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Funding a Smoking Cessation Program for Patients with Crohn's Disease: An Economic Evaluation

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Funding a Smoking Cessation Program for Patients with Crohn's Disease: An Economic Evaluation

by

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Abstract

Crohn's disease (CD) is increasing in incidence and prevalence in Canada. It is diagnosed relatively early in life, and is a life-long burden to those who have it. Numerous risk factors have been associated with the development and exacerbation of CD, but one of the most prevalent modifiable risk factors is smoking; people who smoke have a higher likelihood of developing CD than those who do not smoke. Those who smoke after CD development experience more deleterious events during their disease course compared to those who do not smoke. The health care system does not regularly supply smoking cessation programs for these individuals, nor fund them, even though it has been shown that CD patients have a higher rate of smoking cessation than the general population. **Therefore, the goal of this thesis is to assess the cost-effectiveness of funding smoking cessation programs for incidence cases of CD.**

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Contributions of Authors

SC was involved in conception of the study, design, creation, analysis of model, and writing of final paper. SJH, FC, and GK were involved in the conception of the study and design of the model. They provided guidance with the final analysis and supervised the writing of the final paper. MN assisted with the analysis, and provided assistance with model design. RP, SG, HB, CS, and YL were involved in the overall development and approval of the model, and model inputs.

All authors participated in the final development of the manuscript, and approved it's content.

To the zombie apocalypse, thank you for not happening…

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List of Symbols, Abbreviations and Nomenclatures

CD: Crohn's Disease

IBD: Inflammatory Bowel Disease

Anti-TNF: anti – Tumor Necrosis Factor

NRT: Nicotine Replacement Therapy

CI: Confidence Interval

ICER: Incremental Cost-Effectiveness Ratio

QALY: Quality Adjusted Life Year

WTP: Willingness-To-Pay

PSA: Probabilistic Sensitivity Analysis

BIA: Budget Impact Analysis

Chapter 1: Introduction

1.1 Epidemiology of Crohn's Disease

Crohn's Disease (CD) is an inflammatory bowel disease (IBD), which has been increasing in incidence and prevalence across the world.[1] North America has one of the highest incidence rates at 20.2 per 100,000 person-years, and a prevalence of 319 per 100,000 persons.[1] CD is a complex disease with no definitive cause. The most reproduced environmental risk factor of CD is smoking.[2] Smoking has been found to increase the risk of developing CD and to worsen the prognosis by being associated with more flares, early surgeries, and postoperative recurrence.[3-8]

CD is a life altering disease that is typically diagnosed during an individual's formative and most productive years of life and thus, may cause a considerable burden on the individual.[9] The natural history of CD is characterized by alternating periods of active disease (flare) and remission; further, CD can affect the entire the digestive tract from the mouth to the anus. During a flare most patients experience debilitating symptoms including: nausea, fever, abdominal pain, diarrhea, bleeding, weight loss, anemia, and/or metabolic disturbances. In addition to these symptoms, a patient can also experience complications such as: fibrostenotic obstruction, and penetrating abscess or fistula. These complications are severe and often require immediate surgery to rectify them.

The goal of managing CD is to induce remission of symptoms during an active flare, prevent complications of CD, and maintain remission over time. The two main forms of treatments are medications and surgery. Medications can range from the relatively inexpensive mesalamine, immunosuppressants, and/or corticosteroids, to the substantially

more expensive anti-tumor necrosis factor (anti-TNF) monoclonal antibodies. When medications fail (i.e. medically refractory) or when patients develop a complication of CD, physicians often recommend surgery to remove the diseased portion of bowel. These surgeries can range from segmental bowel resections to complete colectomies (i.e. removal of the entire large intestine). While most patients undergo a primary anastomosis after surgery, some require a permanent ileostomy. Surgery is invasive and exceptionally expensive, costing nearly $21,000 per hospitalization.[10,11] Moreover, surgery does not cure CD as the disease often recurs postoperatively.[7]

Patients with CD are heavy utilizers of the health care system. These patients tend to have more emergency department visits, are hospitalized more, and have more surgeries than the average population. In addition to these resources they also have a heavy utilization of outpatient care, including: visits to gastroenterologists, anti-TNF infusions, and colonoscopies. It is for these reasons that patients with CD tend to have a lower quality of life, even when in remission.

1.1.1 Anti-TNFs

Anti-TNFs are biologics that are commonly used to treat IBD when other conventional therapies such as azathioprine and methotrexate have failed.[12,13] In Canada, the two approved anti-TNFs for CD are infliximab and adalimumab.

Infliximab is induced at 5 mg/kg at 0, 2, and 6 weeks. Primary responders are subsequently prescribed maintenance infliximab, which is dosed every 8 weeks. Patients that lose response to infliximab require dose escalation to 10 mg/kg or dose interval reduction to every 6 weeks. At 1-year approximately 61% of patients are able to attain response with either dosing schedule; 39% of patients attained remission using the 5mg/kg strategy, and

41% with the dose escalation.[14] Adalimumab is induced at 160 mg followed by 80 mg 2 weeks later. Primary responders are subsequently prescribed maintenance adalimumab at 40 mg every second week. Patients who lose response are dose escalated to 40 mg weekly. At 1-year approximately 43% of patients are able to maintain response to treatment every other week, and 49% with weekly infusions.[15] Further to that, successful remission at 1-year is attained in 36% of patients every other week and 41% with weekly doses.[15] Infliximab and adalimumab are relatively safe with infections occurring in approximately 4% and 9% of patients, respectively.[14-16]

Both of these medications are expensive; e.g. the average cost of infliximab therapy for one year of therapy in Canada costs over $29,000.[17] Cost-utility analyses have demonstrated that treatment with either infliximab or adalimumab, as opposed to usual care (e.g. surgery), are associated with higher quality adjusted life years (QALY), but result in incremental cost-effectiveness ratios (ICER) that are higher than the willingness-to-pay (WTP) value of $50,000.[18] Society has accepted a high WTP for the use of anti-TNF in CD because the alternative is recurrent intestinal resections. Thus, anti-TNF therapies have become a standard of medical care for the treatment of CD that improves quality of life and reduces incidence of hospitalization and surgery.

1.1.2 Surgery

While it is preferable to treat patients with medications, sometimes surgery is essential to treat CD. In those patients who are medically refractory, surgery has been shown to improve their quality of life by inducing surgical remission. However, post-operative complications can arise, with an associated morbidity of 23.8% and mortality of 1.2%.[19,20] In addition, surgery does not cure CD. Post-operative recurrence of disease is common, with

one quarter of patients requiring a second intestinal operation within 5 years of their first operation.[21]

A recent meta-analysis shows that the risk of surgery at 1, 5, and 10 years from diagnosis of CD has been decreasing over time.[22] A reduction in the risk of surgery is in part due to advancement of medical management including the advent of immunosuppressants in the 1990's and anti-TNF therapy in the 2000's. The meta-analysis also found that the current risk of surgery within 5 years of diagnosis is 33.3%[22]; this is independent of whether the patient is a smoker or not. However, if a patient does smoke they are more likely to have early surgery, and relapse after surgery.[6,7]

1.1.3 Costs of Crohn's Disease

In Canada, the direct costs (hospitalization, medication, physician visits) associated with IBD exceeded $1.2 billion in 2012, and the indirect (e.g. personal and caregiver work loss) were $1.6 billion.[23] CD is more costly than UC, with direct costs equaling approximately $4,232 per person per year as compared to $3,522[23]; the costs associated with surgery are approximately $21,000 per hospitalization.[10,11] Part of these direct costs are attributed to medications, more specifically anti-TNF therapies, which can costs thousands of dollars per infusion and tens of thousands of dollars per year. Given the high cost of CD, it is important to devise multifaceted approaches to mitigate and deter the rising costs of this disease. One of the major contributors to the exacerbation of CD is smoking, which can increase costs because smoking has been associated with early surgery and/or the prescription of anti-TNF therapies due to increased flaring.[5,6] Since smoking cessation can reduce the risk of exacerbating CD, quitting smoking has the potential to be an inexpensive method to reduce the burden of the CD.

1.1.4 Smoking and Crohn's Disease

Smoking has been the most consistently studied environmental risk factor for CD.[24] Research studies have explored the relationship of smoking on disease development, disease severity, surgical outcomes, postoperative recurrence, and medical efficacy.[3,5,24-26] A study of incident cases in Europe showed that 35.4% of individuals diagnosed with CD were smoking at time of diagnosis; this nearly doubles the prevalence of smoking in the general population, which is less than 20% in North America and most European countries.[27,28] Meta-analyses have demonstrated the smoking increases the odds of developing CD by approximately 2 times the odds of those who never smoke.[3,8] Smoking also worsens the prognosis of CD.[3] Patients who have CD and smoke tend to have worse health outcomes than non-smoking CD patients; they are more likely to flare within the first year, have an early surgery than non-smokers, and relapse after surgery.[5-7] The effect of smoking on anti-TNF responsiveness is conflicting because not all studies demonstrate that smokers have an impaired response to anti-TNF therapies.[26]

Moreover, studies have shown that patients with CD who successfully quit smoking after diagnosis have an improved prognosis. An observational study demonstrated that within 29 months of quitting smoking, an ex-smoker's prognosis becomes equivalent to a patient with CD who never smoked.[5] In addition to the direct benefit of smoking cessation on CD, smoking cessation also improves long-term health outcomes including respiratory diseases (e.g. Chronic Obstructive Pulmonary Disease), cardiovascular diseases, and cancer.[29]

While this data suggests that smoking cessation improves the prognosis of patients with CD, studies evaluating the efficacy of different smoking cessation programs specifically aimed at CD patients are lacking. A multicenter and multi-method smoking cessation study

in CD patients (TABACROHN study) found that 23% of patients were able to successfully quit smoking, which was higher than the general population.[25] This study focused on the use of counseling rather than medications, with approximately 90% of patients receiving only counseling. Thus, the efficacy of pharmacological therapy (e.g. nicotine replacement therapy) on patients with CD is not known.

1.1.4.1 Smoking Cessation Programs

There are five main types of smoking cessation programs: quitting without assistance, counseling, nicotine replacement therapy (NRT), NRT and counseling, and other medications (e.g. varenicline). Quitting without assistance is one of the most difficult methods of quitting and has the lowest success rate of any program, but it is free.[30] Counseling varies from individual counseling, group counseling, to phone based counseling. Individual or group counseling is more effective than no intervention, and more versus less intensive therapy elicit similar responses.[31,32] NRT has numerous forms such as: nicotine patch, gum, inhaler, oral tablets, and nasal spray. Any form of NRT elicits an increased response over no smoking cessation therapy.[33] Also, NRT and counseling has a higher success rate than NRT alone.[32] Finally, varenicline is a nicotinic receptor partial agonist that has been shown to effectively improve smoking cessation when compared to placebo.[34]

1.2 Cost Analysis

Health economics is a subsection of economics, which focuses on healthcare; it studies the allocation of resources in health care, due to their scarcity. Due to scarcity, every allocation decision has an opportunity cost. That is, given we are unable to fund every program for everyone; the programs we do not fund are the opportunity costs of our decisions. Hunink et al. states that "the opportunity cost of a resource consumed in the

provision of a good or service is the value of that resource in its next best alternative" or, to simplify, an opportunity cost is what has to be forgone due to limited resources.[35] To support the allocation of resources to maximize the outcomes achieved from those resources, we perform economic evaluations.

An important component of economic evaluation is the concept of efficiency. Efficiency addresses the resources used and the outcomes attained; it drives the type of economic evaluation we choose as we are interested in the efficiency of various interventions.[36] There are two types of efficiency: technical, and allocative. Technical efficiency looks at the most efficient way to distribute resources to one group of people, whereas allocative efficiency compares multiple groups of people and looks for the way to maximize the well-being of all. When considering technical efficiency we are more concerned with the most efficient way of treating a group of people, independent of possible changes in well-being; the types of economic evaluation which address this are cost-minimization and cost-effectiveness analysis.[36] For allocative efficiency we want to determine how to most efficiently allocate the budget to multiple groups in order to maximize their health; this is addressed through cost-benefit or cost-utility analysis.[36] Before we're able to decide which type of economic evaluation to perform we need to identify which type of efficiency we need to address.

We perform economic evaluations in order to make an educated decision regarding the allocation of limited resources when there is not a clear answer regarding which intervention is the best to fund; it is also a logical, transparent, and quantitative way to evaluate competing interventions. Four types of economic evaluations exist: cost-

minimization analysis, cost-effectiveness analysis, cost-benefit analysis, and cost-utility analysis.

1.2.1 Types of Economic Evaluation

Cost-minimization analysis is a type of economic evaluation that evaluates comparisons that have the same outcome (i.e. kidney dialysis); they are concerned with the least expensive approach. This addresses technical efficiency, as it is concerned with the most cost efficient ways to treat a specific group of patients.

A cost-effectiveness analysis is a combination of the costs associated with one comparator and the outcome attained with that comparator; these are specific to the individual analysis (e.g. units of blood pressure). In this type of analysis the cost per measured outcome gained is evaluated, where the outcome is defined by the researcher, and can range from weight lost to lives saved; this can be referred to as the ICER, and this analysis addresses technical efficiency. The biggest drawback to this type of analysis is the inability to compare one cost-effectiveness analysis to another when the measured outcome differs, and decide where money will be taken from and allocated to a new program; it is difficult to determine whether it is better to have a five unit decrease in blood pressure, or five pound decrease in weight.

Another type of economic evaluation is cost-benefit analysis. In this type of analysis all outcomes are converted and measured in monetary units, then the overall costs of each are measured and compared; this addresses allocative efficiency. The monetary units allocated to the costs and consequences are compared by either ratios or by net benefit or loss between programs.[37]

A cost-utility analysis is similar to cost-effectiveness analysis; however, it integrates a measure of well-being into the analysis, called utilities. Utilities are a measure of a person's well-being in various health-states. A utility is a measure of preference for an individual, and includes morbidity and mortality within one measure.[35,37] The outcome of interest is cost per QALY gained; this ratio is also referred to as an ICER. This type of analysis has the same outcome, QALY, no matter what is being compared and enables us to compare across disparate strategies. A QALY is a combination of a utility value in the health outcome and the amount of time spent in the state.[37] The benefit to this type of analysis is that the cost-utility analysis accounts for the individual's health and well-being, and can capture morbidity and mortality in a single measure; this addresses allocative efficiency.[37] There is also the ability to compare the ICER to a predefined WTP value of $50,000 per QALY gained, as opposed to the outcome in the cost-effectiveness analysis.[38]

Utilizing a cost-utility analysis is an ideal method for analyzing smoking cessation and CD because of the numerous negative health effects that smoking has on this disease. These negative health effects are assessed through utilities in the model. A cost-utility model can capture the effects that smoking has on CD patients, and evaluates the most cost-effective option available for smoking cessation.

1.2.2 Methods in Economic Evaluation

There are two main types of modeling methods: simple trees and Markov models. Simple trees are straightforward models of decision analysis. They are primarily used when taking into account short-term decision models and consequences. However, simple trees are limited in their use (i.e. only for simple decision models) and long-term health assessments

are nearly impossible. Furthermore, simple trees cannot address complex models, probabilities that change over time, or discounting costs.[37]

Markov models take into account time elapses, and are used to account for various health states that a person can be in.[37] These health states have associated cost and utility values that are accrued as time elapses in the model.[37] Modeling IBD cannot normally be done with a simple tree, as there tends to be a longer time component that needs to be evaluated with this disease; especially when looking at the effects of smoking cessation on CD, where the benefits cannot be captured instantaneously. Markov modeling is the best approach when dealing with a disease as complex as CD, and even more important when evaluating smoking cessation among these patients. A Markov model allows us to model CD over extended periods of time, which is important as probability estimates change over time if an individual stops smoking.

The most common method of Markov modeling is the Monte Carlo simulation, where individuals are sent through the model, and transition between health states based on the transition probabilities.[37] Monte Carlo simulation assesses variability and uncertainty in the model, and can be done with first-order or second-order simulation.[35] First-order simulation is based on the individual and the uncertainty around them; we can calculate means and 95% confidence intervals as we attain individual parameters, per person, for each cost and utility.[35] It is the main method used to calculate the means, and 95% confidence intervals, associated with the costs and QALYs of each comparator. Also, first-order simulation allows the use of tracker variables, to track or count outcomes that occur throughout the model; this aspect is ideal for CD-related surgery stratified by smokers or non-smokers.[35] A second-order

simulation (also known as probabilistic sensitivity analysis) accounts for uncertainty around the parameters, sampling estimates from pre-defined distributions.[35,37]

When creating economic models we can either inform the tree based on a randomized control trial (RCT) that has been performed, or use literature to populate the model in a decision analysis; there are benefits and limitations to each. When building a tree with a RCT we have the benefit of utilizing a high quality study, it is transparent, and the costs and outcomes are derived from the same patients.[36] The biggest issues arise from the short time frame these studies run, and these studies do not necessarily mimic what is seen in typical practice (i.e. efficacy versus effectiveness).[36] Using decision analysis allows us to model a longer time frame and address uncertainty, but it is thought to be non-transparent and may be biased by the researcher creating the model.[36] RCTs are mainly used for evaluating medications within CD, but when faced with longer-term issues, which cannot necessarily be addressed through an RCT, using decision analysis when modeling is preferential.

1.2.3 Components of Economic Evaluation

The Canadian Agency for Drugs and Technologies in Health (CADTH) released guidelines in 2006 which outlines numerous components needed to perform an economic evaluation.[38] There are various elements they reference, but some of the main ones are: 1) they study question that is to be addressed, 2) the target population for which the evaluation is aimed, 3) the comparators used, 4) the perspective of the analysis, 5) they time horizon for which the evaluation will run, 6) the type of model that will be used, 7) whether discounting is to be used, and 8) the outcomes to be measured. Each of these plays an important part in creating an economic evaluation, and CADTH outlines these, and a few others, at length in the aforementioned CADTH guidelines.[38]

1.2.4 Model Validity and Uncertainty Analysis

Modeling validity in cost analysis is similar to the validity used in epidemiology, as we evaluate both internal and external validity. Internal validity in economic evaluation ensures that the model is working as it is supposed to; this can be done by running a markov cohort through it or modeling extreme values. External validity is concerned with how well the model mimics what is seen in the population that it is meant to represent; this is done by using a value, external to what is used in the model, and comparing an outcome from the evaluation to that.

In addition to internal and external validity uncertainty analysis is an important component of utilizing a decision analysis model, given that we are using various inputs from literature. There are four main types of uncertainty analysis: sensitivity, threshold, scenario, and probabilistic sensitivity analysis (PSA). Sensitivity analysis can be done varying one, two, or three variables across a possible range of values and we look at the variation to the cost-effectiveness ratio.[36] A threshold analysis is similar to a sensitivity analysis except we only vary one variable across a plausible range, and the outcome is the point at which that variable becomes the most cost-effective option. Scenario analyses are used when there is uncertainty around the parameters used and the model itself; it is done by positing various scenarios and varying the inputs in the model to mimic them. Then the analysis is run again, and we see how the results change in different scenarios. The final type of uncertainty analysis is the PSA; this type of analysis focuses on the uncertainty around all the parameters. It is done by using plausible ranges for numerous variables, create distributions for them, and placing them in the model. The results of this type of analysis are the probability that an intervention will be the most cost-effective, as compared to another

intervention. Each of these types of uncertainty analysis are important to evaluate the model and the outcomes attained.

1.2.5 Budget Impact Analysis

One of the final steps for cost analysis is to perform a budget impact analysis (BIA); this is done to estimate the costs associated with the adoption of an intervention. Using the characteristics and size of the appropriate population, the current care costs, and costs associated with the new care we calculate the approximate costs of a new intervention, and the potential cost savings.[36] Performing a BIA is imperative to the knowledge translation component of cost analysis as it relays to appropriate entities the overall monetary benefits or disadvantages of an intervention.

1.3 Summary: The Problem

Smoking worsens the prognosis of CD by increasing the risk of flares, early surgery, and postoperative recurrence. Consequently, smoking increases the cost of CD by escalating the need for expensive medical therapies (e.g. biologics) and surgery. Moreover, stopping smoking has been shown to improve prognosis and reduce the burden of CD. Thus, smoking cessation offers patients and physicians a potentially cost-minimal approach at improving the natural history of CD. However, smoking cessation is difficult to implement in clinical practice. The largest study to evaluate the efficacy of smoking cessation demonstrated that approximately 25% of CD patients would quit smoking when enrolled into a smoking cessation program.[25] However, a cost-effectiveness comparison across different smoking cessation programs for CD has not been published. Therefore, the aim of this study is to perform a cost-utility analysis of smoking cessation programs for patients with CD.

Chapter 2: Funding a Smoking Cessation Program for Patients with Crohn's Disease: An Economic Evaluation

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Short Running Title: Smoking Cessation in Crohn's Disease

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2.1 Abstract

Background: Patients with Crohn's disease (CD) who smoke are at a higher risk of flaring and requiring surgery. Cost-effectiveness studies of funding smoking cessation programs are lacking. Thus, we performed a cost-utility analysis of funding smoking cessation programs for CD.

Methods: A cost-utility analysis was performed for funding 5 smoking cessation strategies: No Program, Counseling, nicotine replacement therapy (NRT), NRT+Counseling, and Varenicline. The time horizon for the Markov model was five years. The health states included: medical remission (azathioprine or an anti-TNF), dose escalation of an anti-TNF, 2nd anti-TNF, surgery, and death. Probabilities were taken from peer-reviewed literature, and costs (CAN$) for surgery, medications, and smoking cessation programs were estimated locally. Means and 95% confidence intervals were calculated for the costs and Quality Adjusted Life Years (QALY) of each strategy. Threshold, three-way sensitivity, probabilistic sensitivity (PSA) and budget impact analysis (BIA) were done.

Results: Strategies from most to least cost-effective: Varenicline (Cost:$55,614, QALY:3.70), NRT+Counseling (Cost:$58,878, QALY:3.69), NRT (Cost:$59,540, QALY:3.69), Counseling (Cost:$61,029, QALY:3.68), and No Program (Cost:$63,601, QALY:3.67). All strategies dominated No Program. Three-way sensitivity analysis demonstrated that No Program was only more cost-effective when every strategy's cost exceeded 10 times their estimated costs. The PSA showed that No Program was the most cost-effective less than 1% of the time. The BIA showed that any strategy saved the health-care system money over No Program. Funding Varenicline saved $7,987 per CD patient.

Conclusion: Health-care systems should consider funding smoking cessation programs for CD, as they improve health outcomes and reduce costs.

2.2 Background

North America has a high prevalence of the inflammatory bowel diseases (IBD) at ~0.5%, and the incidence continues to rise in most countries.[1] Crohn's disease (CD) imparts a considerable burden on quality of life in the most formative and productive years of life. Patients are often prescribed immunosuppressant and/or biologic therapies in attempt to mitigate the personal health and economic burden of CD. However, these therapies, particularly monoclonal antibodies to anti-tumor necrosis factor (anti-TNF), are expensive. When medical therapies fail, CD patients require intestinal resection. Nearly half of CD patients require a bowel resection within 10 years of diagnosis.[22] In contrast, modulating environmental risk factors that have been shown to influence the prognosis of CD may be a cost-effective approach to improve quality of life and reduce healthcare cost.

Smoking has been consistently recognized as a modifiable lifestyle risk factor that increases the risk of developing CD and worsens the prognosis following diagnosis.[2,8,39-41] CD patients who continue to smoke after diagnosis are more likely to flare, have surgery within 3 years of diagnosis, and are more likely to relapse postoperatively.[4-7] Moreover, individuals who quit smoking have a similar prognosis to CD patients who never smoked.[5]

Smoking cessation interventions are a potentially effective strategy that physicians can utilize to improve the prognosis of CD. When a multi-method smoking cessation program was instituted nearly a quarter of patients with CD were able to successfully quit smoking, which was higher than the success rate of the general population.[25] While this study demonstrated the efficacy of smoking cessation treatment programs for CD patients, these programs require funding. Funding for these types of programs is often a mixed arrangement of public dollars and out of pocket payments from patients. Yet, given the cost of medical and surgical management of

IBD exceeds $2.8 billion annually in Canada, there is a potential cost savings.[23] However, funding smoking cessation programs necessitates either additional funds, or a reallocation of existing resources. Within a fixed budget these resources must be taken from other established health or social programs. The cost-effectiveness of smoking cessation programs has not been studied and these programs are not presently funded by most health jurisdictions. Therefore, the purpose of this study was to evaluate the cost-effectiveness of funding smoking cessation programs for individuals with CD to inform future health policy decisions on this topic.

2.3 Methods

2.3.1 Cost-Utility Analysis

A Markov model was created using decision analysis software (TreeAge Pro 2013) and an incremental cost-utility analysis was performed using a 5-year time horizon. The model ran for 5 years as the probabilities used fit best within that time frame, and extending would have led to uncertainty. Smoking cessation strategies were compared to each other and to a "No Program" strategy. The perspective chosen was the publicly funded health care system, which considers all direct costs to the health care system (e.g. medications and operations) and assumes that the healthcare system pays for all costs incurred during treatment.[38] A discount rate of 5% was applied to all costs and outcomes. The primary outcome was the cost per quality-adjusted life year (QALY) gained associated with each smoking cessation strategy considered. Debugging to assure internal validity was performed using Markov cohort simulation and first-order Monte Carlo simulation was used to determine the number of surgeries.

2.3.2 Model

With the assistance of clinical gastroenterologists, with expertise in IBD (RP, CS, YL, SG, GK), a model was created to mimic the disease progression of CD following diagnosis. The

base case was defined as follows: CD patients that were 1) between the ages of 18 and 35 years; 2) induced into remission using prednisone and azathioprine; 3) using azathioprine to maintain remission; 4) actively smoking at time of diagnosis; and 5) naïve to anti-TNF and to intestinal resection. We then modeled the effect of smoking cessation versus continuing to smoke on CD patients treated with azathioprine, but before starting anti-TNF therapy or undergoing an intestinal resection over a 5-year time period.[13,42] In addition, by looking at anti-TNF and surgery naive patients we evaluated the benefit of quitting smoking on a relatively homogenous population early in the course of their disease.

We considered the following treatment health states: patients on azathioprine; patients on infliximab (or dose escalation); surgery after failing initial infliximab dosage; patients on adalimumab (or dose escalation); surgery (intestinal resections) for medically refractory disease; and death. For each health state the patient either remained in remission or flared leading to a change in medication or surgery. Health state transitions were permitted annually (1-year cycle length). Figure 1 illustrates the structure of the model.

2.3.3 Model Validation

The model was deemed to have good face validity after input and careful review by clinical gastroenterologists with expertise in IBD. We performed extensive debugging exercises to ensure no syntactical errors were present. Finally, to assess external validity we performed first-order Monte-Carlo simulation to count the number of surgeries within No Program, as that was the strategy that models what is currently being done in the health care system. Every time that an individual had surgery it was counted using the tracker in the Monte Carlo analysis. The total number of individuals who had surgery was divided by the total number of individuals put

through the analysis. We compared the probability of surgery within our cohort with the published risk of surgery for CD that was reported in a meta-analysis.[22]

2.3.4 Smoking Cessation Strategies

Table 1 describes the five smoking cessation strategies that were modeled: No Program, Counseling only, nicotine replacement therapies (NRT), NRT+Counseling, and Varenicline.[30,32,34,43] The cost and effectiveness of the smoking cessation strategies ranged from $0 to $459 and 3% to 27.9% quit rates, respectively (Table 1). An adverse event requiring discontinuation of therapy occurs in 3% of individuals prescribed Varenicline which we accounted for in the continuous abstinence estimate in the model.[34]

2.3.5 Clinical Probabilities and Assumptions

The probability of flaring for different clinical scenarios stratified by those who continued to smoke and those who quit smoking are presented in Table 2. Probabilities contained within the model for medically-maintained remission induced by anti-TNFs in the first year of treatment was derived from randomized, double-blinded, controlled trials.[14,15] Maintenance of response of anti-TNF therapies after 1 year was derived from systematic reviews.[44,45] The baseline mortality for CD patients was calculated by using a Canadian population based mortality rate and a pooled standardized mortality ratio for all CD patients[46,47]. The probability of flaring among CD patients who continued to smoke and quit smoking were based on prospective natural history studies of CD patients who quit smoking (Table 2).[5]

Several assumptions were made in the model. All transition probabilities related to anti-TNFs were the same between smokers and ex-smokers, and remained constant over time.[26] This assumption was conservative and if anything favored continuation of smoking. In contrast, the risks associated with flaring while on azathioprine and flaring after surgery differed between

smokers and ex-smokers, and changed over time.[5] Infliximab was modeled as the first anti-TNF prescribed because transition probabilities from infliximab to adalimumab are well defined in the literature.[48] Primary non-responders to infliximab (i.e. first anti-TNF) were transitioned to surgery at 3 months without dose escalation. Secondary non-responders to infliximab were transitioned to adalimumab and subsequently dose escalated prior to surgery.[49] Secondary loss of response to anti-TNF therapy after 1 year of treatment was estimated from systematic reviews for both infliximab and adalimumab.[44,45] Patients with CD who failed a second anti-TNF agent were not prescribed a third anti-TNF agent, but instead went to surgery.

2.3.6 Costs

Throughout the model costs were accrued when a patient was placed on an anti-TNF, dose escalated or had surgery. Dosage costs for infliximab (and its dose escalation) were calculated by using the average weight of 70kg with induction defined as 5mg/kg at 0, 2, and 6 weeks, maintenance defined as 5mg/kg every 8 weeks, and dose escalation defined as 10mg/kg. The cost for the drug was $954.10 per 100 mg vial in Canada and $735.91 per 100mg vial in the United States (US); a $217.12 cost per infusion is included for Canada, and $184.15 in the US.[11,17,50-53] Adalimumab costs were calculated based on a standard dosing schedule with an induction dose of 160mg, 80mg 2 weeks later, a maintenance dose of 40mg every other week, and dose escalation to 40 mg every week. The cost for the drug was $740.36 per 40 mg in Canada, and $928.91 in the US.[17,52,53] Surgery costs were taken from a population-based Canadian study, and inflation adjusted to 2013 CAD dollar by using the Consumer Price Index supplied by Statistics Canada, giving a final cost of $20,877.39.[10,11] For the population in the US the cost of surgery was taken from a review of surgical cases of CD; using the Consumer Price Index supplied by the Bureau of Labor Statistics the final surgical cost was $20,359.92.[52,54]

2.3.7 Utilities

The utilities were taken from Gregor et al, who used a Standard Gamble approach, evaluating patients with CD.[55] Patients started every drug treatment health-state in remission with a utility of 0.88, but a dis-utility of 0.11 was applied when they flared. Patients with chronically active CD disease resistant to therapy remained in a surgery health state where they had a utility of 0.74. The utilities were not varied between smokers and non-smokers because evidence to support a difference is lacking.

2.3.8 Sensitivity Analyses

A threshold analysis was done to look at the effectiveness required to make each smoking cessation strategy dominant. A three-way sensitivity analysis was done for the costs. A number of scenario analyses were completed to test the influence of uncertain variables on the model results. As outlined previously, we conservatively assumed that the efficacy of anti-TNF treatments were similar for the smoking and non-smoking population as studies evaluating the effect of smoking on anti-TNF response durability are controversial.[26] However, a scenario analysis was completed to assess the validity of this assumption. In this scenario analysis we assumed that smokers had a decrease in anti-TNF effectiveness of 10% compared to ex-smokers. The second scenario analysis assessed a greater disutility for flares leading to surgery, and lower utility for the health state "surgery"; decreasing each utility by 0.3. The third scenario analysis utilized pricing of anti-TNFs and surgery in the US where the surgery cost was derived from US literature and was adjusted for inflation.[51-54] Because the cost of the smoking cessation strategies is similar between Canada and the US these costs remained the same. Lastly, we conducted a probabilistic sensitivity analysis (PSA) to account for overall variation in effectiveness of the smoking cessation programs. For each of the probabilities a beta distribution was created,

utilizing the ranges from literature, and the results were displayed in incremental cost-effectiveness scatterplots that contained 95% confidence interval ellipses. The probability that a scenario would occur when No Program was more cost effective than each individual program was calculated from the PSA.

2.3.9 Budget Impact Analysis

The budget impact analysis (BIA) was conducted to estimate the costs to the Canadian healthcare system following the introduction of a smoking cessation program to newly diagnosed CD patients who are smokers. Approximately 5700 individuals are newly diagnosed with CD in Canada every year.[23] For the first BIA we estimated the proportion of adult patients who were current smokers when they were diagnosed with CD using an inception cohort from several European countries (35.4%).[27] The total of the newly diagnosed population who were smokers (35.4%), approximately 2018 individuals, was multiplied by the cost of each smoking cessation strategy to calculate the total required budget. To estimate the costs to the healthcare system we took the total cost per person over the 5 years and multiplied it with the proportion of newly diagnosed CD patients who smoked; the cost savings was calculated by using No Program as the baseline. In actuality, the proportion of current smokers among Canadians with a new diagnosis of CD is not known. Thus, we conducted a second BIA that conservatively estimated that 16% of patients with CD were smokers at diagnosis, which is consistent with the prevalence of Canadians who smoked in 2012.[56] A final BIA was calculated using cost data derived from the US. This BIA assumed a population of 313 million in the US, the incidence of CD is 7.9 per 100,000, and the probability of smoking at diagnosis of 35.4%.[27,57,58]

2.4 Results

2.4.1 Model Validation

When the model was run for 5 years, utilizing a Monte Carlo analysis with 1000 subjects and a tracker variable on surgery, 28.0% of individuals had surgery within the No Program strategy. This is within the 95% CI of the published pooled 5-year risk from 26.3% to 42.1%, indicating that our model is valid.[22]

2.4.2 Cost-Effectiveness

Varenicline dominated all other strategies; Varenicline was the least costly and most effective strategy with a cost savings of $7,987 per person, and a QALY gain of 0.03. No Program was dominated (more costly and less effective) by all other smoking cessation strategies (Table 3 and Figure 2). The costs savings, and QALY gained, for each program as compared to No Program was: NRT + Counseling saved $4,723 and a QALY gain of 0.02, NRT was $4,061 and 0.02, and Counseling was $2,572 and 0.01.

2.4.3 Sensitivity Analysis

2.4.3.1 Threshold Analysis

Varenicline remained the most cost-effective strategy until its effectiveness was reduced below 17.7%. For the other strategies, the threshold for dominance was: >28.3% for NRT + Counseling; >27.8% for Counseling; >27.6 for NRT; and >27.0% for No Program.

2.4.3.2 Three-way Sensitivity Analysis

The threshold cost needed for these programs to be less cost-effective than No Program were: >$5,000 for NRT; >$3,100 for Counseling; >$3,600 for NRT + Counseling; and >$10,000 for Varenicline.

2.4.3.3 Scenario Analysis

Decreasing the effectiveness of anti-TNFs for smokers by 10% did not substantially change the results of the analysis or the dominance of Varenicline (Appendix A). Secondly, when we decreased the utility for the surgical health state (0.74) and dis-utility of flare leading to surgery (-0.11) by 0.3, the result was that the QALY for the strategies overall were lower and the range of the QALYs for the strategies was increased. Though, the costs and order of most to least cost-effective smoking cessation strategy remained the same (Appendix B). The third scenario analysis incorporated costs from the US for anti-TNF therapies and for surgery in the model. We arrived with the same conclusion regarding order of cost and effectiveness. However, the cost differences as compared to No Program ranged from $2,241 to $7,012 (Appendix C).

2.4.3.4 Probabilistic Sensitivity Analysis

When comparing No Program directly to Varenicline at a willingness-to-pay of $50,000 (CAN), No Program was the least cost-effective approach approximately 100% of the time (Figure 3). The incremental cost-effectiveness scatterplots that compares No Program to Counseling, NRT, and NRT+Counseling are presented in Appendices D-F. No Program was the least cost-effective approach approximately 99.9% of the time compared to each of Counseling, NRT, or NRT+Counseling.

2.4.4 Budget Impact Analysis

Assuming that 35.4% of newly diagnosed adults with CD are smokers, the BIA demonstrates that No Program costs the healthcare system $128.3 million dollars in Canada over 5-years.[27] No Program leads to the most costs incurred to the healthcare system when compared to the other smoking cessation strategies (Table 4). For example, funding Varenicline saves the Canadian healthcare system over $16.1 million during the first 5 years of a CD diagnosis. In the

US, the BIA demonstrates that the cost savings for Varenicline exceeds $61 million over 5 years (Appendix G). When the prevalence of smoking at diagnosis of CD was reduced to 16%, the BIA demonstrates that No Program costs the Canadian healthcare system over $58 million over 5 years (Appendix H).

2.5 Discussion

Over a 5-year time period, these programs proved to be cost savings compared to No Program; all programs dominate No Program. This cost-utility analysis demonstrates how important it is for the health care system to fund smoking cessation programs for CD smokers, and not just because it is beneficial in regards to CD it also has long-term health benefits.

Quitting smoking has established benefits for CD patients including improving the prognosis of CD and reducing the risk of long-term health consequences. Despite this universally recognized recommendation, smoking cessation is not common following the diagnosis of CD. In part, the lack of success of smoking cessation in CD stems from the absence of dedicated smoking cessation strategies. While smoking cessation programs require an initial cost commitment, the data from this cost-utility analysis demonstrated that funding any smoking cessation program for CD patients has the potential to save money, when compared to the status quo. Specifically, funding Varenicline has an estimated net savings to the Canadian health care system of $16.1 million over a 5-year period. Thus, this cost-utility analysis provides evidence for healthcare authorities, medical societies, and CD patient advocacy groups to carryout knowledge translation activities that lead to the integration of smoking cessation programs targeted for CD patients.

Recommending smoking cessation has been cited as a quality indicator for good clinical practice; however, guidelines recommending smoking cessation strategies are lacking.[59] In the

Multicenter TABACROHN study, smoking cessation programs directed at patients with CD were successful in nearly one quarter of CD patients who smoked.[25] Smoking cessation in TABACROHN was higher than reported in the general population of smokers, which suggests that CD patients may have an increased willingness to quit.[25,32-34] Increased willingness to quit smoking among CD patients may be influenced by the knowledge that modifying a lifestyle habit directly improves their prognosis of CD. Additionally, CD patients who smoke are typically diagnosed in early adulthood[23] and thus, they have fewer pack-years of smoking than other disease populations targeted for smoking cessation (e.g. a newly diagnosed COPD patient who has smoked for years). Supporting smoking cessation initiatives is a cost-effective measure that may empower CD patients to take action to improve their disease course.

Over three quarters of CD patients in the TABACROHN study did not successfully quit. However, the primary intervention in this study was counseling with nearly 90% of patients not prescribed pharmacological therapy. Thus, combining physician education with prescribing Varenicline has the potential to increase success rate of smoking cessation among CD patients. Future studies are needed to evaluate whether the 29% success rate for Varenicline in the general population would be higher when a CD population is targeted. Improving the success rate of a smoking cessation strategy beyond 29% would have significant additional economic benefits over what we found. For example, increasing the efficacy of smoking cessation strategy to 50% would increase the national savings of smoking cessation in Canada from over $7,900 per CD patient among those treated with Varenicline to over $14,000 per CD patient.

The most cost-effective smoking cessation strategy was varenicline. Physicians who consider prescribing varenicline to patients with CD should be aware of the most common adverse events (i.e. anxiety and nausea).[60-62] Additionally, the FDA issued a warning that

neuropsychiatric symptoms have been reported in patients taking varenicline.[63] However, more recent studies have shown that neuropsychiatric symptoms such as depression and suicidal ideation are not increased when comparing varenicline to placebo.[60-62] In clinical practice, patient preference to avert toxicity may influence choice of smoking cessation strategy. Further, because studies on the effect of varenicline on CD prognosis are lacking, gastroenterologist should follow their patients carefully when prescribing a medication for smoking cessation.

In our model, QALY (i.e. effectiveness) did not vary greatly between the different smoking cessation strategies. The narrow variability of effectiveness across smoking cessation strategies was due to the relatively low efficacy of smoking cessation programs, inconclusive data regarding smoking effects on anti-TNF responsiveness, and the low variation in utilities when comparing remission to flare to surgery. Nevertheless, because anti-TNF therapies and surgery are very expensive compared to maintaining remission on azathioprine alone, even marginal reductions in flares that reduce the need for anti-TNF therapy, dose escalations or need for surgeries translate into impressive cost saving for the healthcare system. Our analysis conservatively demonstrates that targeting newly diagnosed CD patients who smoke with Varenicline could save the Canadian healthcare system approximately $16.1 million across 5 years and in the US approximately $61 million. Importantly, the cost savings have the potential to be considerably higher if the future potential personal and societal costs arising from the long-term complications of smoking such as cardiovascular disease and cancer were also considered.

The results of our model are subject to a number of assumptions that were made. For example, some studies have demonstrated that smoking reduces the efficacy of anti-TNF therapies,[64,65] whereas other studies do not support this association.[66-68] In our model, we conservatively estimated that smoking does not influence anti-TNF efficacy; however, a

sensitivity analysis that reduced the effectiveness of anti-TNF by 10% among smokers led to even larger cost savings for all the smoking cessation strategies. Our base case was a recently diagnosed IBD patient naïve to anti-TNF therapy and surgery and thus, our findings may not be generalizable to prevalent cases of CD who have been smoking for many years. However, while the cost savings and health benefits of smoking cessation might be less among longstanding CD patients who smoke, it is highly likely that improvements in health and reductions in healthcare costs would still be realized when one considers the broader overall benefits of smoking cessation in these patients. Additionally, we did not stratify the CD population by disease severity and phenotype. For example, the cost-effectiveness may be reduced in CD patients with milder disease activity because the probability of flaring is lower. On the other hand the health benefits and cost savings may be higher among those with more severe disease. Also, our model only considered recidivism in the first year, which was accounted for within the smoking cessation studies included in the model. However, the long-term recidivism rate is unlikely to vary across smoking cessation strategies. Moreover, cost-utility analyses by design cannot adequately control for confounding. For example, patients with CD who enroll in smoking cessation program may be more likely to be complaint with their IBD medications. Finally, we only considered CD-specific costs and consequences over a 5-year time horizon as this provided the most reliable data for the model. It is worth stressing however that our findings would have only been strengthened if we had extended the time horizon and considered the additional costs and consequences related to the effects of smoking on cardiovascular disease, chronic lung disease and cancer.

Despite these limitations, our cost-utility modeled appears clinically valid. External validation using a tracker variable for surgery and Monte Carlo simulation demonstrated that the

5-year surgery risk in our model approximated the 5-year surgical risk published in a meta-analysis.[22] In the No Program strategy of our model 28.0% of our CD patients had surgery within 5 years of diagnosis, which was within the 95% confidence interval of the pooled 5-year risk published in the meta-analysis (5-year risk: 33.3%; 95% confidence interval: 26.3% to 42.1%).[22] Further, our scenario analyses, threshold analyses, and PSA demonstrated consistency in the interpretation of our model outputs. Our data robustly demonstrate that funding a smoking cessation program saves money when compared to No Program and thus, provides evidence for healthcare administrators to assess the possibility of instituting interventions aimed at reducing smoking cessation for patients with CD. While the BIA shows the initial funding costs are not inconsequential, the savings realized after only 5 years to the healthcare system are substantial. These savings could be used to fund further research to improve smoking cessation in CD or redirected to support other health promotion programs. The research community should invest in new ways to increase the effectiveness of smoking cessation programs for CD patients because even marginal increases in efficacy have a substantial budget impact.

2.5.1 Conclusion

This cost-utility analysis demonstrates that funding a smoking cessation program directed at CD patients is cost-effective compared to usual standard of care. Health practitioners should actively pursue smoking cessation for their patients with CD. Facilitating smoking cessation is a cost-effective intervention that can empower patients with CD to improve their prognosis by eliminating a modifiable disease determinant, while offering the healthcare system substantial long term cost savings. Health policy decision makers should prioritize funding for smoking cessation programs among patients with CD.

Chapter 3: Conclusion

3.1 Overview of Main Findings

This cost-utility analysis of funding smoking cessation strategies for patients with CD demonstrates the importance of implementing funding for a smoking cessation program. Long-term cost savings are incurred, with minimal investment in the individual programs. In addition, the sensitivity analyses demonstrate that any smoking cessation program dominated the current standard of care (i.e. No Program). Specifically, the most cost-effective approach was the prescription of varenicline. Funding a smoking cessation program utilizing varenicline could save Canada $16.1 million over 5 years.

3.2 Clinical and Public Health Implications

Funding a smoking cessation program for patients with CD provides numerous health benefits outside of the scope of this study. In addition to reducing the deleterious effects of CD, smoking cessation offers long-term benefits including: decreased cancer risk, decreased incidence of lung disease, decreased risk of cardiovascular disease, and decreased mortality.[29]

The BIA done with this study showed that funding a smoking cessation program for patients with CD saves money; funding any program could save approximately $5.1 million over 5 years, which equates to $2,572 per patient. If varenicline was funded, the healthcare system could save $7,987 per patient over 5 years, which equates to approximately $16.1 million in Canada. As the model had a time horizon of only five years these costs do not include those that are associated with the long-term effects of smoking. If the long-term costs were included in the model an even stronger case could be made for funding smoking cessation programs, since these cost savings would be substantial.

The findings presented in this study should help clinicians, health administrators, and policy makers realize the importance of funding smoking cessation programs for CD patients. With this data, policy makers now have evidence to put initial funding into smoking cessation programs aimed at CD patients. While the initial funding will be substantial (i.e. over $384,000 in Canada) the cost-savings in the long-term could counter this cost. Finally, health administrators and clinicians will be able to use this evidence as a guide for smoking cessation programs for CD patients. Clinicians are already aware of the importance of smoking cessation for CD patients, but what this provides is evidence that they can present to their patients in addition to the health benefits they would attain. Moreover, the cost savings do not include the direct savings to patients with CD who do not spend their money on cigarettes. This would help improve the overall care of CD patients and reduce the cost.

Overall, if a smoking cessation program was funded it would improve the long-term outcomes of these individuals and help to relieve the monetary pressure placed on the system by smoking. It would help improve the health of patients with CD and would save the health system money.

3.3 Methodological Challenges and Limitations

One of the biggest limitations of this study was the lack of data regarding smoking cessation for patients with CD. Most studies have been undertaken with members of the general population and do not necessarily represent the CD population, as the general public studied tends to have more pack-years, are older, and may not have a chronic disease directly affected by smoking. To address this limitation a threshold analysis and a PSA were conducted that varied the probability of quitting successfully; reassuringly, both of these analyses showed that funding

any smoking cessation program continued to be more cost-effective than No Program across a wide variation of probabilities.

Another limitation was the conflicting evidence regarding smoking and the effectiveness of anti-TNFs. Studies evaluating the effect of smoking on anti-TNF responsiveness are inconsistent with some showing that smoking decreases the effectiveness of anti-TNF therapies, whereas in other studies smoking did not influence the effectiveness of anti-TNF therapies.[26] Due to this uncertainty, the primary model conservatively estimated that the effectiveness of anti-TNF therapies was the same between smokers and ex-smokers. To evaluate this assumption a scenario analysis was performed that decreased the effectiveness of anti-TNF therapies for smokers by 10%. This scenario analysis made all the smoking cessation strategies even more cost-effective.

While the use of utilities is an advantage to cost-utility analysis, because an individual's well-being is taken into account, it is also a limitation. Use of the utilities attained by the standard gamble, as in this study, does have drawbacks. When people are completing the standard gamble they find it difficult due to the complexity of what is asked (i.e. probability of full health versus death). Also, we assume risk-neutrality even though most individuals are risk averse.[36] The final results of the standard gamble are likely to underestimate the larger probabilities, and then overestimate the smaller probabilities attained.[36] Unfortunately, we are limited to the data that has been published.

3.4 Directions for Future Research

This cost-utility analysis demonstrated that funding a smoking cessation program would improve the quality of life of patients with CD and reduce the cost to the healthcare system. Cost savings could be used to invest in follow-up studies derived from this work.

First, a randomized control trial looking at defining the efficacy of a smoking cessation program for CD patients should be done. Given that the TABACROHN study utilized mainly counseling, a study looking at NRT or varenicline would be beneficial. Given the efficacy of NRT or varenicline, it could be hypothesized that either of these smoking cessation therapies would have higher success rates than those reported in the TABACROHN study.

Second, prospective studies that follow smokers and ex-smokers with CD for longer than 5 years are necessary to evaluate the long-term cost-savings associated with smoking cessation programs. Because a prospective study is costly and time consuming, another option is to conduct a retrospective cohort study using administrative data with information on smoking status and identify those individuals who have quit smoking, and those that have not, and compare the efficacy and costs associated with their treatment (medication and surgical); this could be done with The Health Improvement Network (THIN) database. The THIN database is a comprehensive database from the United Kingdom containing 11.1 million total patients, which is an ideal dataset for epidemiologic research.[69]

Probably the most important task that needs to be undertaken is to perform knowledge translation and exchange that highlights the importance of funding smoking cessation programs, and to disseminate our findings to the appropriate IBD-related entities, such as: Crohn's and Colitis Canada, Alberta Health Services, Canadian Association of Gastroenterology, or Health Canada.

3.5 Conclusion

Smoking cessation has numerous health benefits for patients with CD; both direct short-term benefit on the prognosis of CD and long-term benefit in reducing smoking-related complications. These negative consequences are deleterious towards an individual's health, and

end up costing the health care system a lot of money. It is for these reasons that policy needs to be implemented to fund smoking cessation programs for patients with CD.

Bibliography

1. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology.* 2012;142:46-54.
2. Frolkis A, Dieleman LA, Barkema H, et al. Environment and the inflammatory bowel diseases. *Can J Gastroenterol.* 2013;27:e18-24.
3. Mahid SS, Minor KS, Soto RE, Hornung CA, Galandiuk S. Smoking and inflammatory bowel disease: a meta-analysis. *Mayo Clin Proc.* 2006;81:1462-71.
4. Cosnes J, Carbonnel F, Carrat F, Beaugerie L, Cattan S, Gendre J. Effects of current and former cigarette smoking on the clinical course of Crohn's disease. *Aliment Pharmacol Ther.* 1999;13:1403-11.
5. Cosnes J, Beaugerie L, Carbonnel F, Gendre JP. Smoking cessation and the course of Crohn's disease: an intervention study. *Gastroenterology.* 2001;120:1093-9.
6. Sands BE, Arsenault JE, Rosen MJ, et al. Risk of early surgery for Crohn's disease: implications for early treatment strategies. *Am J Gastroenterol.* 2003;98:2712-8.
7. Reese GE, Nanidis T, Borysiewicz C, Yamamoto T, Orchard T, Tekkis PP. The effect of smoking after surgery for Crohn's disease: a meta-analysis of observational studies. *Int J Colorectal Dis.* 2008;23:1213-21.
8. Calkins BM. A meta-analysis of the role of smoking in inflammatory bowel disease. *Dig Dis Sci.* 1989;34:1841-54.
9. Bernstein CN, Wajda A, Svenson LW, et al. The epidemiology of inflammatory bowel disease in Canada: a population-based study. *Am J Gastroenterol.* 2006;101:1559-68.

10. Bernstein CN, Longobardi T, Finlayson G, Blanchard JF. Direct medical cost of managing IBD patients: a Canadian population-based study. *Inflamm Bowel Dis.* 2012;18:1498-508.

11. Statistics Canada. Consumer Price Index. 2014; Available at: http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/econ09a-eng.htm. Accessed February 19, 2014.

12. Ghosh S. Anti-TNF therapy in Crohn's disease. *Novartis Found Symp.* 2004;263:193-205.

13. Sadowski DC, Bernstein CN, Bitton A, Croitoru K, Fedorak RN, Griffiths A. Canadian Association of Gastroenterology Clinical Practice Guidelines: The use of tumour necrosis factor-alpha antagonist therapy in Crohn's disease. *Can J Gastroenterol.* 2009;23:185-202.

14. Rutgeerts P, Feagan BG, Lichtenstein GR, et al. Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. *Gastroenterology.* 2004;126:402-13.

15. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology.* 2007;132:52-65.

16. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet.* 2002;359:1541-9.

17. Alberta Blue Cross. Alberta Blue Cross Interactive Drug Benefit List. 2014; Available at: https://idbl.ab.bluecross.ca/idbl/load.do. Accessed February 19, 2014.

18. Blackhouse G, Assasi N, Xie F, et al. Canadian cost-utility analysis of initiation and maintenance treatment with anti-TNF-alpha drugs for refractory Crohn's disease. *J Crohns Colitis.* 2012;6:77-85.

19. Frolkis A, Kaplan K, Patel AB, et al. Postoperative complications and emergent readmission in children and adults with inflammatory bowel disease who undergo intestinal resection – A population-based study. *Inflamm Bowel Dis.* 2014; In Press.

20. Al-Darmaki A, Singh S, Frolkis A, et al. Post-operative mortality in Crohn's disease: A systematic review of population-based studies. *Canadian Digestive Disease Week 2014*. Toronto, Canada. 2014.

21. Frolkis A, Lipton DS, Fiest K, et al. Cumulative incidence of second intestinal resection in Crohn's disease: a systematic review and meta-analysis of population-based studies. *Canadian Digestive Disease Week 2014*. Toronto, Canada. 2014.

22. Frolkis AD, Dykeman J, Negron ME, et al. Risk of surgery for inflammatory bowel diseases has decreased over time: a systematic review and meta-analysis of population-based studies. *Gastroenterology.* 2013;145:996-1006.

23. Rocchi A, Benchimol EI, Bernstein CN, et al. Inflammatory bowel disease: a Canadian burden of illness review. *Can J Gastroenterol.* 2012;26:811-7.

24. Lindberg E, Tysk C, Andersson K, Jarnerot G. Smoking and inflammatory bowel disease. A case control study. *Gut.* 1988;29:352-7.

25. Nunes T, Etchevers MJ, Merino O, et al. High smoking cessation rate in Crohn's disease patients after physician advice - The TABACROHN Study. *J Crohns Colitis.* 2012.

26. Narula N, Fedorak RN. Does smoking reduce infliximab's effectiveness against Crohn's disease? *Can J Gastroenterol.* 2009;23:121-5.

27. Burisch J, Pedersen N, Cukovic-Cavka S, et al. Environmental factors in a population-based inception cohort of inflammatory bowel disease patients in Europe - An ECCO-EpiCom study. *J Crohns Colitis.* 2013.

28. Health Canada. Canadian Tobacco Use Monitoring Survey 2012. 2012; Available at: http://www.hc-sc.gc.ca/hc-ps/tobac-tabac/research-recherche/stat/ctums-esutc_2012-eng.php. Accessed December 8, 2013.

29. Jha P, Ramasundarahettige C, Landsman V, et al. 21st-century hazards of smoking and benefits of cessation in the United States. *N Engl J Med.* 2013;368:341-50.

30. Hughes JR, Gulliver SB, Fenwick JW, et al. Smoking cessation among self-quitters. *Health Psychol.* 1992;11:331-4.

31. Stead LF, Lancaster T. Group behaviour therapy programmes for smoking cessation. *Cochrane Database Syst Rev.* 2005:CD001007.

32. Lancaster T, Stead LF. Individual behavioural counselling for smoking cessation. *Cochrane Database Syst Rev.* 2005:CD001292.

33. Stead LF, Perera R, Bullen C, et al. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev.* 2012;11:CD000146.

34. Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database Syst Rev.* 2012;4:CD006103.

35. Hunink M, Glaszious P, Siegel J, et al. *Decision making in health and medicine: Integrating evidence and values*. New York: Cambridge University Press; 2011.

36. Clement F. *MDCH 663: Decision Analysis in Economic Evaluation Course Notes.* Calgary, AB: University of Calgary. Lecture Notes.

37. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. *Methods for the Economic Evaluation of Health Care Programmes: 3rd Edition*. New York: Oxford University Press; 2005.

38. Canadian Agency for Drugs and Technologies in Health. Guidelines for the economic evaluation of health technologies: Canada [3rd Edition]. 2006; Available at: http://www.cadth.ca/media/pdf/186_EconomicGuidelines_e.pdf. Accessed January 29, 2014.

39. Ananthakrishnan AN. Environmental risk factors for inflammatory bowel disease. *Gastroenterol Hepatol (N Y).* 2013;9:367-74.

40. Molodecky NA, Kaplan GG. Environmental risk factors for inflammatory bowel disease. *Gastroenterol Hepatol (N Y).* 2010;6:339-46.

41. Molodecky NA, Panaccione R, Ghosh S, Barkema HW, Kaplan GG, Alberta Inflammatory Bowel Disease C. Challenges associated with identifying the environmental determinants of the inflammatory bowel diseases. *Inflamm Bowel Dis.* 2011;17:1792-9.

42. Loftus EV, Jr. Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. *Gastroenterology.* 2004;126:1504-17.

43. Stead LF, Perera R, Bullen C, et al. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev.* 2012;11:CD000146.

44. Gisbert JP, Panes J. Loss of response and requirement of infliximab dose intensification in Crohn's disease: a review. *Am J Gastroenterol.* 2009;104:760-7.

45. Billioud V, Sandborn WJ, Peyrin-Biroulet L. Loss of response and need for adalimumab dose intensification in Crohn's disease: a systematic review. *Am J Gastroenterol.* 2011;106:674-84.

46. Statistics Canada. Age-Standardized mortality rates by selected causes, by sex. 2009; Available at: http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/health30a-eng.htm. Accessed June 10, 2012.

47. Duricova D, Pedersen N, Elkjaer M, Gamborg M, Munkholm P, Jess T. Overall and cause-specific mortality in Crohn's disease: a meta-analysis of population-based studies. *Inflamm Bowel Dis.* 2010;16:347-53.

48. Ma C, Panaccione R, Heitman SJ, Devlin SM, Ghosh S, Kaplan GG. Systematic review: the short-term and long-term efficacy of adalimumab following discontinuation of infliximab. *Aliment Pharmacol Ther.* 2009;30:977-86.

49. D'Haens GR, Panaccione R, Higgins PD, et al. The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organization: when to start, when to stop, which drug to choose, and how to predict response? *Am J Gastroenterol.* 2011;106:199-212.

50. Kaplan GG, Hur C, Korzenik J, Sands BE. Infliximab dose escalation vs. initiation of adalimumab for loss of response in Crohn's disease: a cost-effectiveness analysis. *Aliment Pharmacol Ther.* 2007;26:1509-20.

51. Bonafede MM, Gandra SR, Watson C, Princic N, Fox KM. Cost per treated patient for etanercept, adalimumab, and infliximab across adult indications: a claims analysis. *Adv Ther.* 2012;29:234-48.

52. Bureau of Labor Statistics. Consumer Price Index (United States of America). 2014; Available at: http://www.bls.gov/cpi/. Accessed February 24, 2014.

53. First Databank, Inc. Whilesale Acquisition costs. 2011; Available at: http://www.firstdatabank.com Accessed Sept 14, 2011. Cited by: Bonafede MM, Gandra SR, Watson C, Princic N, Fox KM. Cost per treated patient for etanercept, adalimumab, and infliximab across adult indications: a claims analysis. *Adv Ther*. 2012;29:234-48.

54. Cohen RD, Larson LR, Roth JM, Becker RV, Mummert LL. The cost of hospitalization in Crohn's disease. *Am J Gastroenterol.* 2000;95:524-30.

55. Gregor JC, McDonald JWD, Klar N, et al. An evaluation of utility measurement in Crohn's disease. *Inflamm Bowel Dis.* 1997;3:265-76.

56. Health Canada. Canadian Tobacco Use Monitoring Survey 2012. 2012; Available at: http://www.hc-sc.gc.ca/hc-ps/tobac-tabac/research-recherche/stat/ctums-esutc_2012-eng.php. Accessed December 8, 2013.

57. Loftus CG, Loftus EV, Jr., Harmsen WS, et al. Update on the incidence and prevalence of Crohn's disease and ulcerative colitis in Olmsted County, Minnesota, 1940-2000. *Inflamm Bowel Dis.* 2007;13:254-61.

58. United States Census Bureau. U.S. and World Population Clock. Available at: http://www.census.gov/popclock/. Accessed December 8, 2013.

59. Nguyen GC, Devlin SM, Afif W, et al. Defining quality indicators for best-practice management of inflammatory bowel disease in Canada. *Can J Gastroenterol Hepatol.* 2014;28:275-85.

60. Anthenelli RM, Morris C, Ramey TS, et al. Effects of varenicline on smoking cessation in adults with stably treated current or past major depression: a randomized trial. *Ann Intern Med.* 2013;159:390-400.

61. Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. *Cochrane Database Syst Rev.* 2013;5:CD009329.

62. Gibbons RD, Mann JJ. Varenicline, smoking cessation, and neuropsychiatric adverse events. *Am J Psychiatry.* 2013;170:1460-7.

63. U.S. Food and Drug Administration. Postmarket Drug Safety Information for Patients and Providers (Varenicline). 2014; Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124818.htm. Accessed May 24, 2014.

64. Parsi MA, Achkar JP, Richardson S, et al. Predictors of response to infliximab in patients with Crohn's disease. *Gastroenterology.* 2002;123:707-13.

65. Arnott ID, McNeill G, Satsangi J. An analysis of factors influencing short-term and sustained response to infliximab treatment for Crohn's disease. *Aliment Pharmacol Ther.* 2003;17:1451-7.

66. Vermeire S, Louis E, Carbonez A, et al. Demographic and clinical parameters influencing the short-term outcome of anti-tumor necrosis factor (infliximab) treatment in Crohn's disease. *Am J Gastroenterol.* 2002;97:2357-63.

67. Fefferman DS, Lodhavia PJ, Alsahli M, et al. Smoking and immunomodulators do not influence the response or duration of response to infliximab in Crohn's disease. *Inflamm Bowel Dis.* 2004;10:346-51.

68. Laharie D, Salzmann M, Boubekeur H, et al. Predictors of response to infliximab in luminal Crohn's disease. *Gastroenterol Clin Biol.* 2005;29:145-9.

69. University College London. THIN Database. 2014; Available at: http://www.ucl.ac.uk/pcph/research-groups-themes/thin-pub/database. Accessed May 19, 2014.

70. Alberta Health Services. Alberta Health Services Job Board. 2014; Available at: http://www.albertahealthservices.ca/careers/. Accessed February 19, 2014.

71. Alberta Health Services. Addiction Centre. 2012; Available at: http://www.addictioncentre.ca. Accessed June 6, 2012.

Figure 1. Bubble diagram of the cost-utility model used in this analysis. The bubble diagram outlines the targeted population, the 5 different smoking cessation strategies, the health states each individual can go through, and the outcomes.

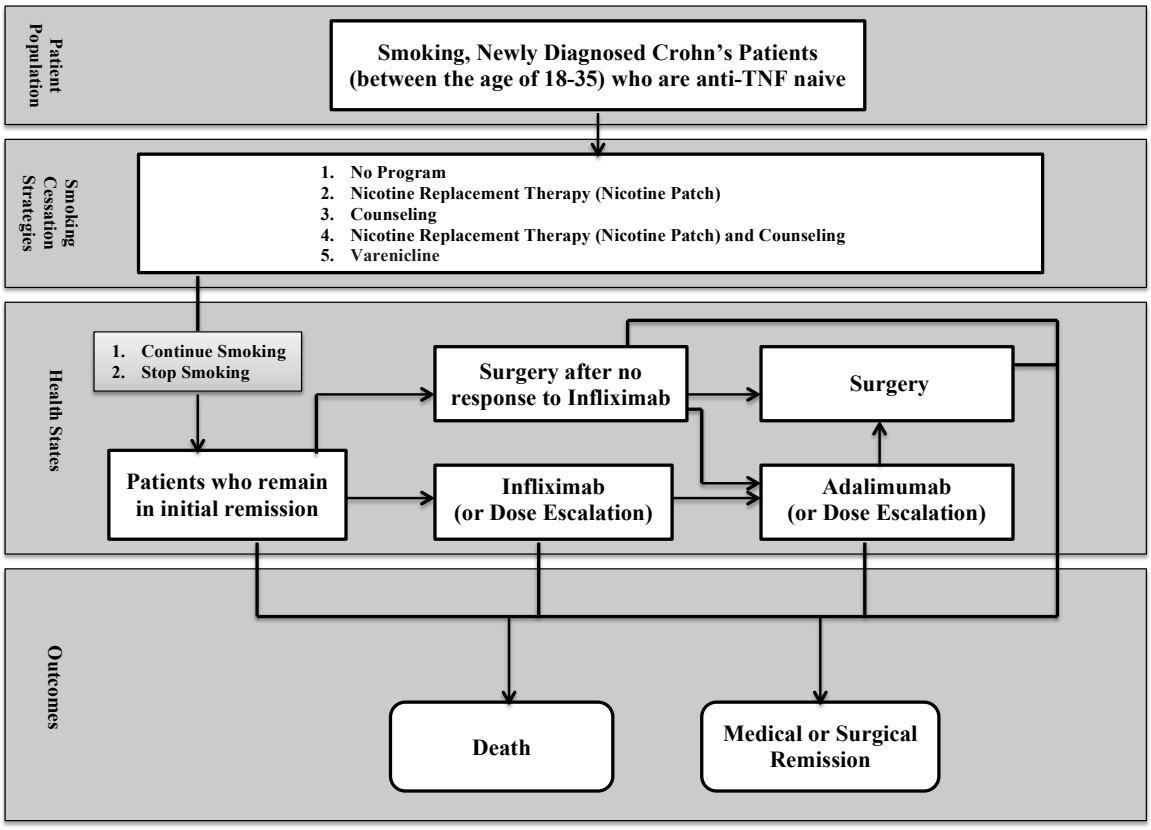


Figure 2. Cost-utility analysis demonstrating that Varenicline is the most cost-effective option. All of the programs dominate No Program.

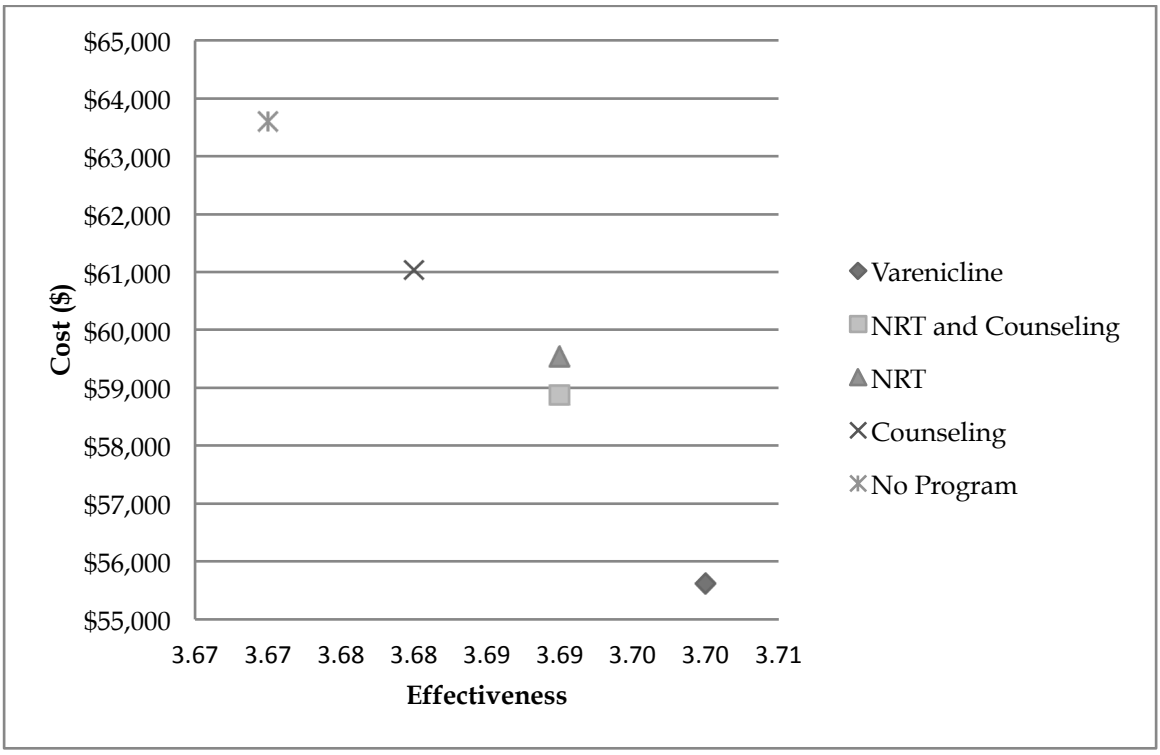


Figure 3. Incremental cost-effectiveness scatterplot comparing No Program to Varenicline, with 95% confidence ellipses and a willingness-to-pay of $50,000 (CAN).

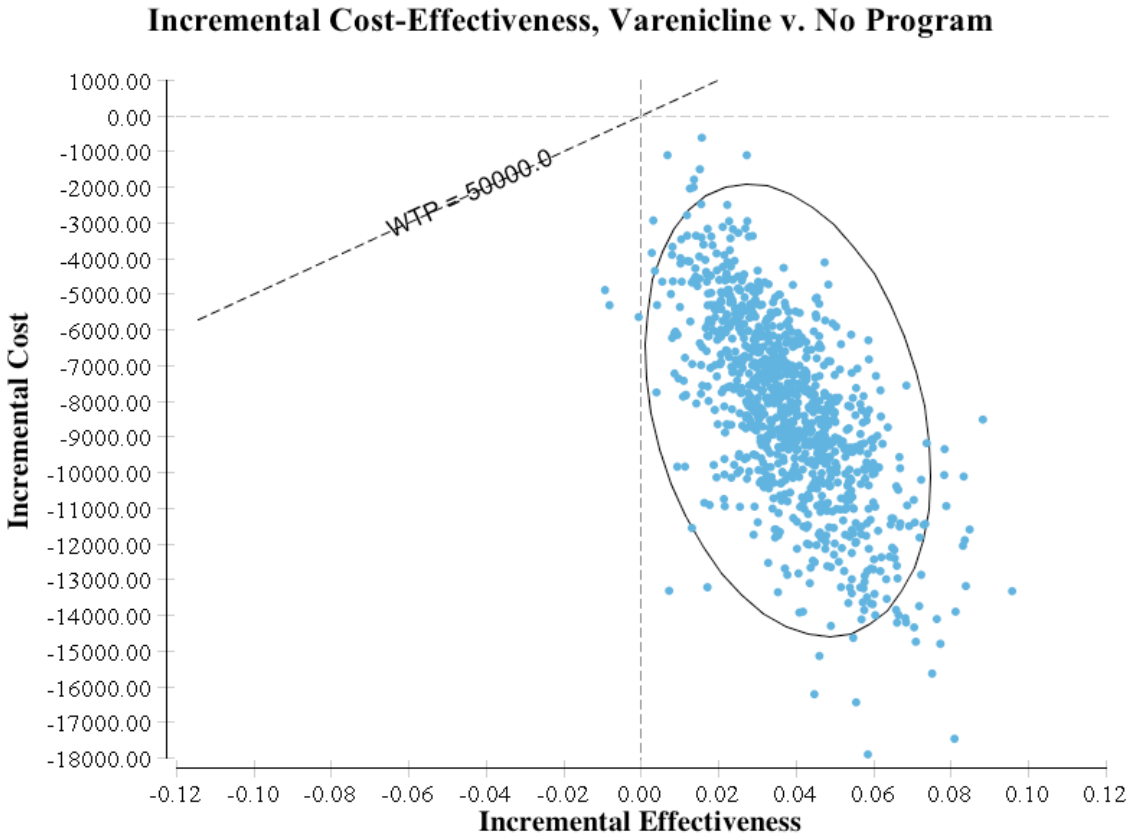


Table 1. The costs and effectiveness of the 5 different smoking cessation programs that were used in the cost-utility model.

Smoking Cessation Strategy	Description	Cost	Effectiveness	Source of Probability of Effectiveness
No Program	Recommendation to quit smoking without any direct Counseling or prescription of a smoking cessation medication. Referent category.	$0.00	3.00%[30]	Observational Cohort
NRT (Nicotine Replacement Therapy)	The nicotine patch is used as NRT because of considerable research on its efficacy, minimal adverse events, and easily quantifiable using standard dosages.	$190.80[17]	15.95%[43]	Systematic Review
Counseling	Individual Counseling once a week for 6 weeks led by a mental health professional	$267.78[70,71]	10.96%[32]	Systematic Review
NRT+ Counseling	A combination of the nicotine patch and individual Counseling.	$458.58[17,70,71]	18.17%[32]	Systematic Review
Varenicline*	Standard dosage of 1 g per day for 12 weeks	$293.33[17]	27.87%[34]	Systematic Review

***** Approximately 3.2% of individuals experience a serious adverse effect while on this medication.[34] Withdrawal due to toxicity and adverse effects was accounted for by using a continuous abstinence estimate that took into account cessation of the strategy due to serious adverse effect.

Table 2. The probabilities of flaring for ex-smokers and current smokers.

	Smokers and Ex-Smokers		Source of Probability
Death	0.007145[46, 47]		Meta-analysis and Statistics Canada
Primary Response to Infliximab (3-month)	0.83[14]		RCT
Remission from Infliximab (1-year)	0.39[14]		RCT
Remission from Infliximab dose escalation (1-year)	0.41[14]		RCT
Remission from adalimumab (1-year)	0.36[15]		RCT
Remission from adalimumab dose escalation (1-year)	0.41[15]		RCT
Maintenance Infliximab response (after 1-year remission)	0.87[44]		Systematic Review
Maintenance Adalimumab response (after 1-year remission)	0.797[45]		Systematic Review
Probability of First Flare in:			
• **Year 1***	0.14[5]	0.31[5]	Observational Cohort
• **Year 2***	0.08[5]	0.39[5]	
Year 3-5*	0.22[5]	0.40[5]	
Probability of flaring after surgery in:			
• **Year 1†**	0.657[7]	0.657[7]	Meta-analysis
• **Year 2†**	0.424[7]	0.657[7]	
• **Year 3-5†**	0.349[7]	0.657[7]	

***** The probability that a patient in remission on azathioprine will flare requiring the initiation of an anti-TNF agent stratified by those who quit smoking versus those who continue to smoke.
† The probability that a patient who experiences a surgically induced remission will flare postoperatively stratified by those who quit smoking versus those who continue to smoke.

Table 3. Results of the Monte Carlo analysis over a 5-year time horizon. The measures of outcome are costs, Quality Adjusted Life Years (QALY) with 95% confidence intervals (CI), and the Incremental Cost-Effectiveness Ratio (ICER).

Strategy	Cost (95% CI)	Cost Difference (compared to No Program)	QALY (95% CI)	ICER
Varenicline	**$55,614** ($52,755-$58,474)	$7,987	**3.70** (3.68-3.73)	0
NRT and Counseling	**$58,878** ($56,050-$61,706)	$4,723	**3.69** (3.66-3.72)	Dominated
NRT	**$59,540** ($56,732-$62,347)	$4,061	**3.69** (3.66-3.71)	Dominated
Counseling	**$61,029** ($58,246-$63,812)	$2,572	**3.68** (3.65-3.71)	Dominated
No Program	**$63,601** ($60,865-$66,337)	$0.00	**3.67** (3.64-3.69)	Dominated

Table 4. Budget Impact Analysis for incident cases of adults newly diagnosed with Crohn's disease in Canada and the prevalence of smoking at diagnosis is 35.4%.

Smoking Cessation Strategy	Initial Cost to Fund	Cost Savings Per Patient	Total Costs Savings Over 5 Years (compared to No Program)
Varenicline	$591,881	$7,987	$16,116,169
NRT + Counseling	$925,323	$4,723	$9,530,069
NRT	$384,996	$4,061	$8,194,286
Counseling	$540,326	$2,572	$5,189,782
No Program	$0	$0	$0

Appendix A. Scenario analysis where the probability of anti-TNF efficacy is reduced by 10% for smokers.

Strategy	Cost (95%CI)	Cost Difference (compared to No Program)	QALY (95%CI)
Varenicline	**$53,993** ($51,284-$56,702)	$7,689	**3.67** (3.64-3.69)
NRT and Counseling	**$56,992** ($54,326-$59,657)	$4,690	**3.65** (3.63-3.67)
NRT	**$57,308** ($54,666-$59,951)	$4,374	**3.65** (3.62-3.67)
Counseling	**$58,765** ($56,132-$61,397)	$2,917	**3.64** (3.61-3.66)
No Program	**$61,682** ($59,098-$64,265)	$0	**3.62** (3.60-3.64)

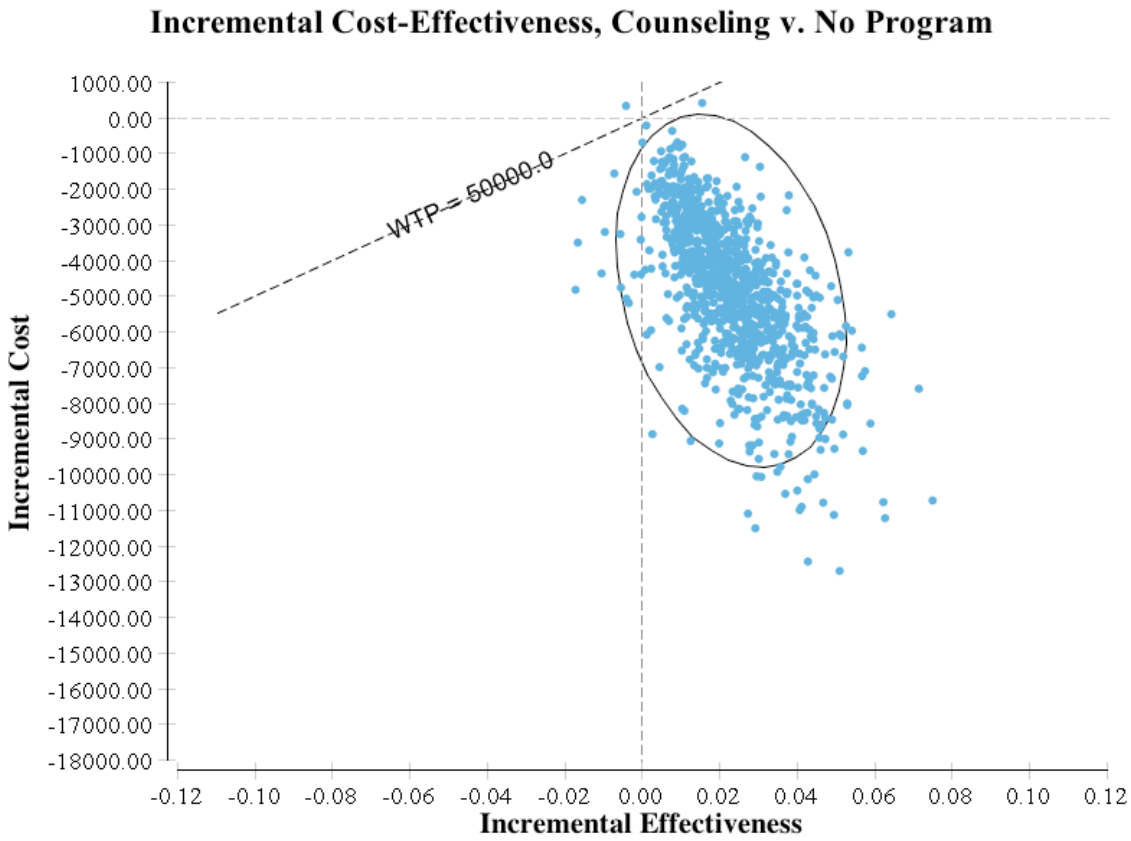
Appendix B. Scenario analysis where utility following surgery is decreased by 0.3 (from 0.74 to 0.44) and the disutility of a flare leading to surgery is decreased by 0.3 (from -0.11 to -0.41).

Strategy	Cost (95%CI)	Cost Difference (compared to No Program)	QALY (95%CI)
Varenicline	**$55,614** ($52,755-$58,474)	$7,987	**3.55** (3.51-3.59)
NRT and Counseling	**$58,878** ($56,050-$61,706)	$4,723	**3.53** (3.49-3.57)
NRT	**$59,540** ($56,732-$62,347)	$4,061	**3.52** (3.48-3.56)
Counseling	**$61,029** ($58,246-$63,812)	$2,572	**3.51** (3.47-3.55)
No Program	**$63,601** ($60,865-$66,337)	$0	**3.49** (3.45-3.53)

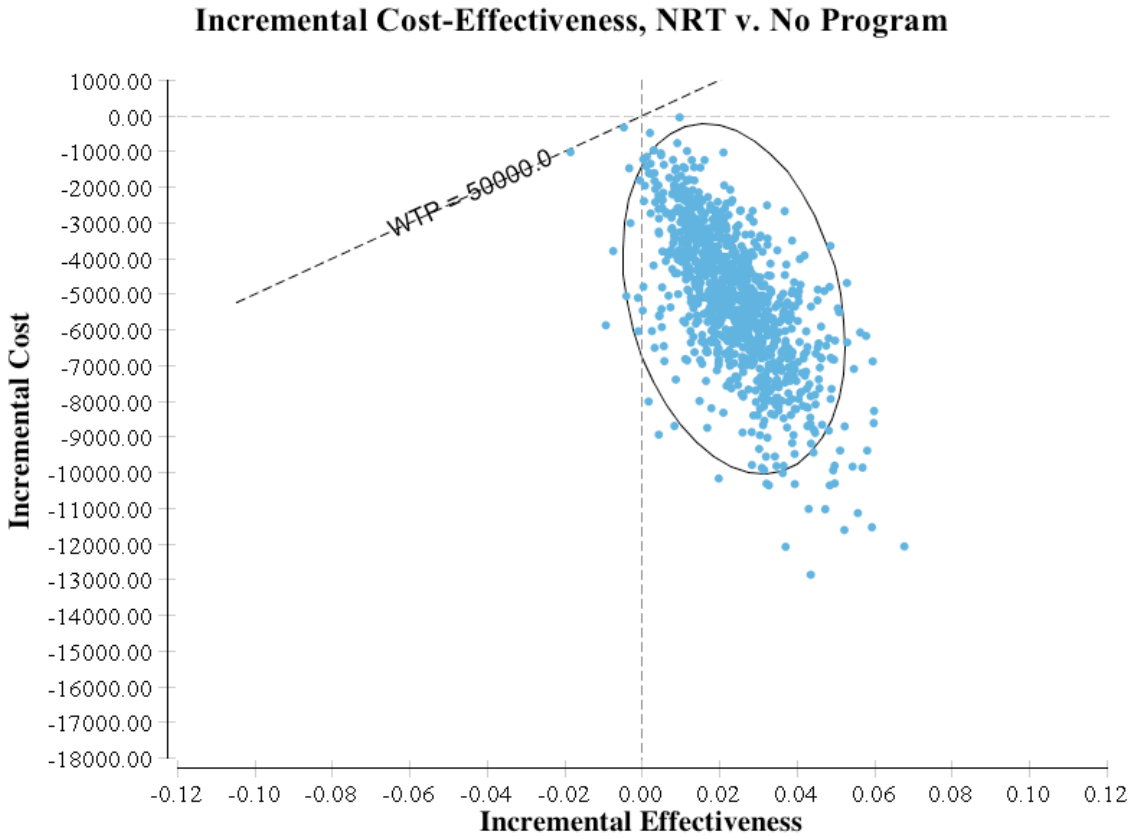
Appendix C. Scenario analysis that used US costs for surgery and anti-TNF therapies.

Strategy	Cost (95%CI)	Cost Difference (compared to No Program)	QALY (95%CI)
Varenicline	**$48,669** ($46,136-$51,202)	$7,012	**3.70** (3.68-3.73)
NRT and Counseling	**$51,568** ($49,065-$54,072)	$4,113	**3.69** (3.66-3.72)
NRT	**$52,136** ($49,648-$54,625)	$3,545	**3.69** (3.66-3.71)
Counseling	**$53,440** ($50,974-$55,906)	$2,241	**3.68** (3.65-3.71)
No Program	**$55,681** ($53,257-$58,106)	$0	**3.67** (3.64-3.69)

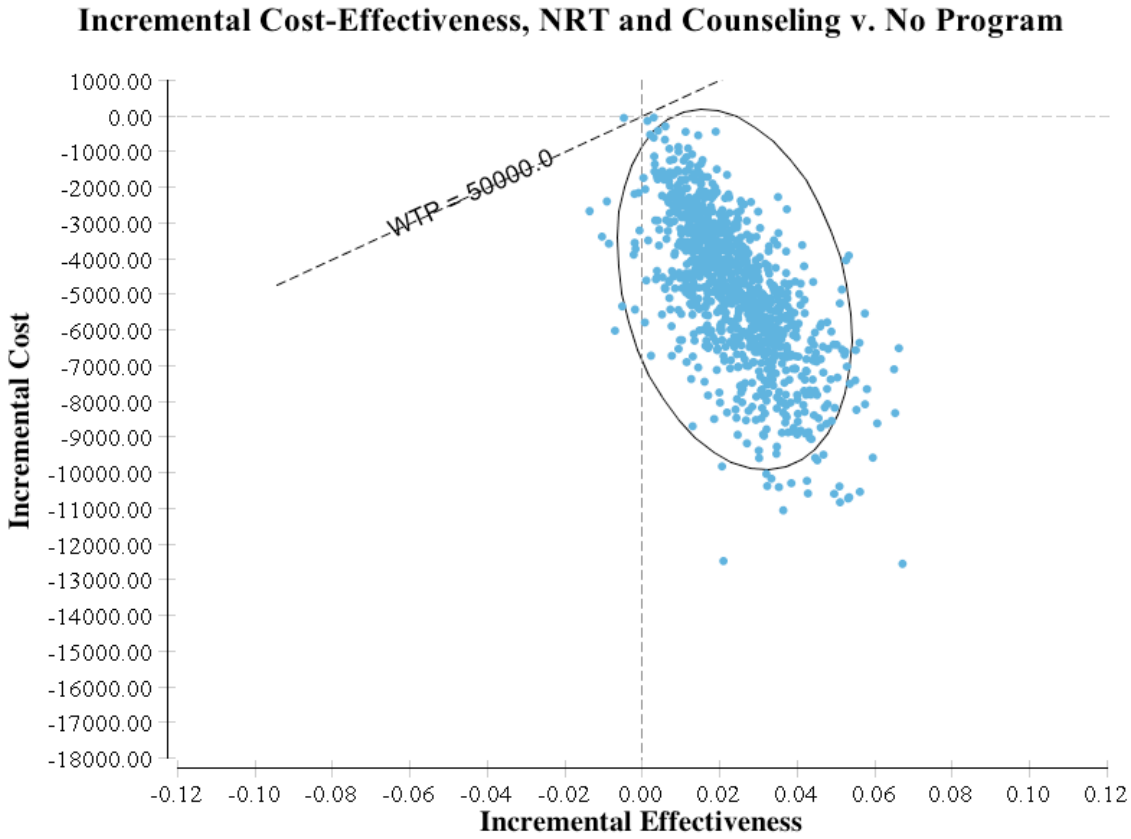
Appendix D. Incremental cost-effectiveness scatterplot comparing No Program to Counseling, with 95% confidence ellipses and a willingness-to-pay of $50,000 (CAN).



Appendix E. Incremental cost-effectiveness scatterplot comparing No Program to Nicotine Replacement Therapy (NRT), with 95% confidence ellipses and a willingness-to-pay of $50,000 (CAN).



Appendix F. Incremental cost-effectiveness scatterplot comparing No Program to Nicotine Replacement Therapy (NRT) and Counseling, with 95% confidence ellipses and a willingness-to-pay of $50,000 (CAN).



Appendix G. Budget Impact Analysis for incident cases of adults newly diagnosed with Crohn's disease in the US and the prevalence of smoking at diagnosis is 35.4%.

Smoking Cessation Strategy	Initial Cost to Fund	Cost Savings Per Patient	Total Costs Savings Over 5 Years (compared to No Program)
Varenicline	$2,567,623	$7,012	$61,380,560
NRT and Counseling	$4,014,115	$4,113	$36,003,262
NRT	$1,670,141	$3,545	$31,031,004
Counseling	$2,343,974	$2,241	$19,618,901
No Program	$0	$0	$0

Appendix H. Budget Impact Analysis for incident cases of adults newly diagnosed with Crohn's disease in Canada and the prevalence of smoking at diagnosis is 16%.

Smoking Cessation Strategy	Initial Cost to Fund	Cost Savings Per Patient	Total Costs Savings Over 5 Years (compared to No Program)
Varenicline	$267,517	$7,987	$7,284,144
NRT + Counseling	$418,225	$4,723	$4,307,376
NRT	$174,010	$4,061	$3,703,632
Counseling	$244,215	$2,572	$2,345,664
No Program	$0	$0	$0