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Article title: Budget impact analysis of adopting primary care-based COPD case detection in the Canadian general population

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Reviewer 1: Mr. Alex Haines, CADTH, Evidence standards

Although a pan- Canadian estimate is useful for context, this may have practical and methodological drawbacks. By running the analysis on a pan- Canadian level this masks a lot of heterogeneity across provinces. COPD prevalence will vary by province but so will smoking rates. This will likely impact the diagnostic accuracy of the strategies given that smoking prevalence from table 1 influence sensitivity and specificity. Given this, the budget impact may be higher or lower in some province (on a per captia basis) such that it may be more affordable/attractive to implement in some provinces and not in others. From a practical standpoint, healthcare funding in Canada mainly happens at the provincial level. If a COPD diagnostic strategy was to be rolled out it would likely happen at the provincial level. Just having a pan-Canadian estimate would not be of particular use to individual provinces who would want to note the budget impact for their jurisdiction.

Potential solution: The analysis could be run with province specific population numbers and prevalence estimates. An assumption could be made that diagnostic accuracy is equivalent across provinces.

However, this would substantially increase the amount of information being reported if the current paper was just replicated for each province. Given that the cost data feeding into the model relies heavily on estimates from BC the analysis could be re-run to just represent BC.

We have provided a discussion of national versus provincial level analysis under the editor's third comment and copy our response below for convenience:

We recognise the valid arguments made for a provincial level analysis. However, there are many reasons for why the analysis should be kept at a national level.

First, reworking the analysis to provincial level is unfortunately not as simple as changing the population size and prevalence estimates.

Population size is an adjustable input parameter in EPIC and will produce a population sample that reflects the demographics of the Canadian population. However, the population demographics module is based on Population Health Model (POHEM) developed by Statistics Canada, a rigorously validated model of risk factors and anthropomorphic and sociodemographic characteristics of the entire Canadian population. This module accommodates for age-sex demographics, population growth, life expectancy, height, weight, and smoking status. Therefore, even if we were to input provincial population size estimates, the sample produced would still be representative, demographically speaking, of the entire general Canadian population. Similarly, COPD occurrence is not modelled within EPIC simply via COPD prevalence estimates. COPD occurrence (in addition to community diagnosis, primary care utilisation, and symptoms) is modelled using data from CanCOLD, a *national*

prospective cohort of patients with COPD and at-risk of COPD. This allows us to account for risk factors in the probability of developing COPD, including age, sex, smoking status, and pack years.

Second, it is not uncommon for Canadian screening studies to be conducted at the national level, particularly when using advanced simulation modelling methodology. The Cancer Risk Management Model which has been used to investigate both lung cancer and colorectal cancer screening options is a national-level model. Such models are extremely complex to develop, and sufficient data is not always available at provincial- level.

Third, even though healthcare funding in Canada occurs at a provincial level, screening guidelines are typically produced nationally (e.g., (3)). Such guidelines require affordability and feasibility assessments to recommend best practice. Therefore, the results of our analysis are of use to policymakers beyond that of providing context.

To summarise, given the modelling framework of EPIC and data availability, a national level analysis is better suited to our methodological framework. Further, national level results for budget impact analyses are common practice and are of significant use to policymakers for recommending guidelines to then be considered at provincial level.

The analysis does not appear to address the implication of overdiagnosis. Figure 3 in appendix 1 shows that a substantial proportion of individuals who do not have COPD are diagnosed with it (~3% reading off the graph). Given that non-COPD patients make up a substantial portion of the population a small
% of misdiagnosis in this group will have significant cost implications. It is unclear if any of the strategies impact the rate of overdiagnosis. This would seem counter intuitive given that figure 1 indicates that no false positives are possible through these testing strategies. Given that current practice results in over diagnosis is this therefore being reduced at all? I may be misinterpreting this however.

Potential solution: it is unclear how the study incorporates the impact of overdiagnosis. If the authors have explored this then this needs to be more transparent in the writing. What is the specificity of 'current practice' for example.

The study assumes that diagnosing an individual with COPD will always lead to incremental costs to the health system. The only savings associated with these diagnostic strategies are from reducing hospitalisation and outpatient visits in those with COPD without a diagnosis. If an individual has COPD and is not diagnosed with it then that may be because they are incorrectly diagnosed with something else, such as asthma for example. In this case the incremental costs of a correct diagnosis would be the difference in COPD management versus asthma management. Treatment costs may even be smaller with COPD versus asthma if the patient was on a biologic for example (cost saving). As the analysis assumes zero treatment costs for those with COPD without a diagnosis that may overinflate the budget impact of these diagnostic approaches.

Potential solution: the analysis should further explore the costs associated with having COPD and not having a correct diagnosis. This may rely on assumptions and clinical expert opinion. This should be explored/tested using scenario analyses.

To clarify, background medical costs are assigned in EPIC based on disease severity (GOLD stage) regardless of diagnosis. Hence undiagnosed COPD patients are still assumed to incur costs associated with their condition. This assumption has been validated by previous observational studies showing that undiagnosed COPD patients still incur healthcare costs (11,12). Following diagnosis, patients are assigned medication (with 70% adherence in the base case) which can decrease costs if treatment prevents an exacerbation.

Mr. Alex Haines raises a valid point regarding the common misdiagnosis between asthma and COPD, but to include it in the analysis would require significant assumptions. A diagnosis of COPD does not necessarily imply the cessation of asthma treatment or the reversal of the asthma diagnosis. Asthma treatment may continue unnecessarily, or patients may genuinely have both conditions (Asthma COPD Overlap). In the case of asthma biologics, these drugs require special authority for public drug coverage which requires objective measures of asthma. Therefore, it is highly unlikely that patients on biologics would be misdiagnosed.

Type of costs looked at in the analysis. The cost of case detection is estimated assuming 34% of the cost of a 15-minute routine primary care visit. For a budget impact analysis this implies that for this cost to be realised the number of GP visits would have to increase to accommodate for this. Or that this case detection would be billed at a rate of $11.91. It may just be that this represents an opportunity cost of GP time, such that the number of GP visits remains the same but time is allocated differently. In an economic evaluation this could be valued as an opportunity cost but in a budget impact analysis this could be misleading. For full transparency the authors should separate this cost out in the case detection row of the results.

Other costs (such as outpatient visits and flow meters) are costs that will be billed and have an impact on health budgets. Time spent asking a questionnaire may or may not appear on a budget depending on how it is incorporated.

Potential solution: If the authors believe this will increase the number of GP visits then they should be explicit and note what impact this would have as that information would be useful to decision makers. If they believe it will be billed at a going rate then they should be explicit about that.

We have followed the advice of the reviewer and have separated out the time-related cost in the results table. The limitations paragraph of the interpretation now includes a brief discussion regarding the uncertainty in how the time-related cost will be billed.

"Third, there is uncertainty in how the time-related cost would be billed. Since we assume case detection to be administered during routine primary care visits, it may not result in budget impact if it does not result in an increase in the length or number of appointments. Conversely, there is an opportunity cost for time spent administering COPD case detection during primary care visits, which is captured by this time cost. We separate out the time-related cost in our budget impact results for full transparency."

Does the analysis assume 100% of individuals diagnosed with COPD have their treatment funded by public drug plans?

Many individuals may not be eligible for public drug coverage or may opt to use their private plan instead.

Proposed solution: the authors should provide an estimate of the proportion of treatment costs funded under a public drug plan. Or be explicit they assume 100% public drug coverage and detail why.

We assume 100% public drug coverage for our analysis. Public drug coverage varies by province, but all provinces have full coverage for adults ≥ 65 years which will account for the majority of COPD patients (13). Further, we have no way of knowing the extent of private insurance by GOLD grade, symptoms, and exacerbation history, which is the criteria used to assign medication type.

Our assumptions for public drug coverage have been added to the methods section of the manuscript.

"We assume 100% public drug coverage since all provinces have full coverage for adults ≥ 65 years which will account for most COPD patients."

I feel the paper could benefit from a more detailed discussion regarding the sensitivity and specificity for each diagnostic strategy given how important this parameter is for the analysis. Also unclear how sensitivity and specificity influence the results. Does specificity even matter if overdiagnosis is not modelled?

Likewise, what is the assumed sensitivity and specificity of current practice?

The sensitivity and specificity values reported in Table 1 are used to model the outcome of the case detection test result. Patients testing positive at case detection are then referred for diagnostic spirometry which we assume to have 100% accuracy. Therefore, the sensitivity and specificity values do not affect overdiagnosis, they only affect the number being referred for diagnostic spirometry (and the balance of true and false positives at case detection). Figure 1 provides a schematic illustrating the case detection pathway and we have added a footnote to Table 1 for clarification.

"[a] Sensitivity and specificity values are derived from the literature and further details have been provided previously. Sensitivity and specificity values relate to the outcome of the case detection test only; patients testing positive are then referred for diagnostic spirometry which we assume to have 100% accuracy."

Within EPIC, the sensitivity and specificity of routine diagnosis is not modelled directly. Instead, we use input data from the CanCOLD study to model the annual probability of routine diagnosis during primary care visits both among COPD patients and non-COPD patients (overdiagnosis). The probability of diagnosis is modelled as a function of sex, symptoms, smoking status, and number of GP visits. Case detection is added as a parameter to the diagnosis equation. The parameter value is such that the average probability of diagnosis equalled the sensitivity of the case detection method (for COPD patients), and the average probability of false positive diagnosis equalled the specificity of the case detection method (for non-COPD individuals).

Where the odds of diagnosis with case detection equals the sensitivity (for COPD patients) and the specificity (for non-COPD individuals), converted to odds.

to odds:

$$\beta_{case\ detection} = \log\left(\frac{1}{n}\sum_{i=1}^{n}\frac{\text{odds of diagnosis with case de}}{\text{odds of routine diagnosi}}\right.$$

The diagnosis module in EPIC has been calibrated to yield a stable proportion of diagnosed patients among COPD individuals approximately equal to that observed in CanCOLD (29.7%). We provide details of the diagnosis module in Appendix 1 and report the validation of routine diagnosis for this analysis specifically at the start of the results section of the main article.

"At baseline the COPD prevalence among Canadians aged ≥40 years was 11.9% and 30.4% of individuals with COPD were diagnosed. These are similar to the COPD prevalence (11.2%) and proportion diagnosed (29.7%) observed in the CanCOLD study (Appendix 1)."

Unclear how adherence is used to influence drug costs. Is 70% applied to the annual drug cost? Does this assume that individual's only pick up 70% of the recommended drug they are on? Additional details regarding this assumption and justification would increase transparency.

Within our modelling assumptions, a 70% medication adherence means that out of 100 patient-years in which a patient was eligible for a medication, they only took it (and therefore received the benefit) in 70 patient-years.
Medication costs are therefore adjusted by 70% for adherence. The values reported in the parameter inputs table (Table 2) are the adjusted costs. A footnote has been added to Table 2 to increase the transparency of our assumptions.
"[a] Annual per-patient treatment costs are weighted by adherence (0.7% in the base case analysis).

[b] Medication adherence of 70% means that out of 100 patient-years in which a patient was eligible for a medication, they only took the medication (and therefore received the benefit) in 70 patient- years."

Some of the costs used to inform the study are very old (2003 over 20 years ago). When cost sources are that old inflation adjustment is unlikely accurate. It is unclear if there is any double counting when separating out exacerbation costs (particularly mild exacerbation costs) with maintenance costs.

There is no double counting of costs. Maintenance costs are those that accrue outside of episodes of exacerbations and include physician visits (generalist and specialists), rehabilitation programmes, laboratory tests and devices, and oxygen therapy. Treatment costs (that is, maintenance treatment and not exacerbation- related treatment) have been deducted from maintenance costs to avoid double counting. A

mild exacerbation is assumed to not require an encounter with the healthcare system and is only assigned the cost of increased medication. This increased medication cost would not be counted under background maintenance costs and are in addition to maintenance treatment costs. We have extended the existing footnotes of Table 2 to increase the transparency of our assumptions.

"[d] Maintenance costs are those that accrue outside of episodes of exacerbations and include physician visits (generalist and specialists), rehabilitation programmes, laboratory tests and devices, and oxygen therapy. Treatment costs (that is, maintenance treatment and not exacerbation- related treatment) have been deducted from maintenance costs to avoid double counting."

We recognise that additional uncertainty is introduced into our cost estimates due to the use of older data sources. The COPD background maintenance costs are sourced from two Canadian studies from 2003 and 2005. We have investigated options for updating these sources but have been unable to find an adequate alternative. We require a detailed micro-costing study stratified by COPD severity GOLD grade that must be specific to Canada, and such studies are rarely conducted.
We performed a scoping literature search in PubMed and found a potentially suitable alternative for maintenance costs from 2012 (14). The costs reported are similar to those used for our analysis. However, this study uses a symptom- based definition for COPD exacerbations whereas EPIC uses an event-based definition of exacerbations (which is based on health service use). Therefore, using this source may result in a miscounting of maintenance and exacerbation costs.

Reporting of thebudget impact is slightly confusing. In the tables negative values indicate savings for the current strategy. Given that the proposal would be to fund a new intervention we should look at the budget impact of that (rather than the budget impact of no change). In appendix 1 I would revert the minus signs to make it clearer where the new strategy will add costs and save money.

We agree that a negative value for cost savings is arguably counterintuitive. However, it is convention for reporting budget impact results. For example, page 26 of the Canadian Budget Impact Analysis Guidelines (15) states:

"The budget impact is equal to the difference between the value of the New Drug Scenario and the Reference Scenario. A positive budget impact value indicates that the introduction of the new drug will result in increased expenditures for the drug plan, while a negative value indicates that the drug plan will save money by adopting the new drug."

Reviewer 2: Dr. James Ted McDonald, University of New Brunswick, Fredericton, Department of Economics

While the costs associated with increased case detection are substantial, the authors note that even a country-wide COPD case detection program would result in an estimated increase in the national health care budget of 0.04% over five years. Thus, while the dollar increase is large, it is a very small proportion of total healthcare expenditure. In making a

case for an expansion of detection, could the authors compare such an outlay to the costs of the implementation of other population- screening programs such as those for colorectal cancer?

We estimate that the programme would account for 0.04% of the budget by 2026, so that's 0.04% per year. We would argue that even 0.04% is quite large for one programme in the context of the entire healthcare budget.

The costs of other population screening programmes in other disease areas are not available in sufficient detail to compare to our analysis.

Other sensitivity checks could include reduced costs assumed for administration of the CDQ and flow meter. For example, could the CDQ be automated and conducted through an app? Could the flow meter test be administered by a trained assistant? Or could the test be administered in a pharmacy?

There are admittedly countless ways a case detection strategy could be implemented.

For this analysis we consider opportunistic primary care-based case detection. EPIC models the rate of primary care visits using input data from the CanCOLD study, and we base uptake of the case detection programme in primary care on lung and colon cancer screening programmes. Using these data sources, we can sensibly model the number of patients administered case detection. Assuming that the case detection test is completed anywhere other than during routine primary care appointments would be inconsistent with our modelling assumptions. In the case of the CDQ, if we were to assume the questionnaire was automated through an app or completed as an online survey, we would incur greater uncertainty with patient participation rates and response bias, since the responsibility of the test is now placed on the patient. In addition, self-administration and GP administration of the CDQ will likely have different sensitivity and specificity values. Up to 50% of adults with airflow obstruction do not recognize or report symptoms or limit physical activity resulting in the masking of symptoms. If a GP is administering the questionnaire, they may be able to ask further questions or provide clarification that can reveal issues the patient has ignored. If we were to assume that the patient completes the CDQ whilst in the waiting room/prior to the appointment/online, or that the Flow Meter is administered by a trained assistant/pharmacist, the follow-up pathway must next be considered. A patient testing positive at case detection would unlikely be immediately referred to outpatient diagnostic services without first speaking with a GP. Thus, a time-related cost would still be incurred, and potentially to a greater degree if the appointment is being made entirely to follow-up the case detection test completed elsewhere. The scope of our study was to evaluate opportunistic primary care-based case detection given the greater availability of evidence on this subject.

Ultimately, the question of the exact method of administering a case detection programme comes down to assumed costs. The Shiny web app for the results of this research allows users to input different cost values and examine their impact on results.

The relatively high rate of community COPD diagnosis without a confirmatory diagnostic spirometry test is noted, as are challenges arising from an increase if the take- up of

diagnostic spirometry testing were to be expanded. These include capacity constraints in facilities and trained personnel as well as access barriers (time, distance) for individuals referred to testing. There may be other reasons as well, including a primary care physician's assessment that a diagnostic confirmatory test is not necessary based on observed symptoms, patient history, other testing (e.g., xray or CT) or an individual's inability to complete the diagnostic testing owing to advanced age and/or respiratory limitations. This apparently is already factored into the baseline as noted on p4 line 55. Could the authors clarify whether the expanded screening excludes or includes such individuals? If included, would a further narrowing of those sent for diagnostic testing substantially reduce total costs?

We assume a 100% completion of outpatient spirometry following positive case detection. We recognise that it is possible that not all patients testing positive at the time of case detection will be referred or attend diagnostic spirometry. However, a diagnosis of COPD can only be confirmed by spirometry. A diagnosis cannot be made on symptoms or patient history alone, and no other test including lung imaging can replace spirometry. We therefore think it is most appropriate to include the necessary step of diagnostic spirometry for the base case of our analysis.

The impact of reduced outpatient spirometry completion on budget impact results can be examined by multiplying the outpatient diagnosis cost by desired adherence in the Shiny web app developed for the results of this analysis.

Dr. James Ted McDonald raises a valid point that some individuals may be unable to complete spirometry, for example if the patient had recently had a heart attack or has uncontrolled high blood pressure, but this would account for a very small number of patients, so we have not included this in our analysis.