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Breathe: A Cost-Effectiveness Evaluation of Breath-Based Lung Cancer Screenings

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Project Title

Breathe: A cost-effectiveness evaluation of breath-based lung cancer screenings

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Introduction

Just How Deadly and Costly is Lung Cancer?

The prevalence and burden of cancers is substantial for societies and their economies.

Current incidence rates of lung cancer in the United States show that per 100,000 population, lung cancer will occur in 49 women and 60 men. Nearly half a million individuals in the United States were diagnosed with lung cancer between 2013 and 2017, and Canadian prevalence rates are similar: nearly 30,000 people are diagnosed with lung cancer each year.

Mortality due to lung cancer is significant as well: approximately 130,000 people in the US and 21,000 people in Canada die annually due to lung cancer.

Costs for treatment are also substantial, totaling about $2 billion per year in Canada, or approximately $70,000 per case. The high cost per case of cancer arises from many factors, central among them the advanced stage at diagnosis of many tumors leading to expensive therapies and treatments, costs for formal and informal caregivers, and life-years lost.

The incidence and high mortality and costs associated with lung cancer show that lowering both the percentage of people receiving lung cancer diagnoses and the costs of treating lung cancer are important issues for our healthcare systems.

Narrowing Down the Problem

Of course, there are many important factors already associated with reducing the causes of lung cancer such as declining smoking rates, as well as treatment costs, such as the development of less-intensive chemotherapies and better therapies. However, one problem that is rarely highlighted is that lung cancer often is not diagnosed until the disease has progressed to a later, less treatable stage: nearly 50% of cases in Canada are first diagnosed as stage IV cancers. By stage IV, lung cancer survival rates diminish substantially, and treatment costs increase significantly. This provides an impetus to get individuals at risk for lung cancer screened early.

Efforts have been made to adjust cancer screening guidelines to meet multiple challenges: detecting cancers earlier, increasing screening for the population-at-risk, and making use of screening technologies such as computerized tomography (CT) scanning machines.

Guidelines from the Canadian Task Force on Preventive Health Care state that adults 55-74 years of age who have a smoking history of 20 pack-years[1] or more, and who either currently

[1] "A pack-year is used to describe how many cigarettes you have smoked in your lifetime, with a pack equal to 20 cigarettes. If you have smoked a pack a day for the last 20 years, or two packs a day for the last 10 years, you have 20 pack-years." (https://shouldiscreen.com/English/pack-year-calculator)

smoke or quit within the past 15 years, should be screened once a year with low-dose CT, up to a maximum of three times total. For individuals who are high-risk and screen positive for lung cancer, a conclusive diagnosis is then completed via biopsy, and if that diagnosis comes back positive, treatments such as surgery, chemotherapy, or radiotherapy are completed, depending on the severity of the lung cancer.

Despite these screening guidelines and other attempts at increasing both knowledge of screenings and accessibility for patients, rates of lung cancer screening are low. Using National Health Interview Survey (NHIS) data in the US, one study estimates that only 262,700 of 6,800,000 smokers eligible for low-dose CT screening received it in a calendar year: a rate of 3.9%.

To increase the accessibility and effectiveness of cancer screenings, better technology is being developed. One specific screening technique – utilizing new breath-based spectrometry, more specifically referred to as continuous wave cavity ring-down spectroscopy (CW-CRDS) – could make screenings for cancers such as lung cancer more widely available than the current standard of care with low-dose CT screens. A question that arises, though, is whether this screening technique is worth investment by healthcare authorities. Canadian provinces have limited money available to spend, and dollars spent should be dedicated to high-value interventions that have a large impact on the health of individuals, preferably at a low cost to the health authorities.

One economic approach used to determine whether an intervention has an optimal mix of both health and cost effectiveness is cost-effectiveness analysis. This method allows researchers to estimate the costs of a new technology, and the health gains from a new technology, for comparison to what is currently being used. If the gains are significant enough – even if a new technology costs more than a current technology – then the new technology will be deemed *cost-effective* and can be recommended on that measure to health authorities. The measure often used is a cost-effectiveness ratio, in which the difference in costs is divided by the difference in effectiveness of the two technologies. When a ratio meets a given threshold, the new technology is cost-effective.

Study Objective and Methodology

The primary objective for this study was to examine whether a breath-based screening for lung cancer would be cost-effective when compared to the current technology for screening, CT screenings. To do so, we ran a simulation measuring cost (cost per patient) and effectiveness (in terms of quality-adjusted life years) for 5,000 people over a five-year period, comparing the outcomes for CT screenings and breath-based screenings.

In preparation for this project, a scoping review was conducted to scan the literature surrounding economic evaluations of lung cancer screening programs. Though we chose to focus on recent work concerning low-dose CT screens, other program interventions were also

included. Studies were retrieved from the literature published between 2015 and 2021 and were required to include an economic component.

Most of the articles selected for inclusion detailed further information on low-dose CT scans. Multiple studies have shown over the years that low-dose CT scans are cost-effective when compared to alternatives such as radiography, or compared to no screening at all, in which case money saved on screening is allocated to increased diagnosis exams.

While CT scans have had cost-effectiveness analyses completed, other technologies such as breath-based lung cancer screening have not been evaluated. This suggests a need to consider economic costs and gains as new technologies are introduced for lung cancer screening. Though the gold standard would involve data tied to a randomized control trial, simulations have and can continue to be completed that serve to evaluate different technologies.

Measuring Cost and Effectiveness

To complete this study, a comparison of equivalent cost measures and equivalent consequences of interventions (i.e., effectiveness) is used. This allows for the two alternatives – breath-based spectrometry screening and CT screening – to be directly compared. For costs, we focus on direct costs that are paid by an agent in the healthcare system, specifically provincial-based health ministries or insurance plans in Canada and government Medicare and private insurance companies in the US. These costs include the cost of completing the screening (using the machine and producing a result) as well as physician time to discuss the screening with the patient and then complete the lung cancer screen and evaluate the results.

The screens can potentially lead to follow-up (if negative but still in a recommended screening group by government guidelines), no follow-up (if a patient does not attend a screening), or a formal diagnosis stage. This formal diagnosis stage incurs costs from a combination of potential further screening and a biopsy of the lung cancer site, with physician and hospital costs incurred. If the diagnosis is positive, lung cancer treatment is then initiated.

Costs can potentially vary based on the stage of lung cancer: stage I cancer is less severe and can be treated with less intense and less costly methods compared to more severe later-stage cancers. The most severe lung cancers may lead to a palliative care option only, which does not incur a significant cost relative to other treatments.

To measure effectiveness, we use quality-adjusted life years (QALYs). These are abstract units that create a life-years gained measure, based on quality of life, from health interventions. They allow us to compare across different interventions without needing to use separate measurements. Other measures can be used, such as life-years gained (number of years society gains from an intervention) or number of lives saved. However, because breath-based spectrometry screening is relatively recent (beginning in the early 1990s), it does not currently have a long enough period of study to provide data for those latter measures.

Monte Carlo Markov Simulation (MCMS)

Several issues can arise when attempting to determine the cost-effectiveness measure. The numbers used for costs, the number of people screened, and cancer treatment effectiveness are based on estimates. Though current values are used, those numbers could change in subsequent years – for instance, if costs decrease or if screening guidelines change. Because of this, a technique called Monte Carlo Markov Simulation (MCMS) is used to model cost and effectiveness. MCMS is used in many cost-effectiveness studies and can be used whether data are derived from clinical trials or from statistical estimates.

MCMS allows for randomness and uncertainty to be considered when looking at a large sample that represents the entire population of those who are eligible for lung cancer screening. In the simulation used in this study, an individual is randomly assigned characteristics and outcomes. Costs for all steps arising from cancer detection and treatment are then summed. These are compared to a quality-of-life estimate (quality-adjusted life years; QALY) that depends on the health of an individual. A cancer-free individual will have a higher QALY than a patient with stage IV lung cancer; both will have a higher QALY than someone who dies of lung cancer (or another cause).

Randomness is introduced as a method to allow variation in the estimates of the model. With some of the model values being uncertain, running multiple estimates using MCMS allows for different values to be averaged together, lowering the risk that one errant estimate causes a distorted cost-effectiveness estimate.

Here, the simulation is run 1,000 times, each with a selection of 5,000 individuals randomly assigned characteristics such as sex, age, and a residence location. These individuals are also given a random probability of having cancer and receive a derived probability that they will be screened in a given year.

From each simulation, costs (cost per patient) and effectiveness (QALYs per patient) over a five-year timeframe are calculated. These are then averaged over the 1,000 simulations. This is done for both the low-dose CT screening pathway and the breath-based screening pathway. These pathways are then compared to determine whether the breath-based screening technology meets a cost-effectiveness threshold, which in this paper and others is designated as a cost of $50,000 per unit of QALY.[2]

[2] Owens, D. K. (1998). Interpretation of cost-effectiveness analysis. *Journal of General Internal Medicine, 13*(10), 716-717. doi: 10.1046/j.1525-1497.1998.00211.x

Results

In Table 1, using baseline statistics and assumptions drawn from recent literature, cost-effectiveness numbers are as follows:

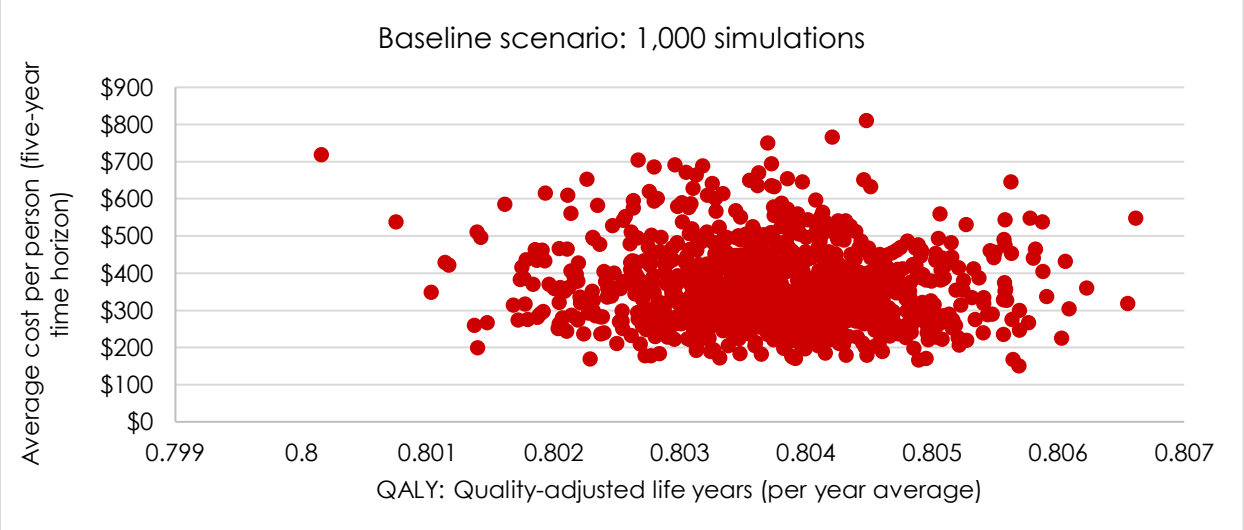
Table 1: Cost-Effectiveness Numbers (Mean) from Baseline Model Simulation

	Cost (Average per person over five years)	**Effectiveness** (Average QALYs per person per year)	**Cost/Effectiveness Ratio**
Low-Dose CT Scan Screening	$290	0.7834	-
Breath-Based Screen (+ low-dose CT scan if positive)	$385	0.8034	-
Incremental Difference	$95	0.0200	$4,750/QALY

Interpreting this table, the cost represents the total amount spent on average for individuals who meet lung cancer screening guidelines over a five-year period. The effectiveness measure represents the average quality of life (QALYs) for a person over the same five-year period. These are calculated for both technologies: the current technology (screening via CT scans) and the proposed new technology for screening (here, breath-based screening, with additional CT scans done only if a positive breath screen is received). The two technologies are then compared (the incremental difference), with a cost-effectiveness ratio calculated. This ratio, at $4,750 per QALY, is well under the generally accepted threshold of $50,000 per unit of QALY for an effective technological intervention.

In Figure 1, for the 1,000 simulations that are completed, we find relatively consistent results: there are few values that are not close to the means calculated in the table above.

Figure 1: Results of Breath-Based Spectrometry Simulations (Baseline Case)



Several alternative scenarios were also completed to see whether the results are sensitive to specific assumptions made for the model. For instance, the timeframe for analysis can be adjusted from five years, or the proportion of those meeting lung cancer guidelines who get screened per year can be adjusted. Almost all of these scenarios still resulted in the cost-effectiveness ratio for breath-based screening being lower than $50,000 per QALY.

One scenario of interest is increasing the proportion of the population being screened. With breath-based screening technology being more widely diffused, and patients not needing to attend hospitals for CT screening, more individuals could be screened. In Table 2, this impacts costs and effectiveness measures:

Table 2: Cost-Effectiveness Numbers Comparing Different Accessibility of Screening Pathways

	Cost (Average 2021 USD per person over five years)	**Effectiveness** (Average QALYs per person per year)	**Cost/Effectiveness Ratio**
Low-Dose CT Scan Screening (assuming 3% per year screening rates)	$290	0.7834	-
Breath-Based Screen (+ low-dose CT scan if positive) (assuming 8% per year screening rates)	$865	0.8008	-
Incremental Difference	$575	0.0174	$33,046/QALY
Different Screening Rates for Breath-Based Spectrometry (compared to 3% low-dose CT scan)			
9%	$1,051	0.7995	$47,263/QALY
10%	$1,167	0.7992	$55,503/QALY
11%	$1,214	0.7985	$61,189/QALY
12%	$1,481	0.7974	$85,071/QALY
13%	$1,675	0.7968	$103,359/QALY

With the higher number of breath-based screenings completed compared to the base case of low-dose CT screening, switching to breath-based screening costs $33,046 per unit of QALY, which is within the generally accepted threshold of $50,000 for cost-effective interventions.

Discussion

Increasing the screening rates, compared to the current screening rates of 3.9% per year, results in a higher incremental cost per QALY. The threshold for $50,000/QALY is reached when breath-based screening rates are between 9%-10% per year, while the $100,000/QALY threshold is reached when breath-based screening rates are between 12%-13% per year.

When the number of screenings within a population increases, several things occur:

- First, costs are higher: more people are being screened each year, with the associated incurred costs.

- Second, the (relatively) less expensive spectrometry screening serves to reduce the need for more expensive low-dose CT screening.

If 10% of the recommended population is being screened each year, given lung cancer is a low-prevalence condition in a given year (at approximately 0.5% rate of incidence per year), the spectrometry pathway saves money by dramatically reducing the need for low-dose CT screening. Potentially having screenings completed earlier (before lung cancer develops to a more severe stage) also results in cost savings.

This highlights a tradeoff which must be considered. Increased testing rates result in higher screening costs (payment rates multiplied by number of tests, plus additional spectrometry screening machines sold) and also result in more cancers being detected. This increases QALYs, as fewer people die of lung cancer. However, the likelihood of discovering lung cancer in a given year is low. Significantly increasing screening rates will result in many negative or false positive screens. This will result in an increased cost, with no concurrent QALY gain.

At a high enough screening rate (over 12%), breath-based spectrometry would no longer be a cost-effective intervention compared to the low-dose CT screening done at current screening rates. At or below a rate of 12% of the recommended population receiving a lung cancer screen in a given year, the increase in costs from more breath-based spectrometry screening is offset by the gains from fewer (high-cost) low-dose CT screens.

As a result, changing sample sizes in the simulations has an impact: the larger the population, the likelier in a given year more people are screened, and the likelier more people are diagnosed with lung cancer. Those who are diagnosed, and hence treated, drive costs higher.

QALY improvements also have an impact: though the improvements may appear to have a small absolute value, the improvements are clinically significant. QALY gains come from more screening results in more cancers detected. Though this results in an initial decrease in QALYs while being treated for cancer, survival results in subsequent healthy-level QALYs. Those levels would have a higher likelihood of being zero (death) had the cancer not been screened.

Limitations

Some facets of this study result in limitations for interpreting these analyses. Since there are no long-run randomized control trials (RCTs), case-control, or observational studies looking at the effectiveness of breath-based screenings for lung cancer, we cannot determine how many lives could be saved via more frequent, more accessible, and more timely screenings. This would be one substantial gain from having more individuals screened early: cancers would be caught in an earlier stage, thereby increasing life expectancy. Specific life-years or lives gained, as well as more precise quality-of-life estimates, can be determined when these long-run studies are completed.

Assumptions are also made regarding increased rates of screening with more accessible technology: the degree of these rates has not been fully determined in the literature or through an RCT. Further research that can be used to update this model in the future includes long-term survival rates, by type of cancer, when breath-based spectrometry is used as a first-line screen; updated numbers on the sensitivity and specificity of breath-based screening; and linkages to healthcare service usage to analyze whether there are differences in utilization between those screened with low-dose CT scans or with breath-based spectrometry.

Conclusion

This analysis shows that in baseline scenarios and through several sensitivity analyses, breath-based spectrometry for lung cancer screening is a cost-effective intervention when compared to the current standard of care using low-dose CT scans. Further research into how breath-based screening can be incorporated, and for longer-term outcomes of breath-based screening, will help to inform more accurate parameter estimates and provide the ability to analyze further scenarios.