Development and validation of the Evaluation Platform In COPD (EPIC): a population-based outcomes model of COPD for Canada

Mohsen Sadatsafavi MD, PhD[1]*, Shahzad Ghanbarian PhD[1]*, Amin Adibi MSc[1], Kate Johnson MSc[1], J Mark FitzGerald MD[2], William Flanagan MSc[3], Stirling Bryan PhD[4,5], Don Sin MD[2]; *for the Canadian Respiratory Research Network#*
*Co-first authors
Other collaborators: Shawn Aaron, Jean Bourbeau, Wan Tan, Teresa To, Penny Brasher, Deirdre Hennessy, Jacek Kopec

1. Faculty of Medicine and Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, British Columbia, Canada
2. Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada
3. Statistics Canada, Ottawa, Ontario, Canada
4. Centre for Clinical Epidemiology and Evaluation, Vancouver Coastal Health Institute, Vancouver, British Columbia, Canada
5. School of Population and Public Health, The University of British Columbia, Vancouver, British Columbia, Canada

Corresponding author: Mohsen Sadatsafavi
Faculty of Pharmaceutical Sciences,
University of British Columbia
7th Floor, 828 West 10th Avenue
2405 Wesbrook Mall
Vancouver, BC Canada V6T 1Z3
Tel: 604.875.5178 | Fax: 604.875.5179
Email: msafavi@mail.ubc.ca

Contact for reprint request: Mohsen Sadatsafavi (msafavi@mail.ubc.ca)

Word count: 4,998 (body), 273 (abstract)

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Abstract

Background: We report the development, validation, and implementation of an open-source population-based outcomes model of Chronic Obstructive Pulmonary Disease (COPD) for Canada.

Methods: Evaluation Platform in COPD (EPIC) is a discrete event simulation model of Canadians 40 years of age or older. Three core features of EPIC are its open-population design (incorporating projections of future population growth, aging, and smoking trends), its incorporation of heterogeneity in lung function decline and burden of exacerbations, and its modeling of the natural history of COPD from inception. Multiple original data analyses, as well as values reported in the literature, were used to populate the model. Extensive face validity as well as internal and external validity evaluations were performed.

Results: The model was internally validated on demographic projections, mortality rates, lung function trajectories, COPD exacerbations, and stability of COPD prevalence over time within strata of risk factors. In external validation, it moderately overestimated rate of overall exacerbations in two independent trials, but generated consistent estimates of rate of severe exacerbations and mortality.

Limitations: In its current version, EPIC does not consider uncertainty in the evidence. Several components such as additional (e.g., environmental and occupational) risk factors, treatment, symptoms, and comorbidity will have to be added in future iterations.

Conclusions: EPIC is the first multi-purpose outcome- and policy-focused model of COPD for Canada. By modeling the natural history of COPD from its inception, it is capable of modeling the outcomes of decisions across the entire care pathway of COPD. Platforms of this type have the capacity to be

iteratively updated to incorporate the latest evidence and to project the outcomes of many different

scenarios within a consistent framework.

Background

Chronic Obstructive Pulmonary Disease (COPD) is one of the most common chronic diseases globally(1).

The prevalence of COPD is increasing in many jurisdictions. Worldwide, the prevalence of COPD has

increased by 44.2% between 1990 and 2005(1). In Canada, a country with a population of 36.7 million

(as of 2017(2)), 17% of the adult population have COPD(3). COPD is characterized by the progressive and

generally irreversible loss of lung function. A defining feature of COPD is the periods of intensified

disease activity, referred to as acute exacerbations(4). Severe exacerbations that require inpatient care

are the second leading cause of hospitalization in Canada, following only childbirth(5). COPD extolls a

substantial economic burden. A Canadian study found the excess direct costs of COPD to be $5,947

(converted to 2015 Canadian dollars) per patient per year between 2001 and 2010, growing by more

than 5% per year(6).

COPD is diagnosed using spirometry, and is defined as the ratio of forced expiratory volume at one

second (FEV_1) to forced vital capacity (FVC) being less than 70%, or alternatively less than the Lower

Limit of Normal (LLN). The widely used Global Initiative for Chronic Obstructive Lung Disease (GOLD)

severity grades are based on the ratio of FEV_1 to its predicted value, with 80%, 50%, and 30% thresholds

separating severity grades I to IV(7). These classifications are common across several other guidelines(7–

9), which has resulted in a large body of evidence relating COPD severity grades to disease outcomes

such as exacerbation rates and costs.

A good understanding of the future burden of diseases and the long-term consequences of clinical and

policy decisions can support the search for efficiency and equity in healthcare(10). In most instances,

objective projection of disease burden and outcomes are based on computer simulations(11). A

common approach to predicting the future burden of diseases and the outcomes of decisions is to

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develop a *de novo* computer model for the specific question at hand(12). For example, different groups

have created cohort-based (e.g., Markov) models of COPD to predict the future costs and outcomes of

COPD in specific countries(13), to evaluate the outcomes of various strategies (e.g., improving smoking

cessation rates, reducing the rate of exacerbations) for reducing the burden of COPD(14), and to

evaluate the cost-effectiveness of bronchodilator therapies across different countries(15). However, this

piecemeal approach has been criticized due to the resulting duplicate efforts, inconsistent assumptions,

and risk of bias due to the influence of stakeholder interests when the model is developed with a

particular research question in mind(16).

An alternative to this approach is to create reference models that can be used for multiple purposes(10).

Reference models are the result of dedicated scientific efforts, typically with more investment

integrated into the overall design, better representation of disease mechanisms and outcomes, more

comprehensive evidence synthesis, and more rigorous validation exercises than the *de novo* models(17).

Once developed, these reference models can be used to evaluate the outcomes of many different

scenarios within a consistent framework. A number of models have been developed for COPD, and a

recent systematic review has identified the strengths and weaknesses of each of the different

platforms(18). The majority of these models (with some exceptions(19)) simulate a cohort of patients

who initially have the disease, and therefore they cannot be used to project the future incidence of the

disease and the impact of preventive scenarios such as changing smoking rates and implementation of

screening programs for earlier detection of COPD.

The Evaluation Platform In COPD (EPIC) was a nationally funded research project with the aim of

creating an open-source, publicly available, population-based 'Whole Disease' COPD model for

epidemiological projections and analysis of a wide range of policies in the Canadian context. The present

paper discusses the concept and overall methodology, assumptions, data sources, and results of internal

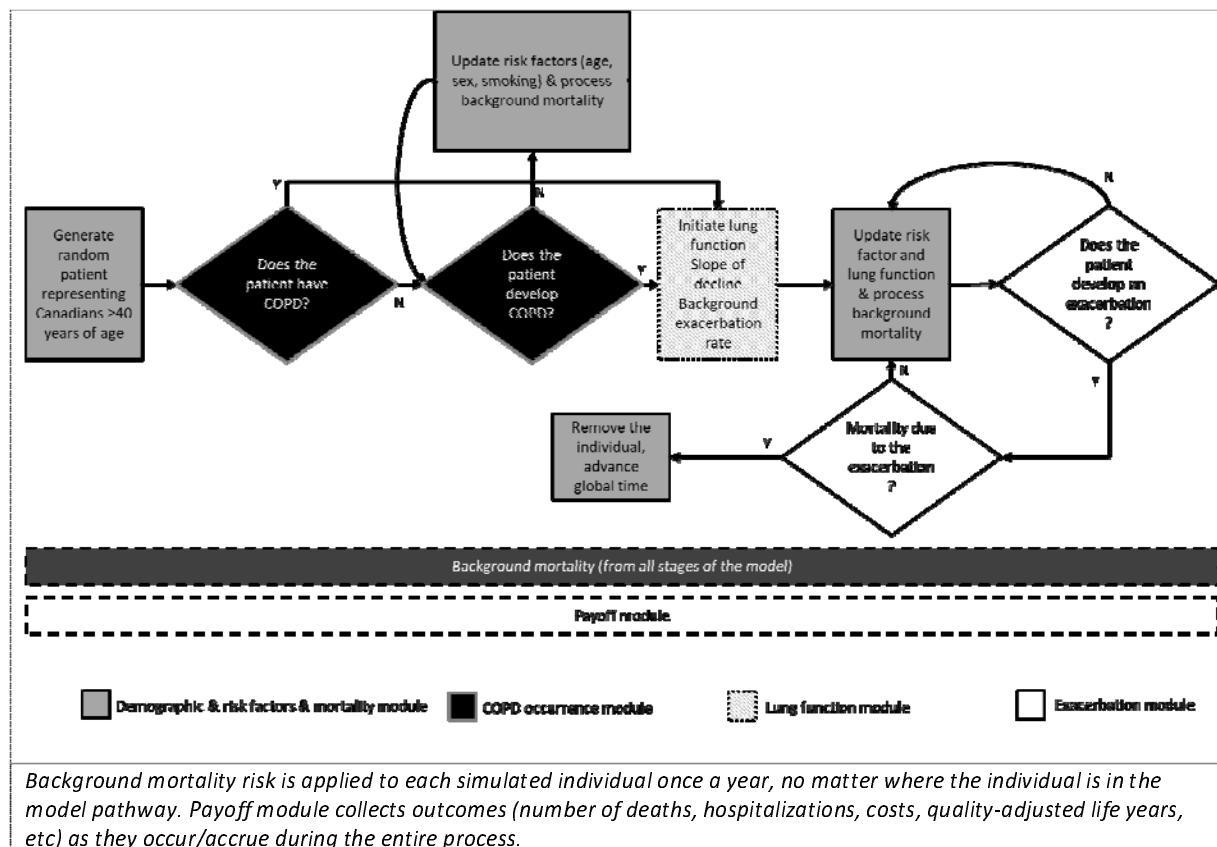and external validation.

Methods

Conceptual framework

The conceptual framework underlying EPIC is that of Whole Disease Modeling(16). This framework

emphasizes modeling the entire pathway of the disease and the transferability of the decision node

across the care pathway of the disease. It also requires the capacity for incorporating interactive

decision nodes, such that implementation of a policy (e.g., the provision of a nationwide screening

program for COPD) will appropriately affect the outcomes of downstream interventions (e.g.,

pharmacotherapy for diagnosed patients)(20).

The investigator team included key stakeholder groups in the research program including clinical

experts, methodologists, and policy makers. We followed guideline recommendations on the proper

conceptualization of a decision-analytic model(21). **Figure 1** provides a schematic illustration of the EPIC

model. The following four features are the core components of the platform: 1) COPD should be

modeled using the reference standard (spirometric definition) so that the model can make projections

about the 'true' burden of COPD and the merits of screening/case detection strategies; 2) lung function

trajectories and acute exacerbations are major factors impacting the natural history of COPD and should

be simulated with high precision as they are ubiquitously the primary end points of clinical trials; 3) EPIC

should realistically model heterogeneity in the natural history of COPD to enable modeling scenarios

pertinent to Precision Medicine (e.g., the use of diagnostic and prognostic biomarkers for COPD

diagnosis and treatment); 4) sex, age, and smoking, the three main risk factors for COPD, should be

modeled explicitly. A consequence of the latter feature is the assumption that any changes in the

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prevalence of COPD over time is due to changes in the distribution of these three risk factors in the population and/or changes in the life expectancy of the population with and without COPD. Input parameters were selected from the sources that would represent 'natural' history of COPD, unaffected by treatment. Additional features of the disease (e.g., symptoms, treatments), other risk factors (such as environmental factors, history of asthma), and comorbid conditions will be added gradually through successive iterations.

Figure 1: Schematic illustration of Evaluation Platform In COPD (EPIC)

Background mortality risk is applied to each simulated individual once a year, no matter where the individual is in the model pathway. Payoff module collects outcomes (number of deaths, hospitalizations, costs, quality-adjusted life years, etc) as they occur/accrue during the entire process.

EPIC is a Discrete Event Simulation (DES) of the general Canadian population. DES models the life history of individuals, one at a time, from entrance into the model to death (or end of the simulation time horizon)(22). The progression occurs during jumps in time (which is a continuous variable) from a set of pre-defined 'events' (e.g., COPD incidence, occurrence of an exacerbation, death – full list is available in

Appendix 1). An individual is defined by a set of 'variables' (such as sex, current age, current FEV_1,

individual-specific rate of FEV_1 decline and rate of exacerbations) whose values determine the rate of

the occurrence of each event, and events in turn affect the value of variables defining the individual.

Time of events were generally sampled from the exponential distribution whose event rates were

functions of an individual's variables. Contrary to cohort-based models (such as the popular Markov

models), individual-specific variables can create a virtually unlimited set of disease states, thus enabling

robust modeling of heterogeneity and complex combination of disease states(22).

Model components and sources of evidence

EPIC can be seen as a series of inter-connected components (modules), each of which models a different

aspect of the disease. Current modules include 1) demographic and risk factors, 2) COPD occurrence

(prevalence and incidence), 3) lung function, 4) exacerbations, 5) costs and quality of life outcomes

(payoffs), and 6) mortality. ***Table 1*** provides the structure of equations for each module. The current

value of parameters (i.e., regression coefficients) are provided in separate tables in the appendices.

<<Table 1>>

1. Demographic and risk factor module

EPIC is a dynamic-population model of Canadian adults ≥40 years of age. As opposed to static models

that simulate follow-up of a closed cohort of individuals for a given time (e.g., 10 years), dynamic-

population models focus on the whole population within a specific date range (e.g., 2020 to 2030) and

include births, deaths, immigration, and emigration. This is instrumental to the accurate modeling of

temporal trends in risk factors such as population aging and changing smoking rates, and

accommodating realistic aspects of policy implementations such as gradual market penetration of new

medications or phased implementation of a population-based intervention such as a COPD screening program.

The demographic module of EPIC was based on Population Health Model (POHEM), a rigorously validated model of risk factors and anthropomorphic and socio-demographic characteristics (e.g., height, weight, smoking status) of Canadians, developed by Statistics Canada. POHEM has performed robustly in multiple internal and external validation challenges(23). Details of the demographic and risk factor module are provided in detail in a separate publication(23), and **Appendix 2** provides an overall description of the demographic module. In summary, individuals are followed over time and new individuals (incident population) enter the model in future years according to the projection of population growth and aging. This module accommodates the projected increase in life expectancy over time through the modification of future life tables. This module is also responsible for modeling smoking-related variables (current smoking status and pack-years of smoking - **Appendix 2**). The smoking pack-years variable is dynamically updated (annually or at the time smoking status changes).

2. COPD occurrence module

This module is responsible for simulating pre-existing and incident COPD. The former refers to COPD that already exists when an individual is first simulated (this is typically for the prevalent population in year 2001, and for immigrants who arrive to Canada after 2001 at older ages), while the latter occurs in simulated individuals as they age, who at the time of creation did not have COPD. COPD was defined as the ratio of FEV_1 to FVC being below its lower limit of normal (LLN)(24). The use of LLN-based definition, as opposed to the fixed (FEV_1/FVC< 0.70) criterion, was based on suggestions from the leading clinical experts in our team reflecting the growing support of the former definition due to its better properties (e.g., association with COPD risk factors)(24). EPIC does not model lung function in the general non-

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COPD population; instead, the occurrence of incident COPD is considered as an event whose risk is determined by the individual's characteristics. Lung function is then modeled in individuals in whom the COPD switch is turned on.

Pre-existing COPD: We used data from the Canadian Cohort of Obstructive Lung Disease (COLD) to assign a binary COPD status to individuals upon their creation. COLD was a nationally representative, population-based cross-sectional study of 3,042 Canadians 40 years of age or older(25). Using these data, we developed sex-specific logistic regression equations for the probability of having COPD as a function of sex, age, and smoking pack-years (**Table 1** and **Appendix 3**).

Incident COPD: The sex-specific hazard of developing COPD was modeled as a log-linear function based on an individual's sex, age, smoking pack-years, and current smoking status (**Table 1** and **Appendix 3**). The incident equation was derived based on a 'steady state' assumption: that COPD incidence is such that COPD prevalence remains stable over time within the strata of risk factors (age, sex, and smoking pack-years). These assumptions establish a mathematical relationship between incidence and prevalence(26). A stochastic optimization approach was adopted to solve for the coefficients in the incidence equation. Details of the calibration process are provided in **Appendix 3**.

3. Lung function module

Once the COPD designation is defined for an individual, an individual-specific initial FEV_1 value and an individual-specific annual rate of FEV_1 decline is assigned. The three components of this module are the initial FEV_1 value for pre-existing (prevalent) COPD cases, initial FEV_1 values for incident COPD cases, and the slope of decline in FEV_1 over time.

For the first two components, we again relied on patient-level data from the nationally representative COLD study(27). Sex-specific linear regression equations were used to estimate FEV_1 given risk factors (**Table 1** and **Appendix 4**). FEV_1 decline was modeled as individualized equations based on the Lung Health Study (LHS, n=5,887), as described in our previous publication(28). These equations performed robustly in internal validation as well as external validation in two independent cohorts(28). In brief, we fitted a random-intercept, random-slope model for FEV_1 decline based on 11 years of data from the LHS with covariates being age, sex, weight, height, and current smoking status (**Table 1** - given that the original equation had other risk variables such bronchial hyper-responsivity not modeled in EPIC, we refitted the original model with reduced variables – results are provided in **Appendix 4**). An additional quadratic term for time was included to capture the potential acceleration in lung function decline over time.

GOLD severity grades: Much of the evidence on COPD outcomes (e.g., costs, quality of life, exacerbation rates) is available according to the GOLD severity grades which are based on FEV_1 to its predicted ratio. Calculating the predicted FEV_1 is based on individuals' age, sex, and height using the National Health and Nutrition Examination Survey equations(29).

4. Exacerbation module

The exacerbation module simulates the exact timing of acute exacerbations of COPD, as well as their severity. Exacerbations were defined in four severity levels according to the event-based definition of exacerbations (which is based on healthcare services use)(30): mild exacerbations are those that result in the intensification of symptoms but do not require an encounter with the healthcare system; moderate exacerbations are those in which patient visits a physician or emergency department but is not hospitalized; severe exacerbations are those that result in hospital admissions; and very severe exacerbations are those that result in admission to the Intensive Care Unit.

We used separate sources for estimating the average rate of exacerbations and between-individual variability (heterogeneity) in rates (**Table 1, Appendix 5**). The average rate was modeled as a function of the GOLD severity grades according to the pooled analysis by Hoogendoorn et. al.(31). The ratio of severe/very severe to total exacerbations was selected from the same study. However, this source did not provide the ratio of mild to moderate or severe to very severe exacerbations. These were selected from a dedicated analysis of a large one-year clinical trial of azithromycin therapy in preventing exacerbations (The MACRO study, n=1,142)(32). The instantaneous rate of exacerbation (hazard) was modeled as a log-linear function of variables; similarly, a proportional odds model was used to assign probabilities for various exacerbation severity levels (**Table 1**).

In EPIC, simulated individuals have their specific rate of exacerbations, as well as their specific probability for an exacerbation, once it occurs, to be at a given level of severity. Empirical evidence supports the presence of such heterogeneity(33). The extent of such heterogeneity was based on our previous work using data from the MACRO study(34). This heterogeneity was modeled through individual-specific (random-effect) intercepts for log-hazard of exacerbation rate and log-odds of exacerbation severity (**Table 1**)(34).

5. Mortality module

This module models death from two sources: due to severe or very severe COPD exacerbations, and background mortality (due to other causes). Background mortality rates were taken from Canadian Life Tables and incorporated the projected declining mortality rates in the future(35). In addition, the probability of death from severe or very severe exacerbations was obtained from the literature (**Table 1**). Explicit modeling of COPD-related mortality in EPIC required calibration of background mortality

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rates so that the combined sources of mortality would produce mortality rates that resemble the sex-specific Canadian life tables. Finally, to avoid implausibly low FEV_1 values, and based on the opinion of the clinical leaders of the team, we assumed individuals would die of a severe exacerbation once they reach an FEV_1 of 0.5.

6. Payoff module

The payoff module assigns costs and health state utility values to events and collects the aggregate population values. These values were chosen from the literature after a dedicated literature review. Details of costs and utility calculations are provided in **Appendix 6**. EPIC currently does not model medical costs and quality of life in the general non-COPD population. Only COPD-specific direct medical costs and utilities are considered. Two cost components are modeled. Annual 'maintenance' costs of COPD are those that accrue outside of episodes of exacerbations. These costs were modeled according to the GOLD grades from previously published studies(36). The second component is costs associated with exacerbations, which were modeled separately for each level of exacerbation severity based on Canadian studies(14,37). All costs are adjusted to 2015 Canadian dollars using the healthcare component of the Consumer Price Index. Similarly, two sets of utilities were modeled: utilities outside exacerbation episodes according to GOLD grades from the published literature, and a direct reduction in QALY associated with exacerbations given their level of severity(36).

Simulation platform

EPIC was programmed in C++. Two copies of the model were developed: one in Statistics Canada's Model Generator, a set of libraries and header files for DES programming implemented in Microsoft® Visual Studio, with pre-existing code representing POHEM(38). An identical open-source and open-access model was developed from scratch with an interface in R (v3.5.1)(39). EPIC code is publicly

available (at http://resp.core.ubc.ca/research/Specific_Projects/EPIC) and can be downloaded and run

as an R package.

Examining face validity and internal validity

We followed the guidelines in establishing validation targets(40). Face validity refers to whether the

model produces sensible results and if changing input parameters affects model output in the expected

direction. Two important sets of face validity targets were the gradient of outcomes across categories of

risk factors (e.g., higher COPD prevalence among ever-smokers than never-smokers), and the stability of

outcomes over time within risk factor strata. Face validity results are not reported here but are available

upon request. Internal validity was assessed by examining if the model produced results that matched

the patterns observed in input data sources or calibration targets. These included **1)** comparing the

simulated population growth and aging with Statistics Canada's projections (validating demographic and

mortality modules), **2)** comparing age-specific all-cause mortality rates with Statistic Canada's life table

estimates (validating the mortality module), **3)** comparing COPD prevalence and GOLD grades by risk

factor groups with estimates from the COLD study (validating the COPD occurrence and lung function

modules), **4)** comparing average and 95% prediction interval of FEV_1 decline with prediction equations

from LHS (validating the lung function module), **5)** comparing the rate of total and severe exacerbations

per GOLD severity grades with the original pooled estimates by Hoogendoorn et. al. (31) and results

from the MACRO study (validating the exacerbation module), and **6)** comparing the average costs and

QALYs across GOLD grades with expected values that are affected by background values and changes

due to the occurrence of exacerbations (validating the pay-off module).

Examining external validity

Ensuring external validity requires examining the model output against results from external sources of

evidence that were not used in the model as input parameters or calibration targets. The external

validity tests were based on the reported outcomes from the placebo arms of two independent clinical

trials: TOwards a Revolution in COPD Health (TORCH)(41) and Understanding Potential Long-Term

Impacts on Function with Tiotropium (UPLIFT)(42). These studies have been used by other COPD

modeling groups as external validity targets and their use here also provides cross-validity tests between

EPIC and existing COPD models(18,19,43–47). The external validity tests involved creating samples that

mimicked the study sample of TORCH and UPLIFT to compare three quantities: rate of overall

exacerbations, rate of severe exacerbations, and percentage of patients who died during follow-up.

Rejection sampling was used to create EPIC samples that matched the baseline characteristics (age, sex,

smoking status, FEV_1, and GOLD grades) of patients in TORCH and UPLIFT (details in **Appendix 7**).

Results

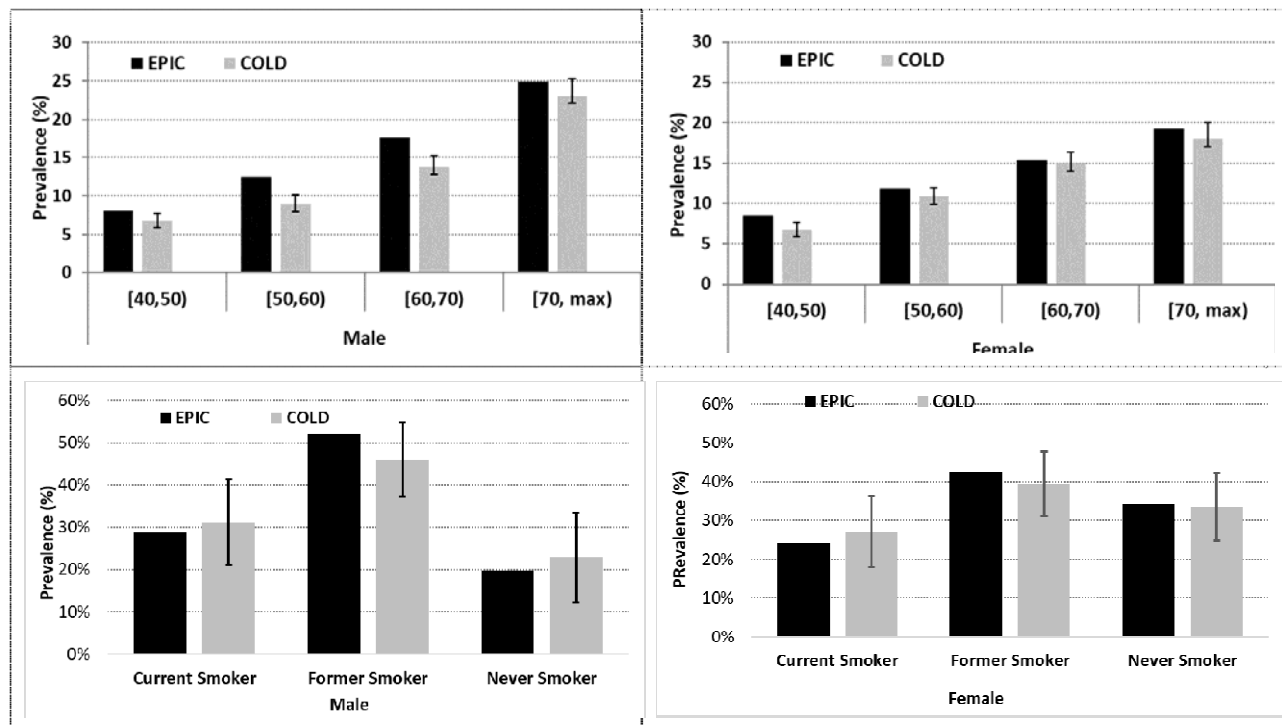## Model calibration and internal validation

Demographic and mortality modules

After incorporating COPD-specific mortality and calibrating background mortality, the model generated

age-specific all-cause mortality rates that were close to the Canadian life tables (**Appendix 2 - Figure**

2.1). The model performed robustly in predicting population growth and aging in the future. **Appendix 2**

- Figure 2.2 presents the simulated (EPIC's) and projected (Statistics Canada's) population growth, as

well as population age pyramid for three exemplary years (2015, 2025, and 2034,).

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COPD occurrence module

After the model was calibrated using the methodology presented in **Appendix 3**, the coefficient for calendar year in the logistic model of COPD prevalence (controlling for sex, age, and smoking) was -0.0004 for males and 0.0001 for females, indicating that the incidence and prevalence equations were coherent. The model performed robustly in replicating the COPD prevalence by sex and age groups as observed in the COLD study (**Figure 2**).

Figure 2: Comparison of the results of EPIC for COPD prevalence by sex and age groups with estimations from COLD data (the source of prevalence equations)

Error bars are 95% confidence intervals. Uncertainty around EPIC output were neglible as simulations were run with large sample sizes.
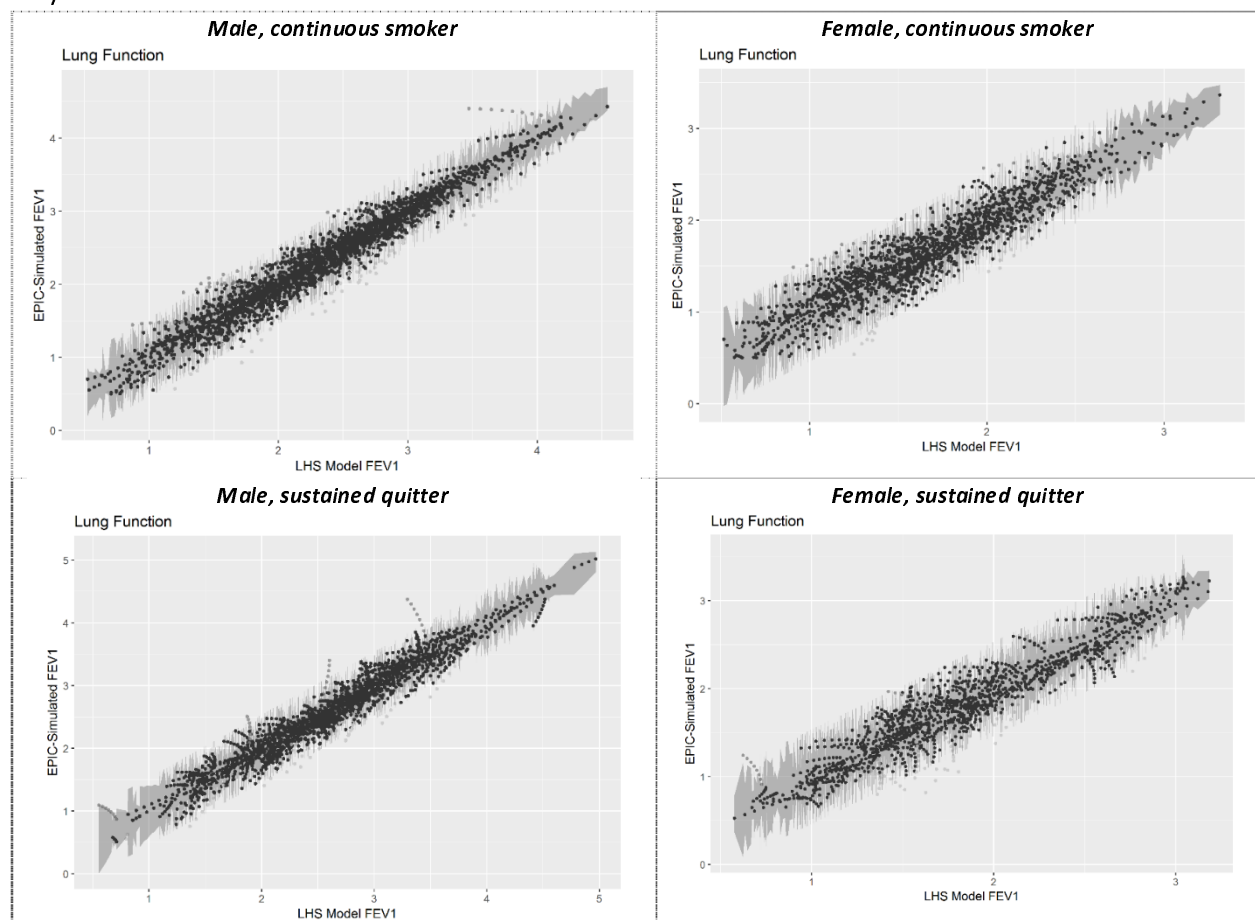
EPIC: Evaluatoin Platform in COPD, **COLD**: Canadial cohort of Obstructive Lung Disease

Lung function module

The equation for FEV$_1$ decline had shown robust internal validity (against LHS) as well as external validity against two independent cohorts. Details of the validation process for FEV$_1$ equations are provided in its

original report(28). Given these results, to validate this module we compared the simulated FEV_1s from

EPIC against the LHS-based equations. ***Figure 3*** presents the results across four subgroups of subjects

(based on permutations of sex and smoking status at baseline). Overall, the FEV_1 values simulated in

EPIC were similar to the LHS-based predictions in terms of the mean and standard deviation across the

range of possible values. The probabilities that the FEV_1 value simulated in EPIC fell within the LHS-based

95% prediction interval were between 94% and 96% for all four subgroups.

Figure 3: Scatterplot of simulated FEV_1s from EPIC versus predicted FEV_1s from LHS equations for up to 11 years
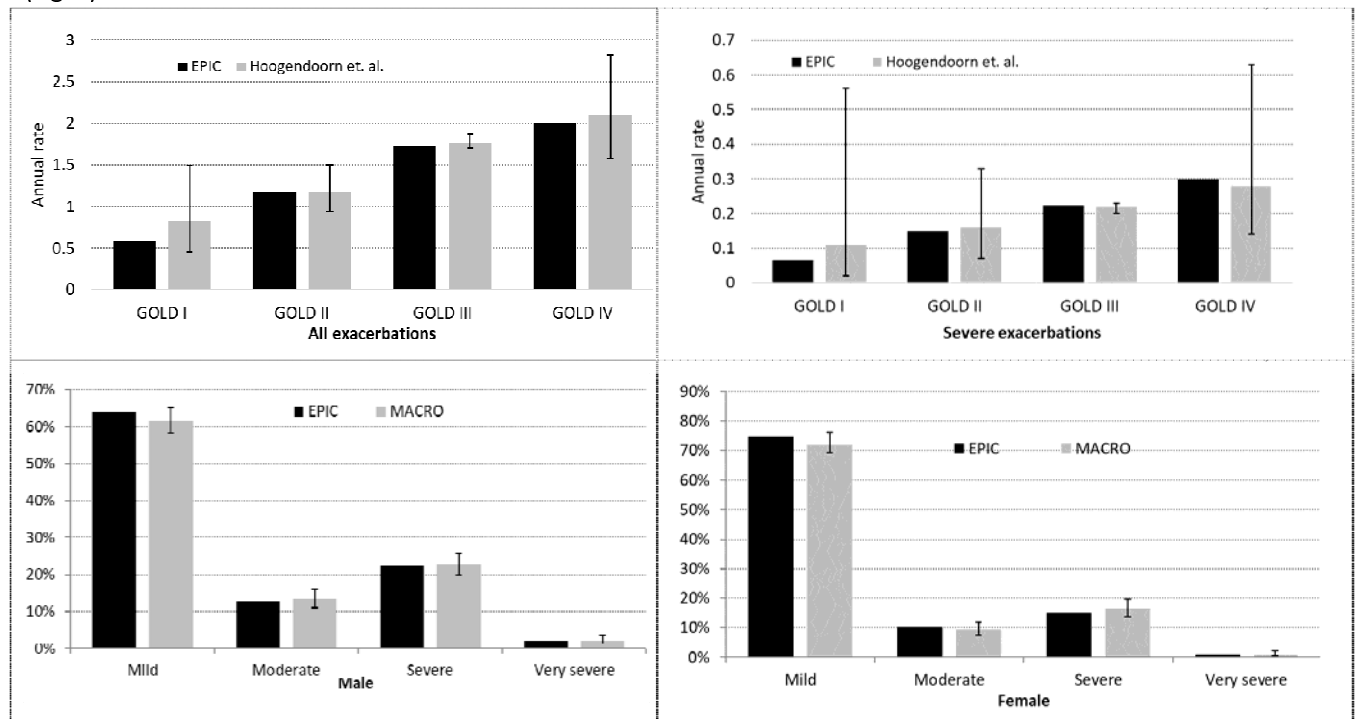

Grey bars are 95% prediction intervals around individual FEV_1 values predicted from LHS equations. Dark grey dots are instances in which the simulated FEV_1 fell within the 95% prediction interval, and light grey dots represent simulated values that fell outside the interval. Graphs are generated based on running the model with 100,000 individuals. For each individual in the model, FEV_1 was sampled once every year. Maximum follow-up was 11 years (LHS follow-up time). In line with the structure of the LHS equations, for this validation task, only individuals who were smokers at baseline (a random date) were followed. At random, individuals either remained smokers throughout follow-up (continuous smokers) or stopped smoking at baseline without any recurrence during follow-up time (former smokers). Simulated individuals die when their FEV_1 reaches 0.5

EPIC: *Evaluation Platform In COPD,* ***LHS:*** *Lung Health Study,* ***FEV_1:*** *Forced Expiratory Volume at one second*

Exacerbation module

Figure 4 shows the EPIC-simulated annual rate of total and severe exacerbations stratified by GOLD

grade compared with those reported in Hoogendoorn et. al. (31). EPIC mildly underestimated the rate of

both total and severe exacerbations in GOLD grade I; nonetheless the simulated values were within the

95% confidence intervals (95%CI) of the original pooled estimates.

Figure 4: Top panel: Comparison of the results of EPIC for the rate of all (left) and severe (right) exacerbations with the pooled estimates from Hoogendoorn et. al. Bottom panel: comparison between the distribution of exacerbation severity between EPIC and MACRO study for males (left) and females (right)

Error bars represent confidence intervals around point estimates. Sampling errors for EPIC-related results are negligible as they are based on a large simulated sample.

EPIC: Evaluation Platform In COPD. MACRO: Azithromycin for prevention of exacerbations of COPD study
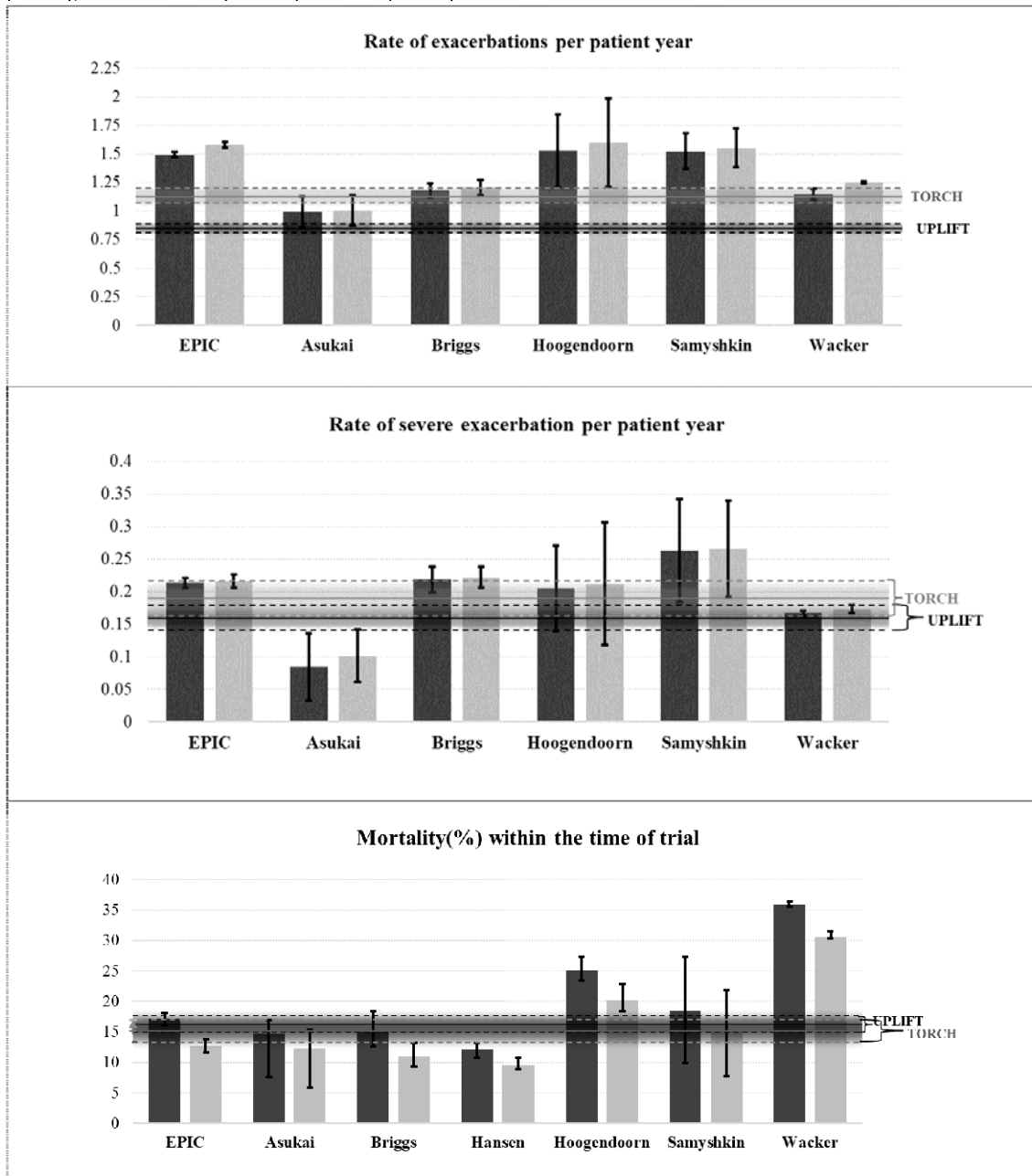
Pay-off module

Appendix 6 – Figure 6.1 provides the results of internal validation of the pay-off module. Back-

calculating costs and QALYs given their background values and the expected rate of exacerbations (of

each level of severity) generated estimates that were close to the output of EPIC.

External validation

After rejection sampling, the baseline characteristics of the simulated sample in EPIC resembled those of

the original samples of TORCH and UPLIFT (*Appendix 7*). *Figure 5* provides the results of external

validation tests.

Figure 5: Comparison of the results of EPIC and five different COPD models with TORCH (light grey bars) and UPLIFFT (dark grey bars) for total exacerbations (top panel), severe exacerbation rate (middle panel), and mortality rate (bottom panel)

After rejection sampling, a total of 3,505 and 5,782 simulated patients remained in the simulated TORCH and UPLIFT groups, respectively.

Error bars are sample confidence intervals for microsimulation models (EPIC and Asukai, first-order uncertainty) while for other models represent uncertainty in outputs due to uncertainty in the model parameters (second-order uncertainty).

EPIC: *Evaluation Platform In COPD,* **TORCH:** *TOwards a Revolution in COPD Health,* **UPLIFT:** *Understanding Potential Long-Term Impacts on Function with Tiotropium*

EPIC, along with two other COPD models (19,47) produced a higher total exacerbation rate than was observed in the UPLIFT trial (1.55/patient-year in EPIC versus 0.85/patient-year in UPLIFT, top panel of *Figure 5*). Similarly, EPIC and the same two models overestimated exacerbation rate in TORCH (1.51/patient-year in EPIC versus 1.13/patient-year in TORCH). EPIC-generated values were outside of the 95%CI of both studies. However, EPIC did replicate the higher exacerbation rate observed in TORCH compared with UPLIFT. EPIC simulated a slightly higher rate of severe exacerbations than was observed in TORCH and UPLIFT (0.21/patient-year in EPIC versus 0.17/patient-year in UPLIFT, and 0.22/patient-year in EPIC versus 0.19/patient-year in TORCH, middle panel of *Figure 5*). EPIC-generated estimate was outside of the 95%CI of UPLIFT. Three other models (19,45,47) generated higher rates than was observed in the trials. EPIC simulated a lower mortality rate over the trial follow-up (12.8%, bottom panel in *Figure 5*) than was observed in TORCH (15.2%); EPIC-generated value was outside of the 95%CI. EPIC generated a similar mortality rate (17.3%) to what was observed in UPLIFT (16.3%).

Discussion

We reported the conceptualization, development, implementation, as well as internal and external validation of a population-based microsimulation outcomes model of COPD in Canada. This platform was developed to provide the capacity to project the burden of COPD given changing risk factors and arrival of new technologies for primary, secondary, and tertiary care prevention. The major components of the model were simulated life trajectories of Canadians, equations describing the incidence and

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prevalence of spirometrically-defined COPD, the individual-specific progression of lung function decline

in COPD, the individual-specific rate and severity of COPD exacerbations, COPD-related mortality rates,

and estimates of costs and quality of life weights associated with different levels of disease severity and

exacerbation status. The use of an open population is a key feature of the model as it provides the

capacity to project future outcomes while considering temporal trends in risk factors such as aging and

smoking. It also enables gradual market penetration of interventions and adoption of policies to be

modeled. This was made possible by access to the population-based cohort in which COPD was defined

spirometrically (as opposed to clinical cohorts that are typically based on convenience sampling of

diagnosed patients in the community). Modeling heterogeneity in key components of the disease

mechanisms (lung function decline and exacerbations) is another important feature of EPIC which

should facilitate the evaluation of scenarios pertaining to complex decision rules for Precision Medicine.

In developing EPIC, we placed a major emphasis on using the most relevant sources of evidence for

different components of the model. This included an extensively validated pre-existing model of socio-

demographic characteristics of the Canadian population and trends in the distribution of risk factors

(e.g., smoking), a secondary analysis of the landmark LHS study for modeling FEV_1 trajectories, a

secondary analysis of a population-based Canadian study for modeling COPD incidence and prevalence,

and a secondary analysis of a recent clinical trial to quantify heterogeneity in the burden of

exacerbations.

Overall, the model performed robustly in face validity and internal validity tests. This should be

reassuring in terms of the validity of the original statistical analyses, model calibration exercises, and

model implementation. It also performed satisfactorily in the external validity of the against two

independent studies that have also been used to validate other COPD models. It overestimated the rate

of overall exacerbation, but its simulated exacerbation rates were similar to two other COPD models.

For rate of severe exacerbations and proportion of patients who died during the follow-up period of

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original studies, its predictions were better aligned with the reported values and were generally around the mid-point of simulated values from five other COPD models. The model replicated the direction of the differences in exacerbation and mortality rates between the two trials, which indicates its responsiveness in propagating changes in risk factors to changes in outcomes.

The limitations of EPIC also need to be mentioned. This work represents the core structure of a COPD 'Whole Disease' model, but much work needs to be done to create a comprehensive COPD outcomes model. While in its current form EPIC is capable of making projections about the future burden of COPD for a broad range of policies, there are many other aspects of COPD which need to be incorporated. Examples include treatment, symptoms, diagnosis, and comorbid conditions. Further, EPIC does not currently incorporate uncertainty in the underlying evidence, which is a goal for the next iteration of this platform. Given that many parameters of EPIC are derived based on calibration techniques, this is not simply a matter of replacing fixed input parameters with their probabilistic equivalent. More sophisticated model calibration techniques might prove useful in this context(48). Further, EPIC is currently limited to modeling the impact of sex, age, and smoking as risk factors for COPD. As such, it cannot currently be used to evaluate scenarios that relate to occupational and environmental exposures or history of asthma. Because lung function in the non-COPD population was not modeled, preventive strategies based on monitoring lung function prior to persistent airflow obstruction cannot be assessed. Similarly, prodromal phase of exacerbations and exacerbation phenotypes (e.g., infectious versus inflammatory) are not currently modeled, limiting the applicability of EPIC in simulating scenarios pertaining to the early detection of exacerbations. Overall, EPIC can currently be used for modeling the outcomes of disease management based on lung function, exacerbation history, and smoking history. However, it cannot provide this capacity for disease management based on symptoms or burden of comorbidity. The planned iterative upgrades should see these features gradually incorporated into the platform.

EPIC is not the first multi-purpose model of COPD. We have previously performed a systematic review of published COPD models that were used for epidemiological projections or economic evaluations(49). The majority of models were created for addressing a specific question (e.g., cost-effectiveness of a novel therapy). However, in some instances, subsequent models were built on previous ones in an iterative fashion. The presence of such an identifiable 'lineage' of models demonstrates the need for, and feasibility of, re-using an existing model for different objectives. Recently, a convention of model developers assessed the consistency of five different models in COPD and their external validity(18,50,51). Putting our developed model in the context of previous reference models is informative. Among the previously reviewed models, only the model by Hoogendoorn et. al., which was developed for the Netherlands, is a dynamic population model(19). EPIC appears to be unique in modeling heterogeneity at the individual level in lung function and the rate and severity of exacerbations. Briggs et. al., developed a model of COPD progression based on the Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE)(52) data (with resource-use estimates from UPLIFT)(45). The model was based on a rigorous practice of model conceptualization(53), and has performed satisfactorily in internal and external validation studies(18,45). A major advantage of this model is its incorporation of multiple aspects of COPD (such as symptoms and six-minute walking distance, a measure of functional capacity). However, reliance on mainly one study (ECLIPSE) makes this model less relevant to the Canadian context, and three-year follow-up of ECLIPSE makes long-term projections less certain.

Predicting the future using the best available evidence is a cornerstone of many disciplines. In healthcare, the use of modeling to reconcile evidence from multiple sources to project the outcomes of decisions is considered "an unavoidable fact of life"(11). Model-based projections can critically inform recommendations for best practices as well as policies. Multi-purpose models that encapsulate concerted efforts in evidence synthesis, validation, and implementation exist for many health

conditions. EPIC adds to the portfolio of such COPD models currently under development by various

groups(51). While EPIC is developed for the Canadian context, many of its components pertain to the

natural history and biology of COPD and are independent of a particular setting. Other components can

be updated (mainly by changing numerical values of input parameters rather than modifying the

structure of equations) with the specifics of a healthcare setting. As such, this platform can have

applicability for other jurisdictions. The recent organized efforts in ensuring external validity and cross-

comparability of such models can help the development of robust platforms that address the ongoing

needs of both the research and policy community.

Table 1: Input parameters (βs) and their related equations in Evaluation Platform In COPD (EPIC)

Parameter(s)	Description	Value(s)	Source/Reference
Demographic and risk factor module			
Demographic variables and risk factors	Sex, age, smoking status, height and weight	Various equations representing the baseline 2001 Canadian population (20 years or older) from 2001 CCHS. See **Appendix 2** for details.	Based on Population Health Model(23)
COPD occurrence module			
COPD prevalence equation	Assigns COPD status to simulated individuals at the time of creation	$logit(p\|sex) = \beta_{0,sex} + \beta_{1,sex} \times age + \beta_{2,sex} \times pack.years$	Regression on COLD data(25) (**Appendix 3**)
COPD incidence equations	Assigns COPD status to simulated individuals who did not have COPD at the time of creation during their time in the model	$log(hazard\|sex) = \beta_{0,sex} + \beta_{1,sex} \times age + \beta_{2,sex} \times pack.years$	Stochastic calibration based on COPD prevalence equations (**Appendix 3**)
Lung function module			
FEV_1 for prevalent cases	Baseline FEV_1 value for individuals who have COPD at the time of creation	$FEV1\|sex \sim Normal\big(\beta_{0,sex} + \beta_{1,sex} \times age + \beta_{2,sex} \times pack.years + \beta_{3,sex} \times height^2, e\big)$	Regression on COLD data(25) (**Appendix 4**)
FEV_1 at incidence	Baseline FEV_1 value for individuals who develop COPD during the time in the model	$FEV_1\|sex \sim Normal\Big(\beta_{0,sex} + \beta_{1,sex} \times age + \beta_{2,sex} \times pack.years + \beta_{3,sex} \times height^2 + \beta_{4,sex} \times \frac{\left(\frac{FEV1}{FVC}\right)}{LLN}, e\Big)$	Regression on COLD data(25) (**Appendix 4**)
FEV_1 decline over time	Models FEV_1 at time t (in years) in the future based on a random-intercept-random-slope model	$FEV_1(t) \sim Normal(Y_0 + Y_1 \times t + Y_2 \times t^2, e)$ $Y_0 = \beta_0 + \beta_1 \times age + \beta_2 \times sex + \beta_3 \times weight + \beta_4 \times height + \beta_5 \times height^2 + \beta_6 \times smoking.status + \beta_7 \times age \times height^2$ $Y_1 = \beta'_0 + \beta'_1 \times age + \beta'_2 \times sex + \beta'_3 \times weight + \beta'_4 \times height + \beta'_5 \times height^2 + \beta'_6 \times smoking.status + \beta'_7 \times age * height^2$	From the Lung Health Study(28) (**Appendix4**)

		$$Y_2 = \beta''_0$$	
Predicted FEV$_1$	Calculated predicted FEV$_1$ value, required for determining GOLD severity grades	$FEV_1.predicted$ $$= \beta_0 + \beta_1 \times sex + \beta_2 \times age + \beta_3 \times height^2$$	From NHANES III(29)
Exacerbation module			
Exacerbation rate	Hazard of exacerbation for the ith individual	$log(hazard) = \alpha_i + \beta_0 + \beta_1 \times age + \beta_2 \times GOLD + \beta_3 \times GOLD_{3+} + \beta_4 \times GOLD_4$ $$\alpha_i \sim Normal(0, v)$$	Pooled estimates from Hoogendoorn et. al.(31); variability estimated form MACRO study(32) (**Appendix 5**)
Severity of exacerbation	Probability that once an exacerbation occurs for the ith individual, it is at a given level of severity	$logit(\pi(S_i < k\,))$ $$= \alpha_i + \beta_{0,k} + \beta_1 \times age + \beta_2 \times sex + \beta_3 \times FEV_1 + \beta_4 \times smokings.tatus + \beta_5 \times pack.years + \beta_6 \times BMI$$ $$\alpha_i \sim Normal(0, v)$$ S_i: severity level (0-3) for the exacerbations of the ith individual. All variables are estimated at the onset of the exacerbation	From Hoogendoorn et. al.(31) and MACRO study(32) (**Appendix 5**)
Mortality module			
Background mortality rate	Death due to non-COPD reasons	Canadian life tables with calibration to remove COPD-specific mortality	Modification of the Canadian life tables(35) such that the combined sources of mortality match the life table values
Mortality due to COPD exacerbations	Short-term mortality due to severe exacerbations	$logit(p) = \beta_0 + \beta_1 \times age + \beta_2 \times severe + \beta_3 \times very.severe$	From (4) and (54). Severe and very severe are dummy-coded variables

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Pay-off module			
Direct maintenance costs of COPD	Annual direct medical costs not associated with exacerbations (in 2015 $CAD)	$cost = \beta_1 \times GOLD_1 + \beta_2 \times GOLD_2 + \beta_3 \times GOLD_3 + \beta_4 \times GOLD_4$	Spencer et. al. (36) and Chapman et. al (55) (**Appendix 6**)
Direct costs associated with exacerbations	Direct medical costs pertaining to an episode of exacerbation according to its level of severity (in 2015 $CAD)	$cost = \beta_1 \times mild + \beta_2 \times moderate + \beta_3 \times severe + \beta_4 \times very.severe$	Mitmann et. al. (37), Canadian Institute of Health Information (56) (**Appendix 6**)
Background utility values in COPD	Health state utility values in patients with COPD according to GOLD grades outsides of an exacerbation episode	$utility = \beta_1 \times GOLD_1 + \beta_2 \times GOLD_2 + \beta_3 \times GOLD_3 + \beta_4 \times GOLD_4$	Spencer et. al. (36) and Rotten-Van Molken et. al. (57) (**Appendix 6**)
Reduction in QALY due to exacerbations	Two sets of regression coefficients (s=0 & s=1) separately modeled reduction in QALY values for mild/moderate and severe/very severe exacerbations which were dependent on the underlying GOLD grade	$\Delta_Q = \beta_{1,s} \times GOLD_1 + \beta_{2,s} \times GOLD_2 + \beta_{3,s} \times GOLD_3 ++ \beta_{4,s} \times GOLD_4$	Spencer et. al. (36), (**Appendix 6**)
EPIC: Evaluation Platform In COPD, **GOLD:** *Global initiative for Obstructive Lung Disease*, **GOLDx:** *Global initiative for Obstructive Lung Disease severity level x (x ranges from 1 to 4 representing mild, moderate, severe, and very severe grade),* **FEV₁:** *Forced Expiratory Volume at one second,* **COPD:** *Chronic obstructive pulmonary disease,* **QALY:** *quality-adjusted life year,* **BMI:** *body mass index,* **MACRO:** *Azithromycin for Prevention of Exacerbations of COPD study,* **NHANES:** *National Health and Nutrition Examination Survey,* **COLD:** *Canadian Cohort of Obstructive Lung Disease,* **$CAD:** *Canadian dollars*			

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