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Title	**Clinical impact and cost-effectiveness of integrating smoking cessation into lung cancer screening: a microsimulation model**
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Reviewer 1	Withheld
Institution	Withheld
General comments	Withheld
Reviewer 2	David Kim
Institution	Tufts Medical Center, Center for Evaluation of Value and Risk in Health, Institute for Clinical Research
General comments	"Modeling the clinical impact and cost-effectiveness of integrating smoking cessation into lung cancer screening." The authors conducted a modeling study to examine the clinical and economic impact of integrating smoking cession into lung cancer screening program in Canada. Given the uncertainty and unavailability of the key data inputs, the authors conducted extensive and comprehensive sensitivity and scenario analyses to provide as much information to inform decision-making. I have major and minor suggestions that may help to improve the study. Major suggestions: - It is hard to understand what data inputs and a range of plausible values are used in the model. For example, screening costs, health-related quality of life measures, specific transition probabilities were not cleared presented. I would recommend the authors to create a data input table with a plausible range of the value when examined in deterministic or probabilistic SA (See my comments below). - - Given some uncertainty in the choice of data input as well as stochastic uncertainty, it would be great if the authors can conduct probabilistic sensitivity analysis to capture the underlying uncertainty of all parameters simultaneously. - As authors acknowledged and examined in the SA, the key assumptions in the model include a recruitment rate (60% in the base case) and an adherence rate (70% in the base case). Can the authors provide a rationale or previous studies to explain why these estimates were chosen as the base case? If no evidence is available to support, the authors may explicitly state that these choices are speculative, and alternatives are examined in SA. - The use of the lower discounting rate (1.5% vs. 3%) generally provides favorable ICERs for preventive interventions with greater downstream benefits. Authors need to justify why 1.5% discount rate is used (authors assumed that no growth in health sector beyond the general inflation – is this a rationale for choosing the lower discount rate?), instead of conventional 3% as recommended by the practice guideline (2nd Panel on cost-effectiveness analysis) and also used by the author's cited previous CEA study of LCS in Canada (reference 7) I see the authors conducted SA on the discounting rate. Wouldn't it make the result more comparable to the other studies if the authors report the result from 3% discounting unless some specific rationale? (Page 10, Line 16-17) - Given the uneven distribution of benefits and costs of the CTS + CS over time, it would be informative to present the results over time. Similar to costs as the intervention cost fluctuates over time. It would be nice to see some graphical representation of the net overall costs, cost offsets, and the intervention costs over time. (be specific whether it is discounted or undiscounted costs) These can be made as Appendix figures, but it would be better than "Data are not shown" and can be very informative to the readers to understand the differential timing of benefits and costs over time. - Also, acknowledged by the authors, smoking is a chronic relapsing condition. In the

	microsimulation model, it wasn't clear how the model incorporates the relapse back to smoking. The authors need to discuss explicitly how the important issue has been incorporated into the model, possibly through using the permanent quit rate, but it may underestimate if not incorporating those who could quit for a while. Minor suggestions: - Page 6, line 47: I feel the use of "reference case" is little confusing since the term is often used to refer a standard set of practice guidelines (e.g., reference case analysis to improve quality and comparability across CEAs). May the authors refer the CTS only as to "the reference strategy or the base case strategy" and CTS + CS as to "alternative strategy?". - Page 12, line 27: it would be more informative if the authors can add per-person (or screened individuals) cost. - Page 12, line 36-43: Are these discounted costs of the program (i.e., net present value of the program in the specified time period) or the undiscounted cost at the year? - Page 16, line 18-23: Is the $50,000/QALY threshold commonly used in Canada? Need to provide a rationale or resource to back this up (or at least citing current literature). - Page 18, line 3-5: A recent literature touched on the issue of implementing risk-targeted incentive programs for lung cancer screening (https://www.healthaffairs.org/doi/abs/10.1377/hlthaff.2018.05148). The findings may also help to guide what are some alternative strategies available to address the budget impact issue and targeted screening.
Author response	Response to reviewer #2, comment #2: Given some uncertainty in the choice of data input as well as stochastic uncertainty, it would be great if the authors can conduct probabilistic sensitivity analysis to capture the underlying uncertainty of all parameters simultaneously. • We request that you conduct probabilistic sensitivity analysis. Response: We have conducted a probabilistic sensitivity analysis, added two graphs (Figures 3 and A5.1) to characterize the joint uncertainty of the cost and effectiveness of smoking cessation and added details about how we conducted the probabilistic sensitivity analysis in Appendix A5. Response to reviewer #2, comment #5: The "permanent quit rate of 2.5% per cessation intervention" seems conservative to me based on my consultation with an expert in this area. So, the implications are that, because the authors used a conservative estimate for the model input, the cost effectiveness estimate that they generated as their output (which was already quite favorable) is likely to be even more so, if the intervention is like others in real life. • This is a key variable and we think you should conduct a more elaborate sensitivity analysis around this (more than the one-way sensitivity analyses). Response: We recognize that both cost of smoking cessation and quit rate are key variables. So, we added more sensitivity analyses. In this version, we have attempted to address the issue in 4 ways: (i) one-way sensitivity analyses varying cost of smoking cessation at different quit rate (Table 3); (ii) a threshold analysis showing the upper limit of smoking cessation cost for it to cost <$50,000 per QALY gained at different quit rate (Figure 2), (iii) two-way sensitivity analyses varying costs and quit rate at the same time (Table A6.1); and (iv) probabilistic sensitivity analysis varying cost and quit rate simultaneously for 10,000 times (Appendix A5). Response to reviewer #2, comment #5: Also, acknowledged by the authors, smoking is a chronic relapsing condition. In the microsimulation model, it wasn't clear how the model incorporates the relapse back to smoking. • Smoking relapse should be taken into consideration in the model. Response: There is no reliable data on the benefits of short-term cessation on long-term outcomes (QALYs and lung cancer). Therefore, we added a sentence in the methods

	stated that we did not model short-term quit rate and relapse and why, and also added that limitation in the limitation section.