $29 increase in the program's annual costs will need to increase the adherence level by approximately 10% in order for the program to be cost-effective. On the other hand, at WTP of $100,000/QALY, each $100

increase in program's annual costs will need to increase the adherence level by at least

10% for the program to remain cost-effective.

Figure 3-5 Results of the scenario analysis at willingness-to-pay value of $50,000/QALY (left panel) and $100,000/QALY (right panel)
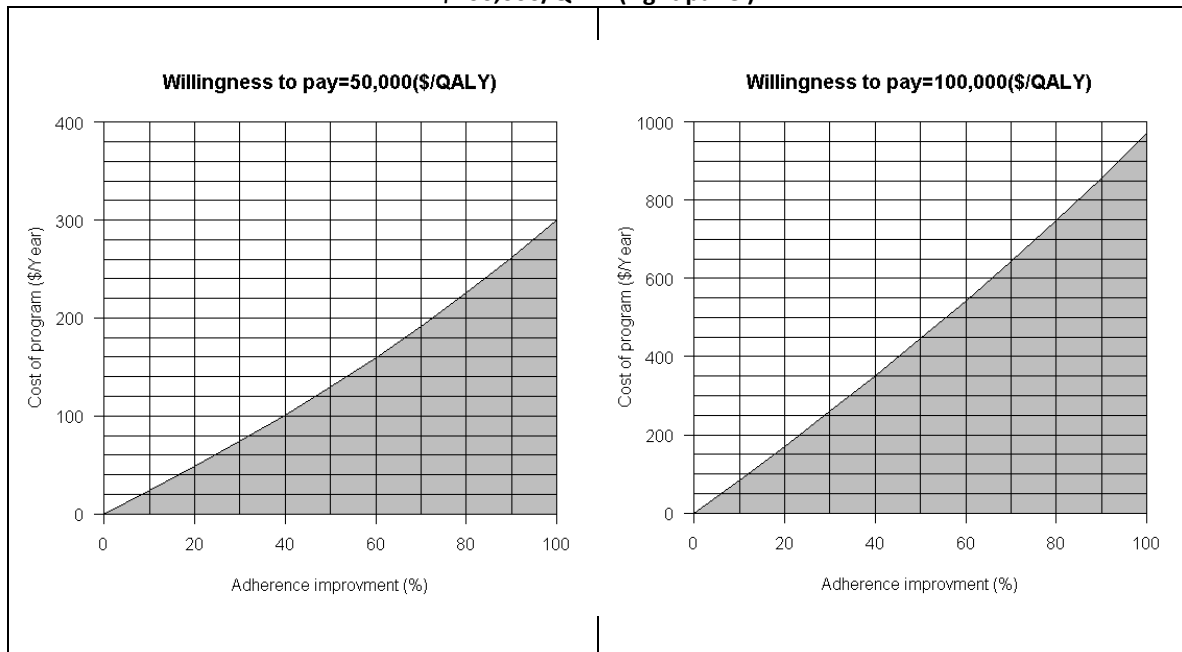
Adherence improvement is relative to the extent of gap between *status quo* level of adherence and *full adherence*. For example, a 50% improvement means the level of adherence after implementing the program will be at the midpoint of adherence between the *status quo* and *full adherence* scenarios within each stratum.

3.4 Discussion

In this chapter, I investigated the health and cost impact of ensuring full adherence to

controller therapies among adults with uncontrolled asthma, and compared it with the

status quo scenario informed by the current level of controller therapy in the US.

Although my *a priori* hypothesis that full adherence to controller therapy will reduce the

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total cost of asthma was not confirmed, I observed a significant improvement in asthma-related outcomes at acceptable costs. Compared to the *status quo*, assuring such full adherence reduced the number of weeks with uncontrolled asthma by 31% and the rate of exacerbations by 40%. My scenario analysis also indicated the potential for adherence interventions to be cost-effective, although such adherence interventions should meet strict cost thresholds. Nevertheless, based on this study, I noticed that still about 23% of asthma patients remain uncontrolled despite full adherence to ICS+LABA. Therefore, to achieve my overall goal to evaluate the population level impact of implementing a strategy to achieve an optimal asthma control, in the next chapter, I am going to evaluate the most cost-effective step up therapy for those uncontrolled asthma patients despite full adherence to ICS+LABA.

Other studies have attempted to evaluate the impact of adherence on the burden of asthma. Many studies have evaluated the cost-effectiveness of a specific intervention resulting in adherence improvement (140–143). While ultimately, specific adherence interventions require their dedicated economic evaluation, such studies would not measure the care gap that exists because of low adherence, as their outcomes are confounded by the specifics of the intervention such as its costs and effectiveness profile. On the other hand, other studies have looked at the economic aspect of adherence, but not its impact on quality of life (144–146), while others have investigated the impact of adherence on asthma-related outcomes, but not costs or quality of life (48,147). Concomitant evaluation of both costs and quality of life

outcomes is required to show cost-effectiveness. Finally, several of the previous studies have been based on the analysis of specific observational or trial data (146), whereas our study was based on the synthesis of evidence from multiple sources, including land mark trials which gives weight to the generalizability of our results.

There were some limitations to this study. Transition probabilities associated with *the full-adherence* scenario were derived based on a one-year randomized trial (131) but were extrapolated over the 10 year time horizon of our study. However, it has been shown that asthma phenotypes are relatively stable over this length of time (148). In addition, controller therapy is not a cure for asthma, and it is the conventional wisdom that continuous, regular controller therapy is required for keeping asthma under clinical control, and that discontinuation of controller therapy is associated with re-emergence of asthma impairment (149). As such, extrapolating the findings of short-term studies is a legitimate action in the absence of long-term data. On the other hand, some studies have suggested that intermittent use of controller medication can, under certain circumstances (150), have the same effect as full adherence, a factor that needs to be evaluated in future research. Furthermore, it is hypothesized that regular controller therapy especially in the early years of asthma in younger patients might have long-term beneficial impact on the natural history of the disease (151). If this is the case, there will be stronger support in favor of ensuring higher adherence to controller therapies especially in the younger population.

The overall impact of a new treatment at the population level is not only determined by its effectiveness but also by the size of the population eligible to receive such a treatment. The pharmaceutical and research community is putting significant efforts into developing new treatments for asthma, but the majority of the new technologies in the pipeline are targeted towards the minority of patients with severe disease. This is despite the fact that access to appropriate controller therapies as well as ensuring adherence to currently available therapies remain a significant problem globally (48). Increasing adherence to currently available medications across the entire spectrum of patients with uncontrolled asthma can potentially provide substantial benefit to the society. Improvement in adherence is an achievable target, as some interventions have resulted in substantial increase in adherence (152,153). My overall conclusion is that there is a substantial lost opportunity due to non-adherence to evidence-based treatments in patients with asthma. Future studies need to evaluate the factors at the patient, care provider, and societal-level that result in sub-optimal adherence and develop cost-effective strategies in improving adherence across the entire spectrum of patients with asthma.

Chapter 4: Cost-effectiveness of Treatments for Moderate to Severe Uncontrolled Asthma

4.1 Introduction

In the previous chapter of this thesis, I showed the tremendous potential for improving asthma outcomes at acceptable costs by improving adherence to controller therapies (inhaled corticosteroids [ICS] with our without long-acting beta agonists [LABA]). While ICS is the mainstay of asthma therapy, some patients with moderate-to-severe asthma do not achieve control even with high dose combination therapy with ICS and LABA (154,155).

There have been some promising developments in terms of new therapeutic options for this subgroup of uncontrolled asthma patients. Omalizumab, which is a humanized monoclonal antibody targeting the IgE, is the first of likely many new biologics available for the treatment of moderate-to-severe allergic asthma, which is limited to atopic subjects with an elevated IgE level within a fairly narrow range (50). Recently, yet another approach to the treatment of this patient population has been proposed. Bronchial thermoplasty (BT) is a technique whereby radiofrequency ablation is applied sequentially to the peripheral sub-segmental airways. The procedure involves three bronchoscopies during which sequentially segmental airways are treated (51). Two randomized controlled trials have shown that BT reduces the rate of asthma exacerbations compared with standard (ICS+LABA) therapy (52,53). A recent follow-up

study has provided some evidence regarding safety and ongoing benefits of BT up to five years after the procedure (156). Nevertheless, there is still uncertainty about BT's long-term health benefits, indicating a need for further studies. In contrast, omalizumab has been shown to have a substantial impact on reducing the number of exacerbations and improving quality of life (157). However, its cost-effectiveness versus BT has not yet been studied.

The purpose of this chapter was to evaluate the cost-effectiveness of omalizumab and BT versus standard therapy over a five year time-horizon in patients with moderate-to-severe allergic asthma who are uncontrolled despite full adherence to ICS+LABA in the US.

4.2   Methods

A probabilistic decision-analytic Markov model was developed to compare the economic and humanistic burden associated with standard therapy, BT, and omalizumab in individuals with moderate-to-severe allergic asthma who remain uncontrolled despite using high dose ICS or ICS+LABA. Since the effect size of BT was informed from studies with, at most, a 5-year follow-up and due to a lack of evidence for the continued efficacy for a longer duration (156), I considered 5 years as the time horizon of the base case analysis. I also reported the cost-effectiveness outcomes over life time, in which I conservatively assigned a declining effect to BT efficacy after the fifth year. In addition, I investigated other time horizons (i.e., 10 years with or without declining effect for BT

after the fifth year, and 5 years with a declining effect for BT after the first year) in the sensitivity analyses. Standard therapy was defined by the Steps 3 and 4 of the Global Initiative for Asthma (GINA) treatment strategy (158). All patients were adults between 18 and 65 years old with an average age of 40 years which is similar to the previous studies evaluating the effectiveness of BT (52). At baseline, all patients were uncontrolled despite using high-dose (≥ 1,000 mcg of fluticasone or equivalent) ICS. Short-acting beta-agonists (SABA) were presumed to be used as a reliever medication by all patients. The primary outcomes of the analysis were the discounted direct costs, discounted quality-adjusted life years (QALYs), and the corresponding incremental cost-effectiveness ratio (ICER) over the 5-year time horizon. ICERs were evaluated at two willingness to pay (WTP) thresholds of $50,000/QALY and $100,000/QALY (159–161). The secondary outcomes were the total number of asthma exacerbations and the proportion of subjects who died. The analysis was from the health-care system perspective and future outcomes were discounted at 3% (162,163).

Model Structure: A probabilistic discrete-time Markov model with five health states was used for this analysis. The structure of the model is informed from previous studies (30–34,36,164). In addition to an absorbing state representing death, I modeled four discrete asthma-related states: exacerbation-free and the following three exacerbation states: 1) requiring oral corticosteroids (OCS); 2) requiring a visit to the emergency department [ED]; and 3) requiring hospitalization. A schematic illustration of the model is provided in Figure 4.1. The cycle length of the model was chosen as a week to allow

modeling of exacerbation as an independent health state (165). I used the statistical

program R 3.1.0 to develop and run the model (139).

Figure 4-1 Schematic Markov states
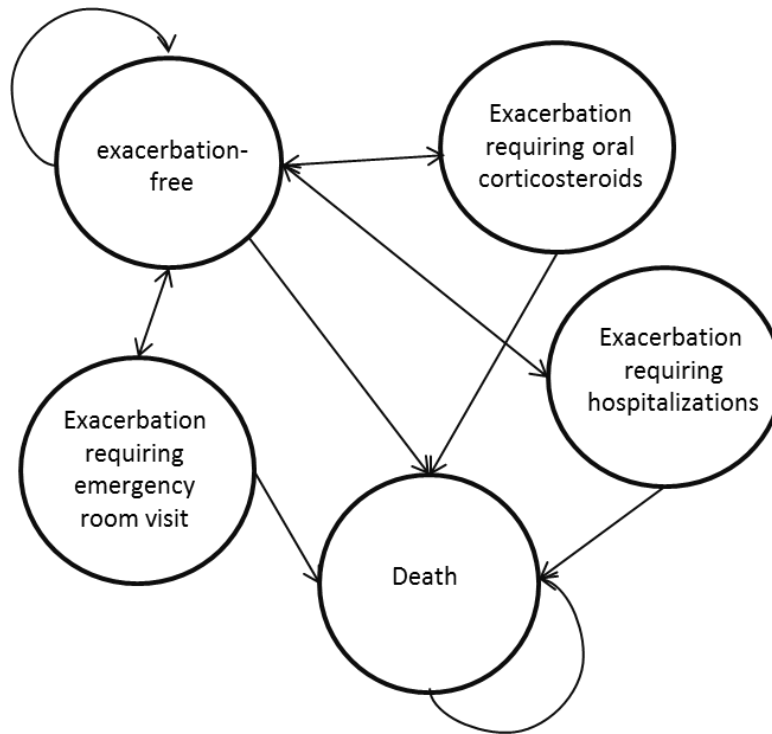
Cycle length is a week.

Model Parameters: Table 4.1 contains all the model parameters including exacerbation

rates associated with interventions, costs of exacerbations (requiring OCS, ED, or

hospitalization), costs of competing interventions (standard therapy, BT, and

omalizumab), and utility values associated with each of the health states. These model

parameters were elicited from published literature, which are described in detail in the

following sections.

Table 4-1 Model Parameters

Parameters	Value	Probability distribution
Age at baseline	40	-
Rate of exacerbation per person-year		
standard therapy		
Exacerbation requiring oral corticosteroids (33,157,166)	1.35	Log-normal(0.29, 0.10)
Exacerbation requiring emergency room visit (157)	0.07	Log-normal(-2.72, 0.10)
Exacerbation requiring hospitalizations (157)	0.06	Log-normal(-2.79, 0.10)
Relative rate of exacerbation per person-year (reference is standard therapy)		
BT		
Exacerbation requiring oral corticosteroids (52,167,168)	0.48	Log-normal(-0.73, 0.09)
Exacerbation requiring emergency room visit (52,167,169)	0.19	Log-normal(-1.64, 0.12)
Exacerbation requiring hospitalizations (52,167,169)	0.30	Log-normal(-1.21, 0.14)
Omalizumab		
Exacerbation requiring oral corticosteroids (33,157,166)	0.63	Log-normal(-0.46, 0.01)
Exacerbation requiring emergency room visit (157)	0.40	Log-normal(-0.92, 0.14)
Exacerbation requiring hospitalizations (157)	0.49	Log-normal(-0.72, 0.12)

Parameters	Value	Probability distribution
Risk of death from hospitalization (30 days) (170)	0.02	Beta(1.10, 43.22)
Background mortality rate (171)	US life tables	None
Cost (2013-$US)		
Treatment costs (per person year)		
Standard therapy (33,172,173)	$2,610	-
Omalizumab (33,157)	$22,700	-
BT *	$14,900	-
Other costs(unit cost) (33,174)		
Exacerbation requiring oral corticosteroids	$130	Γ(100, 0.77)
Exacerbation requiring emergency room visit	$594	Γ(98.01, 0.17)
Exacerbation requiring hospitalizations	$9,900	Γ(100.08, 0.01)
Health state utility values		
Exacerbation-free		
Standard therapy (33,166,175,176)	0.67	Beta(5.92, 2.93)
Utility difference for omalizumab (reference as standard therapy) (177)	0.04	N(0.04, 0.004)
Utility difference for BT (reference as standard therapy) (167)	0.03	N(0.03, 0.02)
Exacerbation requiring corticosteroids (33,175,178)	0.57	Beta(0.51, 0.38)
Exacerbation requiring emergency room visit (33,178)	0.45	Beta(0.36, 0.45)
Exacerbation requiring hospitalizations (33,175,178)	0.33	Beta(0.15, 0.30)

All costs are adjusted to 2013 USA dollars. BT: Bronchial thermoplasty. N(x, y): Normal distribution with mean x and standard deviation y. Γ (x, y): Gamma distribution with shape parameter x, and rate parameter y. Beta(x, y): beta distribution with shape1 parameter x, and shape2 parameter y. Log-Normal(x, y): Log-Normal distribution with log-scale parameter x, and shape parameter y.
*: Calculated based on the costs of three catheters, facility and professional fee, cost associated with

possible hospitalization post BT, and cost associated with possible re-scheduling BT. Cost of three catheters, facility, and professional fee was derived from a published study at $14,100 (38). Cost associated with possible hospitalization post BT was calculated based on 8% chance of hospitalization immediately post BT (52), and $9,900 as a unit cost of hospitalization (33,174) (0.08*$9,900=$792). Cost associated with possible re-scheduling BT was calculated based on 10% chance of re-scheduling (consultation with an expert clinician in our team), and the unit cost of physician visit ($66) (173) adjusted to 2013 US dollars using the US consumer price index (0.1*$66=$6.6).

Transition Probabilities: There is no study directly comparing exacerbation rates between BT and omalizumab. However, there is indirect evidence through comparisons of BT and omalizumab with standard therapy (33,52,157,166). I used data from a meta-analysis by Bousquet et al (157) to inform the relative rates (RRs) of exacerbations requiring ED and hospitalization for omalizumab versus standard therapy. The RR of exacerbations requiring OCS for omalizumab versus standard therapy was informed by Campbell et al (33), which itself was based on the studies by Bosuquet et al (157) and Humbert et al (166). These RRs for exacerbations requiring OCS, ED, and hospitalization were 0.63 (95% credible interval [CrI]: 0.55, 0.73), 0.40 (95% CrI: 0.19-0.82), and 0.49 (95% CrI: 0.25-0.97), respectively.

To determine the RRs of exacerbations for BT versus standard therapy I performed a meta-analysis. For the RR of OCS use, results of the AIR (168) and AIR2 (52) trials were pooled. For the RRs of ED and hospitalization, results of the RISA (169) and AIR2 (52) trials were pooled; Since there were only a few studies informing the efficacy of BT, for constructing the CrIs around its point estimates, between-study variation was borrowed from a meta-analysis of 7 studies of omalizumab with RR of exacerbations as the

outcome (157). However, in a separate probabilistic analysis, I also reported the cost-effectiveness results based on the original 95% CrIs of BT directly estimated from our meta-analysis of BT trials. The pooled RR of exacerbations requiring OCS, ED, and hospitalization from these sources was 0.48 (95% CrI: 0.26, 0.88), 0.19 (95% CrI: 0.10, 0.39), and 0.30 (95% CrI: 0.14, 0.62), respectively. These RRs along with the annual rates of exacerbations in the standard therapy, which were informed from previous studies (33,157,166), were used in the formula, probability=1-exp(-rate/52), to calculate the weekly transition probabilities from exacerbation-free to the three exacerbation states (36).

Costs: All costs were adjusted to 2013 US dollars ($). Cost parameters included costs of standard therapy (controller and reliever medication), BT, omalizumab, and costs of exacerbations stratified by those requiring OCS, ED, and hospitalization. The costs of the three types of exacerbations were derived from previous US studies (33,174).

The costs of standard therapy was calculated based on the published literature (33,172,173). The costs of omalizumab was based on the number of 150mg-vials and administrations needed per year in patients with moderate-to-severe allergic asthma (33,157).

There is still lack of sufficient evidence around costs of BT as a recent technology. For my model I used an average cost estimate of $14,900 per patient. To derive this value, I used a published study to estimate the average cost of three catheters, facility and

professional fee for BT as $14,100 in the US (38), to which I also added the average per patient costs of BT's possible adverse events (i.e., hospitalization post BT and re-scheduling BT procedure). Details of BT's costs are represented in Table 4.1.

Health state utility values (HSUVs): The point estimates and probability distributions assigned to HSUVs are shown in Table 4.1. HSUVs for exacerbation states were informed by representative publications (33,175,178). HSUVs for exacerbation-free state was derived from the Asthma Quality of Life Questionnaire (AQLQ) in the INNOVATE trial (166), and utilities for exacerbation states were derived from a multi-center UK study on moderate-to-severe asthma (178). HSUVs associated with exacerbation states were assumed to be the same across different interventions. On the other hand, I allowed the HSUV of the exacerbation-free state to be different between the three interventions, incorporating the potentially distinct impact of these interventions on symptoms and health-related quality of life outside of the period of exacerbations. The HSUV for the exacerbation-free state under standard therapy was the reference value, upon which changes in HSUV associated with BT and omalizumab were modeled. This reference value of 0.67 has been reported by the National Institute for Health and Care Excellence (NICE) (175), which was calculated based on AQLQ domain scores from INNOVATE study (166) and an algorithm by Tsuchiya et al. (176) to map AQLQ to EQ-5D utility values. The changes associated with omalizumab and BT were estimated from the changes in AQLQ between the respective treatments and standard therapy from the published studies (167,177). I used the same validated algorithm by Tsuchiya et al (176) to convert AQLQ

to HSUVs. This resulted in the point-estimate HSUV of 0.70 (95% CrI: 0.38, 0.95) and 0.71 (95% CrI: 0.39, 0.96) for BT and omalizumab, respectively. In a sensitivity analysis I varied these values to investigate their impact on the outcomes.

Efficacy and adverse events of BT: Even though three studies have already shown the efficacy of BT on reducing the number of exacerbations (52,168,169), there is still substantial uncertainty around BT's real-world effectiveness and its long-term health benefits (167). The three studies have generally used similar methodology. In addition, there might be a risk of bias for effectiveness of BT as two of these three studies did not have a sham intervention for the control arm (167). Furthermore, there are some possible adverse events associated with BT such as requirement for inpatient care after the procedure and need for re-scheduling the procedure in case of asthma symptoms on the procedure day (52). Castro et al. have shown there is 8% chance of hospitalization in the week following BT (52), and since there was no evidence on chance of cancelling and re-scheduling BT in the literature, after a consultation with the expert clinicians of our team, I assigned a chance of 10% for this adverse event.

Analysis: I ran the model separately for standard therapy, BT, and omalizumab, and calculated the average discounted total costs, discounted QALYs, and (undiscounted) number of weeks with exacerbations. The base case results were generated by running the model with the point estimate of parameters.

For probabilistic analysis, I used a Monte-Carlo simulation with 10,000 iterations by randomly sampling from the distribution of model parameters and calculating the outcomes. Probability distributions were assigned to the model parameters based on the literature or expert opinion (i.e., chance of cancelling and re-scheduling BT). The main outcomes of the probabilistic analysis were cost-effectiveness plane (CE-Plane) and cost-effectiveness acceptability curve (CEAC). I additionally calculated the expected value of perfect information (EVPI) at different willingness-to-pay (WTP) values to further quantify the extent of uncertainty and the potential value of future research.

I also carried out detailed deterministic sensitivity analyses to evaluate the robustness of the results against variation in the assumptions and definitions. Specifically, given the uncertainties around the costs of BT, I performed a dedicated sensitivity analysis for this parameter, in which I varied the costs of BT from $8,000 to $30,000.

Other sensitivity analyses included varying other treatment costs, costs of exacerbations, time horizon, rates of exacerbations for standard therapy, RRs of exacerbations, and probability of early hospitalization post BT. In the sensitivity analyses that considered a longer time-horizon beyond five years, I also extrapolated the RR of treatments assuming both of the constant and exponentially declining effects after the fifth year. I also repeated the probabilistic analysis by using the between-study variance estimate for RR of BT from the meta-analysis of BT trials (as opposed to omalizumab trials in the base case analysis).

4.3 Results

Table 4.2 documents the main outcomes of the analysis. Over five years, for standard therapy, the average discounted costs, QALYs, number of exacerbations, and proportion of the population who died were $15,400, 3.08, 7.00, and 0.01, respectively. The corresponding values for BT were $28,100, 3.24, 3.31, and 0.01, and for omalizumab they were $117,000, 3.26, 4.39, and 0.01. My results indicate that omalizumab was the most effective therapy in terms of QALYs gained. Relative to standard therapy, treatment with BT was associated with an ICER of $78,700/QALY, and treatment with omalizumab was associated with an ICER of $552,000/QALY.

In the life time analysis that assumed an exponentially declining effect for BT after the 5th year, the ICER of BT vs. standard therapy, omalizumab vs. BT, and omalizumab vs. standard therapy was $12,500/QALY, $3.15 million/QALY, and $529,000/QALY, respectively.

Table 4-2 The expected value and 95% CrI of outcomes over a five year time frame

Outcome	Standard therapy	BT	omalizumab
Cost (95% CrI)	$15,400($14,700-$16,300)	$28,100 ($27,600-$29,100)	$117,000 ($116,000-$118,000)
QALYs (95% CrI)	3.08(1.64-4.21)	3.24(1.78-4.38)	3.26(1.80-4.40)
Number of oral corticosteroid courses (95% CrI)	6.40(5.27-7.64)	3.15(1.71-5.77)	4.12(3.25-5.14)
Number of emergency department visits (95% CrI)	0.31(0.26-0.38)	0.06(0.03-0.13)	0.13(0.06-0.27)

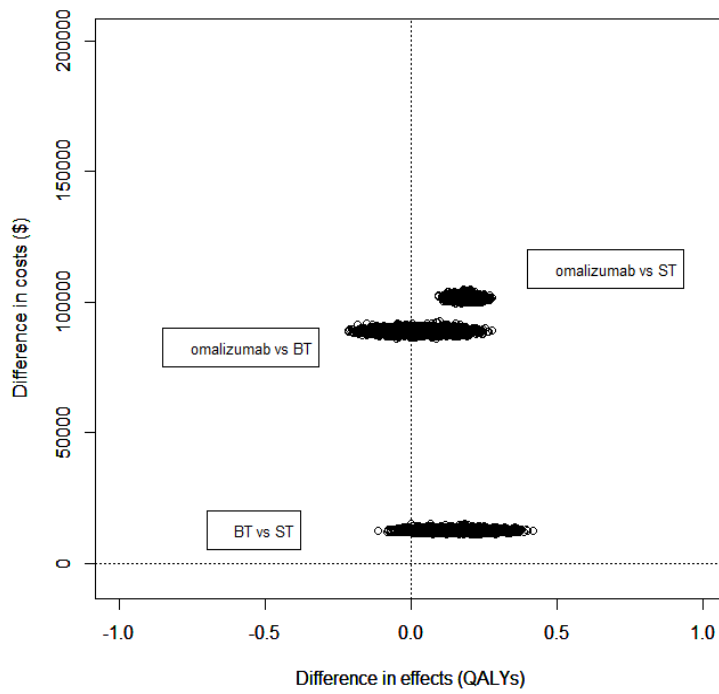| Outcome	Standard therapy	BT	omalizumab
Number of hospitalizations (95% CrI)	0.30(0.24-0.36)	0.09(0.04-0.18)	0.15(0.07-0.30)
Proportion of population died (95% CrI)	0.012(0.010-0.016)	0.011(0.010-0.012)	0.011(0.010-0.014)
ICER			
BT versus standard therapy	Reference	$78,700/QALY	-
Omalizumab versus BT	-	Reference	$3.86 million/QALY
Omalizumab versus standard therapy	Reference	-	$552,000/QALY

BT: bronchial thermoplasty, CrI: credible interval, QALY: quality-adjusted life year, ICER: Incremental cost-effectiveness ratio.

Figure 4.2 shows the results of probabilistic analysis. The CE-planes for BT versus standard therapy, omalizumab versus BT, and omalizumab versus standard therapy are shown in Figure 2(A). Overall, there was substantial uncertainty around comparisons that involved BT. While in the majority of the simulation runs BT was more effective than standard therapy, overall it was associated with higher costs. Also, there was little uncertainty about BT being cost-saving compared with omalizumab, but omalizumab was associated with consistently higher gain in QALYs.

Figure 2(B) shows the CEAC, which indicates the probability of BT being cost-effective was 9% at the WTP of $50,000/QALY and 67% at the WTP of $100,000/QALY. The EVPI at different WTP values is presented in Figure 2(C). EVPI at the WTP of $50,000/QALY was $155 per individual, which increased to $1,530 per individual at the WTP of $100,000/QALY.

Figure 4-2 (A) Cost-effectiveness plane; (B) Cost-effectiveness acceptability curve; and (C) Expected value of information
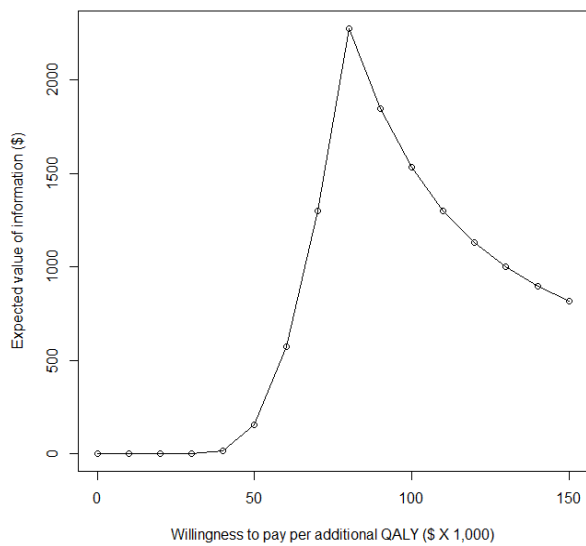
(A)

(B)
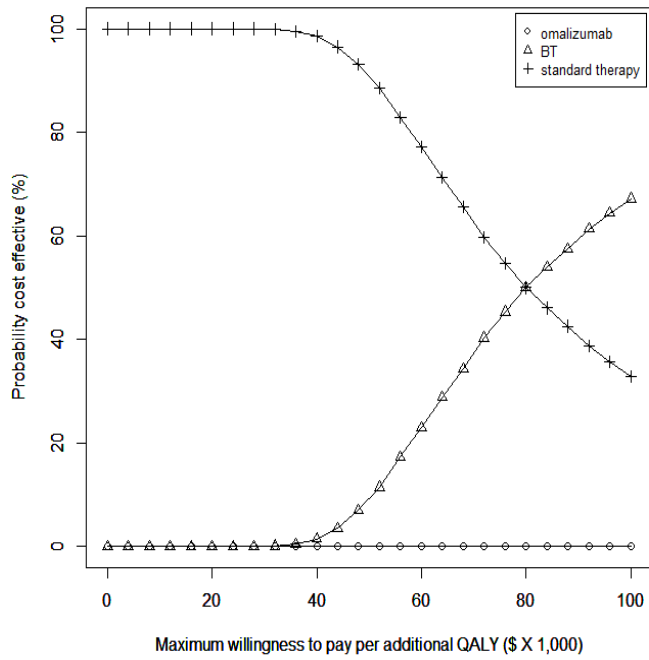
(C)

QALY: quality-adjusted life year, BT: bronchial thermoplasty, ST: standard therapy

Figure 4.3 represents the results of sensitivity analyses, with panel A for BT versus standard therapy and panel B for omalizumab versus BT. As seen in both panels, costs of omalizumab and BT had the most pronounced impact on ICERs. Decreasing the costs of BT and omalizumab by 25% reduced the ICER of BT relative to standard therapy by 28% (to $57,000/QALY), and ICER of omalizumab relative to BT by 29% (to $2.65 million/QALY), respectively. Other sensitivity analyses demonstrated that results were particularly sensitive to the utility of exacerbation-free state for omalizumab and BT. Changing the utility difference between omalizumab and standard therapy from 0.03 to 0.05 (derived based on a Cochrane review on omalizumab (177)) changed the ICER of omalizumab relative to BT from BT being dominated to $1.20 million/QALY. Also, changing the utility difference between BT and standard therapy from 0 (i.e., no change) to 0.06 (based on a Cochrane review on BT (167)) changed the ICER of BT relative to standard therapy from $1.31 million/QALY to $44,700/QALY. In addition, a separate probabilistic analysis, in which the original CrIs for RRs of exacerbations for BT directly estimated from my meta-analysis were used (instead of using the borrowed between-study variation from omalizumab studies), did not change the cost-effectiveness results. In this scenario, the probability of BT being cost-effective vs. omalizumab and standard therapy remained the same as the base case, 9% at the WTP of $50,000/QALY, and 67% at the WTP of $100,000/QALY.

Table 4-3 Sensitivity analysis

(A)
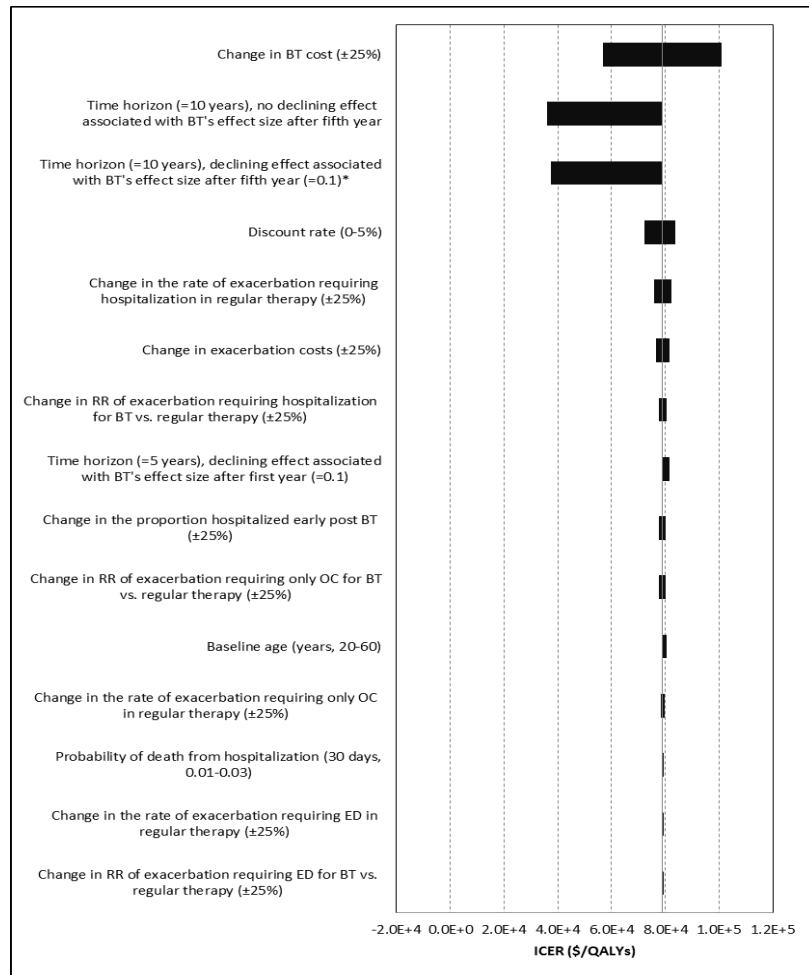
(B)
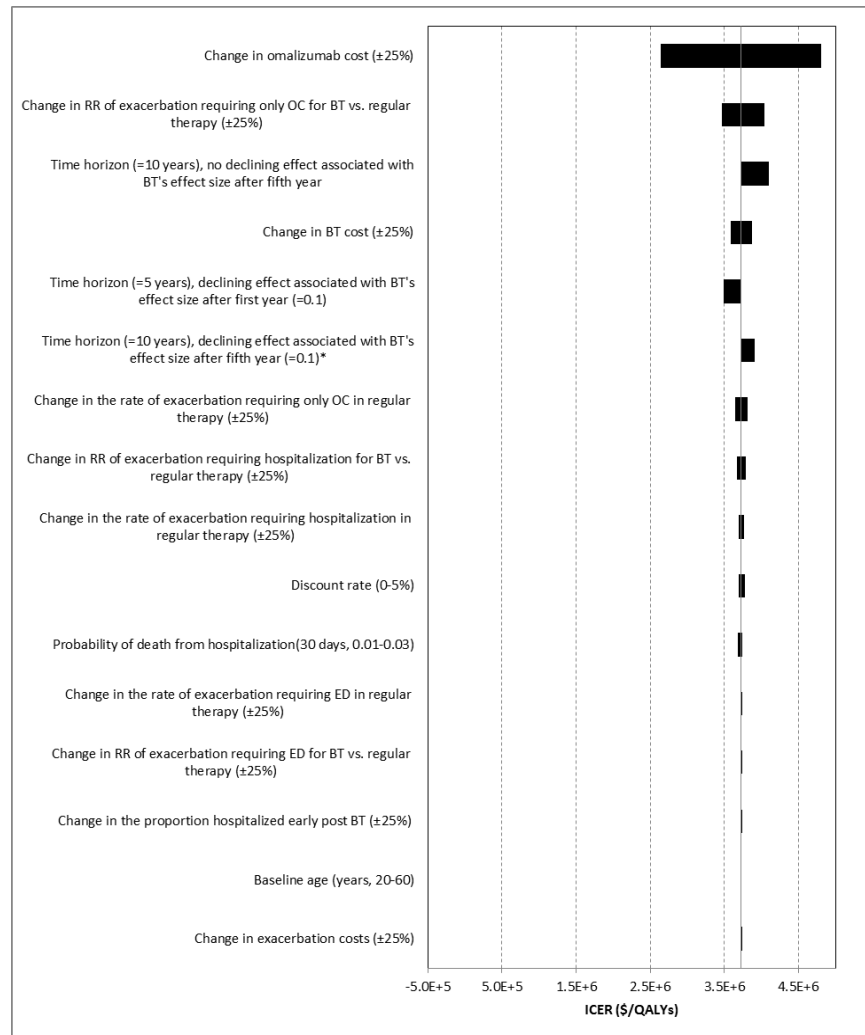
ED: Emergency department, OC: Oral corticosteroids, BT: Bronchial thermoplasty, RR: relative rate, HSUV: health state utility value, ICER: incremental cost-effectiveness ratio.
*: We modeled the declining effect of BT's effect size after fifth year with exponential distribution ($e^{-\lambda t}$).

 Figure 4.4 shows the results of a sensitivity analysis on the costs of BT. In this analysis, I varied the costs of BT from $8,000 to $30,000 per patient and calculated the ICER for BT relative to standard therapy as well as omalizumab relative to BT. Changing the costs of

BT from $8,000 to $30,000 increased the ICER of BT relative to standard therapy from $40,900/QALY to $178,000/QALY, and decreased the ICER of omalizumab relative to BT from $3.99 million/QALY to $3.06 million/QALY. The threshold value for the costs of BT that result in the ICER of BT versus standard therapy being $50,000 and $100,000 was approximately $9,000 and $17,000, respectively.
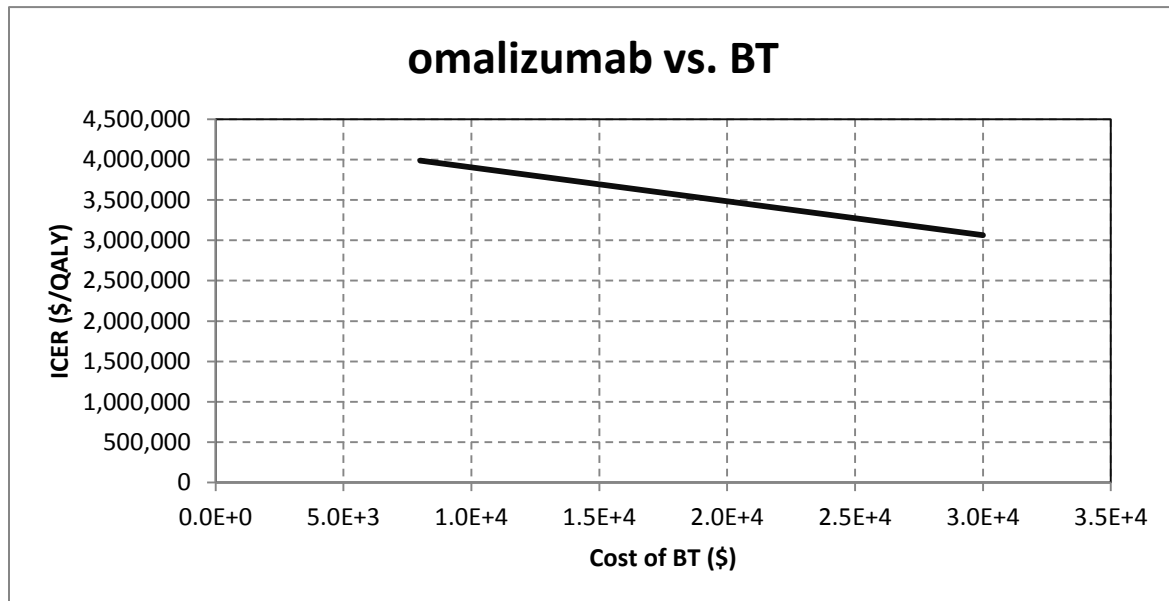
Figure 4-3 Incremental cost-effectiveness ratio as a function of BT's cost: (A) BT versus standard therapy, (B) omalizumab versus BT

(A)

(B)

omalizumab vs. BT
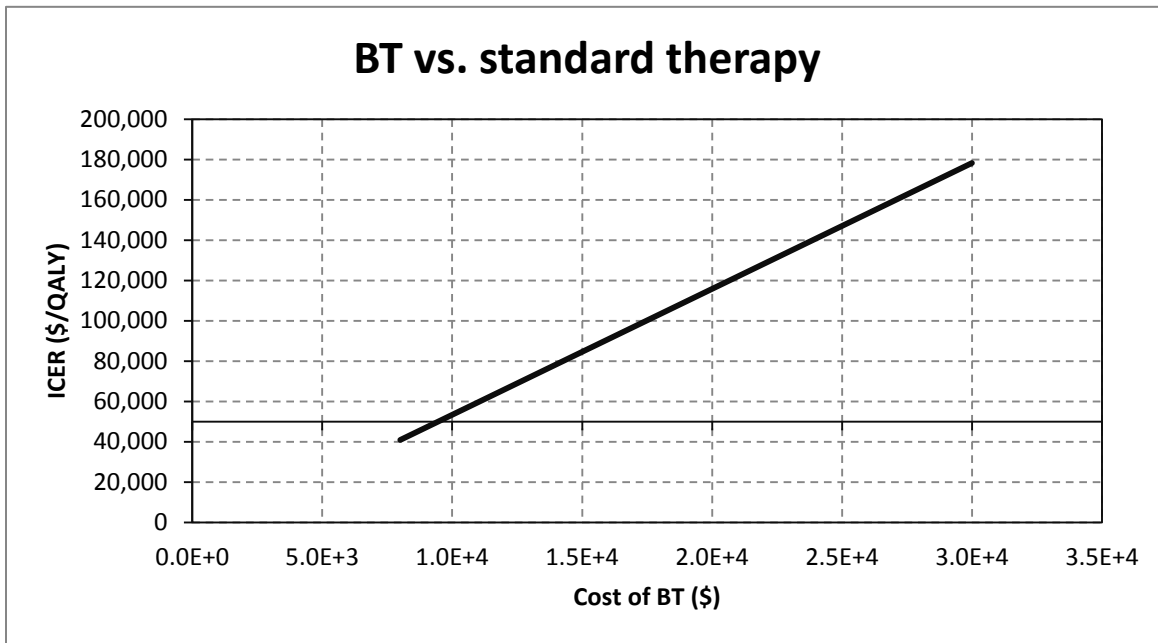
BT: Bronchial thermoplasty, ICER: incremental cost-effectiveness ratio.

4.4 Discussion

In this chapter, I evaluated the cost-effectiveness of novel therapies for the management of uncontrolled asthma among patients who remain uncontrolled despite full adherence to conventional therapies (namely ICS+LABA). Although there is still significant uncertainty around BT efficacy, based on available evidence, this study suggests that BT can be a cost-effective option relative to the other two comparative treatments if the policy makers are willing to pay more than $80,000/QALY. However, this study also demonstrated the presence of substantial uncertainty in the results. The chance of BT being cost-effective compared with omalizumab and standard therapy was

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67% at the WTP of $100,000/QALY. I also showed that in the target population of this study, omalizumab was not cost-effective compared with standard therapy despite being associated with significant clinical improvements. This finding is consistent with the majority of previous evaluations (30–34,36,164). I also developed a freely-accessible web application (available from http://resp.med.ubc.ca/software/ipress/bt-cea/), which provides an interactive framework for users to investigate the results as a function of different input values.

There are some limitations in this study. The effect of treatment on rates of exacerbations and hospitalizations were based on short-term clinical trials (33,157,166), but were assumed to persist over the 5-year time horizon of the study. Nevertheless, there is evidence to support this assumption, which has shown the consistent effect of BT over five years (156). In addition, there is scarce evidence on the optimal duration of omalizumab therapy as in studies of omalizumab, the dosage has often been reduced or the drug has been completely withdrawn in some subjects. As the primary outcome of studies evaluating BT was asthma exacerbations, I constructed my model around asthma exacerbations. My model's health states were similar to those of the Asthma Policy Model (179) and other previously published evaluations (30–34,36,164). Nevertheless, this choice of model precluded me from investigating the effect of interventions on levels of asthma control defined by the guidelines such as GINA (158). It is worth noting that I indirectly considered the effect of treatments on symptom control by incorporating differential impact of treatment on quality of life associated

with exacerbation-free health states. Future studies are needed to investigate the effect of BT on transitioning among levels of control as well as the impact of BT on quality of life aside from its effect on the rate of exacerbations as potentially important parameters determining its cost-effectiveness. In addition, in this study I might have underestimated the uncertainty for HSUVs by converting the AQLQ scores to HSUVs (180); however, in the absence of direct evidence on the final outcome of interest, using intermediate outcomes is a reasonable alternative. I also minimized the risk of bias by applying the same validated mapping algorithm technique (176) to both BT and omalizumab to calculate their impact on HSUVs. For our estimates of treatment effect, I had to rely on existing available evidence from a few BT studies (52,53,168), but due to concerns about homogeneity in the design and included populations of the published studies, I used evidence from omalizumab trials to estimate the between-study variability in the main analysis. There might also be a risk of bias in the point estimate of treatment effect as two (53,168) of these three studies did not include a sham intervention in the control group (167). In addition, the relatively large placebo effect in the sham arms of BT trials might suggest some patients did not receive optimal treatments before entering to the study, making the observed effect of BT less relevant to the context of this evaluation which considers BT after maximum dose of double therapy has failed to achieve asthma control.

Uncontrolled asthma is associated with significant economic and humanistic burden (181). Given the current therapies and the likely arrival of further expensive monoclonal

antibody treatments for severe asthma, it will be important for clinicians and policy makers to develop a framework through which these health technologies can be formally assessed in terms of both costs and health outcomes. In the current and previous chapters of this thesis I tried to identify the most optimal treatment regimens for patients with uncontrolled asthma. The framework adopted in these two studies can be used as a resource to inform policy makers and health-care providers on the benefits of these and other asthma interventions. My overall conclusion is that full adherence to conventional therapies such as ICS+LABA provides the best value for the resources consumed; however, if a patient still remains uncontrolled despite consistent use of high dose ICS+LABA, the addition of BT would be the next best policy move in terms of cost-effectiveness, if policy makers are willing to pay more than $80,000 per QALY.

Chapter 5: Towards Developing a Microsimulation Model of COPD: A Framework for Individualized Prediction of Lung Function Decline in COPD

5.1 Introduction

Although COPD is defined by airflow limitation, the rate of decline of lung function is extremely variable across patients (54,182). Accordingly, data on the rate of change of forced expiratory volume in 1 second (FEV_1), the most commonly used measure of lung function, can be very noisy, often associated with a coefficient of variation that exceeds 1.50 (54). FEV_1 is directly related to severity classifications, Global initiative for Obstructive Lung Disease (GOLD) grades, that determine treatment algorithms (183). However, the relatively poor signal-to-noise ratio of this measurement has made it difficult to risk-stratify patients for progression, especially in mild COPD where differences between the rapid and slow decliners might be difficult to detect. Such risk stratification can help physicians personalize disease management strategies and help researchers design more efficient therapeutic trials.

In this thesis, the identified major care gap in COPD was that the contemporary disease management paradigm is largely based on population-level treatment decisions. For example, guidelines mostly recommend the first line therapy for all individuals with severe COPD, ignoring the tremendous heterogeneity in the disease process and the outcomes. Concordantly, I set my aim to quantify the potential value of precision medicine in COPD; that is, basing the treatment decisions on identifiable individual

characteristics to maximize the benefits and minimize the harms associated with treatment. To achieve this aim, I have faced evidence major gap in the evidence which is lack of quantitative documentation of the level of heterogeneity in lung function decline in COPD. In addition to critically informing the study in the next chapter, a framework for individualized prediction of lung function decline can be of great standalone value in informing clinical care, research, and policy making. For cardiovascular diseases (CVD), prediction tools (e.g., Framingham risk scores (184)) have been available for several decades and have played major roles in clinical, research, and policy domains. Lack of equivalent risk prediction tools and the reduced ability in individualizing disease prevention and management might explain the comparative lack of success in reducing the burden of COPD compared with CVD (185). Therefore, the aim of the research presented in this chapter was to create and externally validate a probabilistic model to predict individualized rate of FEV_1 decline and the corresponding severity grades in COPD.

5.2 Methods

Study population: To derive the prediction equations, I used data from the Lung Health Study (LHS). The details of the LHS design and its major findings have been published elsewhere (186). In summary, the LHS was a multi-center clinical trial, in which 5,887 smokers were randomized to 3 arms of usual care and special intervention (smoking cessation) with or without a bronchodilator (ipratropium). All patients had mild to moderate COPD and were between the ages of 35 and 60 years (186–188). Patients

were excluded if they had any other significant respiratory diseases (186,187). All patients were seen in person on an annual basis for 5 years, and spirometry was performed according to the American Thoracic Society criteria (186). The study was subsequently extended by the addition of an in-person visit at approximately the 11th year of follow-up (189). For this study, I included all individuals without a missing FEV_1 and other independent variables at baseline and with at least one follow-up.

Exposure and outcomes: The predictors were clinical and demographic variables (e.g., sex, age, weight and height), treatment group assignment, methacholine responsiveness (i.e., O'Connor two-point slope (190)), smoking history (in pack-years), and baseline FEV_1. In line with the original analysis of the LHS, individuals were considered continuous smokers if they smoked throughout the first 5 years of follow-up, sustained quitters if they did not smoke in this period, and intermittent quitters if their smoking behavior varied (186). The outcome of interest was the individualized post-bronchodilator FEV_1 for up to 11 years after the baseline visit.

Validation cohort: I determined the external validity of the prediction equations using two independent datasets: the European Respiratory Society Study on Chronic Obstructive Pulmonary Disease (EUROSCOP) and the Pan Canadian Early Detection of Lung Cancer Study (PanCan). EUROSCOP was a multi-center clinical trial that compared inhaled budesonide versus placebo over 3 years in patients with mild to moderate COPD, with recruitment and follow-up between 1992 and 1996 (187), and with spirometry performed every 3 months. The PanCan Study (191) recruited current or

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former smokers with or without COPD and performed spirometry yearly for up to 3 years, with recruitment and follow-up between 2008 and 2013 (192). Because different treatments were used in these trials, external validation was determined only in the placebo arms of these studies. In addition, for external validation in the PanCan Study, I only included patients with FEV_1s between 55% and 90% of the predicted value to be in line with inclusion criterial of LHS and EUROSCOP (186–188).

Statistical analysis: I used a mixed linear regression to model the FEV_1 for each individual. A mixed-effects model enables explicit specification of heterogeneity by assigning random-effect terms to parameters whose effect is variable between individuals. The regression equation was of the form

$$FEV1_t = \beta_0 + \beta.X + \beta'_0.t + \beta'.X.t + \beta''_0.t^2 + (int_{smo} + int_{ipra}) + e,$$

with $FEV1_t$ being FEV_1 at the tth follow-up year, and e representing an independent normally distributed error term. 'X's are the set of covariates (i.e., baseline age, sex, weight, height, height squared, smoking status, O'connor slope, and interaction of baseline age and height squared) as described above. The Intercept, β_0, and slope, β'_0, were modelled as random-effect (to vary across individuals), and other coefficients were modelled as fixed-effect. βs predict the baseline FEV_1 and β's predict the slope of FEV_1 change over time, while β''_0 captures the potential non-linear component of decline, and int_{smo} and int_{ipra} represent smoking cessation and ipratropium interventions that model one-time jump in FEV_1 after the baseline visit for those who received ipratropium

or quit smoking (these two variables were set to zero for all three arms for the baseline visit as baseline FEV_1 was measured before the initiation of interventions)(187). This model connects serial FEV_1 measurements for an individual through a multivariate normal distribution, enabling conditional prediction of future FEV_1 values based on observable characteristics, baseline FEV_1, and potentially previous FEV_1 values.

Using this framework, different models were constructed with different choices of predictors. I used AIC (Akaike Information Criterion) (193) to choose the best predictive model (the final model). From the final model, I calculated the predicted individualized lung function, as well as the range of FEV_1 values around the estimate at the individual level that covers 95% of individuals with similar characteristics (i.e., 95% prediction interval). I also predicted the probabilities of being at different GOLD grades for an individual based on their clinical traits over 11 years and their smoking status (continued smoker versus sustained quitter) during the follow-up time. In addition, I predicted future FEV_1 and GOLD grades by adding a 1-year prior FEV_1 value to other baseline clinical traits (analogous to knowing a previous history of exacerbation, which can enhance prediction of future COPD exacerbations). A variance component analysis was performed to determine the contribution of covariates in explaining the variation of the follow-up FEV_1s. Finally, I evaluated the discriminatory power of the model in predicting future GOLD grades by calculating the C-statistics. GOLD grading classifies lung function decline into four categories: mild ($FEV_1 \geq 80\%$ of predicted), moderate (FEV_1 50 to 79% of predicted), severe (30% to 49% of predicted) and very severe (<30% predicted). I used

NHANES III reference equations for calculating the predicted FEV1s (194), and combined severe and very severe grades together as there were not many predicted values falling into the very severe category.

I performed internal (using LHS) and external validation (using EUROSCOP (195) and PanCan (191)). Because EUROSCOP and PanCan did not measure bronchial responsiveness (i.e., O'Connor slope), I refitted the final model after removing this variable. Validity was assessed in three ways, 1) plotting the observed versus predicted mean FEV_1 at follow-up visits, 2) calculating the root mean squared error (RMSE) of the predicted versus observed FEV_1s (the smaller the RMSE the better the prediction); and 3) determined the coverage probability defined as the proportion of the observed FEV_1 values falling within the 95% prediction interval for that observation (the closer the coverage probability to 95% prediction interval, the better the prediction).

To make the prediction equation accessible to the research and clinical communities, I developed a web application. All analyses were performed in SAS (Version 9.4., SAS Institute, Carey, NC, USA) (196).

5.3 Results

I used data from 5,594 individuals (mean age 48.5 and 63% men). The mean follow-up time was 9.2 years with a combined total of 35,046 visits. Details of the baseline characteristics can be found in Table 5.1.

Table 5-1 Baseline characteristics of patients included in the final model

Variables (n=5,594)	Mean (SD)
Follow up time (years)	9.2 (2.9)
Baseline age (years)	48.4 (6.8)
Baseline FEV1[*] (L)	2.75 (0.63)
FEV1 % predicted	78.47 (9.06)
Weight (kg)	75.9 (15.1)
Height (m)	1.72 (0.09)
Methacholine responsiveness (O'Connor slope) [†]	-12.73 (23.4)
Pack-years of smoking	40 (19)
Sex	
Male	63%
Female	37%
Smoking status by year 5	
Sustained quitters	17%
Intermittent quitters	28%
Continuous smokers	55%

All values are represented in mean (standard deviation) except sex and smoking status. FEV1: forced expiratory volume in 1 second. SD: standard deviation.
*: post bronchodilator.

†: Unit is change in FEV1 per mg/ml change in methacholine concentration.

The final model included the following variables: baseline age, follow-up time, sex, weight, height, height^2, smoking status during follow-up, the O'Connor slope, and smoking and ipratropium interventions. Regression coefficients from this model are presented in Table 5.2. Most of the included variables in the final model were significantly associated with the rate of FEV_1 decline (p-value<0.05). In the final model, 88% of the total variation around the follow-up FEV_1 values was explained by the included clinical covariates and baseline FEV_1. The final model had a C-statistics of 0.90 for follow-up GOLD grades. Within follow-up periods, the C-statistics were 0.92 for year 1 and 2, 0.91 for year 3, 0.90 for year 4, 0.88 for year 5, and 0.85 for year 11.

Table 5-2 Regression coefficients for the slope in FEV1 decline (milliliters per year) contained in the final model

Parameters	Baseline FEV$_1$			Rate of FEV$_1$ decline		
	Effect (ml)	95% CI	P-Value	Effect (ml/year)	95% CI	P-Value
Intercept	1421.2	(-1277.33, 4119.73)	0.3	-177.9	(-456.42, 100.62)	0.2
Baseline age (year)	-5.19	(-17.2, 6.82)	0.4	2.31	(1.06, 3.56)	0.0003
Sex (male vs female)	462.5	(436.71, 488.29)	<.0001	-8.86	(-11.55, -6.17)	<.0001
Weight (kg)	-0.11	(-0.86, 0.64)	0.8	0.15	(0.07, 0.23)	0.0002
Height (m)	-1760.3	(-4729.11, 1208.51)	0.2	74.13	(-232.61, 380.87)	0.6
Height^2 (m^2)	1893.1	(1037.36, 2748.84)	<.0001	11.39	(-77.2, 99.98)	0.8
Continuous smoker[*] (vs. sustained quitters)	-77.22	(-88.73, -65.71)	<.0001	-25.79	(-28.29, -23.29)	<.0001
Intermittent quitter[*] (vs. sustained quitters)	-41.31	(-53.92, -28.7)	<.0001	-10.02	(-12.79, -7.25)	<.0001
O'connor slope[†]	2.61	(2.24, 2.98)	<.0001	0.2	(0.16, 0.23)	<.0001
Baseline age* height^{2} [‡]	-8.2	(-12.2, -4.2)	<.0001	-0.92	(-1.34, -0.5)	<.0001
Time (year)	NA	NA	NA	-0.44	(-0.59, -0.29)	<.0001
Parameters	**Effect on one time jump in FEV$_1$**					
Intervention (smoking)	27.35	(18.78, 35.92)	<.0001			
Intervention (ipratropium)	33.71	(24.05, 43.37)	<.0001			

95% CI: 95% confidence interval, FEV1: forced expiratory volume in 1 second, variables of this table will predict the rate of FEV1 decline ($i.e., FEV1\ (y) - FEV1\ (0) = y * (intercept + \beta1 * x1 + \beta2 * x2 + \cdots) + \beta * intervention + \varepsilon$, where y represents the year, 'x's are the set of covariates, and ε representing an error term).
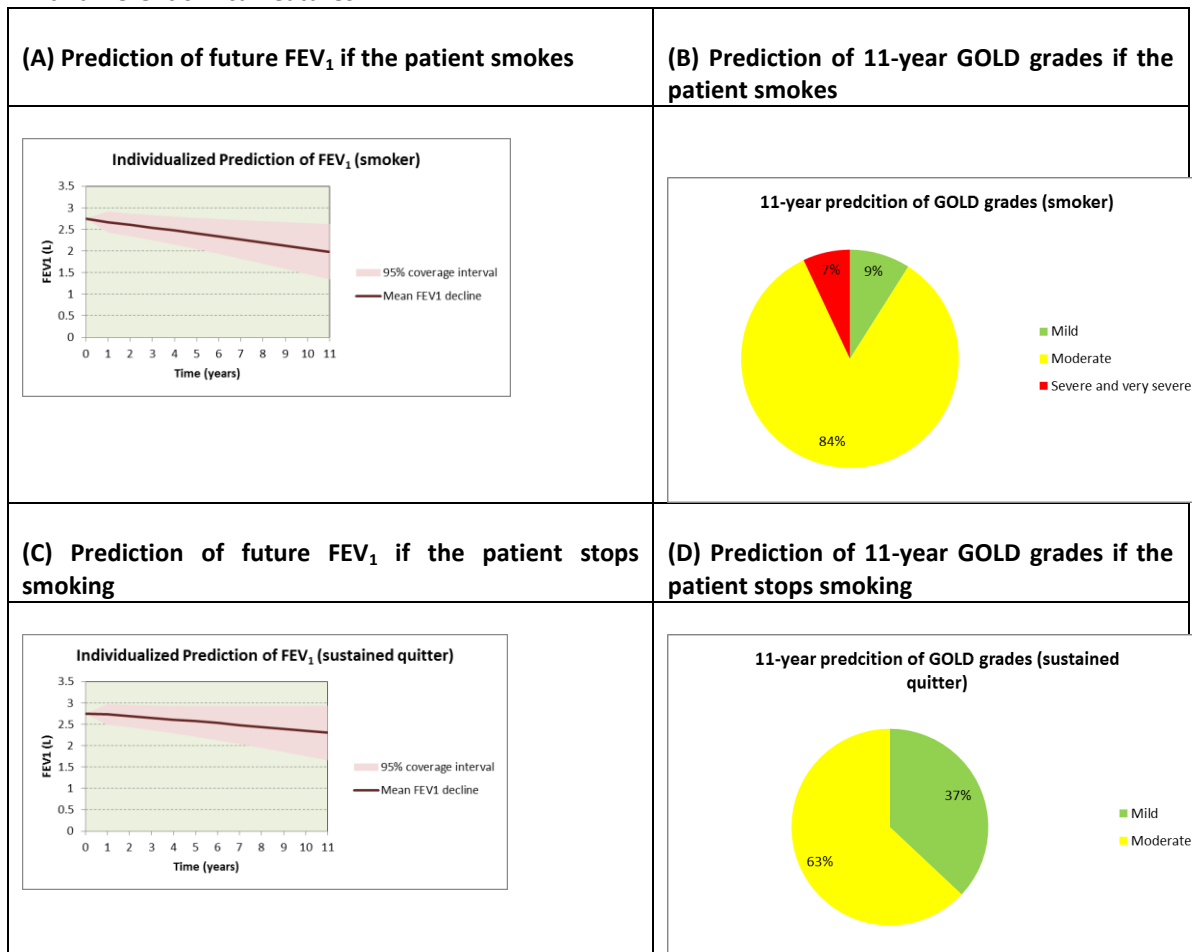
*: dummy variable.

†: Measure of hyperresponsiveness. This variable is log transformed.

Figure 5.1 shows an example of prediction of lung function decline and the corresponding GOLD grades stratified by future smoking behavior for an exemplary patient with a baseline FEV_1 of 2.75 L. Based on these figures, if the patient continues smoking, over 11 years the average rate of decline would be 70 ml/year, with a 95% prediction interval of -11 to -128. If the patient stops smoking, the expected decline rate would be -40 ml/year with a 95% prediction interval of -98 ml/year to +18 ml/year. In terms of GOLD grades, there would be 9%, 84%, and 7% chance that the patient remains in mild, transitions to moderate, or transitions to severe/very severe COPD, respectively, if he continues to smoke. These transitions can be significantly improved if the patient quits smoking, with almost no chance of becoming severe/very severe, and a 37% and 63% chance of remaining in mild or transitioning to moderate COPD, respectively. Incorporation of a previous FEV_1 value for this patient will reduce the width of the prediction interval. This effect is more pronounced in short-term prediction: the width of the prediction interval is reduced by 38%, and 30%, for the 1st and 2nd year prediction, respectively.

Figure 5-1 Results of prediction: (A) Mean estimate and 95% prediction interval for future FEV_1 based on baseline FEV_1 and clinical traits for an exemplary patient (55 year old male, continuous smoker, baseline FEV1 of 2.75 L, weight of 75 kg, and height of 170 cm with baseline FEV1 of 2.75 L) when smokes, **(B)** 11-year prediction of GOLD grades for the exemplary patient when smokes, **(C)** Prediction of FEV_1 for the exemplary patient when stops smoking, **(D)** 11-year prediction of GOLD grades for the exemplary patient when stops smoking.

This is an illustrative case only. The reader can use the online FEV_1 calculator (at http://resp.med.ubc.ca/software/ipress/epic/fev1pred) to estimate future FEV_1 decline in patients with different clinical features.

(A) Prediction of future FEV_1 if the patient smokes	**(B) Prediction of 11-year GOLD grades if the patient smokes**
(C) Prediction of future FEV_1 if the patient stops smoking	**(D) Prediction of 11-year GOLD grades if the patient stops smoking**

FEV1: forced expiratory volume in 1 second, COPD: Chronic Obstructive Pulmonary Disease.

5.4 Validation

Internal validation using LHS: Figure 5.2 panels A and B present the expected against observed mean FEV_1 at follow-up visits for continuous smokers and quitters, respectively. The RMSE for both smokers and non-smokers was 0.24, and the actual coverage probabilities of the 95% prediction intervals were 94% and 93%, respectively.

External validation using EUROSCOP: There were 542 patients (72% male, baseline age of 52.5 years old, and baseline FEV_1 of 2.56 L (73.23% predicted)) in the placebo arm of EUROSCOP. Figure 5.2-panel C shows the replication data in this cohort. The RSME in this cohort was 0.22, and the actual coverage probability of 95% prediction interval was 91%.

External validation using PanCan: There were 940 patients with COPD in PanCan (59% male, baseline age of 63 years of age, and baseline FEV_1 of 2.21 L). Figure 5.2-panel D and panel E present observed versus predicted values for FEV_1 decline for current smokers and ex-smokers, respectively. For current smokers, RMSE and the actual coverage probability of 95% prediction interval were 0.25 and 90%, respectively; whereas for quitters, these values were 0.19, and 93%, respectively.

Figure 5-2 Validation of the model: (A) Internal validity, LHS smokers, (B) Internal validity, LHS non-smokers, (C) External validity, EUROSCOP smokers (it only included smokers), (D) External validity, PanCan smokers, (E) External validity, PanCan non-smokers

(A)

(B)

(C)

(D)

(E)
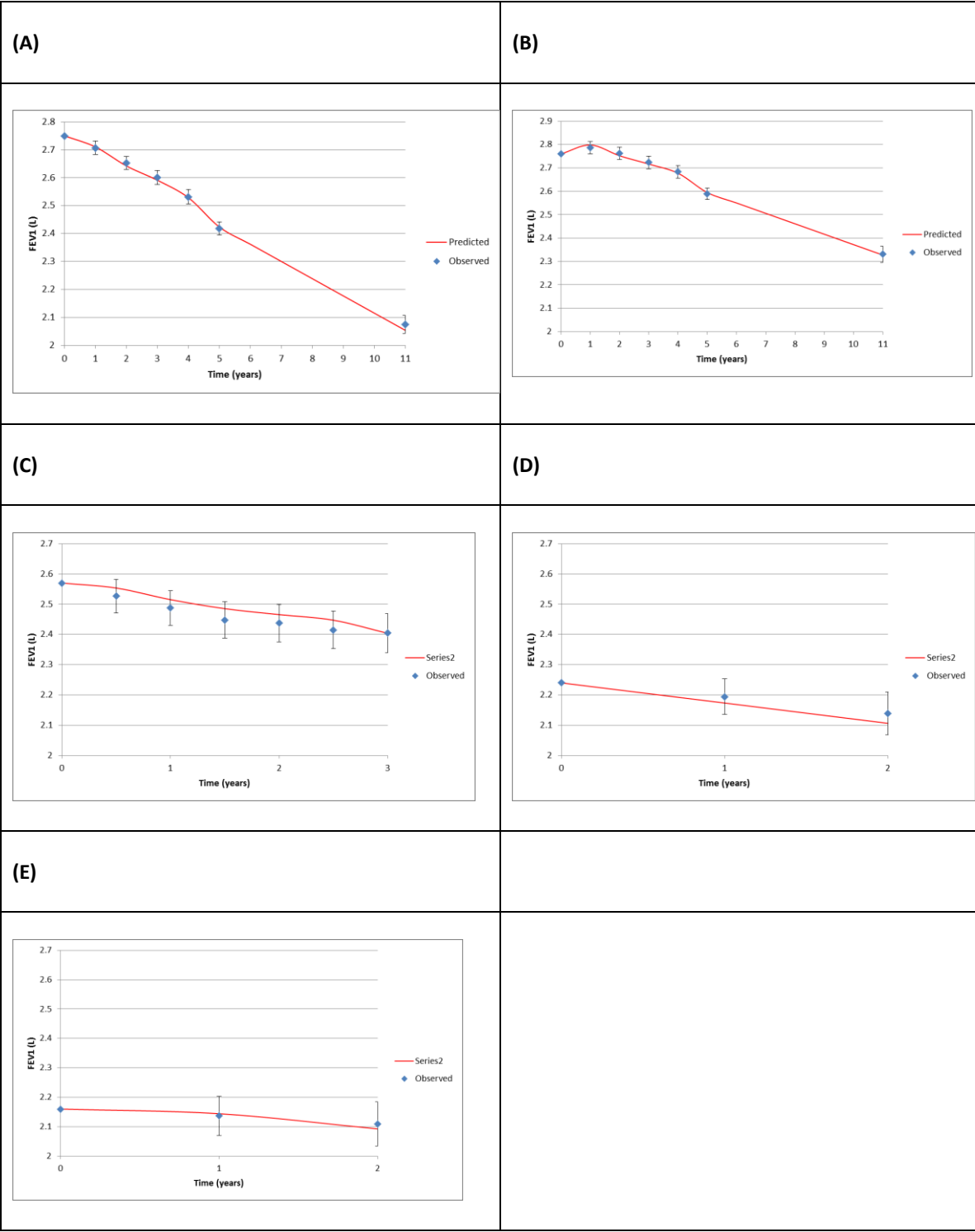
RMSE: root mean squared error, FEV1: forced expiratory volume in 1 second, EUROSCOP: European Respiratory Society Study on Chronic Obstructive Pulmonary Disease, PanCan: the Pan Canadian Early Detection of Lung Cancer study.

Web application: Using prediction equations, I developed a Web-based application (at http://resp.med.ubc.ca/software/ipress/epic/fev1pred). This tool enables the prediction of future FEV_1 values and GOLD grades for up to 11 years using clinical variables that can be collected at the point of care. The tool also allows users to incorporate, from external sources, the effect of pharmacologic interventions such as bronchodilators in terms of one-time increase in FEV_1.

5.5 Discussion

In this chapter, using data from LHS, I developed equations that enable individualized probabilistic prediction of FEV_1 decline for up to 11 years based on readily available clinical features at the point of care in patients with mild to moderate COPD. My results are consistent with the original data by Fletcher and Peto that showed continuous smokers on average experienced a faster decline than non-smokers (197), and subsequent studies that demonstrated the tremendous heterogeneity in COPD (197,198). I also validated the robustness of our equations in two independent data sets, EUROSCOP and PanCan. The latter is a more contemporaneous study, compared with LHS and EUROSCOP, that assures the relevance of our prediction for modern COPD patients. I will use the results of this chapter to build a micro-simulation model of COPD to quantify the value of personalizing medicine in COPD in the next chapter.

The framework developed in this chapter will allow clinicians to risk-stratify patients with mild-to-moderate COPD in terms of their future lung function decline and to identify rapid progressors, who can be targeted for close follow-up and intervention (e.g. smoking cessation programs). Other potential applications of such a prediction tool is to promote the design of efficient clinical trials of interventions to modify disease progression by improving the signal-to-noise ratio of the FEV_1 decline variable and reducing the sample size. The latter is achieved in two ways: by providing estimates of residual variance for sample size calculation that remove the effect of heterogeneity due to observable characteristics, and by enriching the recruitment by patients who are most likely to experience rapid decline in lung function. In addition, the development of the web-based tool can enable rapid translation of the study's findings into clinical practice and research designs.

There were some limitations in this study. First, LHS did not image patients with thoracic computed tomography (199); thus the impact of emphysema on the rate of FEV_1 decline could not be incorporated into our model. Second, the determinants of FEV_1 are likely to be very complex with multiple interactions, and while we examined the performance of several models, they are inevitable simplified versions of the underlying disease process. Third, my model is applicable to patients with mild to moderate COPD when the opportunities for disease modification are the greatest. However, it may not be generalizable to patients with more severe disease. Moreover, my equations may not be generalizable to individuals with asthma-COPD overlap syndrome, lifetime non-smoking

COPD patients, or to patients whose predominant risk factor is biomass or other forms of indoor or outdoor pollution.

The present study can be seen as a step towards creating a quantitative framework for outcome predictions in COPD. The present work was focused on FEV_1, and did not incorporate other meaningful endpoints in COPD. However, it has the potential to be expanded, incorporating exacerbations and mortality as watershed COPD events that are affected by the degree of lung function impairment. For other conditions such as CVDs, such frameworks have been in place for decades, allowing for evidence-based decision making at the clinical and policy levels, as well as more informed design of clinical trials (200). Given the high and escalating burden of COPD, it is time to develop similar frameworks for this disease.

Chapter 6: Quantifying the Value of Personalizing Medicine in COPD

6.1 Introduction

Lung function decline, characterized as the changes over time in the forced expiratory volume in 1 second (FEV_1), is the hallmark of COPD pathology and a critical marker of disease progression. Cut-offs on the ratio of FEV_1 to its predicted value define the Global initiative for Obstructive Lung Disease (GOLD) severity grades, a central component of contemporary clinical practice in COPD (183). While gradual decline in FEV_1 is a hallmark of the disease, the rate of FEV_1 decline is substantially different across COPD patients (54). As shown in the previous chapter, a proportion of the variability in the rate of FEV_1 decline can be explained by easily verifiable characteristics such as baseline severity of the disease, smoking status, height, and weight (56). This means stratification of treatment decisions based on such factors can potentially improve efficiency of COPD care (56).

Between-individual variability (heterogeneity) refers to the differences in individuals' characteristics that can influence the outcomes of medical decisions (56). Conventionally, decisions on the adoption of health technologies have been made at the population-level (or at most at a few identifiable subgroups within the population) (201). Generally, uncertainty around the outcomes of decisions in a random individual from a target population stems from multiple sources: the inevitable unpredictability of outcomes due to chance, the uncertainty in the individual's characteristics that

determines the outcome (heterogeneity), and the uncertainty due to our lack of knowledge about the population-level parameters (parameter uncertainty). Among these three sources, the latter two can be controlled by the decision maker. Parameter uncertainty can be overcome by collecting further evidence (e.g., conducting a clinical trial to learn about the average treatment effect). Between-individual variability can be accounted for by stratifying the treatment based on the observed characteristics of the individuals. While the role of parameter uncertainty in medical decision making has been extensively explored, the theoretical and empirical research on efficient decision making in the presence of heterogeneity is less studied. In 2003, Coyle et al. provided a framework for stratified cost-effectiveness (202). Also, more recently, the value of moving from the population-level towards individual-level decision making has been recognized, and metrics have been developed in the medical decision making literature to quantify the benefit of such a paradigm shift (57). In COPD, there appears to be a significant window of opportunity in making treatment decisions more refined based on patients' characteristics (individualized care) (55–57). In this chapter, I aimed at quantifying the value of characterizing heterogeneity and individualizing treatments in COPD.

6.2 Methods

Model: I developed a probabilistic microsimulation (individual level sampling) model of COPD to predict the discounted 20-year costs and QALYs associated with various maintenance COPD therapies.

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Table 6.1 provides the value of input parameters along with their probability distributions. A key set of input parameters are those characterizing FEV_1 decline. To estimate these parameters, I used prediction equations for lung function decline in COPD patients, developed in the previous chapter. Other parameters of the model were derived from published literature, and were assigned two levels of probability distribution, representing parameter uncertainty and between-individual heterogeneity, details of which can be found in Table 6.1.

Table 6-1 Model parameters and their probability distributions. All costs are adjusted to CAN 2011 dollars

Parameter	Value [Probability distribution or 95% credible interval]
*Age**	48.4 [μ~N(48.4, 0.09)] [N(μ, 6.8)]
*Sex**(male as 1 vs. female as 0)	0.63 [p~B(19714486, 11578349)] [Bern(p)]
*Weight**(kg)	75.9 [μ~N(75.9, 0.2)] [N(μ, 15.1)]
*Height**(m)	1.72 [μ~N(1.72, 0.001)] [N(μ, 0.09)]
*Smoker**(yes as 1 vs.no as 0)	[p~B(17211059, 14081776)] [Bern(p)]
*Intermittent quitter**(yes as 1 vs.no as 0)	[p~B(8761994, 22530841)] [(1-smoker)* Bern(p)]
*Baseline FEV$_1$**(L)	2.75 [μ~N(2.75, 0.008)] [N(μ, 0.63)]
Rate ratio of exacerbation(reference=placebo)† (203–205)	
ICS	0.811 [0.719-0.908]
LABA	0.867 [0.783-0.959]
ICS+LABA	0.700 [0.622-0.787]
LAMA	0.743 [0.667-0.822]
Background mortality rate (206)	US life tables
Rate of total exacerbations (207) (a*exp[b+c*FEV$_1$ % predicted])	
a	0.960

Parameter	Value [Probability distribution or 95% credible interval]		
b (intercept), c (coefficient of FEV$_1$ % predicted)	0.981, -0.009 [MVN(mu=(0.981, -0.009), sig=$\begin{bmatrix} 0.132496 & -0.00227 \\ -0.00227 & 0.000049 \end{bmatrix}$)]		
Rate of severe exacerbations (207) *(a*exp[b+c*FEV$_1$ % predicted])*			
a	1.072		
b (intercept), c (coefficient of FEV$_1$ % predicted)	-1.043, -0.013 [MVN(mu=(0.981, -0.009), sig=$\begin{bmatrix} 0.817216 & -0.0176 \\ -0.0176 & 0.0004 \end{bmatrix}$)]		
	Per COPD stages		
	mild	**moderate**	**severe or very severe**
Healthcare contacts (annual rate) [‡] (208)			
General practitioner (GP) visit	0.80	1.03	5.43
Specialist visit cost	0.75	1.25	2
Utilities [§] (209)			
Baseline	0.81 [B(310.84,72.91)]	0.72 [B(160.56,62.44)]	0.67 [B(58.58,28.86)]
Minor exacerbation	0.72 [B(362.16,140.84)]	0.658 [B(163.87,85.17)]	0.475 [B(46.91,51.84)]
Major exacerbation	0.519 [B(323.39,299.71)]	0.447 [B(22.10,27.34)]	0.408 [B(39.01, 56.60)]
Indirect maintenance cost (annual CAN dollars) (209–211)	$36 [Γ(16, 0.4444)]	$215 [Γ(16, 0.0744)]	$524 [Γ(16, 0.0305)]
Indirect exacerbation cost (annual CAN dollars) (209–211)			
Minor exacerbation	$40 [Γ(16, 0.4)]	$80 [Γ(16, 0.2)]	$134 [Γ(16, 0.1194)]
Major exacerbation	$1,625 [Γ(16, 0.0098)]	$3,250 [Γ(16, 0.0049)]	$5,417 [Γ(16, 0.0029)]
Direct Medication cost (212)			
Inhaled corticosteroids (ICS)	$450		
Long-acting beta-agonists (LABA)	$500		
ICS+LABA	$1,000		
Long-acting muscarinic agents (LAMA)	$750		
Direct exacerbation cost (annual CAN dollars) (209)			
Minor Exacerbation	$161 [Γ(16, 0.0994)]		
Major Exacerbation	$6,501 [Γ(16, 0.0024)]		
GP visit cost (208)	$70 [Γ(16, 0.2286)]		
Specialist visit cost (208)	$90 [Γ(16, 0.1778)]		

FEV$_1$: forced expiratory volume in 1 second, GP: general practitioner, ICS: Inhaled Corticosteroids, LABA: Long Acting Beta Agonist, LAMA: Long Acting Muscarinic Agents. N(x,y)=normal distribution with mean x and standard deviation y. MVN(*mu*,*sig*)=multi-variate normal distribution with mean vector *mu* and variance and covariance matrix *sig*. B(x,y)=beta distribution with shape1(alpha) parameter x, and shape2 (beta) parameter y. Γ(x, y): gamma distribution with shape parameter x and rate parameter y. Bern: Bernoulli distribution.

*: Based on Lung Health Study (LHS). For age normal distribution was truncated with lower limit of 30 years old and upper limit of 75 years old. For weight distribution was a truncated normal with lower limit of 45 kg and upper limit of 110 kg. For height distribution was a truncated normal with lower limit of 1 m and upper limit of 2 m. For baseline FEV$_1$ distribution was a truncated normal with lower limit of 1 L and upper limit of 4 L.

†: Estimated based upon 10,000 random samples from posterior distributions in a network meta-analysis,

Five interventions were modeled. These were no maintenance therapy, and maintenance therapy with inhaled corticosteroids (ICS), long-acting beta-agonists (LABA), combination of inhaled corticosteroids and long-acting beta-agonists (ICS+LABA), and long-acting muscarinic antagonists (LAMA). Based on the literature and the expert opinion, treatments in COPD have not been shown to modify the lung function, and so their effectiveness was modeled through the reduction in the rate of exacerbations (73,74,85,87–92,97–99,103,105,107,108). Even though Tricco et al did not show the assumption of class effects (213), there was a recent network-meta analysis by Mills et al. that supported the class effect (214).

The natural history of COPD was modeled through decline in FEV_1, which was then converted to GOLD severity grades as mild (grade I), moderate (grade II), severe (grade III) or very severe (grade IV) (183). The time horizon was 20 years (56), and future costs and quality-adjusted life years (QALYs) were discounted at the rate of 3% (162,163). The model was implemented in the statistical programming environment R v3.2.2 (139).

The framework: Let x be the value of a heterogeneous parameter in the population (e.g., slope of FEV1 decline). The heterogeneity of the parameter is modeled through a probability distribution, identified by a type and indexed by a set of distribution parameters, as

$$x{\sim}Distribution(Parm1, Parm2, \dots).$$

The value of the parameters is typically estimated from the literature or from the expert if there is no evidence in the literature. In both circumstances, there is uncertainty around the parameter values for this distribution, which in itself is identified by a probability distribution (parameter uncertainty):

$$Parm1{\sim}Distirbution(\ Hyper-parm1, Hyper-parm2, \dots),$$

$$\dots$$

The model inputs are therefore the so called 'hyper-parameters', parameters that index the probability distribution of second-order parameters.

Estimating the value of characterizing heterogeneity: I used the Value of Heterogeneity (VoH) framework that was introduced by Espinoza et al (57). Espinoza et. al. explain how VoH quantifies the gain in net benefit by moving the decision from the population level to subgroup levels, and devise relevant metrics that capture such benefits. The original framework is based on finite, discrete subgroups (e.g., categories of baseline severity). The framework is developed for the ubiquitous situation that parameter uncertainty also exists. I expanded this framework for infinite number of subgroups based on patients' individualized clinical traits, as we were interested in quantifying the additional value of treatment stratified by baseline lung function and other patient characteristics.

The VoH can be calculated by subtraction of the expected value of perfect information for the average population ($EVPI$) from the total expected value of perfect information for considering S_n infinite patients' subgroups ($EVPI(S_n)$) based on their clinical traits, which can be formulated as

$$VoH = EVPI(S_n) - EVPI$$

$$= \left(E_{x,y_x} \, Max_i \, NB_i(x, y_x) - Max_i \, E_{x,y_x} \, NB_i(x, y_x) \right)$$

$$- \left(E_x \, Max_i \, E_{y_x} \, NB_i(x, y_x) - Max_i \, E_{x,y_x} \, NB_i(x, y_x) \right)$$

$$= E_{x,y_x} \, Max_i \, NB_i(x, y_x) - E_x \, Max_i \, E_{y_x} \, NB_i(x, y_x)$$

$$= \int_x \int_{y_x} Max_i \, NB_i(x, y_x) \, P(x, y_x) \, dy_x \, dx$$

$$- \int_x Max_i \int_{y_x} NB_i(x, y_x) \, P(y_x|x) \, dy_x \, P(x) \, dx,$$

where NB_i represents the net benefit for the ith treatment, and x, and y_x represent the population-level and individual-level parameters, respectively. The subgroups that define the disease states, S_n, are based on combination of all variables that determine the characteristics of an individual. As uncertainty can never be completely removed, and treatment cannot fully be individualized based on all available patient-level variables, the estimate of VoH provides an upper bound on the value of moving the decision from the population to the individual-level.

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Implementation: In order to calculate the outcomes and evaluate the double-integral mentioned above, I performed a probabilistic analysis (PA) in a microsimulation model resulting in a two-level Monte-Carlo simulation framework. In the outer level, parameter uncertainty was modeled through sampling from the second-order probability distributions. In the inner level, given a set of population parameters, between-individual heterogeneity was modeled by sampling from the distribution of heterogeneous parameters (e.g., age, sex, height, weight, smoking status, baseline FEV1, and lung function decline).

Finally, I calculated the value of characterizing heterogeneity and precision medicine in COPD using the above-mentioned equation. Specifically, I calculated the $EVPI$ for the average population (i.e., when a treatment with the highest net benefit is determined for a population), and subtract it from the EVPI for infinite patients' subgroups, $EVPI(S_n)$) (i.e., when a treatment with the highest net benefit is determined for an individual patient based on his/her clinical traits), at two thresholds for willingness-to-pay (WTP) values of $50,000/QALY and $100,000/QALY.

6.3   Results

Table 6.2 quantifies heterogeneity for model outputs, costs, QALYs, and number of exacerbations for all five interventions across individuals. For example, for ICS, there was substantial heterogeneity in terms of outcomes. While the average costs were $51,535 over the time horizon, the interval that contained 95% of the individuals was

$7,338 to $161,364. Similarly, the average QALYs, and number of exacerbations for ICS was 9.821, and 21.436, respectively, while their 95% interval was 2.506 to 12.316, and 3.216 to 42.213, respectively. Variation of these outcomes for other interventions is detailed in Table 6.2.

Table 6-2 Model outcomes along with their 95% confidence interval

	Placebo	ICS	LABA	ICS+LABA	LAMA
Costs ($)	54,137 (4,948, 187,129)	51,535 (7,338, 161,364)	54,899 (7,836, 172,033)	53,947 (9,339, 150,225)	52,579 (8,464, 154,250)
QALYs	9.687 (2.461, 12.238)	9.821 (2.506, 12.316)	9.781 (2.493, 12.292)	9.901 (2.531, 12.363)	9.869 (2.521, 12.343)
Number of exacerbation	26.343 (3.971, 51.276)	21.436 (3.216, 42.213)	22.892 (3.437, 44.847)	18.51 (2.774, 36.434)	19.69 (2.953, 38.742)

ICS: inhaled corticosteroids, LABA: long-acting beta-agonists, LAMA: long-acting muscarinic antagonists, QALYs: quality-adjusted life years.

Table 6.3 represents the results of the value of heterogeneity analyses. As shown, for WTP of $50,000/QALY, the EVPI for considering patient subgroups was calculated as $3,491/person. In addition, the EVPI for average population was calculated as $2,226/person, which resulted in $1,265 (the difference between $3,491 and $2,226) per person for the value of characterizing heterogeneity.

Also, for the WTP of $100,000/QALY, the EVPI when considering subgroups and EVPI for average population was calculated as $2,787, and $2,027, respectively. This resulted in the value of heterogeneity as $760 per person.

Table 6-3 Value of individualizing treatments in COPD

Parameters	WTP of $50,000/QALY	WTP of $100,000/QALY
EVPI for infinite patient subgroups	$3,491	$2,787
EVPI for average population	$2,226	$2,027
Value individualizing treatment	$1,265	$760

WTP: willingness-to-pay, EVPI: expected value of perfect information, EVPPI: expected value of partial perfect information.

6.4   Discussion

In this chapter, I showed the value of personalizing medicine in a case study of COPD. The value of characterizing between-individual heterogeneity and personalizing medicine in COPD was estimated as $1,265 per person at WTP of $50,000/QALY. In other words, this study suggests that the value of shifting treatment decisions in COPD from the population-level to individual-level is up to $1,265 per person over 20 years. Given the substantial number of COPD patients in Canada, policies that advocate such a shift in COPD management can be associated with significant benefits to the society.

Indeed, the reported values provide an upper bound on the value of such a policy shift. This is because I simulated decisions that are made fully at the individual level, capturing the full heterogeneity in the disease process. For example, the rate of FEV1 decline, estimated from the prediction equations developed in the previous chapter, has a random-effect component specific to each person. It is difficult to verify the value of this source of unexplained heterogeneity at the individual level, yet they are incorporated in

the VoH analysis. My intention in this work was to provide an upper estimate for VoH. It is likely that with more research (e.g., the discovery of novel biomarkers), higher share of heterogeneity will be explained by observable characteristics, moving towards realization of the estimates made in this work.

There are recent studies attempting to develop the necessary methodology in quantifying the value of personalized medicine. A previous study by Vemer et al. quantified heterogeneity and distinguished it from the population-level uncertainty in decision-analytic models (56). In addition, other applied cost-effectiveness studies have partly or fully accounted for heterogeneity in their analyses through results stratification for different COPD patients' sub-groups (75,76,85,86,94,95,104,113). The work developed by Espinoza et. al. provides the most appropriate framework for the applied research conducted here, as it enables separating the effect of heterogeneity from parameter uncertainty in determining the model output and estimation of the value of decision making at the subgroup level.

There are some limitations in this study. Treatment effects were informed from studies with limited duration; but in this study, they were assumed to be consistent over 20 years. However, my assumption was in concordance with other published studies in COPD (73,74,85,87–92,97–99,103,105,107,108). In addition, although I tried to be as exhaustive as I could in capturing and reflecting heterogeneity and that for building my model, I resorted to one of the most comprehensive and largest trails of COPD, the LHS,

my choice of variables was restricted to the LHS. Future studies are needed to further characterize heterogeneity and its determinants in COPD.

Using the results of the previous chapter, in this chapter, I built a micro-simulation model of COPD to achieve my overall goal of quantifying the value of personalizing medicine in this disease. The results can be an informative source of evidence for health economists and policy makers to appreciate the value of shifting from population-based to individualized disease management in COPD. The framework developed in this study can also be useful for developing health technologies (e.g., novel biomarkers) that can be used to further explain variability in COPD course and outcomes.

Chapter 7: Conclusions

7.1 Overview of Results and Contributions

In this thesis, I developed mathematical decision-analytic models of asthma and COPD to evaluate strategies aimed at closing three important care gaps in these two major respiratory diseases with substantial burden (13,60).

My overall goal in the asthma-related research component was to investigate how pharmacotherapy can be optimized to improve asthma outcomes. Given the low adherence to the current standard asthma therapies, I investigated whether or not ensuring full adherence to the standard controller medications in asthma would be cost-effective (care gap 1). The issue of whether or not improving adherence to current asthma therapies can improve asthma outcomes at the population level has been the subject of much debate (120,121). Addressing this issue required a comprehensive model development practice with broad interdisciplinary knowledge in different fields such as disease epidemiology, mathematics, data analysis, and computer programming. In the study presented in Chapter 3, I showed that improving adherence to the standard controller medications could be associated with substantial gain in QALYs, but also at additional costs resulting in a minimum of $24,515/QALY when full adherence is achieved at no additional costs for any adherence-improvement intervention. This sets the lower limit for the ICER of any adherence-improvement intervention in asthma. I also showed that full adherence can reduce the number of exacerbations and

hospitalizations by 40%. Nevertheless, we noticed that almost 23% of asthma patients still remained uncontrolled despite full adherence to the standard therapies (i.e., ICS+LABA). As the next step, I investigated the most cost-effective treatments for those patients whose asthma remains uncontrolled despite full adherence to the standard therapy. For this patient subgroup, I developed another decision model, modeling transitions across levels of asthma exacerbation, based on which I showed the addition of bronchial thermoplasty to the standard controller medications would be cost-effective if policy makers are willing to pay more than $80,000/QALY. I developed an interactive Web application to communicate the results of this study to stakeholder. Through these two studies, I contributed to asthma research by developing decision-analytic models through probabilistic Monte Carlo simulations to assess the most optimal treatment strategy for asthma (215).

For COPD, my overall goal was to assess the value of individualizing treatments, given that COPD is a very heterogeneous disease (56). Traditionally, management decisions in COPD have been informed by population-level inference (e.g., average treatment effect from clinical trials). Concordantly, the treatment recommendations have also largely been formulated for the whole population, or at most across a few broad subgroups (e.g., GOLD grades). To demonstrate the potential benefits of personalized medicine in COPD, I aimed for creating a microsimulation model incorporating both parameter uncertainty and heterogeneity. However, early in the course of this work, I encountered a methodological challenge and a gap in evidence in terms of the need for the

quantification of individualized lung function trajectories. To address this gap, I used 11-years data of the Lung Health Study in a mixed-effects regression framework to create such equations. The equations were externally validated using data from two other COPD studies. In addition to the utility of such equations, reported in Chapter 5, this prediction framework can be of substantial standalone value in patient care and policy making and can be a stepping stone towards the development of outcomes prediction frameworks for COPD. Such outcomes prediction frameworks can be powerful decision tools for clinicians and policy makers in optimizing practice standards and policies in prevention, diagnosis, and management of COPD.

Having overcome this data gap, in Chapter 6, I developed a mathematical decision-analytic model to quantify the value of personalizing treatments in COPD. In this study, I showed that the value of individualizing treatments is $1,265 per a COPD patient. This sets an upper bound on the value of precision medicine in COPD. Considering the prevalence of COPD in Canada, the population-level estimate of value would be $2 billion. The methodology, model structure, and input values used in this study can be expanded to quantify the value of stratified treatment based on specific set of patient characteristics of disease biomarkers. This thesis has therefore contributed to COPD research and care by creating an individualized predictor of lung function decline, and quantifying the maximum societal benefit of personalized treatment in COPD.

7.2 Strengths and Limitations

I used the state-of-the-art statistical techniques and incorporated the latest recommendations in decision analysis to build the models used in this thesis. The models I developed have the required versatility and flexibility to address different 'what if' scenarios pertaining to the defined research objectives. I tried to populate the models with the most up-to-date and highest quality evidence from multiple sources to reflect the current status of our collective knowledge. When needed, I got access to the world-class data to estimate critical input parameters or to examine the external validity of key equations used in the model. Finally, I had access to a multi-disciplinary research group and could solicit their expert opinion and insight throughout evidence synthesis, model development, and validation phases. I attempted to fully account for uncertainty in the evidence through modeling uncertainty around all model parameters, and propagate the uncertainty from model inputs to outputs using probabilistic analyses.

Inevitably, there were some limitations in some aspects of the research in this thesis. Some parameters in the asthma models (chapters 3 and 4) were mostly informed from clinical trials with short follow-up time, and thereby, there was a lack of robust data that would cover the entire time horizon of analysis. I performed the decision analyses based on a longer, more reasonable, time horizon to provide meaningful evidence on cost-effectiveness. Such extrapolations were based on rational mathematical and clinical assumptions and were further evaluated in sensitivity analyses. However, extrapolation beyond available data required strong assumptions about the time-dependency of the

estimated parameter (e.g., treatment effect). When appropriate and once confirmed by expert clinicians in our team, I conservatively assigned a declining effect for extrapolated treatment effect beyond the follow-up time of the clinical trials. For instance, there were only three trials for effect size of BT for treatment of severe asthma with some evidence for its sustainability over five years (156); therefore, after a careful consultation with expert clinicians in our team, I ran the model for more than five years considering a declining effect for BT's effect size after the fifth year. Another challenge I faced over the course of model developments was lack of data on the correlation between model parameters. As identified in my systematic review of the literature, most of the developed models for asthma and COPD have been population-based. Once moving into the realm of microsimulation, many parameters need to be specified that characterize variability in traits across individuals. For instance, for COPD, I had to assign to each patient an individual-specific rate of lung function decline and rate of COPD exacerbation. There is no evidence on the correlation between these set of parameters, and there were no data available to estimate such correlations. By default, those correlations were set to zero but I appreciate the importance of future research on the empirical value of such parameters.

7.3   Knowledge Translation

Throughout my thesis research, I strived to put a strong emphasis on knowledge translation. In particular, I attempted to make the results of the evaluations available to a wide range of stakeholders. In addition to publications in peer-reviewed journals, I

have tried to reach out to the knowledge user community through presentations at relevant conferences (e.g., Canadian Agency for Drugs and Technologies in Health (CADTH) and American Thoracic Society (ATS)), and, importantly, to make the entire modeling platform accessible to the broad user community. Decision analytic models have been criticized for being black boxes, leaving stakeholders and end-users with the set of assumptions imposed on them by the developers and the selected set of results presented in publications and reports. I tried to overcome this limitation by making my asthma and COPD models accessible to the research community. For this purpose, I developed interactive Web applications for two models pertaining to Chapters 4 and 5. These Web applications provide a user-friendly interface for users to explore different combination of input parameters, perform customized sensitivity analyses, and run variety of alternative policy scenarios. As an example, for my asthma cost-effectiveness model, I built an online framework allowing users to have access to the inputs and outputs of the model simultaneously. The users can change any input of the model and examine the outputs instantaneously. Graphical presentation of model output facilitates the evaluation of results. The address to the Web link is at (ipress.resp.med.ubc.ca/bt2/). Figure 7.1 shows a snapshot of this web application.

Figure 7-1 Online web app for asthma cost-effectiveness model

Cost-effectiveness of standard therapy, bronchial thermoplasty, and omalizumab
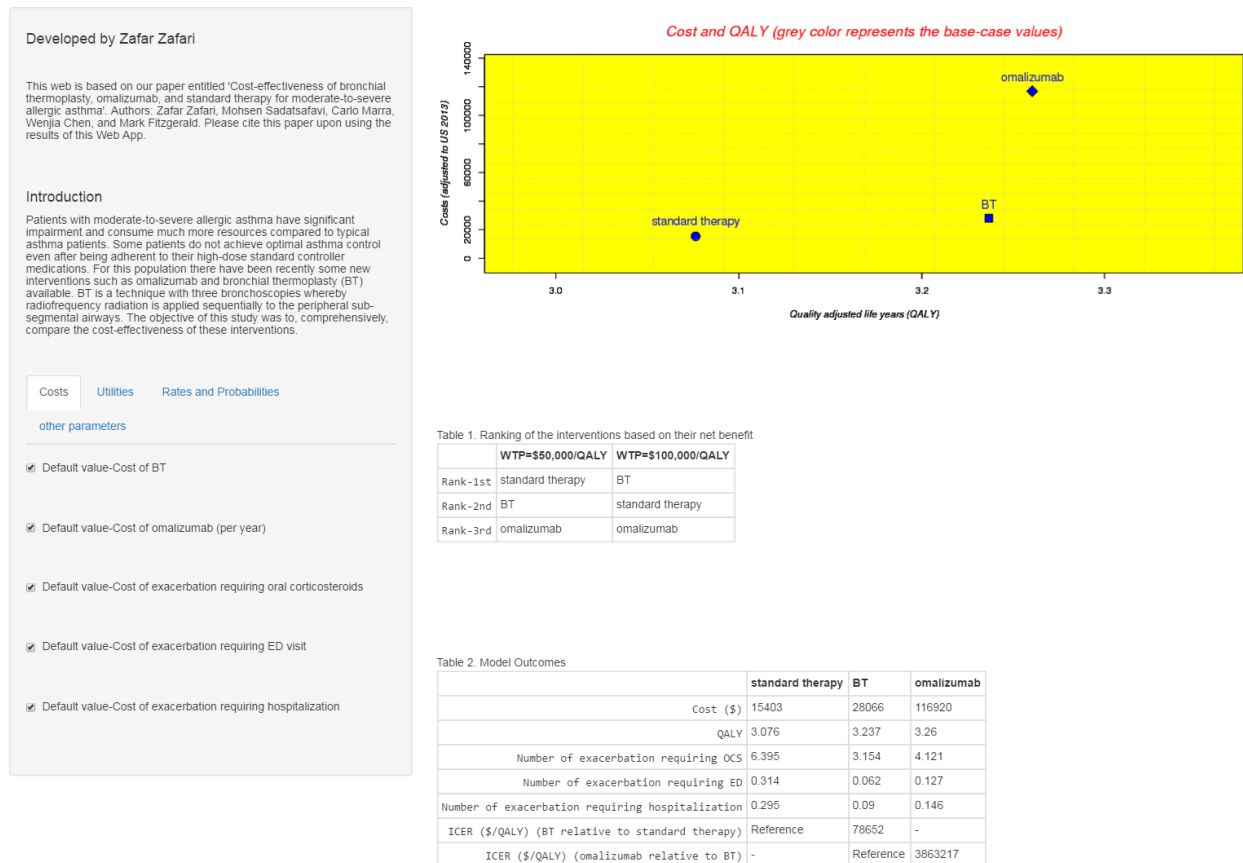
In addition, for the research on creating individualized prediction models for lung function decline in COPD, presented in Chapter 5, I developed an online Web application freely accessible to the clinicians, policy makers, and the research community through the link "http://resp.med.ubc.ca/software/ipress/epic/fev1pred/". Using this Web app, the users can input the clinical traits of a COPD patient such as age, sex, weight, height, and smoking status, and investigate their future lung function decline. Based on this lung function calculator, a potentially rapid decliner COPD patient can be simply distinguished from a slow decliner, and accordingly, an appropriate medicine or

treatment program could be identified for him/her. This lung function calculator could

also have a potential impact on reducing sample size for the future COPD clinical trials

by identifying the more appropriate patient population target using this web app. Figure

7.2 represents a snapshot of this web app.

Figure 7-2 Online web app for COPD prediction model
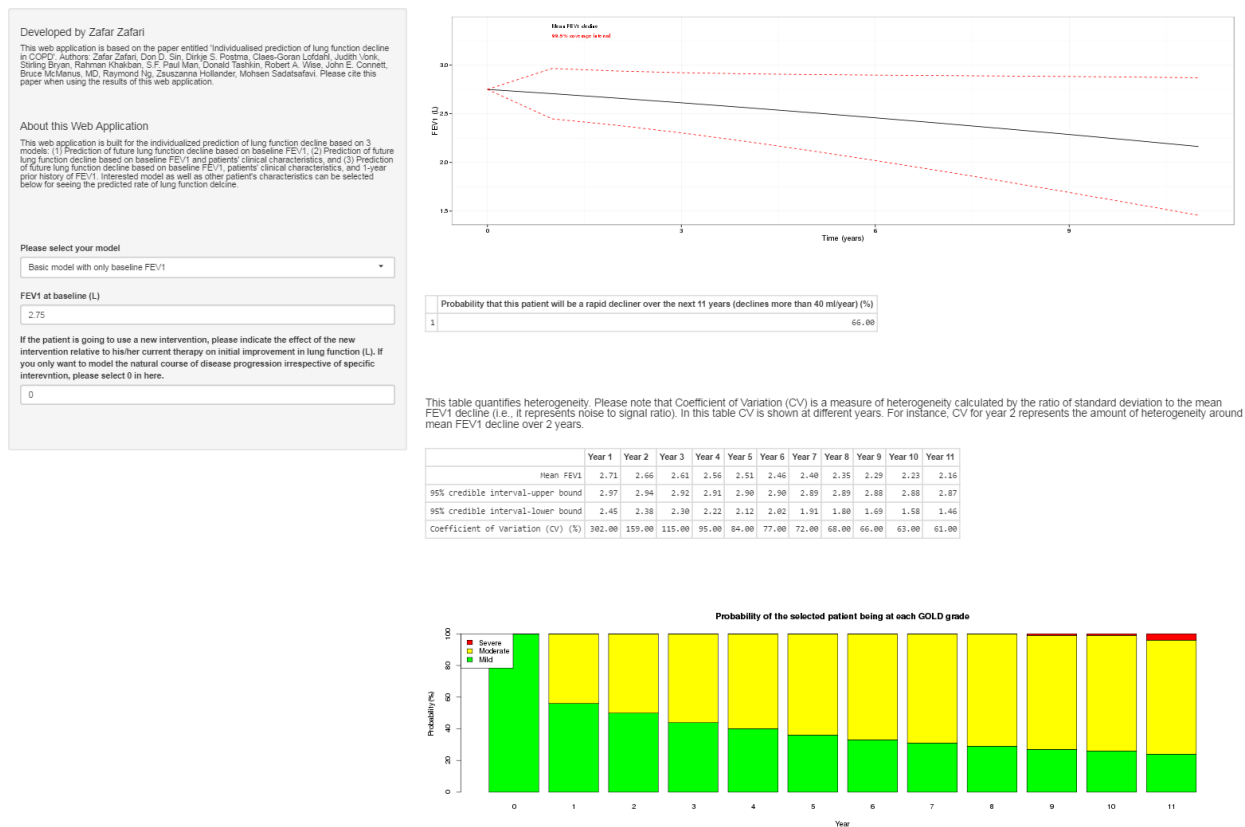
7.4 Future Research Directions

Co-morbid conditions are common in both asthma and COPD and constitute a significant component of the disease burden (61). Future studies should expand the presented framework by the inclusion of comorbidity in evaluating the cost-effectiveness of health technologies in asthma and COPD. Empirical research should concordantly fill large gaps that currently exist around the interaction between asthma/COPD and comorbidity (e.g., relation between COPD severity and comorbidity) or the impact of treatment for the main disease on the burden of comorbidity. Furthermore, there is an emerging consensus that asthma is an independent risk factor for COPD, and individuals whose COPD has stemmed from a previous asthma (asthma-COPD overlap syndrome) can have a significantly different disease trajectory than those with COPD alone (216). Future studies should therefore consider such interaction between asthma and COPD to inform policies in both diseases. In terms of modeling, a promising line of future research is the framework of 'whole disease modeling' that can consider the entire disease pathway, enabling the evaluation of multiple decisions and their interaction.

While building an individual-level model of COPD, I encountered major issues in terms of populating the model with values from the literature. While I overcame some of these challenges by performing original studies to estimate critical parameter values, still more research is required to address some other ongoing issues in individual-level modeling. An important item is the need for the evaluation and reporting of the

correlation among parameters representing different aspects of the disease (e.g., the correlation between exacerbation rate and severity in COPD). In addition, the clinical research community should also embrace the importance of providing more nuanced measures of treatment effect and other disease parameters that move beyond population-averaged metrics and towards individualized measures and associations that enable precision medicine.

Although the significant role of modeling practice in health-care has been highlighted by many authorities (26), there has not been much investment and advancement in the methodology of modeling in health-care and appreciation of its importance compared to the other fields such as finance or environmental sciences. I believe much additional research needs to be done to expand modeling techniques for future research in healthcare. This requires close collaborations between health-care research methodologists, statisticians, and clinicians. I also believe more efforts are needed towards improving transparency of the model development process and the accessibility of the models. Innovative paths for transparency and knowledge translation that improve access to model-based evaluations and facilitate the communication of results in non-technical ways could go a long way towards maximizing impact.

7.5   Concluding Remarks

Chronic non-infectious diseases are now a major source of morbidity and mortality across the globe (13,60). Efforts in combating the burden of these diseases are currently

hampered by two major roadblocks. The first is our failure in effective translational research in brining innovations out of the research labs into clinical and public health reals, and the second is our failure in effective use of innovations and technologies despite their availability because of critical lack of evidence on their real world effectiveness and efficiency (217). My thesis was a set of coherent studies particularly attacking the second roadblock in the context of asthma and COPD, two common chronic respiratory diseases that rank very highly in terms of their economic and humanistic burden in Canada and in many other jurisdictions in the world.

On a broader scale, I hope this thesis can send an important message to policy makers and the research community by demonstrating the role of modeling in addressing challenging care gaps. When there is a need for consolidating data from multiple sources to project long-term outcomes of different decisions and policies, decision-analytic modeling could be among the best tools for informing policy. Other disciplines (e.g., climate research, strategic national policy making) have been relying on such techniques for several decades to inform investments and critical decisions. The stakes are high in health-care, and the use of objective tools to inform how limited resources for patient care and health research should be spent will be associated with significant benefit to the society.

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Appendices

Appendix A: Supplementary Material for Chapter 1

A.1 Search Strategy for asthma models

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
----
1   asthma/ or asthma, aspirin-induced/ or asthma, exercise-induced/ or asthma, occupational/ or status asthmaticus/ (112337)
2   asthma$.tw. (129169)
3   wheez$.mp. (11113)
4   reactive airway disease.mp. (292)
5   (allergic adj5 respirator$).mp. (2254)
6   (chronic adj5 respirator$).mp. (11421)
7   (airway$ adj3 inflam$).mp. (15448)
8   (whistl$ adj10 chest).mp. (43)
9   (short$ adj10 breath).mp. (6188)
10   (tight$ adj10 chest).mp. (1206)
11   Dyspnea/ (16954)
12   Bronchial Diseases/ (8309)
13   Respiratory Tract Diseases/ (20089)
14   (respiratory adj3 (hypersen$ or inflam$ or obstruct$)).mp. (12882)
15   excessive airway narrowing.mp. (46)
16   (antiasthma$ or anti-asthma$).mp. (11005)
17   ((Bronchial$ or respiratory or airway? or lung?) adj4 (Hypersensittiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp. (53639)
18   Bronchial Spasm/ (4206)
19   bronchospas$.mp. (4961)
20   (bronch$ adj3 spasm$).mp. (4402)
21   or/1-20 (254408)

22   Cost-Benefit Analysis/ (65285)
23   models, economic/ or models, econometric/ (11519)
24   markov chains/ (11054)
25   Computer Simulation/ (154778)
26   decision support techniques/ (14568)
27   Monte Carlo Method/ (22312)
28   Decision Trees/ (9415)
29   Models, Theoretical/ (119723)

30   cost-effectiveness.mp. (41787)
31   cost effective.mp. (62324)
32   cost utility.mp. (3133)
33   (simulation adj5 model$).mp. (25528)
34   monte carlo.mp. (40938)
35   (microsimulation or micro simulation).mp. (678)
36   (markov adj5 (model? or framework)).mp. (9614)
37   mathematical model.mp. (23536)
38   ((model$ adj3 (approach$ or study or simulat$)) and economic).mp. (2439)
39   discrete event? simulation.mp. (428)
40   (economic? adj1 (evaluation? or analysis or model$)).mp. (18964)
41   Decision-analytic$ model$.mp. (1605)
42   decision model?.tw. (1607)
43   Cost-effectiveness.kw. (1650)
44   cost evaluation.mp. (297)
45   economics/ or resource allocation/ or health care rationing/ (41597)
46   (decision tree? and model$).tw. (2452)
47   (individual sampling adj3 model$).mp. (8)
48   or/22-47 (509530)

49   21 and 48 (2804)

50   exp asthma/ (112337)
51   ec.fs. [Economics] (361172)
52   50 and 51 (1928)

53   **49** or 52 (4149)

54   limit 53 to yr="2014 -2015" (434)

55   (201401$ or 201402$ or 201403$ or201404$ or 201405$).ed. [Entry Date] (254376)
56   (201505$ or 201506$ or 201507$ or201508$ or 201509$ or 2015010$ or 201511$ or 201512$).ed. [Entry Date] (508181)
57   55 or 56 (762557)
58   54 not 57 (299)
59   (2014$ or 2015$).dc. [Date created] (2199871)
60   53 and 59 (443)
61   60 not 54 (25)
62   58 or 61 (324)
63   limit 62 to English language (306)
64   comment/ or editorial/ or letter/ or news/ (1632375)
65   63 not 64 (293)

Database: Embase <1980 to 2016 April 12>
Search Strategy:
----
1   asthma/ or allergic asthma/ or aspirin exacerbated respiratory disease/ or asthmatic state/ or exercise induced asthma/ or extrinsic asthma/ or intrinsic asthma/ or mild intermittent asthma/ or mild persistent asthma/ or moderate persistent asthma/ or nocturnal asthma/ or occupational asthma/ or severe persistent asthma/ (210318)
2   asthma$.tw. (178240)
3   wheez$.mp. (24033)
4   reactive airway disease.mp. (425)
5   (allergic adj5 respirator$).mp. (3168)
6   (chronic adj5 respirator$).mp. (16765)
7   (airway$ adj3 inflammation).mp. (20653)
8   or/1-7 (266639)

9   economic evaluation/ or "cost benefit analysis"/ or "cost control"/ or "cost effectiveness analysis"/ or "cost minimization analysis"/ or "cost of illness"/ or "cost utility analysis"/ (239849)
10   Cost consequence analys$.mp. (175)
11   mathematical model/ or statistical model/ (210442)
12   stochastic model/ (8325)
13   Monte Carlo method/ (26701)
14   hidden markov model/ (1928)
15   population model/ (2896)
16   computer simulation/ (96256)
17   probability/ (64162)
18   sensitivity analysis/ (79402)
19   simulation/ (99050)
20   computer model/ (35304)
21   Decision-analytical model$.mp. (252)
22   discrete-event simulation.mp. (707)
23   Markov Model$.mp. (11045)
24   cost-effectiveness.tw. (57289)
25   cost effective.tw. (83299)
26   cost utility.tw. (4632)
27   (simulation adj5 model$).tw. (22028)
28   monte carlo.tw. (32356)
29   (microsimulation or micro simulation).tw. (1036)
30   (markov adj5 (model? or framework)).tw. (12988)

31   mathematical model.tw. (26161)
32   ((model$ adj3 (approach$ or study or simulat$)) and economic).tw. (2974)
33   discrete event? simulation.tw. (674)
34   (economic? adj1 (evaluation? or analysis or model$)).tw. (17825)
35   Decision-analytic$ model$.tw. (2449)
36   decision model?.tw. (2246)
37   cost evaluation.tw. (447)
38   (decision tree? and model$).tw. (3832)
39   (individual sampling adj3 model$).tw. (15)
40   discrete event simulation model/ (4)
41   or/9-40 (850247)

42   8 and 41 [COPD and Economic Modeling] (7058)

43   (letter or note or editorial or conference abstract).pt. (4261870)
44   42 not 43 (5454)

45   (201406$ or 201407$ or 201408$ or 201409$ or 201410$ or 201411$ or 201412$).dd. (776823)
46   (201501$ or 201502$ or 201503$ or 201504$).dd. (813190)
47   45 or 46 (1590013)
48   44 and 47 (368)

49   limit 44 to yr="2014 -2015" (719)
50   49 not 47 (422)
51   2016$.em. (714272)
52   50 not 51 (355)
53   (201505$ or 201506$ or 201507$ or 201508$ or 201509$ or 201510$ or 201511$ or 201512$).dd. (1165603)
54   52 not 53 (102)

55   48 or 54 (470)

56   20150$.em. (332209)
57   ("201510" or "201511" or "201512" or "201513" or "201514" or "201515" or "201516").em. (456371)
58   56 or 57 (788580)
59   44 and 58 (202)

60   or/48,54,59 (480)
61   limit 60 to English language (462)
62   medline.cr. (9969266)

63   61 not 62 (345)

Appendix B: Supplementary Material for Chapter 2

B.1 Search Strategy for COPD models

MEDLINE (Ovid)
Feb. 26, 2015

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
----
1   pulmonary disease, chronic obstructive/
2   bronchitis, chronic/ or pulmonary emphysema/
3   Bronchitis/
4   Bronchiolitis/ or bronchiolitis obliterans/ or cryptogenic organizing pneumonia/
5   (bronchiolitis or bronchitides or bronchitis).tw.
6   chronic obstructive pulmonary disease.tw.
7   COPD.tw.
8   Lung Diseases, Obstructive/
9   limit 8 to yr="1980 -2001"
10   emphysema/ or mediastinal emphysema/
11   subcutaneous emphysema/ or alpha 1-antitrypsin deficiency/
12   emphysema.tw.
13   obstructive lung disease?.tw.
14   COAD.tw. [chronic obstructive airway disease]
15   chronic lung disease?.tw.
16   obstructive airway disease?.tw.
17   or/1-7,9-16
18   Cost-Benefit Analysis/
19   models, economic/ or models, econometric/
20   markov chains/
21   Computer Simulation/
22   decision support techniques/
23   Monte Carlo Method/
24   Decision Trees/
25   Models, Theoretical/
26   cost-effectiveness.mp.
27   cost effective.mp.
28   cost utility.mp.
29   (simulation adj5 model$).mp.

30   monte carlo.mp.
31   (microsimulation or micro simulation).mp.
32   (markov adj5 (model? or framework)).mp.
33   mathematical model.mp.
34   ((model$ adj3 (approach$ or study or simulat$)) and economic).mp.
35   discrete event? simulation.mp.
36   (economic? adj1 (evaluation? or analysis or model$)).mp.
37   Decision-analytic$ model$.mp.
38   decision model?.tw.
39   Cost-effectiveness.kw.
40   cost evaluation.mp.
41   economics/ or resource allocation/ or health care rationing/
42   (decision tree? and model$).tw.
43   (individual sampling adj3 model$).mp.
44   or/18-43
45   17 and 44 [COPD and Economic Modeling]
46   Pulmonary Disease, Chronic Obstructive/
47   ec.fs. [Economics]
48   46 and 47 [COPD and Economic Modeling]
49   45 or 48
50   limit 49 to yr="1980 -current"
51   limit 50 to English language

Embase (Ovid)
April 13, 2015

Database: Embase <1974 to 2015 April 10>
Search Strategy:
----
1   chronic obstructive lung disease/
2   bronchitis/
3   chronic bronchitis/ or laryngotracheobronchitis/ or tracheobronchitis/
4   bronchiolitis/
5   bronchiolitis obliterans/
6   obstructive airway disease/
7   lung emphysema/ or hypertranslucent lung/ or lung bulla/ or lung cyst/
8   emphysema/
9   subcutaneous emphysema/
10   pneumomediastinum/ [mediastinal emphysema]
11   bronchitis.tw.
12   (bronchiolitis or bronchitides or bronchitis).tw.

13   chronic obstructive pulmonary disease.tw.
14   airflow obstruction?.tw.
15   COPD.tw.
16   emphysema.tw.
17   obstructive lung disease?.tw.
18   COAD.tw. [chronic obstructive airway disease]
19   chronic lung disease?.tw.
20   obstructive airway disease?.tw.
21   obstructive lung disease?.tw.
22   obstructive respiratory disease?.tw.
23   obstructive respiratory tract disease?.tw.
24   obstructive bronchopulmonary disease?.tw.
25   or/1-24
26   economic evaluation/ or "cost benefit analysis"/ or "cost control"/ or "cost effectiveness analysis"/ or "cost minimization analysis"/ or "cost of illness"/ or "cost utility analysis"/
27   Cost consequence analys$.mp.
28   mathematical model/ or statistical model/
29   stochastic model/
30   Monte Carlo method/
31   hidden markov model/
32   population model/
33   computer simulation/
34   probability/
35   sensitivity analysis/
36   simulation/
37   computer model/
38   Decision-analytical model$.mp.
39   discrete-event simulation.mp.
40   Markov Model$.mp.
41   cost-effectiveness.tw.
42   cost effective.tw.
43   cost utility.tw.
44   (simulation adj5 model$).tw.
45   monte carlo.tw.
46   (microsimulation or micro simulation).tw.
47   (markov adj5 (model? or framework)).tw.
48   mathematical model.tw.
49   ((model$ adj3 (approach$ or study or simulat$)) and economic).tw.
50   discrete event? simulation.tw.
51   (economic? adj1 (evaluation? or analysis or model$)).tw.
52   Decision-analytic$ model$.tw.
53   decision model?.tw.

54   cost evaluation.tw.
55   (decision tree? and model$).tw.
56   (individual sampling adj3 model$).tw.
57   discrete event simulation model/
58   or/26-57
59   25 and 58 [COPD and Economic Modeling]
60   (letter or note or editorial or conference abstract).pt.
61   59 not 60
62   limit 61 to yr="1980 -Current"
63   limit 62 to English language
64   medline.cr.
65   63 not 64
66   62 not 63
67   66 not 64 [Non-English]