Estimating the Cost-Effectiveness of Evidence-Informed Primary Care:

A Micro-simulation Analysis of Cancer Screening and Diabetes Management

Final Report

July 12, 2011

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Glossary of terms

Term	Definition
Physician Integrated Network	A Manitoba primary care renewal initiative
Electronic medical record	Medical records held in electronic rather than paper form
Primary care indicator	Indicators meant to measure primary health care activity such as disease screening, or testing
Cost-effectiveness analysis	Analysis of the cost of producing the outcomes of a program or other initiative, often involving a comparison of alternative approaches to delivery
Decision analysis	Analytical approach that examines individual decision making in the face of chance events and various incentives
Markov modelling	Model where individuals transition between a number of fixed states, often over a fixed time period
Quality adjusted life year	A measure of annual life extension, which is prorated from 0 to 1 based on an individual's health during that period
Health determinants	Factors, such as socio-economic status, which influence individuals' health outcomes
Tree diagram	A representation of decision-making process where branches identify possible courses of action and outcomes
Recursive model structure	A fixed model structure where all possible starting and ending states are identical, through which simulated individuals can move repeatedly
State-based modelling approach	Simulation modelling approach that includes a relatively large number of states through which individuals may transition, and a relatively small number of possible events between each transition
Event-based modelling approach	Simulation modelling approach that includes a limited number of states through which individuals may transition, and a relatively large number of possible events between each transition
Inner loop simulation	A single micro-simulation of an entire population often producing average outcome values for these individuals
Outer loop simulation	Multiple micro-simulations of the same population producing average outcome values for each individual, at each simulation, which are aggregated to identify an average from among these averages
Switch-point	In the context of the current study, a cost structure at which average simulated costs per individual are identical under both the baseline and counterfactual modelling approaches
Sub-tree	A portion of a larger decision tree, often involving a series of related events
Tracker variable	A variable used in micro-simulations to identify simulated individuals who have experienced specific events

Acknowledgements

This report benefitted significantly from the advice provided by various clinical and subject matter experts throughout Manitoba. The following individuals were instrumental to the work, and provided ongoing support throughout the project:

- Alan Katz
- Paul Komenda
- Marion Harrison

In addition, the following individuals offered insight into aspects of the modelling undertaken in this study, as these related to their areas of expertise:

- Ethel MacIntosh
- Greg Finlayson
- Debrah Wirtzfeld
- Robert Lotocki

The input of all those listed above is greatly appreciated.

Executive summary

The Physician Integrated Network (PIN) is a Manitoba primary care renewal initiative, with four objectives:

- to improve access to primary care
- to improve providers' access to and use of information
- to improve the work life for all primary care providers
- to demonstrate high-quality primary care with a specific focus on chronic disease management

Group practice sites in the province that are involved with PIN use electronic medical records to track a range of primary care clinical process quality indicators. Where possible, these are based on evidence-based primary care indicators developed by the Canadian Institute for Health Information (CIHI). The selected primary care indicators capture recommended screening and chronic disease management processes within six clusters:

- prevention
- diabetes management
- asthma management
- congestive heart failure management
- hypertension management
- coronary artery disease management

A PIN Evaluation Plan[1] was developed to measure the impact of the initiative on patient care and provider satisfaction, with reference to the identified PIN objectives, within the context of primary care renewal in Manitoba and Canada. Data analysis and qualitative interviews with providers and patients before and after the implementation of PIN have informed, and continue to inform, the future direction of the initiative and primary care renewal in the province of Manitoba. In addition to these PIN evaluation activities, there has been interest in pursuing further analysis examining the cost-effectiveness of screening practices aligned with CIHI guidelines and improved chronic disease management that have been implemented by PIN. The results from this cost-effectiveness analysis (CEA) should complement rather than supersede other information considered when assessing primary care renewal.

In 2010, Manitoba Health contracted a feasibility study for a CEA related to the initiative. The feasibility study examined techniques for assessing the extent of cost avoidance arising from increased primary prevention (screening) and chronic disease management activities. In particular, the CEA examined selected primary care activities measured by some of the CIHI primary care indicators. The study showed that such CEA was feasible and a full study was commissioned.

[1] More information on the PIN evaluation plan is available at http://www.gov.mb.ca/health/phc/pin/plan.html

This report presents the methodology and findings from this subsequent work. While not strictly speaking a CEA of the PIN initiative, the report explores potential cost avoidance from increasing rates of screening and management involving four distinct diseases. These include:

- colorectal cancer
- cervical cancer
- breast cancer
- diabetes

Two factors drove the selection of these diseases. The first was the initial feasibility of modelling each disease progression. The second was the importance of each disease process to primary care renewal in Manitoba. For each of the three cancers, the disease progression was quite linear and not heavily dependent on individual behaviour. This is unlike diseases like lung cancer, the progression of which may depend heavily on smoking cessation or other behavioural change that is not necessarily guaranteed for much for the population. While the diabetes modelling was supported by strong evidence in the literature, diabetes management is also a provincial priority, given its high incidence and prevalence in Manitoba.

The current study takes a decision analysis approach to cost-effectiveness modelling. Decision analysis simulates individual decision-making and various chance events from a real world setting, in order to identify outcomes of specific courses of action. In the context of the current study, the models view individuals as experiencing chance events such as testing positive or negative for cancer over a number of annual cycles. Throughout these simulated years, individuals accumulate various costs, allowing one to determine the cost implications of the model. In very simple terms, and again referencing cancer screening, the research asks whether regular screening identifies cancers earlier, placing individuals on a lower-cost care trajectory, and if this lower cost of care offsets the general cost estimations of increased screening across the eligible population.

It is important to understand the specific nature of the costs modelled in this research. In general, comprehensive preventive practice and chronic disease management in primary care is seen as contributing to avoidance of the following three categories of cost associated with disease:

- Net costs to the payer such as health insurance, government, and individual costs
- Lost economic benefits such as wages and taxes
- Costs in terms of quality of life for both patients and those around them

This study only examines the first category of costs. The advantage of conducting the analysis using only the health system costs is that it focuses on an essential question posed by government. What cost avoidance may result by committing spending to screening and chronic disease management? In an era of competing priorities within health care services and among the public sector interests, this is clearly a central question. It should certainly not be the only decision criteria, but before a course of screening and chronic disease management is finalized, it is important to understand the possible fiscal implications.

The models used in the current analysis attempt to estimate the potential cost avoidance of undertaking cancer screening and diabetes management associated with indicators aligned with CIHI's evidence-based Primary Health Care indicators and hereafter referred to as 'PIN indicators.' The cancer modelling examines average individual cancer-related medical costs

when different proportions of the population undergo consistent screening, as outlined by the PIN indicators. By examining how these average costs change as the percentage of the population undergoing screening changes, it is possible to assess the potential cost avoidance from primary care practitioners adopting a screening approach aligned with the PIN indicators. The diabetes modelling, by contrast, attempts to assess whether improved diabetes management practices in primary care—moving individuals from a state of uncontrolled diabetes to controlled diabetes—may avoid the health system costs associated with the management and treatment of major diabetic complications.

The main cancer modelling results compare the costs of primary care practitioners achieving full adherence to PIN screening guidelines among the targeted Manitoba population to screening situations that represent various other states that do not meet PIN screening guidelines. In one case, the PIN screening practice by primary care physicians is compared to a situation where no Manitobans undergo regular screening. In a second case, PIN screening practice is compared to a situation where primary care practitioners screen individuals at the current rate in Manitoba. Since there remains some uncertainty about the costs associated with various aspects of the cancer models, the cost-effectiveness assumed two additional cost structures to explore these results. The first additional structure uses more exhaustive and higher cost figures for cancer treatment, based on estimates found in other jurisdictions, while the second examined a cost structure where estimated costs per individual were identical regardless of the screening approach. Diabetes modelling followed that of the cancer models as closely as possible. This was based on comparing a scenario where there was a 70% chance of an individual exhibiting diabetic control among a simulated Manitoba population to one where all individuals were able to exhibit diabetic control.

Summary of results

In terms of the three cancers examined in the CEA, breast and colorectal cancer readily show the potential for cost avoidance through the alignment of primary care screening practice to PIN screening guidelines for breast and colorectal cancers. Under the high cost scenario described above, the breast cancer CEA model suggests a potential avoided cost of $2,581,200 over no screening, and a potential avoided cost of $717,000 over current screening practice over a 25-year period. The colorectal cancer CEA model shows even greater avoided costs, with corresponding results for $57,511,800 and $10,662,300 over the same number of years. By contrast, the cervical cancer CEA model shows increased health system costs through the alignment of primary care screening practice to PIN screening cervical cancer guidelines under all scenarios and assumptions. The low incidence of this condition means that the costs of delivering a program of cervical cancer screening in Manitoba are not recovered by the reduced costs associated with earlier cancer detection.

In reference to diabetes, the research shows that increasing an individual's likelihood of diabetic control from 70% to 100% generates a total avoided cost of $1.1 million over a 40-year period. However, it is critical to recognize that these results include only the financial costs involved in managing the consequences of diabetes-related health complications. They do *not* include the financial costs involved in implementing interventions aimed at managing diabetic control. Much of the control involves patients being able to alter diet and exercise and follow medication protocols. For many, powerful social and economic factors preclude their participation in the treatment protocols and many lack the resources required to maintain critical levels of health

determinants. Only if the avoided costs resulting from a given increase in diabetic control exceed the value of increased expenditures required to carry out these interventions can it be argued that these interventions avoid costs. The inclusion of potential intervention costs in the CEA for diabetes was beyond the scope of this study.

The CEA outlined in this report represents an important step in providing concrete evidence of the benefits of primary care practice alignment with evidence-based clinical guidelines beyond those commonly found in the literature. Several future steps are desirable. The main body of the report discusses these extensions of the analysis in more detail.

Interpreting the main report results

The CEA undertaken as part of this study compares results from simulations of PIN screening and chronic disease management to simulations of alternative primary health care prevention approaches. The tables that present the main results of these comparisons include two important financial figures.

- The first figure notes cost avoidance or additional costs, per simulated individual, over the entire length of the simulations.
- The second figure notes the total cost avoidance or additional costs, for all simulated individuals together, over the length of the simulations.

The following table presents results from the comparison of two hypothetical simulations of 160,000 individuals over 25 years. In one case, no individuals screen for cancer, and in the other, individuals screen as outlined under PIN. The two financial figures identified directly above are highlighted for clarity below.

Additional cost, per simulated individual, over 25 years

Cost-effectiveness results example	
Description	**Cost per individual**
No cancer screening simulation over 25 years	$400.00
Full PIN screening simulation over 25 years	$450.00
Difference	$50.00
Count of simulated individuals	**Total estimated additional or avoided costs**
Simulation of 160,000 individuals	$8,000,000 additional cost

Additional cost, for 160,000 individuals, over 25 years

These tables and the full results of the CEA analysis are discussed in more detail in the main body of this report.

1.0 Introduction

The Physician Integrated Network (PIN) is a Manitoba primary care renewal initiative with four objectives:

- to improve access to primary care
- to improve providers' access to and use of information
- to improve the work life for all primary care providers
- to demonstrate high-quality primary care with a specific focus on chronic disease management

The initiative began in 2006, and as of spring 2011, entered its second demonstration phase. It currently involves approximately 130 family doctors, at 13 fee-for-service group practice sites in urban and rural Manitoba, caring for a total of about 150,000 patients. All groups include a minimum of five family physicians and have electronic medical records (EMRs).

Throughout the first two phases of PIN, change-management funding was provided to each group to support and facilitate the creation of a plan to meet the PIN objectives. Phase 1 required intensive work related to the implementation and utilization of EMRs to support primary care practice, to ensure quality indicator data were available for monitoring and reporting, and to ensure that practice changes and primary care quality achievements could be measured. Since it began, the initiative has undertaken extensive evaluation and has received some benefits evaluation funding from Canada Health Infoway.

As noted above, PIN practice settings all use EMRs and have tracked a range of primary care clinical process quality indicators where possible, based on evidence-informed primary care indicators developed by the Canadian Institute for Health Information (CIHI). The selected primary care indicators—simply referred to as the PIN indicators throughout this report—focus on recommended screening and chronic disease management processes. These indicators are grouped into the following six clusters:

- prevention
- diabetes management
- asthma management
- congestive heart failure management
- hypertension management
- coronary artery disease management

Trial indicators for depression screening are also being tested at two sites, and access indicators are under development. PIN indicators track rates of testing, screening, or preventative care activity such as immunization for specific populations. For example, under the prevention cluster, the cervical cancer screening indicator identifies the percentage of the 18 to 69-year-old female population having undergone a Pap test in the past 36 months. Increasing the rates of these preventative care activities supports avoidance and early identification of pathology. The focus on the chronic disease management clinical processes aims to support the management of chronic disease, providing more opportunity for early intervention and disease management. This may then reduce the incidence of certain preventable diseases and help manage the progression and burden of illness of certain chronic conditions.

Participating clinics generate quarterly data extracts that track indicator achievement over time. These data are used to provide useful practice information to clinicians and to determine the clinic's Quality Based Incentive Funding (QBIF), based on a pay-for-performance model. QBIF funding is provided over and above the fee-for-service funding—an approach undertaken to explore and evaluate a blended funding approach in primary care. Physician group practices have discretion to use the funding to meet PIN objectives, and most have chosen to add other healthcare professionals to their team. Feedback to date has suggested that the majority of family physicians have identified that the use of inter-professional teams has assisted their groups in addressing the PIN objectives.

Further information on PIN can be found at http://www.gov.mb.ca/health/phc/pin/index.html.

1.1 PIN evaluation

A PIN Evaluation Plan was developed to measure the impact of the initiative on patient care and provider satisfaction, with reference to the identified PIN objectives within the context of primary care renewal in Manitoba and Canada. The Evaluation Plan was developed in collaboration with the PIN team and Dr. Alan Katz of the Department of Family Medicine, the University of Manitoba, and the Manitoba Centre for Health Policy. Data analysis and qualitative interviews with providers and patients before and after the implementation of PIN have informed, and continue to inform, the future direction of the initiative and primary care renewal progression in the province of Manitoba.[2]

In addition to these PIN evaluation activities, there has been interest in pursuing an analysis of the cost-effectiveness of increasing rates of preventative care services and improved chronic disease management. Early detection and intervention, and stringent chronic disease management have the potential to reduce disease development and progression, and to avoid some of the costs of more intensive treatment at advanced stages of disease. However, it is not well understood to what extent, and to what degree, this is the case, given the complexity of accounting for additional costs of early intervention and ongoing management. That said, cost-effectiveness alone will not drive further investment in these types of services. Other considerations include clinical evidence, individual patient benefit, net system benefit, and provincial priorities in policy and strategic health system management. Such an analysis is, however, an important component in assessing value and system benefit.

1.2 The current study

In 2010, PIN contracted a feasibility study for a cost-effectiveness analysis (CEA) related to the initiative. The feasibility study, carried out by PRA Inc., examined techniques for demonstrating cost avoidance from increased primary care prevention practice and chronic disease management activities. In particular, it examined those activities measured by the indicators discussed above.

The feasibility study determined that a Markov modelling approach could be used to demonstrate the cost-effectiveness of the various levels of testing, screening, or preventative activity encompassed by the Manitoba PIN. Using screening for colorectal cancer as an example, the feasibility study outlined the model development, data collection, and cost estimation work

[2] More information on the PIN evaluation plan is available at http://www.gov.mb.ca/health/phc/pin/plan.html

needed to support future analyses. The feasibility study resulted in a subsequent CEA using a similar Markov modelling approach. Engaged via a request for proposals process, PRA conducted this work on behalf of Manitoba Health via Manitoba eHealth. Manitoba eHealth is administratively housed within the Winnipeg Regional Health Authority, but has a province-wide mandate to facilitate health care delivery transformation through the use of information and communications technology (ICT) for health system users in Manitoba.

This report presents the methodology and findings from this subsequent work. While not strictly speaking a CEA of the PIN initiative, the report explores potential cost avoidance from increasing rates of screening and management involving four distinct diseases. These include:

- colorectal cancer
- cervical cancer
- breast cancer
- diabetes

Two factors drove the selection of these diseases. The first was the feasibility of modelling each disease progression. The second was the importance of each as an area of primary care focus in Manitoba.

It is important to reiterate that the study discussed in this report is not an analysis of PIN itself. Rather, the study assesses potential cost avoidance as a result of selected primary care interventions, including screening for three types of cancer and improved diabetes management. These are a subset of the activities outlined under the PIN indicators discussed above.

1.3 Approach to defining cost-effectiveness

Readers should note that this report only examines potential medical system cost avoidance from primary care activities. Cost-effectiveness studies in health commonly use quality adjusted life years (QALYs) as an outcome measure. Under this approach, cost-effective interventions are those that produce the greatest extension in QALYs per dollar of expenditure. The use of QALYs presents the value of any health intervention solely from the perspective of the patient and the value he or she attaches to the result of the intervention.

Two other measures of cost are also common in the literature. The first attempts to incorporate private costs incurred by individuals as a result of health conditions in model outcomes. This approach may attempt to assess various private costs including the emotional cost on caregivers, the extra costs imposed on the family, and the economic losses that may occur when caregivers must withdraw partially or totally from the workforce.

A second approach involves attempting to extend CEA to include numerous social costs. For example, these may include the economic and productive loss as a result of premature death. It could also incorporate direct costs to society including increased disability and insurance payments. This is typically a much broader approach to analysis requiring complex assumptions about the relationship of medical conditions to multiple aspects of the economy.

Under either of these approaches, complexities arise because cost categories are not always mutually exclusive. For example, reductions in quality of life may derive from the loss of

income, but also from the need to withdraw from a career that may have intrinsic value. Until the relationship among QALYs and private and economic losses is clarified, using these categories in the same analysis risks double counting and overstating the cost of disease and therefore the benefit arising from disease avoidance or health and wellness.

The advantage of conducting the current analysis using only the health system costs is that it focuses on the essential question posed by government. What cost avoidance may result by committing spending to achieving evidence-based screening practice and chronic disease management in primary care? In an era of competing priorities within health and among the public sector interests, this is clearly a central question. It should certainly not be the only decision criterion, but it is important to understand the possible fiscal implications in the course of policy implementation.

1.4 Guide to the report

The remainder of this report includes six sections. The first provides general preliminary comments on the mechanics and interpretation of the cost-effectiveness modelling. The next four include specific additional detail on the four Markov models developed for the study. They also provide results from simulations undertaken using these models. The final section provides concluding remarks and a general discussion of the work. It also outlines possible ways to improve the current models and discusses areas for future work.

2.0 The modelling approach

The current study takes a decision analysis approach to cost-effectiveness modelling. Decision analysis simulates individual decision-making and various chance events from a real world setting, in order to identify outcomes of specific courses of action. In a medical context, it is often used to examine specific medical practices or processes across the continuum of care. For example, it may help identify the most effective or least costly course of treatment among a number of available options (Detsky, Naglie, Krahn, Naimark, & Redelmeier, 1997, p. 123).

The first step in any decision analysis involves creating a model that accurately represents the real world situation under study. Although there are a number of ways to approach this modelling, one commonly used in the medical and other literatures involves creating a decision tree. A decision tree maps out the relevant choices, chance events, and outcomes facing an individual. The following figure presents an example of a simple decision tree for a patient presenting to a physician who is a candidate for Fecal Occult Blood Testing (FOBT) to detect colon cancer.

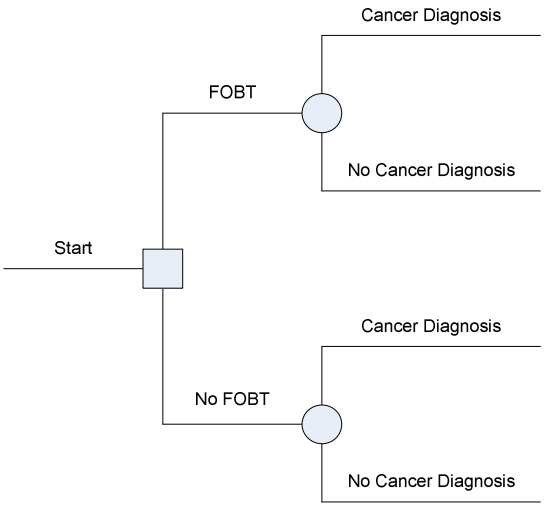

Figure 1: A simple decision tree

The example above represents—in a highly simplified way—the decision to order FOBT and its possible outcomes. Three features are important to this decision tree. They include:

- Decision nodes – squares in Figure 1
- Chance nodes – circles in Figure 1
- Branches – lines in Figure 1

Decision nodes represent those actions that are under the control of individuals in the real world. In this case, it is the decision of the physician to order and the patient to undertake or not undertake FOBT. Chance nodes represent events that are outside the control of these same individuals. Here, it is the chance of a particular diagnosis following testing or not testing. Branches represent various events that follow from either of the two nodes. In the example above, these would include testing, not testing, diagnosis of cancer, and no diagnosis of cancer.

Clearly, it is impossible to identify and represent all possible events facing individuals in the real world. Thus, a decision tree simplifies the range of options to only those that are relevant to the analysis at hand. The example above greatly simplifies reality. However, in models that are more accurate, there is careful consideration of relevant events. For example, cost-effectiveness models may abstract from events that have no bearing on costs. This makes the model tractable with a finite and manageable number of events, while not invalidating the model's findings.

To make this decision tree model functional, it must be populated with probabilities and outcomes. With finite decision tree models such as the one in Figure 1, decision nodes do not typically have associated probabilities. Rather, these determine optimal courses of action based on the other information in the model. Chance nodes, by contrast, are associated with probabilities for each subsequent event. This could include, for example, the chance of a positive or negative diagnosis after either undergoing FOBT or not. Figure 2 shows this below.

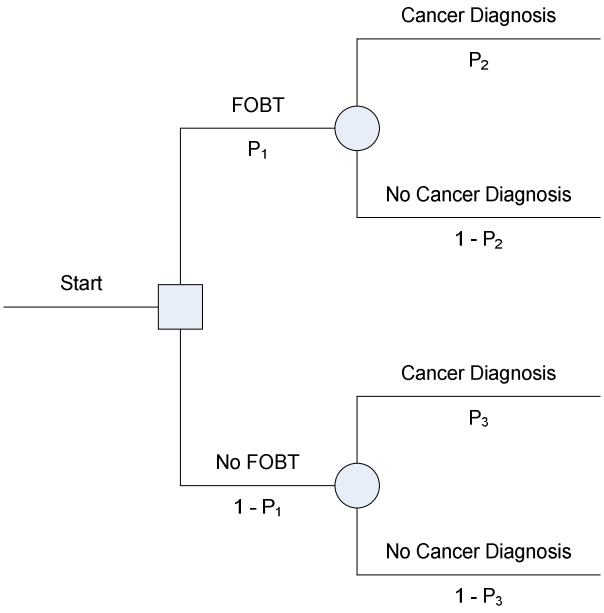

Figure 2: A simple decision tree with probabilities

Each of the events discussed above would then have associated outcomes. These might include costs—such as the discrete costs for the FOBT itself—or perhaps some measure of utility. These outcome values and probabilities therefore help identify an optimal choice between FOB testing and not testing.

Beyond its simplicity, the decision tree in Figure 1 has major limitations. Among the most important is the fact that it only considers each of the events represented in the model once. Therefore, in the model above, individuals would make the decision to undergo FOBT based on physician advice/orders only once, and then have the chance of a cancer diagnosis, again, only once. Clearly, this does not represent reality, as individuals may undergo screening a number of times during their life, and have the chance of a cancer diagnosis at many different times. It is this repeated sequence of events, common to primary care activities, that is missing from the model. To add this critical element, it is necessary to change the approach to the CEA modelling slightly.

Markov modelling involves developing a recursive model structure that adds the missing element noted above. It does so by repeating a finite model structure over a number of iterations or cycles. In each cycle, individuals start in a particular state—such as being healthy—and transition into others—such as having cancer. Transitions in this type of model are based on probabilities taken from real world data. For example, the probability of undertaking the transition noted above could be based on observed cancer diagnoses in a given year.

It is possible to use the tree diagrams discussed above in a Markov modelling approach with some changes. A finite number of states define the start and end of the model to represent the states through which an individual may transition. Choice nodes must then include probabilities indicating the likelihood of an individual undertaking a particular choice—or the risk/probability of a particular outcome to occur. While one may vary these to assess the impact of different decision-making processes in the design of a simulation, they remain fixed while running simulations. The following figure demonstrates how the tree diagram from Figure 2 may be made recursive.

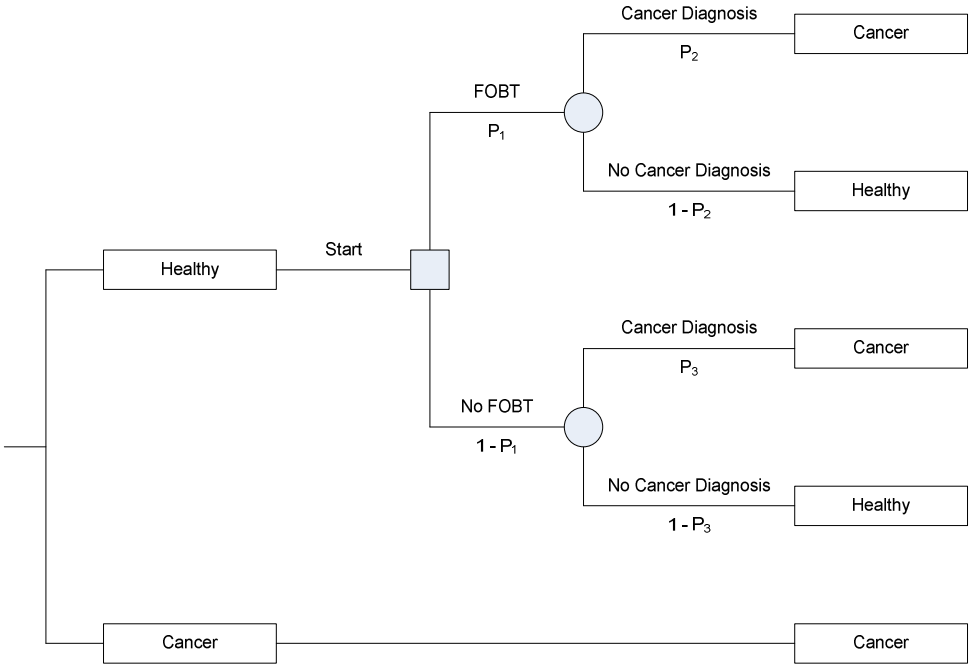

Figure 3: Recursive tree diagram

This recursive model allows for a Monte Carlo simulation approach to analysis. Simply put, this involves simulated individuals travelling through the model for a number of cycles. Individuals' movements through the model depend entirely on the probability of particular events and random number draws from a probability distribution. To understand this process, one can think of a chance event with two mutually exclusive outcomes, such as the chance of a cancer diagnosis where an individual may either receive a positive diagnosis or not.

In these types of models, probabilities are typically defined as values from 0 to 1, with 1 representing a 100% probability of an event occurring and 0 representing a 0% probability. The example above presents two possible events, one of which must occur—cancer diagnosis or no diagnosis. If the chance of being diagnosed with cancer were 10%, it would be assigned a value

of .10. Since one of the two events must occur, the chance of not being diagnosed with cancer would be assigned a value of .90.

A random draw in the range of 0 to 1 would then determine which event would occur during the simulation. In the example above, a random number from 0 to .10 would imply a cancer diagnosis. Values greater than .10 would imply no diagnosis. This process repeats at each node in the model to determine the simulated individuals' courses of action across the continuum of care defined by the simulation decision tree.

As individuals travel through a number of model cycles, they accumulate outcomes associated with various events. For example, costs may cumulate to create a total cost of medical care associated with repeated FOBTs. In addition, models that are more complicated may assign simulated individuals tracker variables following specific events. These tracker variables are helpful when attempting to identify the instance of certain events or incorporate history into the model. For example, a tracker variable may increase in value by one each time an individual undergoes screening in order to determine the average number of times all individuals screen.

By appropriately defining the length of time covered by each model cycle, and the number of cycles that an individual must travel through, it is possible to model a variety of real world situations. Simulating a number of individuals allows one to build up a distribution of cumulative outcomes across a population. This allows one to make statistical statements about the situation modelled.

2.1 Modelling mechanics

As mentioned, the current study applies the Markov modelling approach above to four different disease processes. Recall that these include:

- colorectal cancer
- cervical cancer
- breast cancer
- diabetes

To assess cost-effectiveness, the models attempt to estimate the potential cost avoidance associated with primary care alignment to evidence-based screening guidelines and chronic disease management associated with the PIN indicators for the disease processes above—at various rates in the population. For example, the colorectal cancer model examines average individual cancer-related medical costs when different proportions of the population undergo consistent two-year FOBT screening. By examining how these average costs change as the percentage of the population undergoing screening changes, it is possible to assess the potential cost avoidance from adopting this screening approach.

The indicators associated with each of the disease processes above are as follows.

Table 1: Cost-effectiveness results example

Disease process	Associated indicator(s)	Measure
Cervical cancer	Cervical cancer screening (PAP testing)	- Percentage of female core patients 18 to 69 years of age without PAP exemptions (hysterectomy, not sexually active) who have had a PAP test in the past 36 months
Colorectal cancer	Colon cancer screening (FOBT and colonoscopy)	- Percentage of core patients 50 to 74 years of age who have had a FOBT in the past 24 months or colonoscopy in the last 10 years
Breast cancer	Breast cancer screening (mammography testing)	- Percentage of female core patients 50 to 69 years of age without mammography exemptions (e.g., radical mastectomy) who have had a mammography test within the past 24 months
Diabetes	HGB A1C	- Percentage of core patients with diabetes who have had the HGB A1C test in the past 12 months
	Nephropathy screening	- Percentage of core patients with diabetes who have had nephropathy screening in the past 12 months
	Fundoscopic exams	- Percentage of core patients 15 years of age and over with diabetes who have had a fundoscopic exam or a referral for a fundoscopic exam within the last 12 months
	Foot exams	- Percentage of core patients 18 years of age and over with diabetes who have had a foot exam in the past 12 months or with documented peripheral neuropathy
	Full fasting lipid profile screening	- Percentage of core patients 18 to 74 years of age with diabetes who have had a full fasting lipid test in the past 12 months
	Blood pressure testing	- Percentage of core patients 18 years of age and over with diabetes who have had a blood pressure measurement taken in the past 12 months
	Obesity/overweight screening	- Percentage of core patients 18 years of age and over with diabetes who have received an obesity/overweight screening in the past 12 months

* Note: The diabetes model in this study models diabetic control and not these management processes specifically.

Due to differences in the nature of the four disease processes, it is possible to identify two generic variations in the model structure. The three cancer models all share a similar state-based model structure. For all three cancers, the CIHI primary care guidelines call for explicit screening procedures leading to the classification of cancers into stages, followed by treatment and surveillance testing. The models include these steps as separate events with associated probabilities of specific outcome and costs, after which individuals transition into a number of fixed states. For example, someone may be either screened or not. If screened, they may be cancer-free or classified into one of five cancer stages. After their treatment is complete, they would transition into a post-treatment surveillance state. This was possible in the models largely because these events and states are limited and mutually exclusive in a given cycle.

Diabetes management is quite a different process and is associated with a number of potentially co-occurring microvascular and macrovascular events. Their potentially co-occurring nature means that these are not mutually exclusive in a given cycle. Modelling every possible combination to make each state mutually exclusive would result in a tree diagram that is too complex to operate as a functional model. Thus, the diabetes model adopted an acute event approach to modelling.

Under this approach, there are only three states explicitly defined—a controlled diabetic state, an uncontrolled diabetic state, and death. All potentially co-occurring disorders were included in the model as events representing either an acute complication or the progression of a disorder. For example, the model included the possibility of stroke and retinopathy progression in each cycle. The probabilities and costs associated with these events depend on both the simulated individual's state at the start of the cycle and their history of events in past cycles. For example, the probability of a stroke would increase if a simulated individual had a stroke in the past. Similarly, costs and probabilities would change with each disorder progression event.

The controlled and uncontrolled diabetic states used in the modelling were defined based on three underlying risk factors identified by a set of test results. These tests were associated with a subset of the diabetes-related PIN indicators and examined haemoglobin A1C levels, systolic blood pressure levels, and total cholesterol / high-density lipoprotein ratios. Both states were defined by fixed levels of each, with the uncontrolled state being associated with worse results for all three. Although it would have been preferable to have each of these test results vary freely during the simulation, the nature of the model meant that this was not possible. Given this limitation, the controlled and uncontrolled states were defined to most accurately reflect the distribution of diabetic patients in Manitoba, within the limitations of the data available for the analysis.

To do so, the analysis operated under the expert advice that a haemoglobin A1C level of 8.0 represented a reasonable breakpoint, separating diabetics of higher and lower risk of associated complications. A distribution of haemoglobin A1C test results from a major lab in Manitoba were examined, averaging above and below 8.0 to define haemoglobin A1C levels for the model's controlled and uncontrolled states. The newly defined controlled and uncontrolled haemoglobin A1C levels were compared to target values in the Manitoba Diabetes Treatment Guidelines and conventional levels as defined in the literature.

This comparison provided percentage differences between the controlled and uncontrolled levels and those in the guidelines and the literature. The percentage differences were then used to prorate the conventional and target systolic blood pressure levels and the total cholesterol / high-density lipoprotein ratios from the diabetes guidelines and literature to similarly controlled and uncontrolled points. These, along with the controlled and uncontrolled haemoglobin A1C levels, then defined the controlled and uncontrolled states in the models. As noted above, these states helped determine aspects of the diabetes model's functionality. Additional details regarding this calculation process are provided in the sections that follow and in the accompanying appendices.

2.2 Modelling principles

The cancer and diabetes models examine two distinct hypotheses about primary care activities. All three cancer models attempt to explore the premise that increased screening activities can lead to cost avoidance for Manitoba Health. This idea rests on the notion that if individuals are regularly screened, cancers will be detected at earlier stages than cancers diagnosed after individuals develop symptoms and present to their doctors. The critical assumption under screening is that all else being equal, earlier stages of cancer are generally the easiest and least costly to treat. Thus, identifying cancers sooner rather than later saves treatment costs.

However, increasing screening in Manitoba has at least two cost implications that complicate the apparently straightforward logic suggested above. First, increased screening is not free, and these additional costs may undermine the avoided costs from early diagnosis and treatment. This is particularly true for low incidence cancers and when screening targets much of the population. Second, increased screening may identify greater numbers of cancer patients in the population. The additional cost of treating these individuals may undermine the avoided costs noted above. The cancer models developed in this study attempt to identify under what circumstances potential avoided costs outweigh potential additional costs, and the extent to which these reflect what is expected with alignment to evidence-based screening practices in Manitoba's PIN.

The diabetes model, by contrast, attempts to identify the cost avoidance from moving individuals in the Manitoba population from a state of uncontrolled diabetes to one of controlled diabetes. Given that complications—both microvascular and macrovascular—are more common among those who do not have diabetic control, moving a greater percentage of individuals into a controlled state will reduce the amount of costly medical interventions required as a result of these complications. At the same time, it is possible that individuals under diabetic control, with fewer complications yet living longer, will incur ongoing costs throughout their lifetime that outweigh the avoided costs from a reduction in their number of complications.

Additionally, the diabetes-related testing indicated by PIN indicators is associated with additional costs of implementation and increased ongoing testing costs. Unfortunately, at this point, there is little information to accurately calculate these costs or suggest the extent to which these PIN activities of testing an array of clinical indicators may affect diabetic control positively in the Manitoba population in isolation of population and community-based education initiatives and individual access to diabetes care management and resources. As such, the diabetes modelling in this study presents possible cost avoidance, which, provided PIN evidence-based testing activities are proven effective at increasing diabetic control among the Manitoba population, may offset the costs of implementation and ongoing operation. In addition, the diabetes modelling undertaken as part of this study does not examine the concept of a pre-diabetic state, the idea of maintaining individuals in this state, or the possible avoided costs associated with this type of activity.

2.3 Interpreting results

Each of the cancer models developed as part of this study is associated with four types of results as follows:

- Inner loop results
- Cost distribution results
- Cancer stage distribution results
- Cost-effectiveness results

The *inner loop results* are presented to help readers understand the overall simulation process for each cancer model. They show individual costs from the progress of a set number of Manitobans through the model, over a specific time, following the current screening practice typical in Manitoba. As the discussion below will indicate, the models use an annual cycle. Each year, some individuals are screened, diagnosed, and treated. Others may never screen but will perhaps present with cancer symptoms eventually leading to a diagnosis. Many individuals may pass through all simulation years without being diagnosed and only accumulate costs from screening. Others may never screen, yet will remain symptom free throughout the simulation, thereby incurring no costs at all.

The range of patterns discussed above will produce a variety of individual costs. The inner loop results include the mean, minimum, maximum, standard deviation, and quartile values for these costs. These help readers understand the distribution of individual costs calculated by the models. For example, a mean value of $450.00 would suggest that cancer screening, follow-up testing, and treatment under this scenario cost, on average, $450.00 per simulated individual over the entire simulation period.[3]

The *cost distribution results* supplement the inner loop results by providing a more detailed representation of costs. Histograms present the distribution of these costs for the overall simulated sample and two additional subgroups. These subgroups include those who were diagnosed with cancer and those who were not. This helps readers understand the difference in costs between these two groups.

The *cancer stage distribution results* include the percentage of individuals from the preliminary simulation scenario that are diagnosed with each stage of cancer. These results are compared with current cancer diagnosis rates from Manitoba to ensure that the models have reasonable face validity. While one would not expect these two sets of figures to align perfectly, particularly given the length of the simulations and the treatment of recurrent cancers in the models, some similarity is expected. If these two sets of values do not align, there are likely some features of the models that do not fully capture the provincial situation.

The *cost-effectiveness results* include two main tables. These compare the costs resulting from simulations of the full implementation of PIN evidence-based screening practice among the targeted Manitoba population to counterfactual screening situations.[4] In one case, PIN screening is compared to a situation where no Manitobans undergo regular screening. In a second case, PIN screening practice is compared to a situation where individuals screen at a rate currently

[3] All simulations discount costs at five percent per simulation year. Thus, all results are in present value.
[4] Appendix C includes corresponding results from the scaled implementation of CIHI screening.

prevalent in the province. The tables then present the difference between the per-individual cost under each scenario and the total additional cost or avoided cost from full alignment to PIN evidence-based screening practice, based on the number of individuals used in the simulation.

Using a series of hypothetical costs calculated from a 25-year simulation, this tabular presentation would appear as follows.

Table 2: Cost-effectiveness results example

Description	Cost per individual
No cancer screening simulation over 25 years	$400.00
Full PIN screening simulation over 25 years	$450.00
Difference	$50.00
Count of simulated individuals	**Total estimated additional or avoided costs**
Simulation of 160,000 individuals	$8,000,000 additional cost

Here, the first simulation where no individuals screen for cancer produces an average cost of $400.00 per individual. With the full alignment to PIN evidence-based screening practice simulation producing an average cost of $450.00 per individual, this would imply a cost of $50.00 per individual to move from no screening to the PIN screening approach. With 160,000 individuals under either simulation scenario, this would imply a total additional cost of $8,000,000 over a 25-year period.

Here, it is important to emphasize that these represent average costs among all simulated individuals and total costs calculated based on these averages. As the discussion above suggests, certain simulated individuals will incur considerable costs as a result of not screening and being diagnosed with a late stage cancer. As with their real world counterparts, these individuals could have avoided many treatment costs by undergoing regular cancer screening. However, this study does not attempt to identify the most advantageous results from screening among the Manitoba population. Rather, it explores the aggregate effect of evidence-based primary care in the province as a whole, making these average and total figures the most relevant to the analysis.

Since there remains some uncertainty about the costs associated with various aspects of the cancer models, the cost-effectiveness tables present the comparisons above assuming two additional cost structures. This cost sensitivity analysis is important to the full understanding of the cost-effectiveness of evidence-based primary care. The first additional structure uses more exhaustive cost figures for cancer treatment, based on estimates found in other jurisdictions. Since many of these jurisdictions are in the United States (US), costs will include additional items and mark-ups—due, for example, to the profit margins implicitly embedded in all US costs—making it likely that these exceed the total costs typical in Manitoba.[5] The results are included to suggest an upper bound on possible cost avoidance in Manitoba, were all local costs taken into consideration. If, under this cost structure, the full alignment to PIN screening procedures does not result in cost avoidance relative to the other scenarios, there is little to support the cost-effectiveness of the PIN screening guidelines if fully implemented across primary care practitioners in Manitoba.

[5] Appendix D includes a full listing of the items explicitly included in these larger treatments costs.

In situations where this inflated cost structure suggests cost avoidance as a result of primary care practice alignment to PIN screening for breast, colorectal, and cervical cancer, a final cost structure is examined. This structure is developed by calculating the difference between the initially identified treatment costs and those of the inflated cost structure. These differences are then adjusted proportionally until a switch-point is found where there is no discernable cost difference between primary care practice alignment to PIN screening and the counterfactual screening approaches. The scaling for each situation will be a percentage of the calculated difference between 0% and 100%. Thus, a 50% scaling would represent costs of cancer treatment 50% of the way between the initially identified costs and those of the larger costs estimates from other jurisdictions.

Since the exact costs of cancer treatment in Manitoba are not well understood in the current study, the switch-point serves an important purpose. It suggests the degree of confidence with which one can assert that PIN screening will result in cost avoidance in Manitoba. For example, a switch-point at 25% would suggest that the addition of only a few further treatment costs to the initial study estimates would result in avoided cost from PIN screening—something quite plausible in the context of the work. By contrast, a switch-point at 95% would suggest that cost avoidance in Manitoba is far less likely, given the amount of increased treatment cost required to produce this type of result.

Readers should note that average cost per individual figures reported in the cost-effectiveness tables are the result of an *outer loop* simulation process. Since there is a considerable range of possible costs in each model, the variance associated with the estimated average cost per individual from any single simulation is quite high. To produce average cost figures with smaller variances, each simulation scenario is repeated a number of times. The average cost values from these repeated simulations are collected to form a distribution of averages. The average of these averages is then reported in the cost-effectiveness tables. This outer loop simulation process has the advantage of smoothing out any outlier simulation results.[6]

The presentation of the diabetes results follows those of the cancer models as closely as possible. Inner loop results use a scenario where there is a 70% chance of diabetic control among a simulated Manitoba population. This 70% chance is based on the percentage of the lab test result population discussed above that fell below a haemoglobin A1C level of 8.0. A histogram of individual costs from this simulation is then included in the results. Although the results section does not include the prevalence of each co-occurring disorder, the cost-effectiveness section does compare the results from the preliminary simulation scenario to one where all individuals are under diabetic control. This comparison suggests the cost avoidance—in terms of the treatment of diabetic complications—possible, if all diabetic individuals in the province could be moved to this controlled state.

[6] This is analogous to the use of bootstrapping or re-sampling in statistical estimation.

3.0 Modelling and results

The following four subsections present each of the CEA models, along with their associated results. Each subsection introduces its associated tree diagram structure, the data upon which its transition probabilities and costs are based, as well as any assumptions required in the models. The results present cost-effectiveness results under a number of modelling scenarios.

3.1 Breast cancer

The breast cancer model has many similar characteristics to the cervical and colorectal cancer models. Each cancer model follows the same basic format: individuals begin in a healthy or non-cancer state and then transition through the various sub-trees based on probabilities. Over many cycles—defined as one year in the models—they will transition to various other health states and incur different kinds of medical costs. This section covers each sub-tree of the breast cancer model in detail.

Figure 4 presents the "sorting" sub-tree of the breast cancer model. This sub-tree only functions during the first cycle of the Monte Carlo simulations. It separates individuals into PIN and non-PIN screening groups based on a fixed probability at model node 1 below. Altering the probability at this first node allows one to change the percentage of the simulated population in either group, and test the effects of different rates of related PIN primary care activities in the population.

Once assigned to a group, simulated individuals are assigned a tracker variable that governs their subsequent screening activity. ***PIN screeners*** are aligned to a primary care practice that adheres strictly to the PIN indicator screening guidelines during subsequent model cycles. In the case of breast cancer, this will involve mammography testing once every two years. ***Non-PIN screeners*** are aligned to a primary care practice that undergoes screening with a different frequency, with the analysis exploring two alternatives.

However, prior to sorting individuals into PIN and non-PIN screening groups, the sub-tree identifies a small proportion of PIN screeners (5%) who are at a high risk of breast cancer due to family history or genetic predisposition, and assigns a different tracker to the members of this group. As per the guidelines of the Manitoba Breast Screening Program (MBSP), these high-risk individuals will screen every year during the simulation (CancerCare Manitoba, 2010a, p. 15).

The model assumes that an individual will be either a PIN screener or a non-PIN screener for the entire simulation. It does not allow individuals to switch between the two types of screening behaviour. It is also important to note that this sub-tree is merely the sorting stage of the model and does not actually represent a full year. Therefore, the patients do not age and there is no chance of death during the sorting cycle.

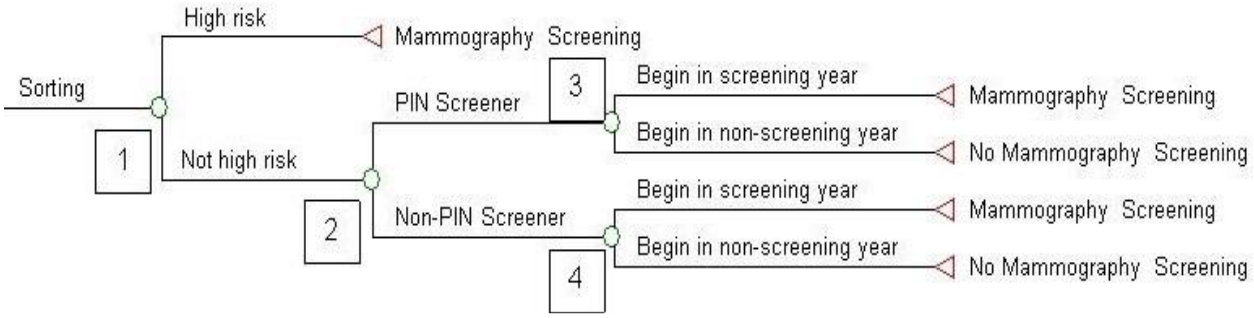

Figure 4: Breast cancer PIN screener sorting sub-tree

After sorting the groups, the model transfers each person to another state in the model, governed by the probabilities shown in Table 3.

Table 3: Transition probabilities and costs for breast cancer: "PIN screener sorting" sub-tree

Node # or Cost	Description	Estimate	Source
Transition probabilities			
1	Whether the individual is at a high risk of breast cancer	High risk: 0.05 Not high risk: 0.95	CancerCare Manitoba (2010a), p. 15
2	Whether the person is a PIN screener or a non-PIN screener	Variable	One can vary the proportion of PIN screeners to observe differences in cost-effectiveness.
3	Whether the PIN screener begins the first cycle by screening or not screening	Begin by screening: 0.500 Begin by not screening: 0.500	Assumption: for simplicity, the model assumes that in the starting year, half of the PIN screeners are in their screening year, and half of them are not.
4	Whether the non-PIN screener begins the first cycle by screening or not screening	Begin by screening: 0.500 Begin by not screening: 0.500	Assumption: for simplicity, the model assumes that in the starting year, half of the non-PIN screeners are in their screening year, and half of them are not. If one wishes to define non-PIN screeners as those who never screen, then all of the non-PIN screeners go to the non-screening branch instead.
Costs			
N/A	N/A	N/A	N/A

Figure 5 presents the "No Mammography Screening" sub-tree of the breast cancer model. In this sub-tree, individuals do not undergo a screening test, but may still develop symptomatic cancer and receive a diagnosis of cancer stages 1 through 4. Based on advice from medical consultants, stage 0 cancers are unlikely to be symptomatic, so the model assumes that symptoms only occur for stages 1 through 4.

If an individual does not develop cancer, they will either screen or not screen next cycle. A "logic node" denoted with an "L" below is a specific form of chance node and governs this transition. Logic nodes function by checking whether certain conditions exist, and then transferring individuals to different branches based on those conditions. This logic node checks whether an individual is a PIN screener by using the PIN screener tracker they were assigned at the beginning of the simulation. If they are a PIN screener, then this individual is one who screens every two years, so the logic node directs them to screen the following year as per the PIN guidelines. If the logic node determines that they are a non-PIN screener, then it directs them to either screen or not screen in the following year, as governed by other probabilities. For example, if attempting to compare PIN screening to no screening whatsoever, then "non-PIN" individuals always have no probability of screening in the next cycle. If one is comparing PIN screening to another type of screening behaviour (such as current screening trends), then "non-PIN" represents this behaviour and follows the probabilities listed in Table 4.

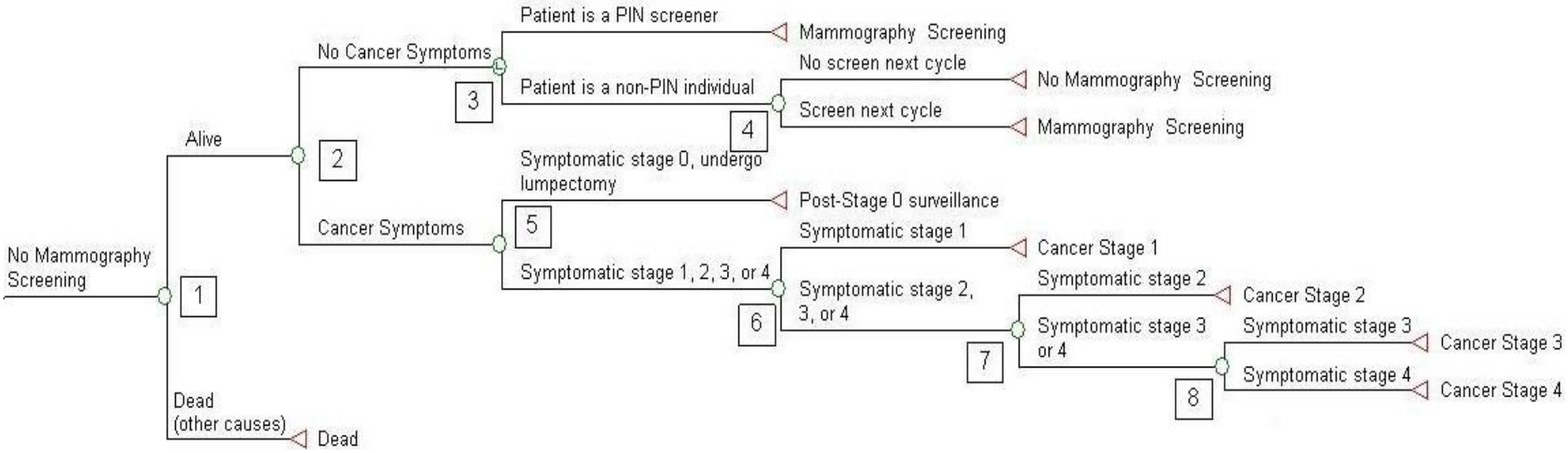

Figure 5: No Mammography Screening sub-tree

Table 4: Transition probabilities and costs for breast cancer: "No Mammography Screening" sub-tree			
Node # or Cost	**Description**	**Estimate**	**Source**
Transition probabilities			
1	Whether the individual survives or dies from any cause other than breast cancer	Age-dependent	Statistics Canada (2010a) contains age-dependent mortality data. The model calculates the age of each person and assigns them the appropriate chance of mortality.
2	Chances of developing cancer symptoms: based on 1) 800 new cases of breast cancer predicted per year by the Canadian Cancer Society; and 2) the fraction of these individuals who will be identified without screening, based on the participation rates in the MBSP	0.00510	CancerCare Manitoba (2010a), p. 11; Canadian Cancer Society (2010a); Manitoba Health (2009a), p. 11 The result was calculated by dividing the expected number of symptomatic (non-screening) cancer cases by the proportion of the female population aged 50–74 that are not expected to undergo a mammography test.
3	Logic node: whether patient is a PIN screener	Dependent on initial PIN screener probabilities	Using the tracker variables, the logic node divides those who are PIN screeners from those who are not and directs them to the appropriate branch.
4	Given that the patient is a non-PIN screener, the chances that they will screen next year	If the non-PIN screeners never screen, then the probability is zero. If the non-PIN screeners follow current screening trends, then: Screen 24 months after last screen: 0.383 Screen 36 months after last screen: 0.667 Screen >36 months after last screen: 0.500	CancerCare Manitoba (2010a), p. 13: for up to 36 months No data available for further than 36 months from last screening, so the model assumes a probability of 0.500 until the patient screens again
5	Given that the patient has cancer symptoms, the likelihood of stage 0 versus all other stages	0.000	Assumption from the medical experts: stage 0 cancers are asymptomatic
6	Given that the patient has cancer symptoms of a stage between 1 and 4, the likelihood of it being stage 1 cancer	0.145	Heitman et al. (2010), p. 4 (symptomatic stage breakdown for colorectal cancer used as a proxy for breast cancer due to lack of breast cancer data)
7	Given that the patient has cancer symptoms of a stage between 2 and 4, the likelihood of it being stage 2 cancer	0.4164	Heitman et al. (2010), p. 4
8	The likelihood of stage 3 or 4 cancer	Stage 3: 0.561 Stage 4: 0.439	Heitman et al. (2010), p. 4
Costs			
N/A	N/A	N/A	N/A

Figure 6 presents the "Mammography Screening" sub-tree of the model. In this sub-tree, patients undergo a mammography test and can experience a number of different results. A positive (abnormal) mammography test will lead the patient to undergo a series of follow-up diagnostic tests, including a diagnostic mammography test, clinical breast exam, biopsy, and a surgical consultation. The model assumes that the patient will always comply with the follow-up tests due to the amount of media attention surrounding breast cancer issues, and a heightened awareness of the risks of the disease. The follow-up tests can either reveal a false positive (benign finding) or a cancer diagnosis. If a patient is diagnosed with cancer, they transition to a cancer state. The exception is stage 0 cancer, which can be treated with a lumpectomy within a short time period. This allows the patients to transition directly to a post-treatment surveillance state.

Most of the mammography tests will be negative (normal). In reality, there would be an incidence of false negative tests—particularly for less advanced cancers. These individuals would presumably receive a cancer diagnosis at a later date based on symptoms or another mammography test. However, this process is not compatible with the modelling approach. Patients would only screen in this branch if they were asymptomatic. Whether the individual begins the cycle without cancer, or with an asymptomatic cancer, it is unlikely that they will develop cancer symptoms within the same year. In other words, the only chance they have at identifying a cancer during the cycle is through the screening and follow-up tests. The model does not allow for them to have a second chance in the same year to identify cancer through symptoms. Therefore, with this modelling approach, a person with a false negative test would be unaware that they have cancer, and would face the same screening decision for the next cycle, as would a cancer-free individual.

When a patient completes their screening and there is no detectable cancer present, they must decide whether to screen the following year. A logic node once again determines their behaviour. If a patient was identified as high-risk at the beginning of the simulation, then the logic node will direct them to screen every year. If they are a regular PIN screener, they will only screen once every two years, so they will not screen the following cycle. If they are a non-PIN screener, their screening behaviour is governed by other probabilities.

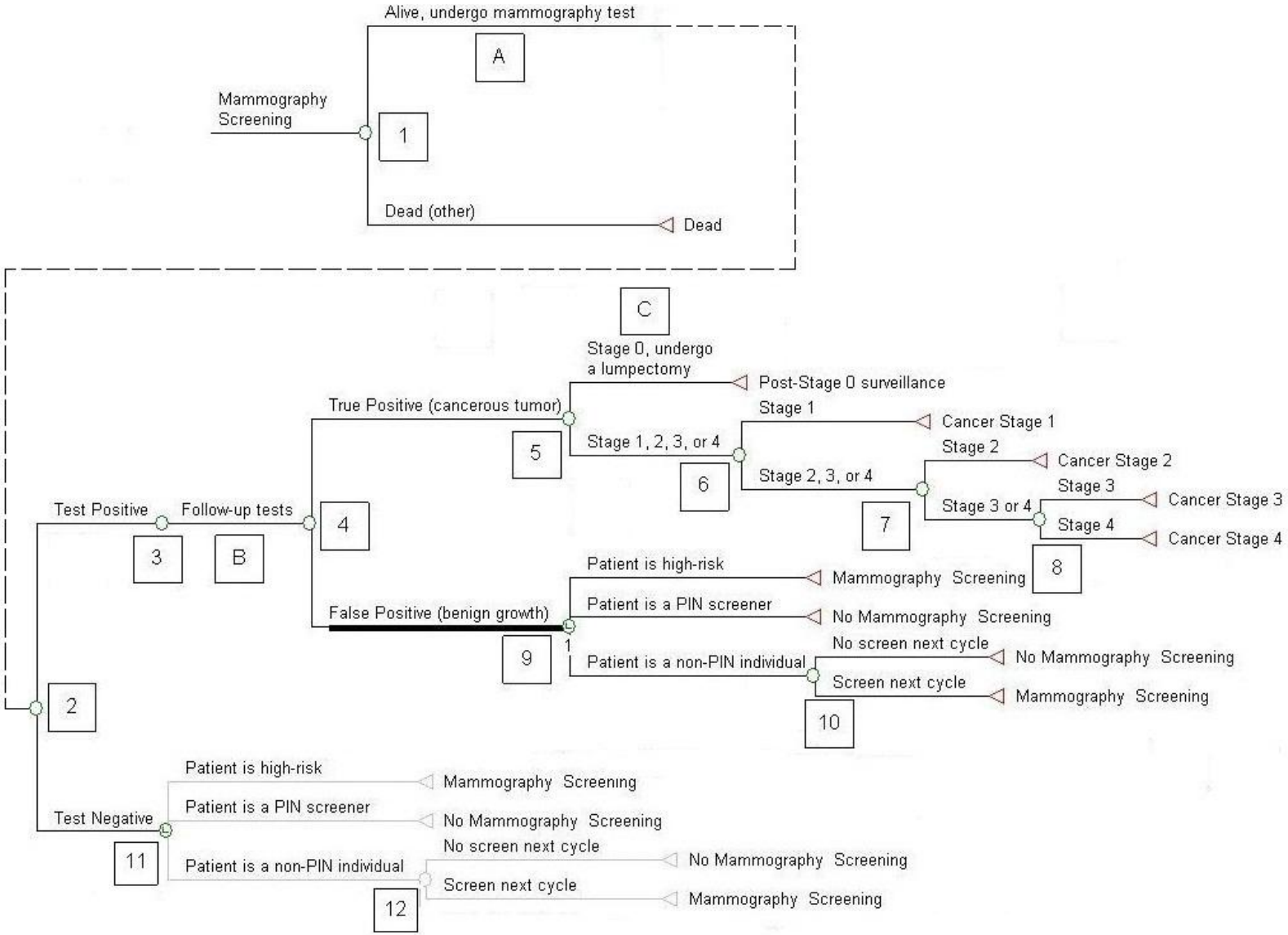

Figure 6: Mammography Screening sub-tree

Table 5 lists the probabilities and costs associated with this sub-tree.

Table 5: Transition probabilities and costs for breast cancer: "Mammography Screening" sub-tree

Node # or Cost	Description	Estimate	Source
Transition probabilities			
1	Whether the individual survives or dies from any cause other than breast cancer	Age-dependent	Statistics Canada (2010a) contains age-dependent mortality data. The model calculates the age of each person and assigns them the appropriate chance of mortality.
2	Positive (abnormal) or negative (normal) mammography test	Abnormal mammography: 0.04962	CancerCare Manitoba (2010a), p. 22
3	Chance of follow-up test compliance, given a positive mammography test	1.00	Assumption from medical experts: According to the experts, there is a great deal of medical attention on breast cancer. The public has a heightened awareness of the risks of the disease, so the model assumes they will always comply with the follow-up tests.
4	True positive or false positive (whether the follow-up tests confirm cancer is present)	False positive (benign growth): 0.888	CancerCare Manitoba (2010a), p. 22
5	Given that the patient has cancer between stages 0 to 4, the likelihood of stage 0 cancer	0.187	CancerCare Manitoba (2010a), p. 22
6	Given that the patient has cancer between stages 1 to 4, the likelihood of stage 1 cancer	0.640	CancerCare Manitoba (2010a), p. 22
7	Given that the patient has cancer between stages 2 to 4, the likelihood of stage 2 cancer	0.861	CancerCare Manitoba (2010a), p. 22
8	The chances of stage 3 or 4 cancer	Stage 3: 0.600 Stage 4: 0.400	CancerCare Manitoba (2010a), p. 22
9, 11	Logic node: this determines whether the patient is high-risk, a PIN screener, or a non-PIN screener	Variable	Determined through initial probabilities
10, 12	Given that the patient is a non-PIN screener, the likelihood of screening the following cycle	0.063	CancerCare Manitoba (2010a), p. 13
Costs			
A	Mammography test	$27 (professional fee)	Manitoba Health (2010a), p. T-12
B	Follow-up tests after an abnormal mammography (diagnostic mammography test, biopsy, and surgical consultation)	$96	CancerCare Manitoba (2010a), p. 18; Manitoba Health (2010a), p. T-1, T-11, T-22
C	Stage 0 treatment (lumpectomy)	$280	Manitoba Health (2010a), p. E-3

Figure 7 depicts the cancer states in the breast cancer model. Although the figure consists of only one sub-tree, each stage of cancer from 1 to 4 has its own sub-tree in the actual model. Stage 0 does not have a cancer state, since the treatment (a lumpectomy) takes a short amount of time after diagnosis, so the patient can undergo the procedure and then transition to post-treatment surveillance. When patients receive a cancer diagnosis of stage 1 to 4, they transition to the respective cancer state and the model assumes it takes no more than one year for them to complete their treatment. They undergo treatment for their type of cancer and then either survive and transition to post-treatment surveillance; die of cancer, after unsuccessful treatment; or die of other causes.

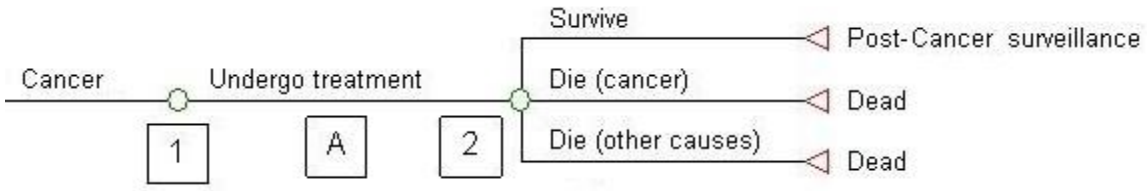

Figure 7: Breast cancer sub-tree

Table 6 lists the associated probabilities and costs.

Table 6: Transition probabilities and costs for breast cancer: "Cancer" sub-trees

Node # or Cost	Description	Estimate	Source
Transition probabilities			
1	Patient with cancer undergoes treatment	1.00	Assumption
2	Whether the patient survives treatment, dies of cancer, or dies of other causes	Survives: dependent on the probabilities below	The probability of survival is what is left over after subtracting the probabilities of dying from cancer and dying from other causes
		Death from cancer (within 1 year of diagnosis): Stage 1: 0.005 Stage 2: 0.042 Stage 3: 0.170 Stage 4: 0.557	http://www.cancerresearchuk.org/
		Death from other causes: age-dependent	Statistics Canada (2010a)
Costs			
A	Cost of treating stage 1: Partial mastectomy and axillary node dissection, simple radiation treatment (1 course), single agent chemotherapy (1 course), sentinel lymph node biopsy	Stage 1: $1,913	Manitoba Health (2010a), pp. A-50, B-22, B-23, E-3, I-1
	Cost of treating stage 2: Partial mastectomy and axillary node dissection, intermediate radiation treatment (2 courses), chemotherapy (2 courses), sentinel lymph node biopsy	Stage 2: $2,568	Manitoba Health (2010a), pp. A-50, B-22, B-23, E-3, I-1
	Cost of treating stage 3: modified radical mastectomy, complex radiation treatment (3 courses), chemotherapy (3 courses), sentinel lymph node biopsy	Stage 3: $4,027	Manitoba Health (2010a), pp. A-51, B-22, B-23, E-3, I-1
	Cost of treating stage 4: modified radical mastectomy, extensive radiation treatment (4 courses), extensive chemo (4 courses), sentinel lymph node biopsy	Stage 4: $5,413	Manitoba Health (2010a), pp. A-51, B-22, B-23, E-3, I-1

Figure 8 presents the post-treatment surveillance state. Each type of cancer has its own surveillance state, including stage 0 cancer. The model assumes that after their cancer treatments, patients spend five years in the surveillance state. In this state, patients undergo surveillance tests involving diagnostic mammography tests and clinical breast exams. Each year they may die from complications of cancer, based on cancer mortality statistics. They may also experience a recurrence of cancer. If this occurs, it means that the cancer has come back and spread to other parts of the body, so it is defined as a stage 4 cancer.

If the patients survive for five years, they transition back to the mammography screening state, but due to the fact that they are cancer survivors, the model assigns them a high-risk tracker so that they will screen every year.

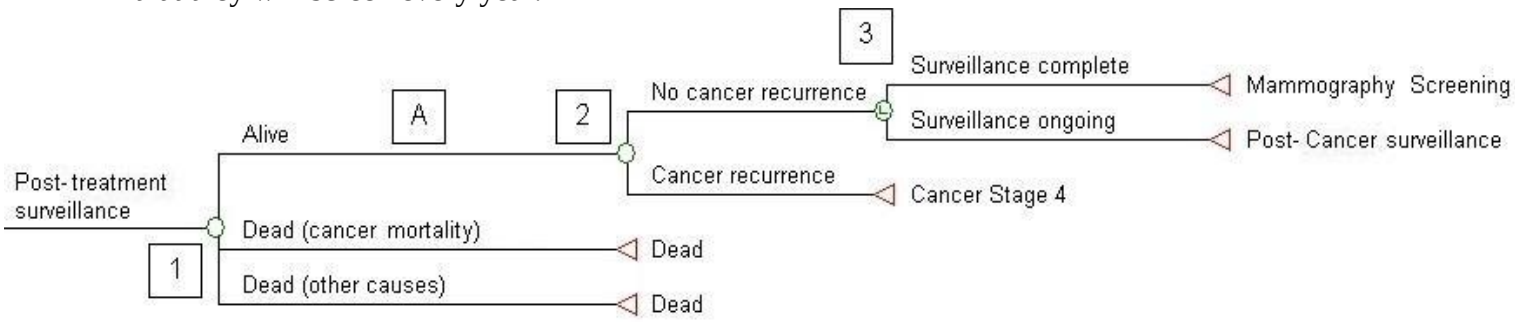

Figure 8: Breast cancer post-treatment surveillance sub-tree

Table 7 lists the associated probabilities and costs.

Table 7: Transition probabilities and costs for breast cancer: "Post-treatment surveillance" sub-tree

Node # or Cost	Description	Estimate	Source
Transition probabilities			
1	Whether the patient survives, dies from cancer, or dies from other causes	Survives: dependent on the probabilities below	The probability of survival is what is left over after subtracting the probabilities of dying from cancer and dying from other causes.
		Cancer death (listed as the expected proportion of mortality after 5 years): Stage 0: 0.000 Stage 1: 0.081 Stage 2: 0.271 Stage 3: 0.497 Stage 4: 0.870	http://www.cancerresearchuk.org/
		Death from other causes: age-dependent	Statistics Canada (2010a)
2	Likelihood of a cancer recurrence	Chance of recurrence per year: Stage 0: 0.002 Stage 1: 0.002 Stage 2: 0.020 Stage 3: 0.040 Stage 4: 0.060	Assumption from medical experts
3	Whether the patient completes their post-treatment surveillance	5 years	After five years, the patient completes their surveillance and transitions to mammography screening.
Costs			
A	Post-treatment surveillance cost (diagnostic mammography once a year and clinical breast exam twice a year)	$212	Manitoba Health (2010a), pp. A-1, T-11

3.1.1 Results

As noted above, the cost-effective analysis in this study is performed using Monte Carlo simulation. As per the relevant PIN indicator, the simulation contains women in Manitoba between the ages of 50 and 69 in 2010, totalling 143,400 individuals (Statistics Canada, 2010c, p. 188). The distribution of the ages is based on the ages of the screeners provided in CancerCare Manitoba's (2010a) biennial report on the MBSP (p. 12). Note that while the PIN indicator for breast cancer suggests that women between the ages of 50 and 69 be screened, the MBSP recently began inviting women up to age 74.

Table 8 presents the results of an inner loop simulation with 143,400 individuals in the breast cancer model. In this simulation, the entire cohort followed an approximation of current screening trends, based on CancerCare Manitoba's (2010a) biennial report on the MBSP (p. 13).

Table 8: Breast cancer inner loop results

Statistic	Value
Mean cost per individual	$2,080
Standard deviation	$6,252
Minimum cost	$0
First quartile	$131
Second quartile (median)	$165
Third quartile	$223
Maximum cost	$118,027

The simulation provides some insight into the possible outcomes of the model. For example, the minimum cost of $0 would represent an individual who never screened and never developed breast cancer. The relatively low costs in the first, second, and third quartiles show that many cost observations will be low, since only a fraction of the individuals in the model actually developed breast cancer. On the other hand, the maximum cost of $118,027 likely represents an individual who developed cancer, underwent expensive treatment, and then experienced a recurrence, leading to more treatment.

Below are three histograms that depict the outcomes of the simulation above. Figure 9 shows the cost distribution of everyone in the model. The vast majority of observations fall under $500, so the higher costs can barely be seen on the diagram. Figure 10 shows the cost distribution for individuals who developed breast cancer, where most of the costs fall under $50,000, but a few very high costs lie along a "tail" to the right. Figure 11 depicts the distribution for people without cancer, where the costs are substantially lower, because they only include screening costs.

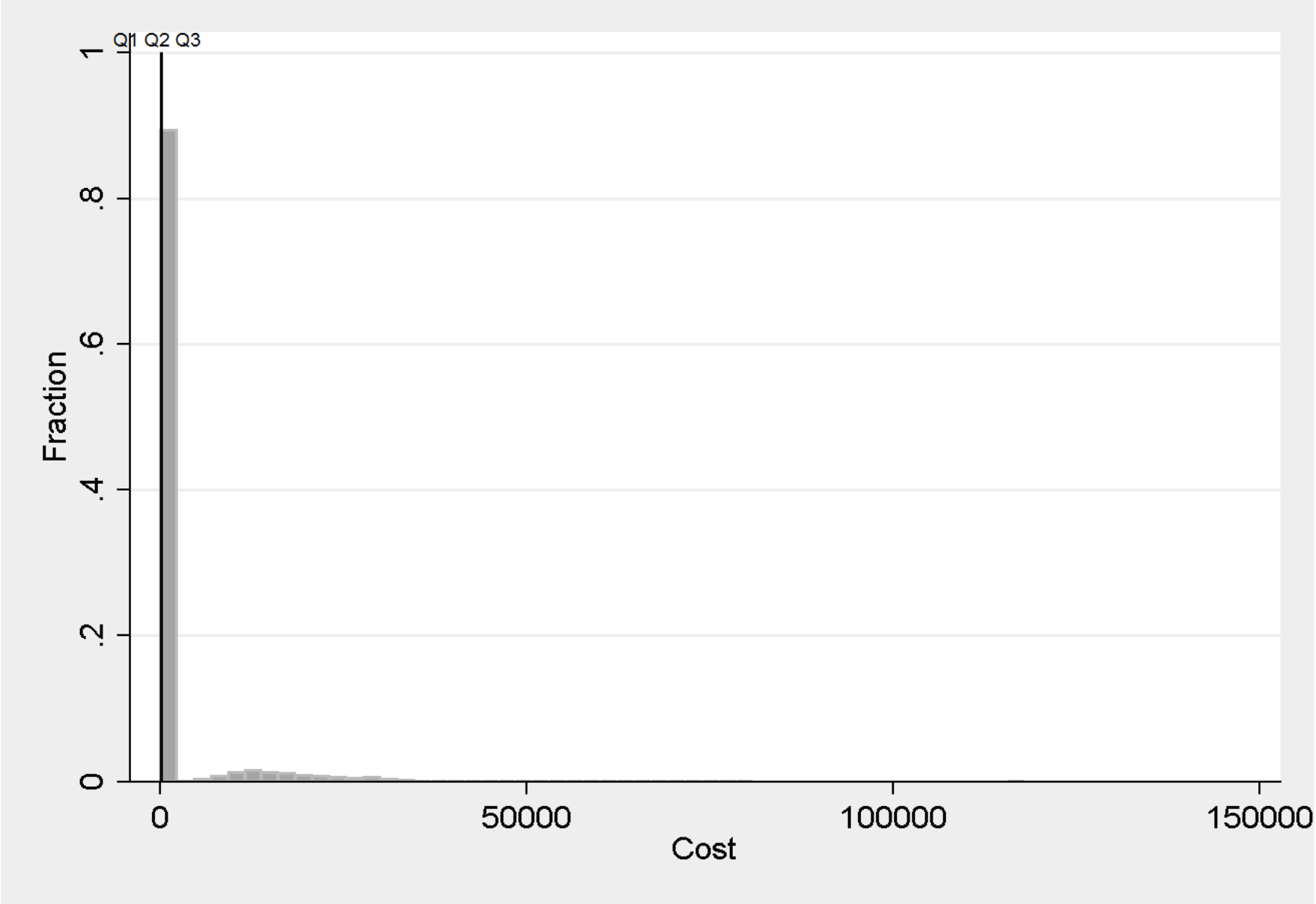

Figure 9: Breast cancer cost distribution, aggregate

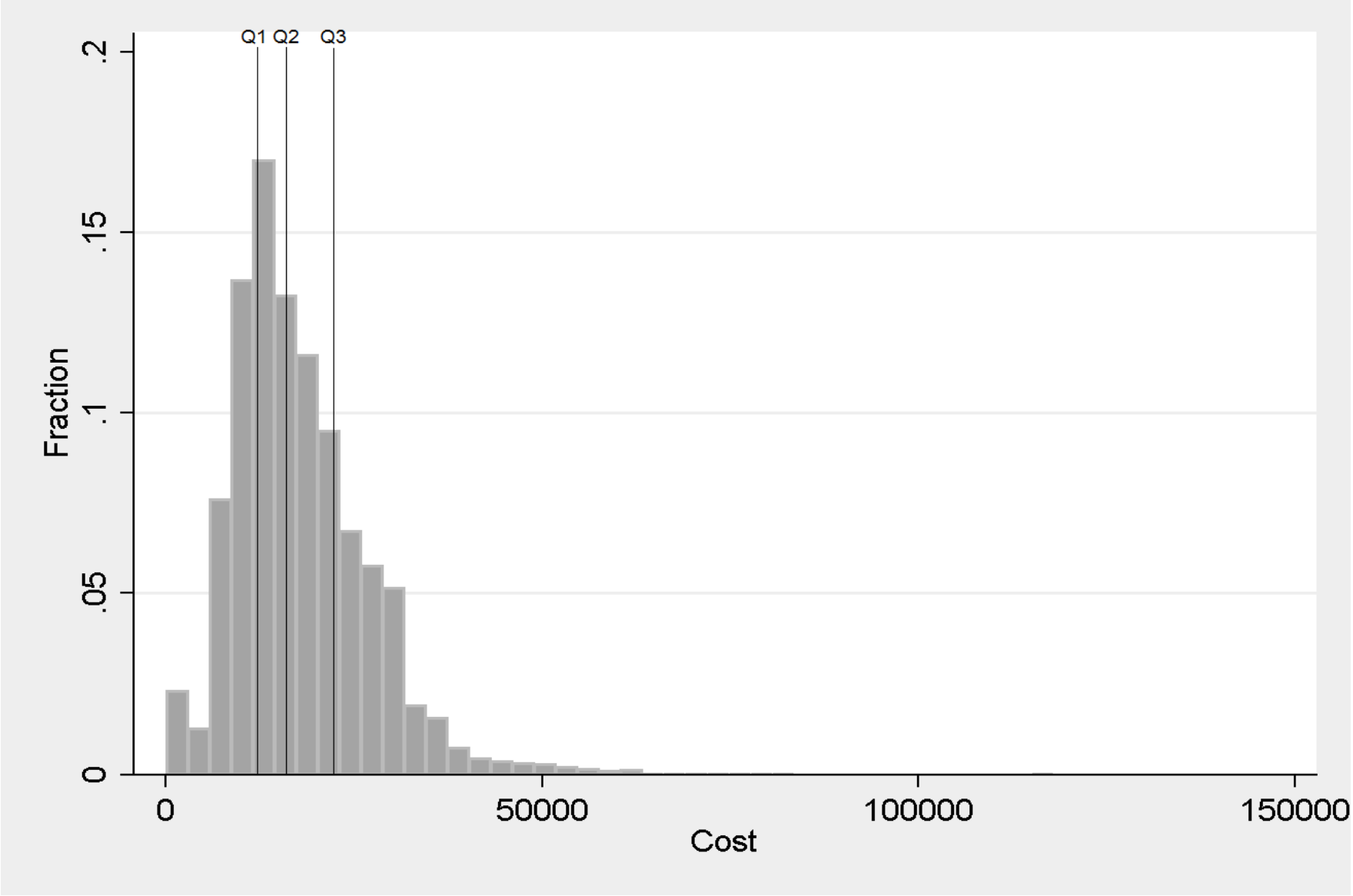

Figure 10: Breast cancer cost distribution, all individuals with cancer

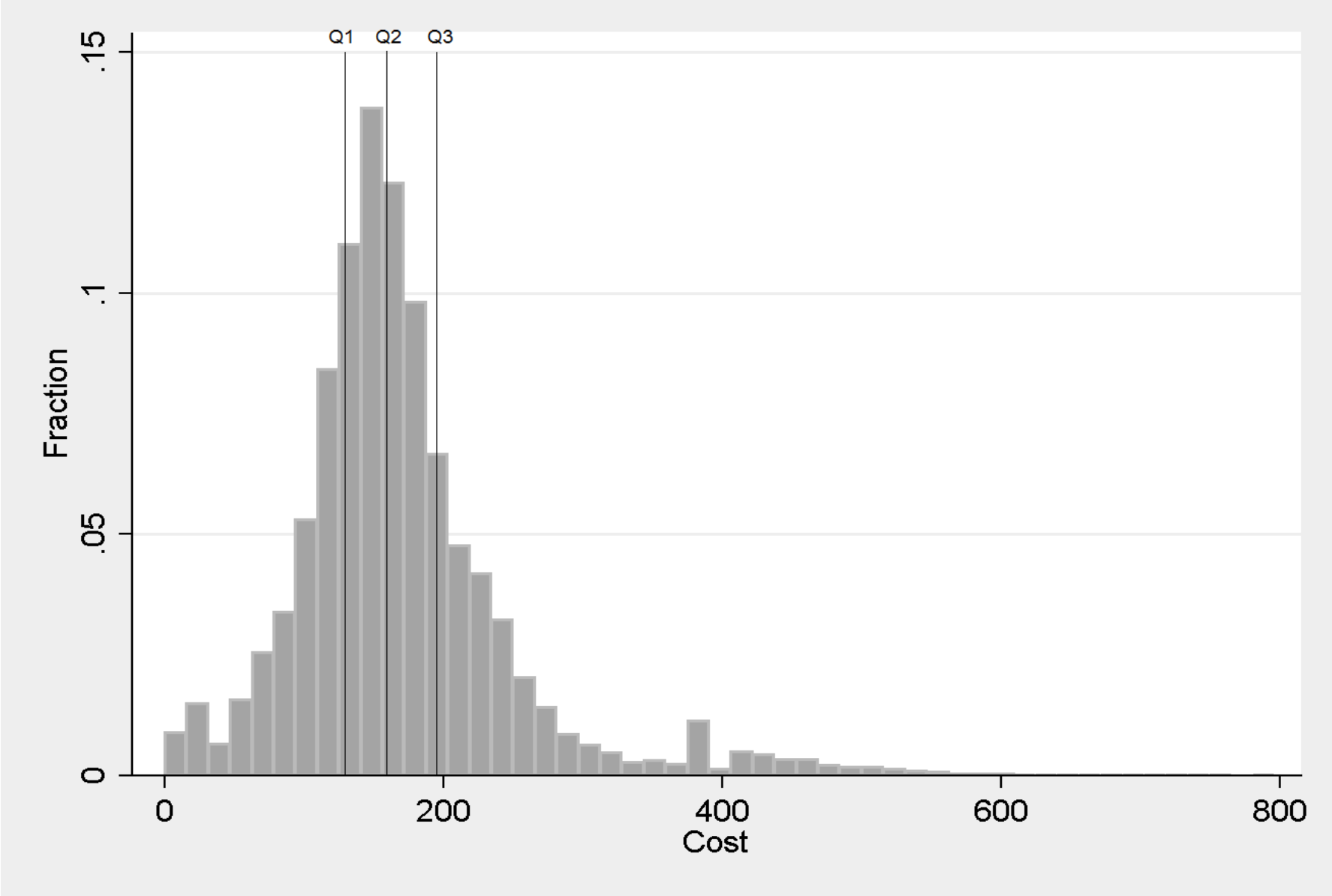

Figure 11: Breast cancer cost distribution, all individuals without cancer

The simulation recorded the number of cancer diagnoses received by individuals in the cohort over 25 years, broken down by stage of cancer. The program kept track of the highest level cancers diagnosed, so if an individual had stage 2 cancer, but then experienced a cancer recurrence, they were labelled as having stage 4 cancer. The distribution of the cancer stages was as follows:

Table 9: Breast cancer stages in the cohort

Health state	Percentage
No cancer	89.18
Stage 0	0.95
Stage 1	3.39
Stage 2	3.10
Stage 3	1.63
Stage 4	1.74

Given that the model used information from the biennial MBSP report for the prevalence of breast cancer, there is some degree of similarity expected in the simulated prevalence of cancer. Essentially, the simulation used the annual probability of developing cancer extrapolated from the report (CancerCare Manitoba, 2010a, p. 22) for each year. For example, according to the report, about 0.5% of people were diagnosed with cancer (0.1% with stage 0 and 0.4% with invasive) over the screening period. Over a 25-year time period, using the same yearly probability, one would expect that about 88.22% of the cohort would remain cancer-free. This is reasonably close to the 89.18% reported in the simulation.

The simulation also correctly predicts that about 31% of invasive cancers are stage 2 (CancerCare Manitoba, 2010a, p. 25), but it generates a much lower proportion of stage 1 cancers than expected, and generates somewhat more stage 3 and 4 cancers than expected. This difference is most likely due to the fact that the CancerCare Manitoba probabilities refer to people undertaking a mammography test. The simulation includes these people as well as non-screeners, who can receive a symptomatic diagnosis. For this group, lower stages are less likely than higher stages, which could account for the overall difference. Another feature that could explain the difference is the fact that the simulation accounts for cancer recurrences over 25 years. For example, an individual could develop stage 1 cancer, but then experience a recurrence, labelling them as having stage 4 cancer instead of stage 1.

As mentioned in Section 2, when one introduces an outer loop to the Monte Carlo simulation, the program can generate a much more refined estimate of cost-effectiveness. Table 10 presents a number of results from the breast cancer simulations. In each case, it lists the cost per individual when there is no screening, versus the cost per individual when everyone follows the PIN screening indicators associated with PIN. It then calculates the difference when switching from non-PIN to PIN screening, which will represent either an additional cost or an avoided cost per individual. Finally, it multiplies the additional or avoided cost per individual by the total number of individuals in the cohort (143,400) to calculate the total additional or avoided costs.

Table 10: Breast cancer cost-effectiveness results (no screening versus PIN screening)			
Description	**Original simulation**	**Refined cost-estimate simulation**	**Switch-point**
	Cost per individual	**Cost per individual**	**Cost per individual**
No cancer screening simulation over 25 years	$263	$2,063	$1,882
Full PIN screening simulation over 25 years	$410	$2,045	$1,882
Difference	$147	$18	$0
Count of simulated individuals	**Total estimated additional or avoided costs**	**Total estimated additional or avoided costs**	**Total estimated additional or avoided costs**
Simulation of 143,400 individuals	$21,079,800 additional cost	$2,581,200 avoided cost	$0

In the table above, the original simulation uses a limited number of screening and treatment costs specific to Manitoba. However, these greatly understate what are likely the full costs for each event and state in the model. With these costs, the PIN screening is not cost-effective compared to no screening whatsoever, leading to an increased cost of about $21.1 million over the 25-year simulation period.

The refined simulation incorporates a greater number of cancer costs obtained from the literature, but which are based on information from other jurisdictions. These serve as "upper bounds" for each cost category and are suggestive of the full costs in Manitoba. With these cost figures, the screening behaviour associated with PIN is cost-effective compared to no screening whatsoever, leading to an avoidance of costs in the amount of $2.6 million.

The switch-point results present the average cost at which there is virtually no difference between the two screening procedures. These results are produced by calculating the differences between event and state costs in the original and refined simulations, and then proportionally scaling these costs down until the simulations produce these equivalent results. In the case of breast cancer, the switch-point results are produced at 90% of the difference between the original and refined model costs.

Table 11 presents the same information as Table 10, except instead of including a no cancer screening scenario, it includes current trend cancer screening versus PIN cancer screening.

Table 11: Breast cancer cost-effectiveness results (current trend screening versus PIN screening)			
	Original simulation	**Refined cost-estimate simulation**	**Switch-point**
Description	**Cost per individual**	**Cost per individual**	**Cost per individual**
Current trend cancer screening simulation over 25 years	$380	$2,050	$1,882
Full PIN screening simulation over 25 years	$410	$2,045	$1,882
Difference	$30	$5	$0
Count of simulated individuals	**Total estimated additional or avoided costs**	**Total estimated additional or avoided costs**	**Total estimated additional or avoided costs**
Simulation of 143,400 individuals	$4,302,000 additional cost	$717,000 avoided cost	$0

With the costs in the original simulation, PIN screening was not cost-effective compared to current trends, generating an extra cost of $4.3 million. With the costs in the refined simulation, PIN screening behaviour is cost-effective compared to current screening activity, generating a cost avoidance of about $0.72 million.

3.2 Cervical cancer

The cervical cancer model has many similar characteristics to the breast cancer model. The basic mechanics are identical: after the program divides the individuals in a cohort between PIN and non-PIN screening groups, the simulated patients progress throughout the model and transition to various health states, based on probabilities. However, the models have some very different structural characteristics. The Pap test in the cervical cancer model can have a number of different results, and the disease progression differs from that of breast cancer. In addition, the screening guidelines associated with the PIN initiative recommend that women between the ages of 18 and 69 have a Pap test every three years, which differs from the two-year intervals in the breast cancer model. This section presents each sub-tree of the cervical cancer model in detail.

Figure 12 presents the sorting sub-tree of the cervical cancer model. As in the breast cancer model, this sub-tree serves to separate members of the cohort into PIN screeners and non-PIN screeners. Once one chooses the preferred proportion of PIN screeners, the program sorts and distributes them among the screening and non-screening sub-trees. Unlike the rest of the cycles, this process does not represent a full year of time, so the patients do not age, and there is no chance of death during the sorting. The program assumes that an individual is either a PIN screener or a non-PIN screener for the entire simulation; there is no switching between groups. The PIN screeners will have a Pap test every three years as per the PIN guidelines. Non-PIN screeners can be defined either as individuals who never screen, or individuals who are aligned with a primary care practice that follows current screening trends. The current trends are based on screening retention rates from a statistical report on the Manitoba Cervical Cancer Screening Program (MCCSP) (CancerCare Manitoba, 2006, pp. 11, 22). Table 12 lists the probabilities associated with the sorting sub-tree. Note that while the breast cancer model had a high-risk group, the medical experts advised that a high-risk group for cervical cancer would not be applicable.

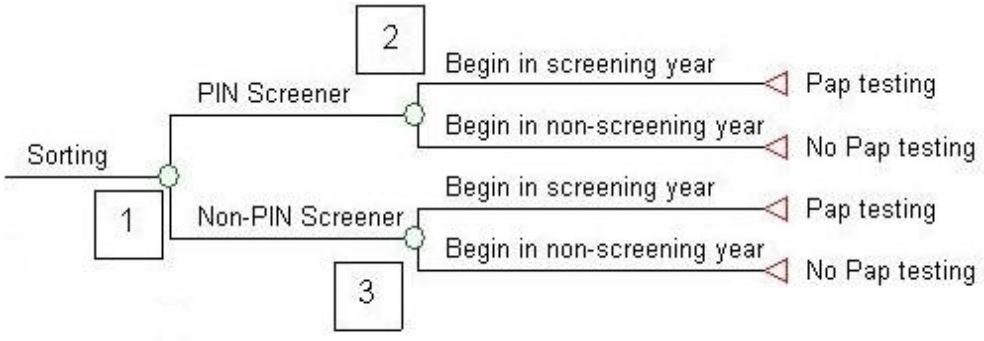

Figure 12: Cervical cancer PIN screener sorting sub-tree

Table 12: Transition probabilities and costs for cervical cancer: "PIN screener sorting" sub-tree			
Node # or Cost	**Description**	**Estimate**	**Source**
Transition probabilities			
1	Whether the individual is a PIN screener or a non-PIN screener	Variable	One can vary the proportion of PIN screeners to observe differences in cost-effectiveness.
2	Whether the PIN screeners begin the first cycle by screening or not screening	Begin by not screening: 0.500	Assumption: for simplicity, the model assumes that in the starting year, half of the PIN screeners are in their screening year and half of them are not.
		Begin by screening: 0.500	
3	Whether the non-PIN screeners begin the first cycle by screening or not screening	Begin by not screening: 0.500	Assumption: for simplicity, the model assumes that in the starting year, half of the non-PIN screeners are in their screening year, and half of them are not. If one wishes to define non-PIN screeners as those who never screen, then all of the non-PIN screeners go to the non-screening branch instead.
		Begin by screening: 0.500	
Costs			
N/A	N/A	N/A	N/A

Figure 13 depicts the "No Pap testing sub-tree" of the cervical cancer model. This sub-tree works in a very similar way to the "No Mammography Screening sub-tree" of the breast cancer model. However, in the cervical cancer model, there is a chance of a hysterectomy from causes other than cervical cancer at the beginning of every non-cancer health state. If a patient who has not had cancer receives a hysterectomy, the program assumes that they are no longer at risk of cervical cancer. In this case, the patient transitions to a hysterectomy state, where they remain for the rest of their life. The other difference with the cervical cancer model is that since the PIN guidelines recommend screening once every three years, the PIN screeners will remain in the non-screening branch for two years, rather than a single year. All individuals in this branch have a small probability of developing cancer symptoms for stages 1 to 4, assuming again that stage 0 cancer is asymptomatic. Table 13 presents the associated probabilities.

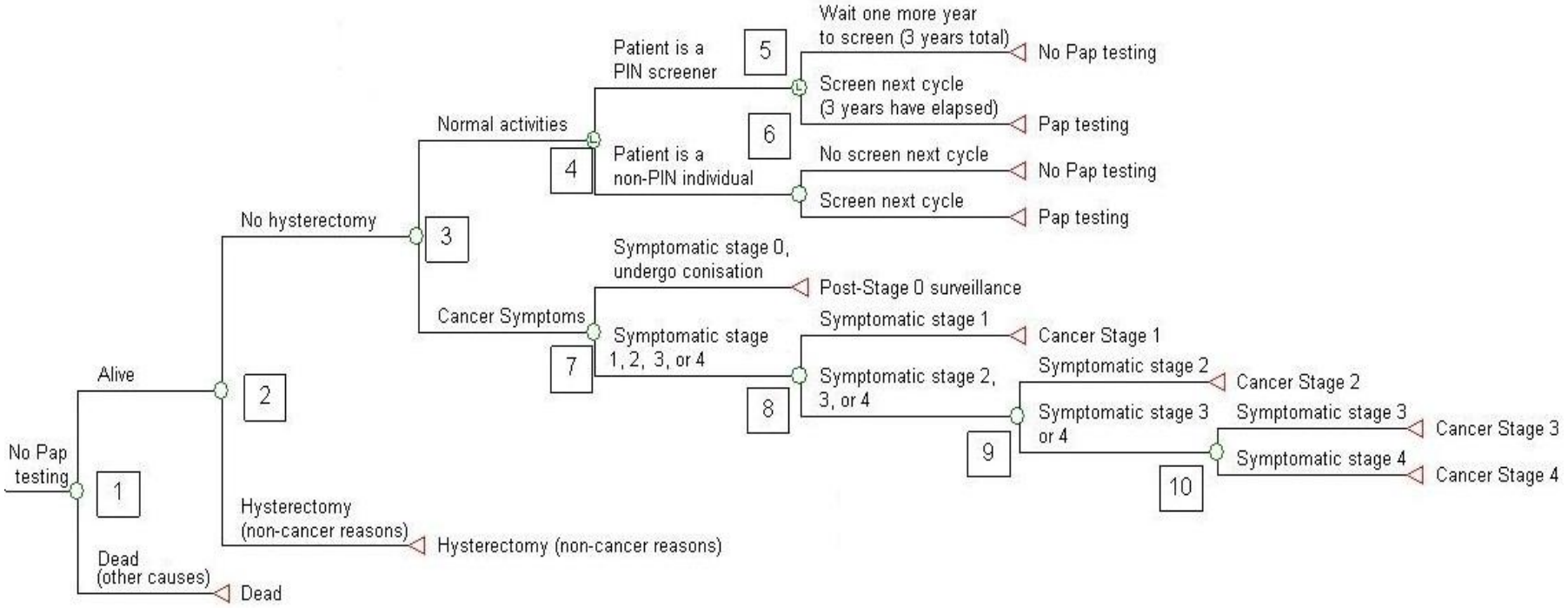

Figure 13: No Pap testing sub-tree

Table 13: Transition probabilities and costs for cervical cancer: "No Pap testing" sub-tree			
Node # or Cost	**Description**	**Estimate**	**Source**
Transition probabilities			
1	Whether the individual survives or dies from any cause other than cervical cancer	Age-dependent	Statistics Canada (2010a) contains age-dependent mortality data. The model calculates the age of each person and assigns them the appropriate chance of mortality.
2	Chances of a hysterectomy	By age group: 18-25: 0.000 30-34: 0.007 35-39: 0.013 40-44: 0.029 45-49: 0.035 50-54: 0.092 55-59: 0.084 60-64: 0.086 65-69: 0.144 70-74: 0.137 75-79: 0.126 >79: 0.127	Chuck (2010), p. 172
3	Chances of developing cancer symptoms: based on 1) 1,300 new cases of cervical cancer predicted in Canada by the Canadian Cancer Society (approximately 47 in Manitoba); and 2) the fraction of these individuals who will be identified without screening, based on the participation rates in the MCCSP	0.000116	CancerCare Manitoba (2006), p. 9; Canadian Cancer Society (2010b); Manitoba Health (2009a), p. 11; Statistics Canada (2010b) The result was calculated by dividing the expected number of symptomatic (non-screening) cancer cases by the proportion of the female population aged 18–69 that are not expected to undergo a Pap test.
4	Logic node: whether patient is a PIN screener	Dependent on initial PIN screener probabilities	Using the tracker variables, the logic node divides those who are PIN screeners from those who are not, and directs them to the appropriate branch.
5	Logic node: for PIN screeners, whether it has been three years since their last Pap test	3 years	As per the PIN guidelines, PIN screeners will screen if it has been three years since their last Pap test.
6	Given that the patient is a non-PIN screener, the likelihood that they will screen next cycle	If the non-PIN screeners never screen, then the probability is zero. If the non-PIN screeners follow current screening trends, then: Screen 24 months after last screen: 0.553 Screen 36 months after last screen: 0.289 Screen >36 months after last screen: 0.500	CancerCare Manitoba (2006), pp. 11, 22: for up to 36 months No data available for further than 36 months from last screening, so at this point the model assumes a probability of 0.500 until the patient screens again
7	Given that the patient has cancer symptoms, the likelihood of stage 0 versus all other stages	0.000	Assumption from the medical experts: stage 0 cancers are asymptomatic
8	Given that the patient has cancer symptoms of a stage between 1 and 4, the likelihood of it being stage 1 cancer	0.145	Heitman et al. (2010), p. 4 (symptomatic stage breakdown for colorectal cancer used as a proxy for cervical cancer due to lack of cervical cancer data)
9	Given that the patient has cancer symptoms of a stage between 2 and 4, the likelihood of it being stage 2 cancer	0.4164	Heitman et al. (2010), p. 4
10	The likelihood of stage 3 or 4 cancer	Stage 3: 0.561 Stage 4: 0.439	Heitman et al. (2010), p. 4
Costs			
N/A	N/A	N/A	N/A

Figure 14 presents the Pap testing sub-tree. Like the previous sub-tree, there is a chance of death from other causes and a chance of a hysterectomy from non-cancer causes, but to save space on the page, the figure does not include these. In this sub-tree, patients undergo a Pap test and can experience many different results. Firstly, the Pap test may be unsatisfactory for sampling, so the patient will be invited back for a repeat Pap test. The patient may decline this test and then decide whether to screen next cycle. If the second Pap test is unsatisfactory, the patient will go for a colposcopy and biopsy. The model assumes that patients will always comply with a colposcopy. After a satisfactory Pap test, there are a number of possible results, including normal, atypical squamous cells of undetermined significance (ASC-US); low-grade squamous intraepithelial lesions (LSIL); atypical squamous cells – cannot rule out high-grade squamous intraepithelial lesions (ASC-H); high-grade squamous intraepithelial lesions (HSIL); atypical glandular cells (AGC); adenocarcinoma in situ (AIS); or carcinoma. For the results of ASC-US and LSIL, the patient will be invited for a repeat Pap test before going for a colposcopy. These lesions have a high probability of regressing on their own. For all other Pap test results, the patient proceeds to a colposcopy.

In Figure 14, the [+] symbols indicate another sub-tree that has been "rolled up" to save space. This symbol appears after "colposcopy and biopsy," and Figure 15 depicts this sub-tree in detail. Table 14 presents the probabilities and costs associated with the Pap test sub-tree.

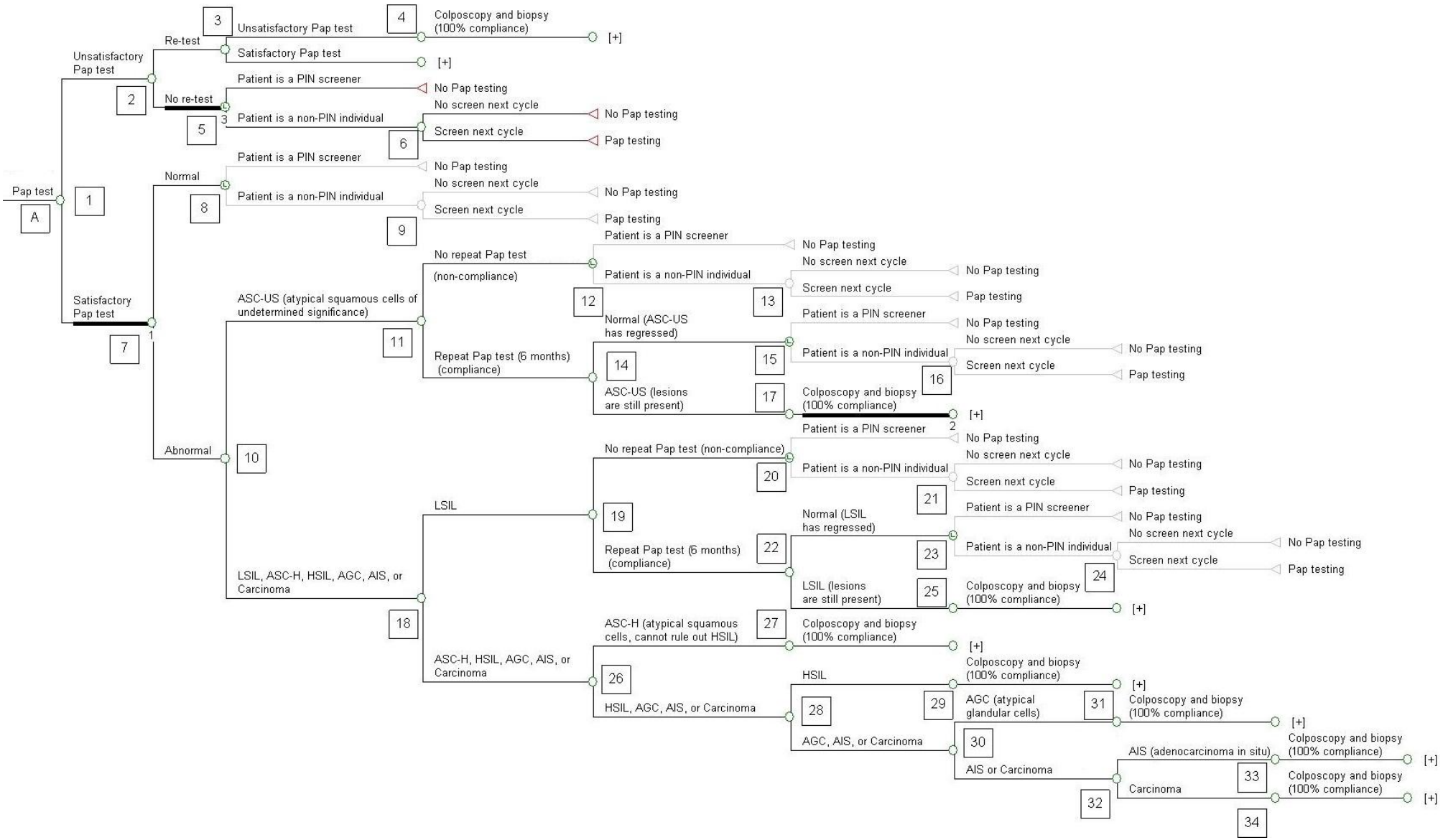

Figure 14: Pap testing sub-tree

Table 14: Transition probabilities and costs for cervical cancer: "Pap testing" sub-tree			
Node # or Cost	**Description**	**Estimate**	**Source**
Transition probabilities			
1, 3	Chances of a satisfactory or unsatisfactory Pap test	Unsatisfactory: 0.0227	CancerCare Manitoba (2006), p. 11
2, 11, 19	Whether the patient complies with a repeat Pap test	Compliance: 0.95	Assumption
4, 17, 25, 27, 29, 31, 33, 34	Patient compliance with a colposcopy and biopsy, given an abnormality	Compliance: 1.00	Assumption
5, 8, 12, 15, 20, 23	Logic node: whether the patient is a PIN screener or a non-PIN screener	Variable	One can vary the proportion of PIN screeners to observe differences in cost-effectiveness.
6, 9, 13, 16, 21, 24	Given that the patient is a non-PIN screener, the likelihood of screening next year	0.229	CancerCare Manitoba (2006), pp. 11, 22
7	Likelihood of a normal or abnormal Pap test	Normal: 0.9181	CancerCare Manitoba (2006), p. 11
10	Given the Pap test is abnormal, the likelihood of ASC-US versus all other results	0.235	CancerCare Manitoba (2006), p. 11
14	Likelihood of ASC-US regressing	0.800	Assumption from medical experts
18	Given LSIL, ASC-H, HSIL, AGC, AIS, or carcinoma, the likelihood of LSIL	0.426	CancerCare Manitoba (2006), p. 11
22	Likelihood of LSIL regressing	0.800	Assumption from medical experts
26	Given ASC-H, HSIL, AGC, AIS, or carcinoma, the likelihood of ASC-H	0.545	CancerCare Manitoba (2006), p. 11
28	Given HSIL, AGC, AIS, or carcinoma, the likelihood of HSIL	0.9068	CancerCare Manitoba (2006), p. 11
30	Given AGC, AIS, or carcinoma, the likelihood of AGC	0.867	CancerCare Manitoba (2006), p. 11
32	Likelihood of AIS or carcinoma	0.500 0.500	Assumption
Costs			
A	Pap test cost	$47	Manitoba Health (2010a), p. A-34

Figure 15 presents the colposcopy and biopsy sub-tree of the cervical cancer model. There is a colposcopy sub-tree for every abnormal Pap test result. The probabilities in these sub-trees will vary, depending on the type of abnormal Pap test result. The colposcopy results can be normal, cervical intraepithelial neoplasia (CIN 1 or CIN 2/3), or cancer. In general, the more serious the Pap test result, the more likely that the colposcopy and biopsy will reveal cervical lesions or cancer. Table 15 lists the probabilities and costs associated with this sub-tree.

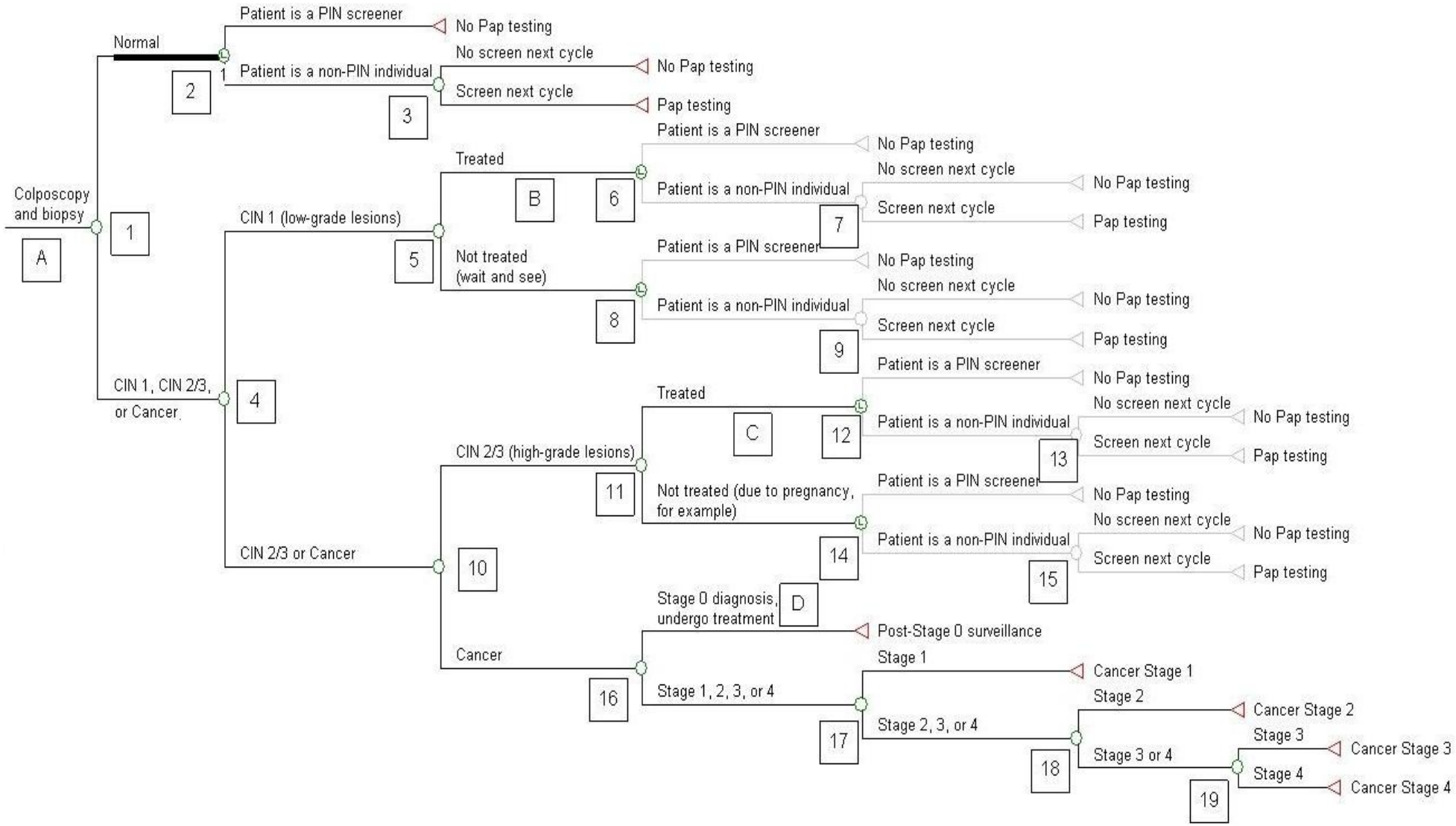

Figure 15: Colposcopy and biopsy sub-tree

Table 15: Transition probabilities and costs for cervical cancer: "Colposcopy and biopsy" sub-tree			
Node # or Cost	**Description**	**Estimate**	**Source**
Transition probabilities			
1	Probability of a normal colposcopy and biopsy result	Given unsatisfactory or ASC-US: 0.440 Given LSIL: 0.265 Given ASC-H: 0.353 Given HSIL: 0.173 Given AGC: 0.730 Given AIS: 0.000 Given carcinoma: 0.000	CancerCare Manitoba (2006), pp. 15–17 (values for AIS and carcinoma assumed due to lack of data)
2, 6, 8, 12, 14	Logic node: whether the patient is a PIN screener or a non-PIN screener	Variable	One can vary the proportion of PIN screeners to observe differences in cost-effectiveness.
3, 7, 9, 13, 15	Given that the patient is a non-PIN screener, the likelihood of screening next year	0.229	CancerCare Manitoba (2006), pp. 11, 22
4	Given CIN 1, CIN 2/3, or cancer, the likelihood of CIN 1	Given unsatisfactory or ASC-US: 0.741 Given LSIL: 0.701 Given ASC-H: 0.471 Given HSIL: 0.375 Given AGC: 0.704 Given AIS: 0.000 Given carcinoma: 0.000	CancerCare Manitoba (2006), pp. 15–17 (values for AIS and carcinoma assumed due to lack of data)
5	Whether the physician treats CIN 1 in a patient	0.200	Assumption from medical experts
10	Given CIN 2/3 or cancer, the likelihood of CIN 2/3	Given unsatisfactory or ASC-US: 0.966 Given LSIL: 0.964 Given ASC-H: 0.927 Given HSIL: 0.812 Given AGC: 0.525 Given AIS: 0.000 Given carcinoma: 0.000	CancerCare Manitoba (2006), pp. 15–17 (values for AIS and carcinoma assumed due to lack of data)
11	Whether the physician treats CIN 2/3 in a patient	Age-dependent pregnancy rates (not treated if pregnant)	Assumption from medical experts: CIN 2/3 is almost always treated, unless there is a pregnancy. Pregnancy rates obtained from Statistics Canada (2005).
16	Given cancer, the likelihood of stage 0 compared to stages 1 to 4	Given unsatisfactory or ASC-US: 0.500 Given LSIL: 0.450 Given ASC-H: 0.400 Given HSIL: 0.300 Given AGC: 0.500 Given AIS: 1.000 Given carcinoma: 0.000	CancerCare Manitoba (2006), pp. 15–17 (values for AIS and carcinoma assumed due to lack of data)
17	Given stage 1, 2, 3, or 4, the likelihood of stage 1	Given unsatisfactory or ASC-US: 1.000 Given LSIL: 1.000 Given ASC-H: 0.917 Given HSIL: 0.429 Given AGC: 1.000 Given AIS: 0.000 Given carcinoma: 0.750	CancerCare Manitoba (2006), pp. 15–17 (values for AIS and carcinoma assumed due to lack of data)

Table 15: Transition probabilities and costs for cervical cancer: "Colposcopy and biopsy" sub-tree			
Node # or Cost	**Description**	**Estimate**	**Source**
18	Given stage 2, 3, or 4, the likelihood of stage 2	Given unsatisfactory or ASC-US: 0.000	CancerCare Manitoba (2006), pp. 15–17 (values for AIS and carcinoma assumed due to lack of data)
		Given LSIL: 0.000	
		Given ASC-H: 1.000	
		Given HSIL: 0.750	
		Given AGC: 0.000	
		Given AIS: 0.000	
		Given carcinoma: 0.333	
19	Given stage 3 or 4, the likelihood of stage 4	Given unsatisfactory or ASC-US: 0.000	CancerCare Manitoba (2006), pp. 15–17 (values for AIS and carcinoma assumed due to lack of data)
		Given LSIL: 0.000	
		Given ASC-H: 0.000	
		Given HSIL: 0.500	
		Given AGC: 0.000	
		Given AIS: 0.000	
		Given carcinoma: 0.500	
Costs			
A	Colposcopy and biopsy cost	$88	Manitoba Health (2010a), p. N-2
B	Cost of treating CIN 1	$64	Manitoba Health (2010a), p. N-3
C	Cost of treating CIN 2/3	$143	Manitoba Health (2010a), p. N-3
D	Cost of treating stage 0 cervical cancer (conization)	$169	Manitoba Health (2010a), p. N-3

Figure 16 depicts the hysterectomy state of the cervical cancer model. This state serves to absorb patients who have a hysterectomy for reasons other than cervical cancer. Since the model assumes these patients are no longer at risk of developing cervical cancer, they remain there until they die from other causes. Table 16 shows the associated probabilities.

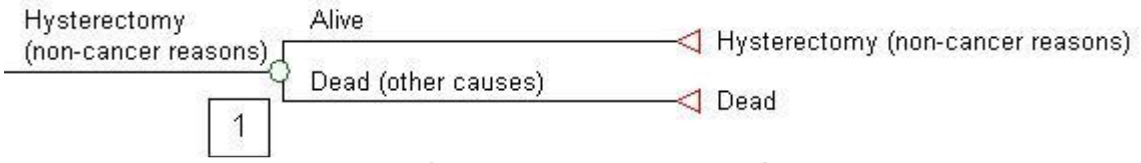

Figure 16: Hysterectomy sub-tree

Table 16: Transition probabilities and costs for cervical cancer: "Hysterectomy" sub-tree			
Node # or Cost	**Description**	**Estimate**	**Source**
Transition probabilities			
1	Whether the individual survives or dies from any cause other than cervical cancer	Age-dependent	Statistics Canada (2010a) contains age-dependent mortality data. The model calculates the age of each person and assigns them the appropriate chance of mortality.
Costs			
N/A	N/A	N/A	N/A

Figure 17 depicts the cancer states in the cervical cancer model. Although the figure consists of only one sub-tree, each stage of cancer from 1 to 4 has its own sub-tree in the actual model. Like the breast cancer model, stage 0 does not have a cancer state, since the treatment takes a short amount of time after diagnosis. Instead, patients with stage 0 cancer transition directly to post-treatment surveillance after undergoing treatment. When patients receive a cancer diagnosis of stage 1 to 4, they transition to the respective cancer state, and the model assumes it takes no more than one year for them to complete their treatment. They undergo treatment for their type of cancer and then either survive and transition to post-treatment surveillance; die of cancer, after unsuccessful treatment; or die of other causes. Table 17 lists the associated probabilities and costs.

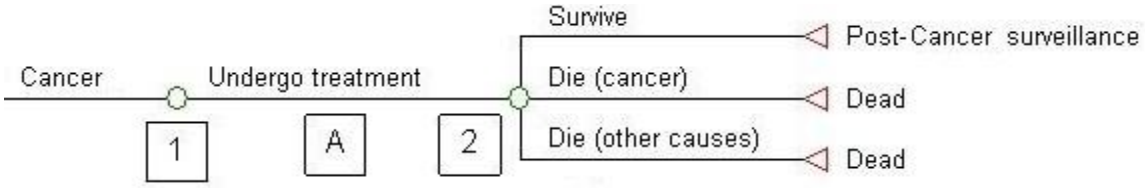

Figure 17: Cervical cancer sub-tree

Table 17: Transition probabilities and costs for cervical cancer: "Cancer" sub-trees			
Node # or Cost	**Description**	**Estimate**	**Source**
Transition probabilities			
1	Patient with cancer undergoes treatment	1.00	Assumption
2	Whether the patient survives treatment, dies of cancer, or dies of other causes	Survives: dependent on the probabilities below	The probability of survival is what is left over after subtracting the probabilities of dying from cancer and dying from other causes.
		Death from cancer: Stage 1: 0.005 Stage 2: 0.042 Stage 3: 0.170 Stage 4: 0.557	http://www.cancerresearchuk.org/ (breast cancer survival data used as a proxy due to lack of cervical cancer survival data)
		Death from other causes: age-dependent	Statistics Canada (2010a)
Costs			
A	Cost of treating stage 1: hysterectomy (assumed 50% of cases), conization, simple radiation treatment (1 round), single agent chemotherapy (1 round)	Stage 1: $547	Manitoba Health (2010a), pp. A-50, B-22, B-23, N-3
	Cost of treating stage 2: hysterectomy (assumed 50% of cases), intermediate radiation treatment (2 rounds), chemotherapy (2 rounds)	Stage 2: $1,049	Manitoba Health (2010a), pp. A-50, B-22, B-23, N-3
	Cost of treating stage 3: hysterectomy (assumed 100% of cases), complex radiation treatment (3 rounds), chemotherapy (3 rounds)	Stage 3: $2,541	Manitoba Health (2010a), pp. A-51, B-22, B-23, N-3
	Cost of treating stage 4: hysterectomy (assumed 100% of cases), extensive radiation treatment (4 rounds), extensive chemotherapy (4 rounds)	Stage 4: $3,897	Manitoba Health (2010a), pp. A-51, B-22, B-23, N-3

Figure 18 presents the post-treatment surveillance state. Each type of cancer has its own surveillance state, including stage 0 cancer. The model assumes that after their cancer treatments, patients spend five years in the surveillance state. In this state, patients undergo surveillance tests by following up with their physicians. Each year, they may die from complications of cancer, based on cancer mortality statistics. They may also experience a recurrence of cancer. If this occurs, it means that the cancer has come back and spread to other parts of the body, so it is defined as a stage 4 cancer. The key assumption is that any cancer recurrence counts as a stage 4 cancer. If the patients survive for five years, they transition back to the Pap testing state. Table 18 lists the associated probabilities and costs.

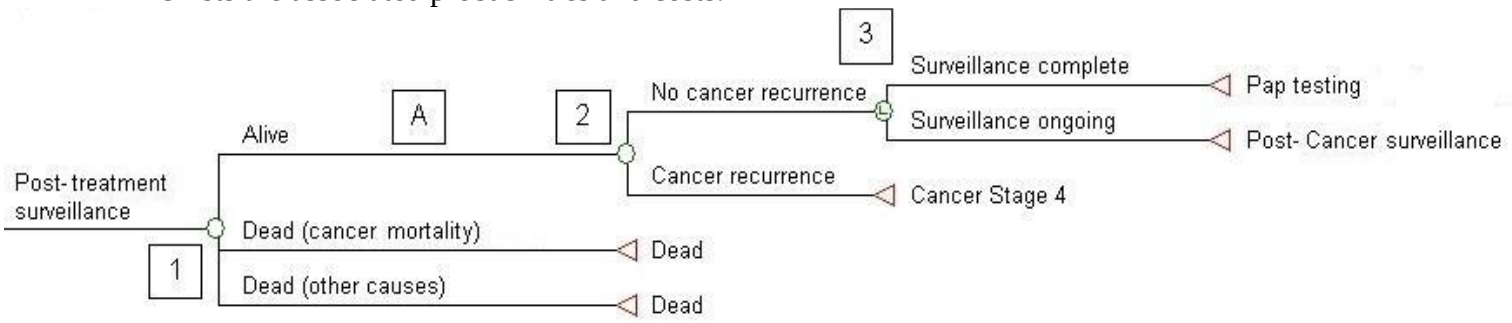

Figure 18: Cervical cancer post-treatment surveillance sub-tree

Table 18: Transition probabilities and costs for cervical cancer: "Post-treatment surveillance" sub-tree

Node # or Cost	Description	Estimate	Source
Transition probabilities			
1	Whether the patient survives, dies from cancer, or dies from other causes	Survives: dependent on the probabilities below	The probability of survival is what is left over after subtracting the probabilities of dying from cancer and dying from other causes.
		Cancer death (listed as the expected proportion of mortality after five years): Stage 0: 0.000 Stage 1: 0.081 Stage 2: 0.271 Stage 3: 0.497 Stage 4: 0.870	http://www.cancerresearchuk.org/ (breast cancer survival data used as a proxy due to lack of cervical cancer survival data)
		Death from other causes: age-dependent	Statistics Canada (2010a)
2	Likelihood of a cancer recurrence	Chance of recurrence per year: Stage 0: 0.002 Stage 1: 0.002 Stage 2: 0.020 Stage 3: 0.040 Stage 4: 0.060	Assumption from medical experts
3	Whether the patient completes their post-treatment surveillance	5 years	After five years, the patient completes their surveillance and transitions to Pap testing
Costs			
A	Physician visits: 4 times a year for years 1–2, 3 times a year for years 3–4, and 2 times in year 5	$47 per visit	Manitoba Health (2010a), p. A-34

3.2.1 Results

As noted above, the cost-effective analysis in this study is performed using Monte Carlo simulation. As per the relevant PIN indicator, the simulation contains women in Manitoba between the ages of 18 and 69 in 2010, totalling 409,040 individuals (Statistics Canada, 2010c, p. 188). The distribution of the ages is based on the ages of the screeners provided in CancerCare Manitoba's (2006) statistical report on the MCCSP (p. 11).

Table 19 presents the results of an inner loop simulation with 409,040 individuals in the cervical cancer model. The individuals followed current screening trends extrapolated from CancerCare Manitoba's (2006) statistical report on the MCCSP (pp. 11, 22).

Table 19: Cervical cancer inner loop results

Statistic	Value
Mean cost per individual	$279
Standard deviation	$1,880
Minimum cost	$0
First quartile	$104
Second quartile (median)	$173
Third quartile	$249
Maximum cost	$46,197

The simulation provides some insight into the possible outcomes of the model. For example, the minimum cost of $0 would represent an individual who never screened and never developed cervical cancer. The relatively low costs in the first, second, and third quartiles show that many cost observations will be low, since only a fraction of the individuals in the model actually developed cervical cancer. On the other hand, the maximum cost of $46,197 likely represents an individual who developed cancer, underwent expensive treatment, and then experienced a recurrence, leading to more treatment.

Below are three histograms that depict the outcomes of the simulation above. Figure 19 shows the cost distribution of everyone in the model. Because cervical cancer has a relatively low incidence, the vast majority of observations fall under $500, so the higher costs are not visible. Figure 20 shows the cost distribution for individuals who developed cervical cancer, where most of the costs fall under $30,000, but a few very high costs lie along a "tail" to the right. Figure 21 depicts the distribution for people without cancer, where the costs are substantially lower, because they only include screening costs over the simulation period.

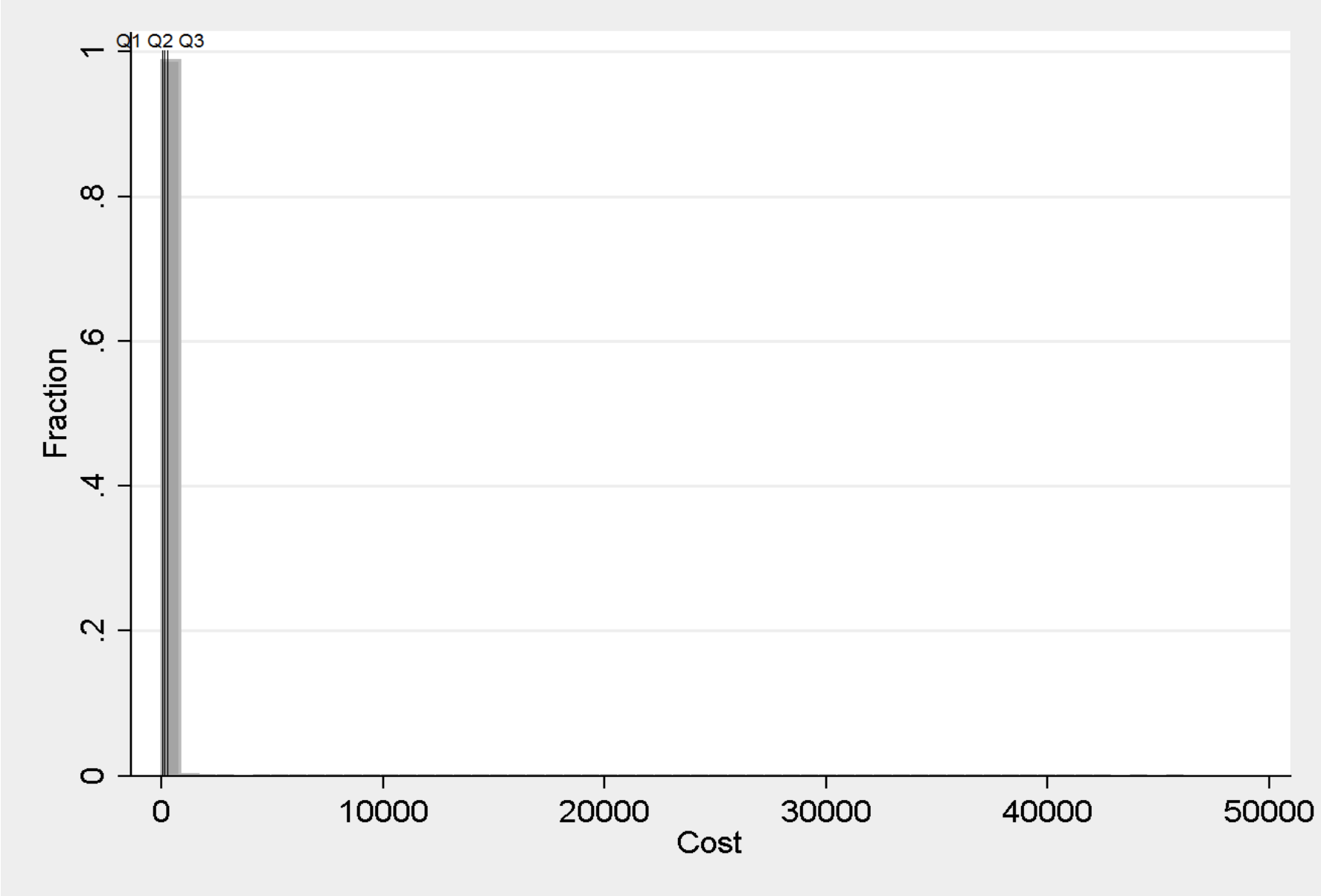

Figure 19: Cervical cancer cost distribution, aggregate

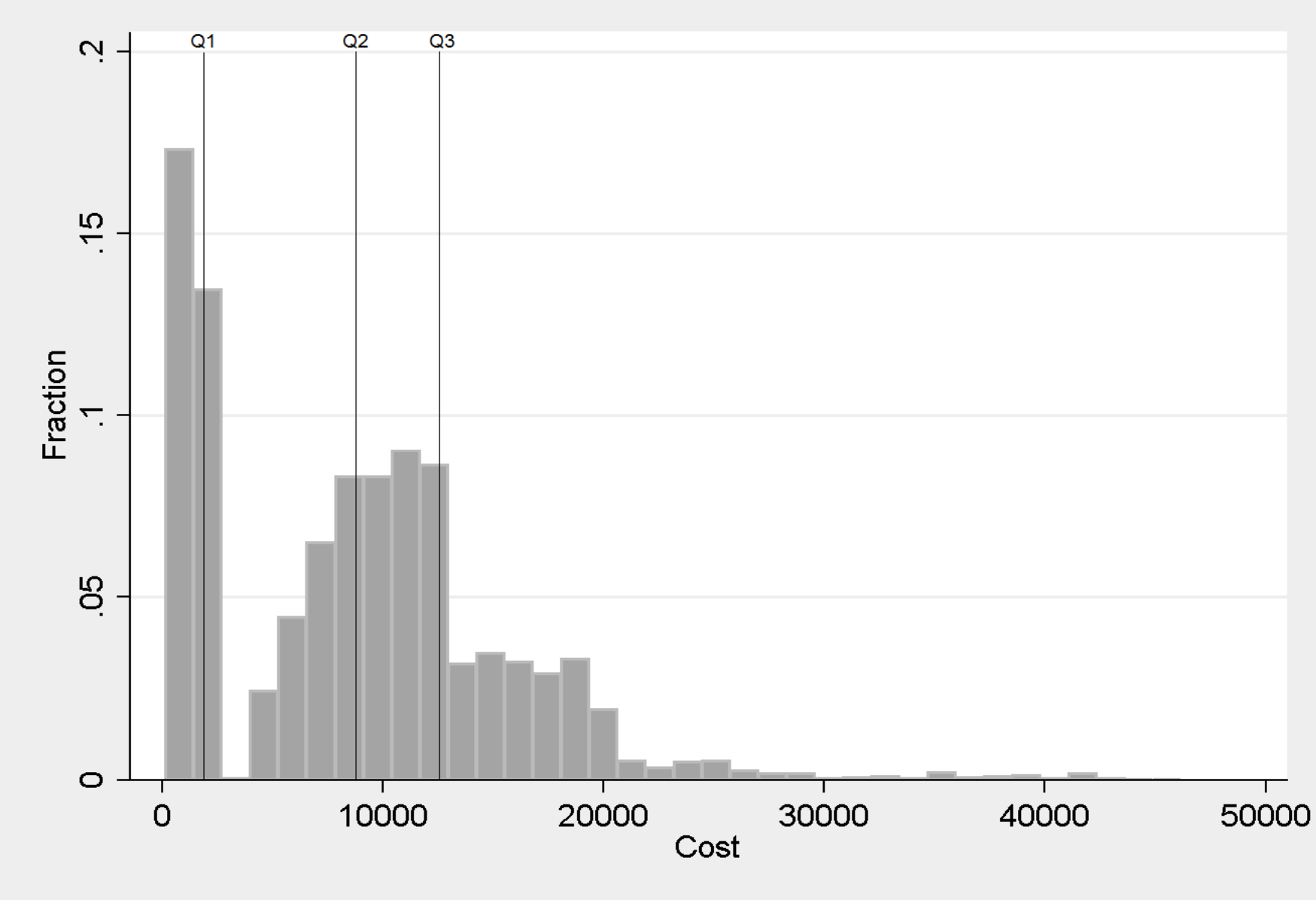

Figure 20: Cervical cancer cost distribution, all individuals with cancer

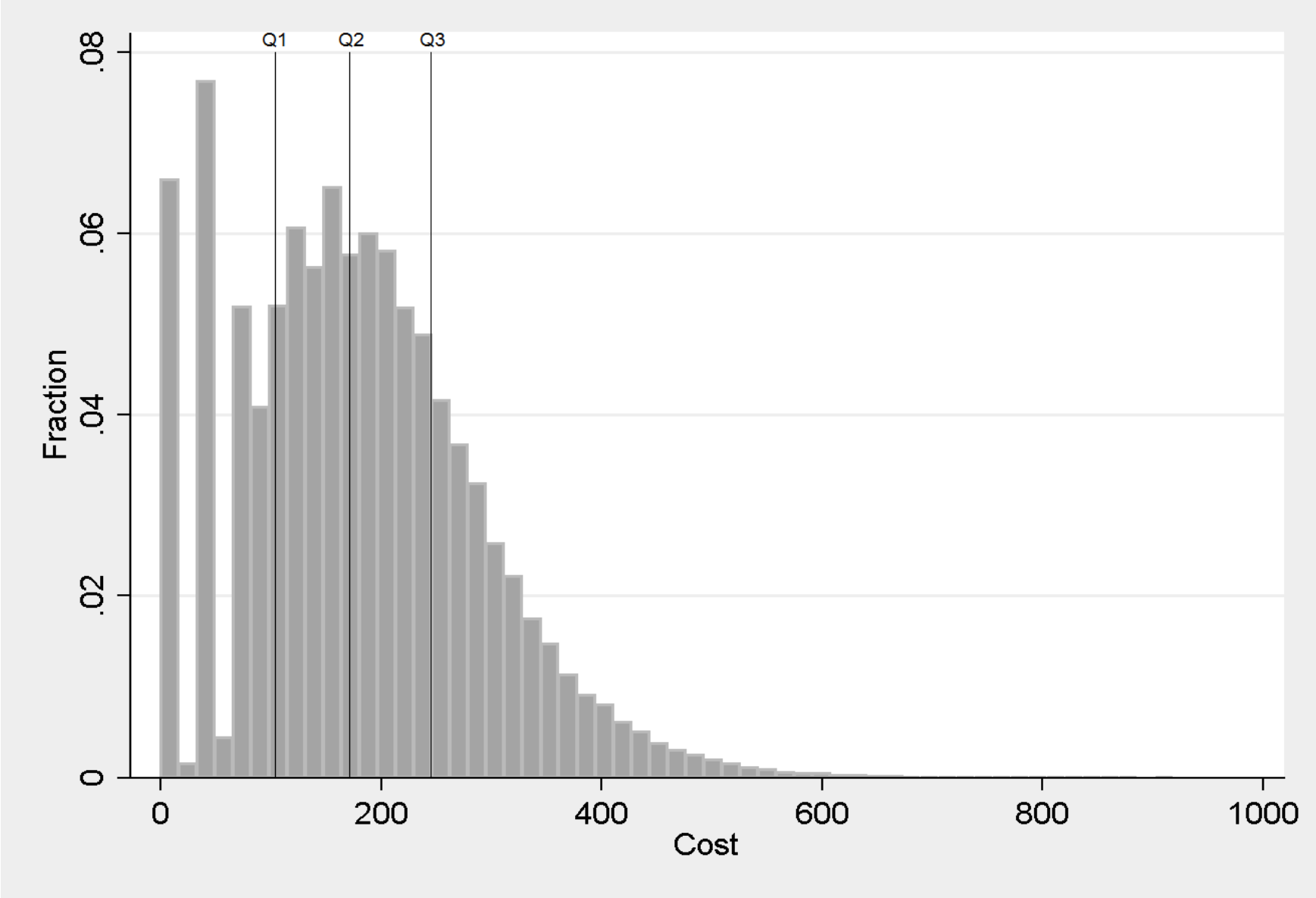

Figure 21: Cervical cancer cost distribution, all individuals without cancer (screening costs only)

The simulation recorded the number of cancer diagnoses received by individuals in the cohort over 25 years, broken down by stage of cancer. The program kept track of the highest level cancers diagnosed, so if an individual had stage 2 cancer, but then experienced a cancer recurrence, they were labelled as having stage 4 cancer. The distribution of the cancer stages was as follows:

Table 20: Cervical cancer stages in the cohort

Health state	Percentage
No cancer	98.84
Stage 0	0.35
Stage 1	0.42
Stage 2	0.24
Stage 3	0.06
Stage 4	0.08

Given that the model used information from the MCCSP report for the prevalence of cervical cancer, there is some degree of similarity expected in the simulated prevalence of cancer. Essentially, the simulation used the annual probability of developing cancer extrapolated from the report (CancerCare Manitoba, 2006, pp. 12, 15–17) for each year. For example, among about 175,000 Pap tests in 2005 and about 180,000 in 2006, only about 0.025% were associated with cervical cancer (CancerCare Manitoba, 2006, p. 11). Over a 25-year time period, using the same yearly probability, one would expect that about 99.38% of the cohort would remain cancer-free. This is reasonably close to the 98.84% reported in the simulation.

Compared to breast and colorectal cancer, cervical cancer has a very low incidence. With such small percentages, it is very difficult to compare the simulations with the actual data. However, as in the breast cancer model, it is likely that this model understates lower stages and overstates higher stages, because it includes both screeners and non-screeners. Again, this is likely explained by the fact that for individuals in their non-screening year who could develop symptomatic cancer, the likelihood of a higher stage of cancer is greater.

As mentioned in Section 2, with an outer loop to the Monte Carlo simulation, the program can generate a much more refined estimate of cost-effectiveness. Table 21 presents a number of results from the cervical cancer simulations. In each case, it lists the cost per individual when there is no screening, versus the cost per individual when everyone follows the PIN screening indicators. It then calculates the difference when switching from non-PIN to PIN screening, which will either represent an additional cost or avoided cost per individual. Finally, it multiplies the additional or avoided cost per individual by the total number of individuals in the cohort (409,040) to calculate the total additional or avoided costs.

Table 21: Cervical cancer cost-effectiveness results (no screening versus PIN screening)

Description	Original simulation	Refined cost-estimate simulation
	Cost per individual	Cost per individual
No cancer screening simulation over 25 years	$3	$23
Full PIN screening simulation over 25 years	$268	$385
Difference	$265	$362
Count of simulated individuals	**Total estimated additional or avoided costs**	**Total estimated additional or avoided costs**
Simulation of 409,040 individuals	$108,395,600 additional cost	$148,072,480 additional cost

As in Section 3, the original simulation results are based on limited cost information. With these costs, the screening behaviour associated with PIN is not cost-effective compared to no screening whatsoever, leading to an increased cost of about $108.4 million. Again, the refined simulation refers to the new costs obtained in the literature. With these figures, the screening behaviour associated with PIN is still not cost-effective compared to no screening whatsoever, generating a cost of about $148.1 million. Unlike the breast cancer model, there is no switch-point, because even with the upper bound costs in place, the simulation still does not find screening aligned with PIN indicators to be cost-effective.

Table 22 presents the same information as Table 21, except instead of including a no cancer screening scenario, it includes current trend cancer screening versus PIN cancer screening.

Table 22: Cervical cancer cost-effectiveness results (current trend screening versus PIN screening)

Description	Original simulation	Refined cost-estimate simulation
	Cost per individual	Cost per individual
Current trend cancer screening simulation over 25 years	$195	$285
Full PIN screening simulation over 25 years	$268	$385
Difference	$73	$100
Count of simulated individuals	**Total estimated additional or avoided costs**	**Total estimated additional or avoided costs**
Simulation of 409,040 individuals	$29,859,920 additional cost	$40,904,000 additional cost

With the costs in the original simulation, PIN screening was not cost-effective compared to current trends, generating an extra cost of $29.9 million. With the costs in the refined simulation, PIN screening behaviour is still not cost-effective compared to current screening behaviour, generating about $40.9 million in costs. Once again, there is no switch-point for the cervical cancer model. Unlike the breast cancer model, the cost-effectiveness results shown here indicate that according to the simulations, PIN-type screening is not cost-effective in any of the scenarios, almost entirely because small screening costs across the entire population are not offset by the avoided costs of treating earlier stages of a low incidence cancer.

3.3 Colorectal cancer

The colorectal cancer model has the same basic mechanics as the breast and cervical cancer models. After the program sorts a cohort of patients into PIN and non-PIN screeners, they progress throughout the model, transitioning to different branches and health states based on probabilities. To sort the cohort into different groups, the model uses a sorting sub-tree with probabilities defined as the percentage of PIN versus non-PIN screeners. For example, if one wishes to run a simulation where half of the patients in the cohort are PIN screeners, then they may set the proportion of PIN screeners to 0.5, and allow the remainder to follow a different type of screening behaviour. As in the breast cancer model, there is a small "high-risk" group, containing individuals who screen every year. Since this sub-tree is only a sorting tool, there is no chance of death and patients do not age. Once again, the program assumes that once a patient is sorted into one of the screening groups, their screening behaviour will remain associated with that group for the entire simulation.

Figure 22 presents the sorting sub-tree and Table 23 lists the associated probabilities.

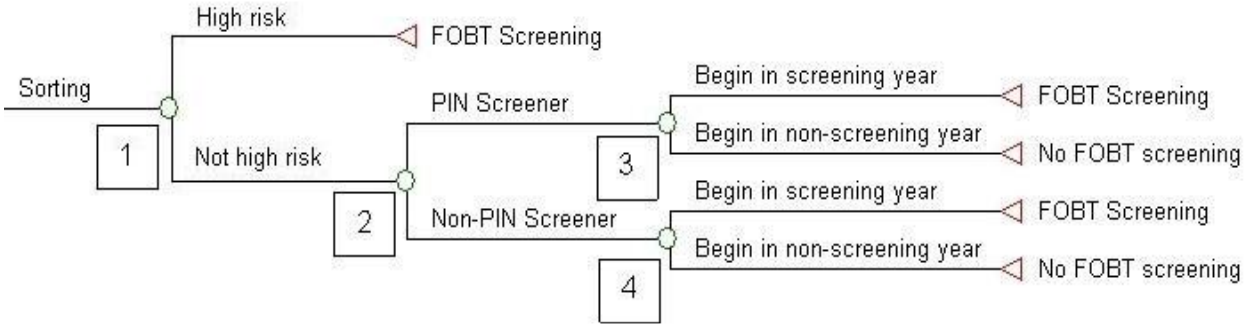

Figure 22: Colorectal cancer PIN screener sorting sub-tree

Table 23: Transition probabilities and costs for colorectal cancer: "PIN screener sorting" sub-tree			
Node # or Cost	**Description**	**Estimate**	**Source**
Transition probabilities			
1	Whether the individual is at a high risk of colorectal cancer	High risk: 0.05 Not high risk: 0.95	Assumption
2	Whether the individual is a PIN screener or a non-PIN screener	Variable	One can vary the proportion of PIN screeners to observe differences in cost-effectiveness.
3	Whether the PIN screeners begin the first cycle by screening or not screening	Begin by screening: 0.500 Begin by not screening: 0.500	Assumption: for simplicity, the model assumes that in the starting year, half of the PIN screeners are in their screening year and half of them are not.
4	Whether the non-PIN screeners begin the first cycle by screening or not screening	Begin by screening: 0.500 Begin by not screening: 0.500	Assumption: for simplicity, the model assumes that in the starting year, half of the non-PIN screeners are in their screening year, and half of them are not. If one wishes to define non-PIN screeners as those who never screen, then all of the non-PIN screeners go to the non-screening branch instead.
Costs			
N/A	N/A	N/A	N/A

Figure 23 presents the non-screening sub-tree of the colorectal cancer model. In this sub-tree, patients do not screen, and will simply continue with their normal activities. However, there is a small chance of developing cancer symptoms and receiving a diagnosis of stage 1 to 4 colorectal cancer. The model assumes that stage 0 cancers are asymptomatic, so there is no chance of receiving a diagnosis of stage 0 in this sub-tree. If the patient does not develop symptomatic cancer, then a logic node governs their screening decision. The logic node identifies the patient as either a PIN screener or a non-PIN screener, based on where the program sorted them in the sorting cycle. If the patient is a PIN screener, they strictly adhere to the PIN guidelines. If they are not, they screen based on other probabilities. Table 24 lists the associated probabilities.

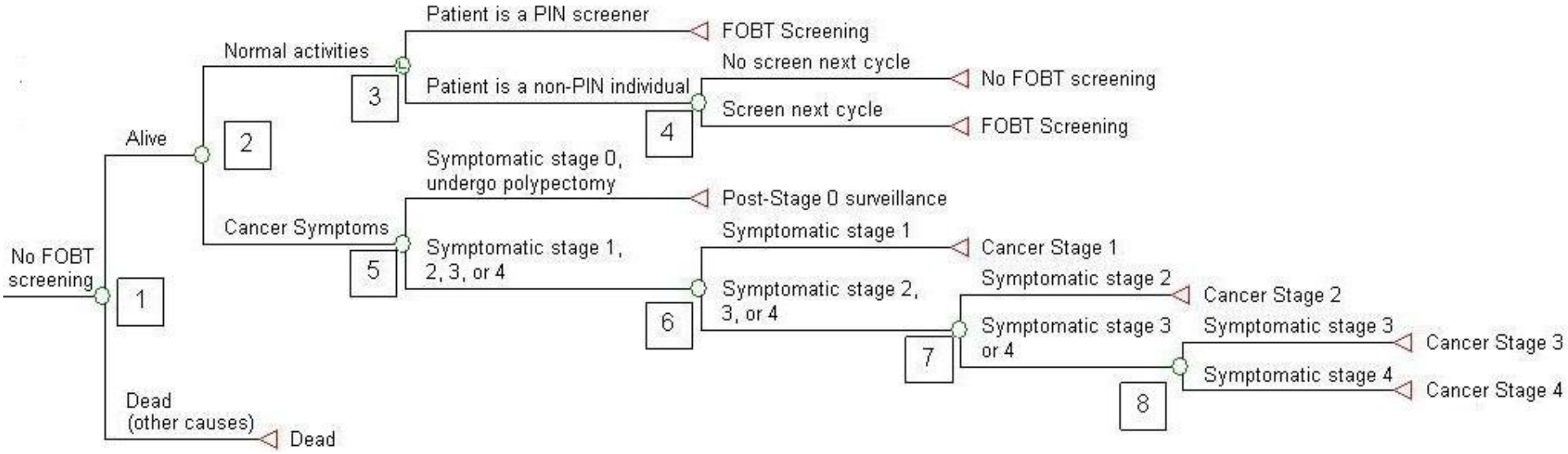

Figure 23: No FOBT screening sub-tree

Table 24: Transition probabilities and costs for colorectal cancer: "No FOBT screening" sub-tree			
Node # or Cost	**Description**	**Estimate**	**Source**
Transition probabilities			
1	Whether the individual survives or dies from any cause other than colorectal cancer	Age-dependent	Statistics Canada (2010a) contains age-dependent mortality data. The model calculates the age of each person and assigns them the appropriate chance of mortality.
2	Chances of developing cancer symptoms	0.0051	Assumption: breast cancer data used as a proxy for colorectal cancer due to lack of data
3	Logic node: whether patient is a PIN screener	Dependent on initial PIN screener probabilities	Using the tracker variables, the logic node divides those who are PIN screeners from those who are not and directs them to the appropriate branch.
4	Given that the patient is a non-PIN screener, the chances that they will screen next year	If the non-PIN screeners never screen, then the probability is zero. If the non-PIN screeners follow current screening trends, then: Screen 24 months after last screen: 0.383 Screen 36 months after last screen: 0.667 Screen >36 months after last screen: 0.500	Assumption: breast cancer data used as a proxy for colorectal cancer due to lack of data. The CancerCare Manitoba colorectal cancer screening program is too new to collect reliable participation and re-screening estimates.
5	Given that the patient has cancer symptoms, the likelihood of stage 0 versus all other stages	0.000	Assumption from the medical experts: stage 0 cancers are asymptomatic
6	Given that the patient has cancer symptoms of a stage between 1 and 4, the likelihood of it being stage 1 cancer	0.145	Heitman et al. (2010), p. 4
7	Given that the patient has cancer symptoms of a stage between 2 and 4, the likelihood of it being stage 2 cancer	0.4164	Heitman et al. (2010), p. 4
8	The likelihood of stage 3 or 4 cancer	Stage 3: 0.561 Stage 4: 0.439	Heitman et al. (2010), p. 4
Costs			
N/A	N/A	N/A	N/A

Figure 24 depicts the FOBT screening sub-tree of the colorectal cancer model. In this sub-tree, patients undergo an FOBT and can experience a number of results. If the patient has a negative FOBT, they will either screen or not screen the following cycle, as determined by their screening behaviour. In reality, there would be an incidence of false negative tests—particularly for less advanced cancers. False negatives are treated the same way as they are in the breast cancer model. After a false negative test, a patient would presumably receive a cancer diagnosis at a later date based on symptoms or other tests. However, this process is not exactly compatible with the modelling approach. Individuals only screen in this branch if they are asymptomatic. Whether the individual begins the cycle without cancer, or with an asymptomatic cancer, it is unlikely that they will develop cancer symptoms within the same year. In other words, the only chance they have at identifying a cancer during the cycle is through the screening and follow-up tests. The model does not allow them to have a second chance in the same year to identify a cancer through symptoms. Therefore, with this modelling approach, a person with a false negative test would be unaware that they have cancer, and would face the same screening

decision for the next cycle as would a cancer-free individual. Based on this, the models abstract from false negatives.

Patients in this sub-tree may also receive a positive result on their FOBT. Their physician would then prompt them to undergo a colonoscopy. However, there is a chance that the patient will not comply with this follow-up test, and decide to either screen or not screen the following cycle. A positive FOBT does not necessarily mean that the individual has cancer, so many people with a positive FOBT and no colonoscopy will continue to be healthy. Other people with a positive FOBT but no colonoscopy could develop cancer symptoms, but presumably not in the same year, so the patient simply faces the screening decision in this cycle. The reasoning for this is similar to false negatives. Whether the patient begins a cycle with no cancer, or an asymptomatic cancer, the program assumes they will not develop symptoms in the same cycle.

If the patient complies with the colonoscopy, the results could be normal, which would indicate a false positive, or possibly some other colorectal disease. After a normal colonoscopy, the PIN indicator associated with this screening process would cause a patient to drop out of screening for 10 years, due to the risk reduction provided by the test. However, according to Manitoba screening guidelines, an individual with a normal colonoscopy would drop out of screening for five years (CancerCare Manitoba, 2010b, p. 15). This model follows the Manitoba guidelines, so patients in this category spend five years in a "colonoscopy" state before returning to normal screening.

Alternatively, the patient could receive a cancer diagnosis between stages 0 and 4. A stage 0 cancer would be treated with a polypectomy during the colonoscopy, and the patient would proceed directly to a post-treatment surveillance state. Any stage 1 to 4 cancer would require a longer treatment period, so the patient would spend the next cycle (one year) undergoing treatment in a cancer state. Table 25 lists the probabilities and costs associated with this sub-tree.

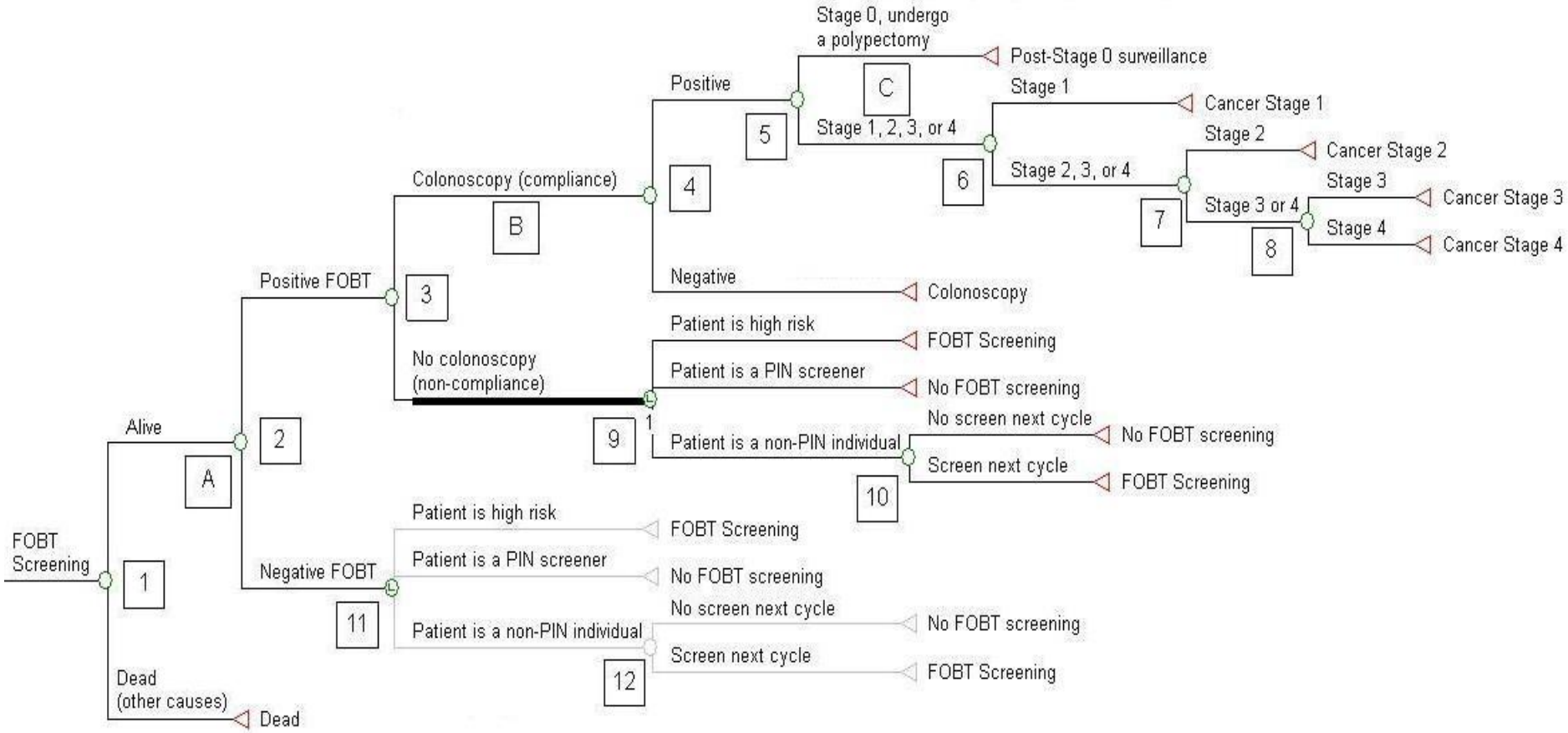

Figure 24: FOBT screening sub-tree

Table 25: Transition probabilities and costs for colorectal cancer: "FOBT Screening" sub-tree			
Node # or Cost	**Description**	**Estimate**	**Source**
Transition probabilities			
1	Whether the individual survives or dies from any cause other than colorectal cancer	Age-dependent	Statistics Canada (2010a) contains age-dependent mortality data. The model calculates the age of each person and assigns them the appropriate chance of mortality.
2	Probability of a positive or negative FOBT	Positive: 0.03	CancerCare Manitoba (2010b), p. 31
3	Whether the patient complies with a follow-up colonoscopy after a positive FOBT	Compliance: 0.95	CancerCare Manitoba (2010b), p. 7
4	Probability of a positive or negative colonoscopy	Normal colonoscopy: 0.422	CancerCare Manitoba (2010b), p. 7
5	Given that the patient has cancer, the likelihood of stage 0 cancer versus all other stages	0.831	CancerCare Manitoba (2010b), pp. 7, 42
6	Given stage 1, 2, 3, or 4, the likelihood of stage 1	0.305	Heitman et al. (2010), p. 4
7	Given stage 2, 3, or 4, the likelihood of stage 2	0.458	Heitman et al. (2010), p. 4
8	The chances of stage 3 or 4 cancer	Stage 3: 0.645 Stage 4: 0.355	Heitman et al. (2010), p. 4
9, 11	Logic node: whether an individual is high-risk, a PIN screener, or a non-PIN screener	Variable	Determined through initial probabilities
10, 12	Given that the patient is a non-PIN screener, the likelihood of screening in the following cycle	0.063	Assumption: breast cancer re-screening statistics used as a proxy for colorectal cancer, since the CancerCare Manitoba colorectal cancer screening program is too new to collect reliable estimates
Costs			
A	Cost of the FOBT	$16	Manitoba Health (2010a), p. V-5; Heitman et al. (2010), p. 6
B	Cost of the colonoscopy	$211	Manitoba Health (2010a), p. J-8
C	Cost of the polypectomy	$95	Manitoba Health (2010a), p. J-8 (the polypectomy is done during the colonoscopy, so the $95 cost already factors in the cost of the colonoscopy)

Figure 25 presents the colonoscopy sub-tree of the colorectal cancer model. Patients with a normal result on a colonoscopy transition to this state and remain for five years before returning to normal screening. While the PIN indicator associated with this screening process recommends a 10-year withdrawal from the program, Manitoba guidelines specify a five-year withdrawal (CancerCare Manitoba, 2010b, p. 15). Table 26 lists the probabilities associated with this sub-tree.

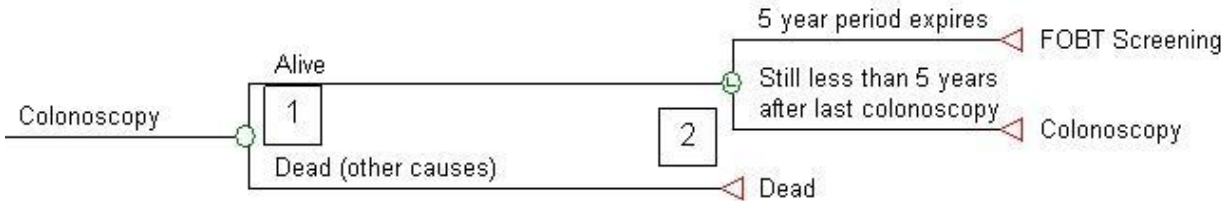

Figure 25: Colonoscopy sub-tree

Table 26: Transition probabilities and costs for colorectal cancer: "Colonoscopy" sub-tree			
Node # or Cost	**Description**	**Estimate**	**Source**
Transition probabilities			
1	Whether the individual survives or dies from any cause other than colorectal cancer	Age-dependent	Statistics Canada (2010a) contains age-dependent mortality data. The model calculates the age of each person and assigns them the appropriate chance of mortality.
2	Logic node: if five years have elapsed, the patient returns to the normal screening process	5 years	CancerCare Manitoba (2010b), p. 15
Costs			
N/A	N/A	N/A	N/A

Figure 26 depicts the cancer states in the colorectal cancer model. Although the figure consists of only one sub-tree, each stage of cancer from 1 to 4 has its own sub-tree in the actual model. Like the breast cancer and cervical cancer models, stage 0 does not have a cancer state, since the treatment takes a short amount of time after diagnosis. Instead, patients with stage 0 cancer transition directly to post-treatment surveillance after undergoing treatment. When patients receive a cancer diagnosis of stage 1 to 4, they transition to the respective cancer state, and the model assumes it takes no more than one year for them to complete their treatment. They undergo treatment for their type of cancer and then either survive and transition to post-treatment surveillance; die of cancer, after unsuccessful treatment; or die of other causes. Table 27 lists the associated probabilities and costs.

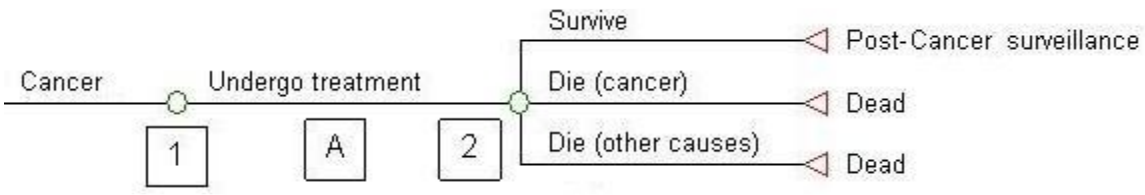

Figure 26: Colorectal cancer sub-tree

Table 27: Transition probabilities and costs for colorectal cancer: "Cancer" sub-trees			
Node # or Cost	**Description**	**Estimate**	**Source**
Transition probabilities			
1	Patient with cancer undergoes treatment	1.00	Assumption
2	Whether the patient survives treatment, dies of cancer, or dies of other causes	Survives: dependent on the probabilities below	The probability of survival is what is left over after subtracting the probabilities of dying from cancer and dying from other causes
		Death from cancer: Stage 1: 0.005 Stage 2: 0.042 Stage 3: 0.170 Stage 4: 0.557	http://www.cancerresearchuk.org/ (breast cancer survival data used as a proxy due to lack of colorectal cancer survival data)
		Death from other causes: age-dependent	Statistics Canada (2010a)
Costs			
A	Cost of treating stage 1: enterotomy (colon) or local excision (rectum), simple radiation treatment (1 round), single agent chemotherapy (1 round)	Stage 1: $772 (cost of surgery weighted by 75% colon cases and 25% rectal cases)	Manitoba Health (2010a), pp. A-50, B-22, B-23, J-14, J-15 Assumption from medical experts: 75% of colorectal cancers are in the colon, and 25% are in the rectum
	Cost of treating stage 2: minor colectomy (<50%) (colon) or resection (rectum), intermediate radiation treatment (2 rounds), chemotherapy (2 rounds)	Stage 2: $1,782 (cost of surgery weighted by 75% colon cases and 25% rectal cases)	Manitoba Health (2010a), pp. A-50, B-22, B-23, J-14, J-15 Assumption from medical experts: 75% of colorectal cancers are in the colon, and 25% are in the rectum
	Cost of treating stage 3: minor colectomy (<50%) or resection (rectum), complex radiation treatment (3 rounds), chemotherapy (3 rounds)	Stage 3: $3,186	Manitoba Health (2010a), pp. A-51, B-22, B-23, J-14, J-15 Assumption from medical experts: 75% of colorectal cancers are in the colon, and 25% are in the rectum
	Cost of treating stage 4: major colectomy (>50%) (colon) or anterior resection with anastomosis (rectum), extensive radiation treatment (4 rounds), extensive chemotherapy (4 rounds)	Stage 4: $4,952	Manitoba Health (2010a), pp. A-51, B-22, B-23, J-14, J-15 Assumption from medical experts: 75% of colorectal cancers are in the colon, and 25% are in the rectum

Figure 27 presents the post-treatment surveillance state. Each type of cancer has its own surveillance state, including stage 0 cancer. The model assumes that after their cancer treatments, patients spend five years in the surveillance state. In this state, patients undergo surveillance tests by following up with their physicians. Each year, they may die from complications of cancer, based on cancer mortality statistics. They may also experience a recurrence of cancer. If this occurs, it means that the cancer has come back and spread to other parts of the body, so it is defined as a stage 4 cancer. The key assumption is that any cancer recurrence counts as a stage 4 cancer. If the patients survive for five years, they transition back to the FOBT screening state. However, due to their history of colorectal cancer, the model labels them as high-risk patients, and as a result they screen every year. Table 28 lists the associated probabilities and costs.

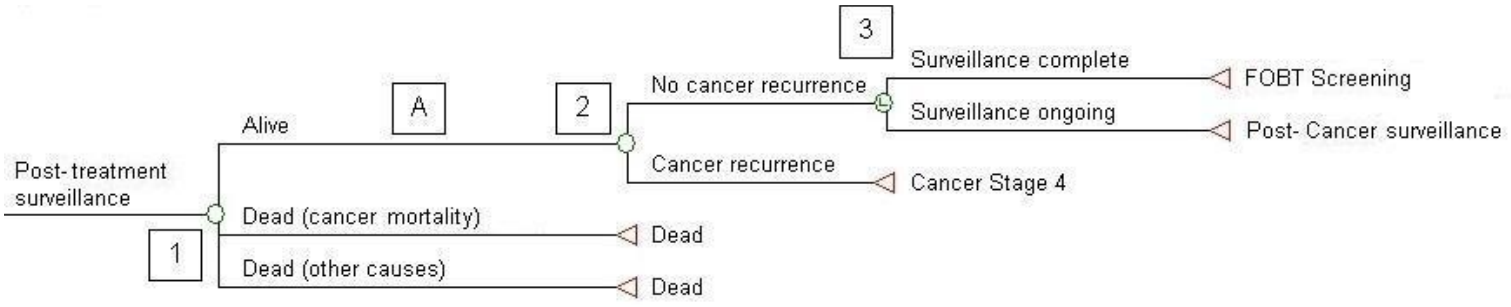

Figure 27: Colorectal cancer post-treatment surveillance sub-tree

Table 28: Transition probabilities and costs for colorectal cancer: "Post-treatment surveillance" sub-tree			
Node # or Cost	**Description**	**Estimate**	**Source**
Transition probabilities			
1	Whether the patient survives, dies from cancer, or dies from other causes	Survives: dependent on the probabilities below	The probability of survival is what is left over after subtracting the probabilities of dying from cancer and dying from other causes.
		Cancer death (listed as the expected proportion of mortality after five years): Stage 0: 0.000 Stage 1: 0.081 Stage 2: 0.271 Stage 3: 0.497 Stage 4: 0.870	http://www.cancerresearchuk.org/ (breast cancer survival data used as a proxy due to lack of colorectal cancer survival data)
		Death from other causes: age-dependent	Statistics Canada (2010a)
2	Likelihood of a cancer recurrence	Chance of recurrence per year: Stage 0: 0.002 Stage 1: 0.002 Stage 2: 0.020 Stage 3: 0.040 Stage 4: 0.060	Assumption from medical experts
3	Whether the patient completes their post-treatment surveillance	5 years	After five years, the patient completes their surveillance and transitions to FOBT screening.
Costs			
A	Carcino-embryonic antigen (CEA): every 3 months for years 1–3; Colonoscopy: scope in years 1 and 3; Physician visit: every 3 months for years 1–3, every 6 months for years 4–5; Computed axial tomography (CT) scan: 1 per year for years 1–3	CEA: $24 Colonoscopy: $211 Physician visit: $72 CT: $104	CancerCare Manitoba (2010d), p. 2; Manitoba Health (2010a), pp. A-7, J-8, T-5, V-11

3.3.1 Results

Table 29 presents the results of an inner loop simulation with 323,100 individuals in the colorectal cancer model. In this simulation, the entire cohort followed an approximation of current screening trends, using a proxy of the trends found in CancerCare Manitoba's (2010a) biennial report on the MBSP (p. 13). The model uses this proxy because the Colorectal Screening Program is too new to obtain reliable screening behaviour data.

Table 29: Colorectal cancer inner loop results

Statistic	Value
Mean cost per individual	$1,387
Standard deviation	$4,807
Minimum cost	$0
First quartile	$70
Second quartile (median)	$89
Third quartile	$183
Maximum cost	$92,477

The simulation provides some insight into the possible outcomes of the model. For example, the minimum cost of $0 would represent an individual who never screened and never developed colorectal cancer. The relatively low costs in the first, second, and third quartiles show that many cost observations will be low, since only a fraction of the individuals in the model actually developed colorectal cancer. On the other hand, the maximum cost of $92,477 likely represents an individual who developed cancer, underwent expensive treatment, and then experienced a recurrence, leading to more treatment.

Below are three histograms that depict the outcomes of the simulation above. Figure 28 shows the cost distribution of everyone in the model. The vast majority of observations fall under $300, so the higher costs can barely be seen on the diagram. Figure 29 shows the cost distribution for individuals who developed colorectal cancer, where most of the costs fall under $30,000, but a few very high costs lie along a "tail" to the right. There is also a large concentration of very low costs due to the low cost of treating stage 0 cancer (a polypectomy during a colonoscopy). Figure 30 depicts the distribution for people without cancer, where the costs are substantially lower, because they only include screening costs.

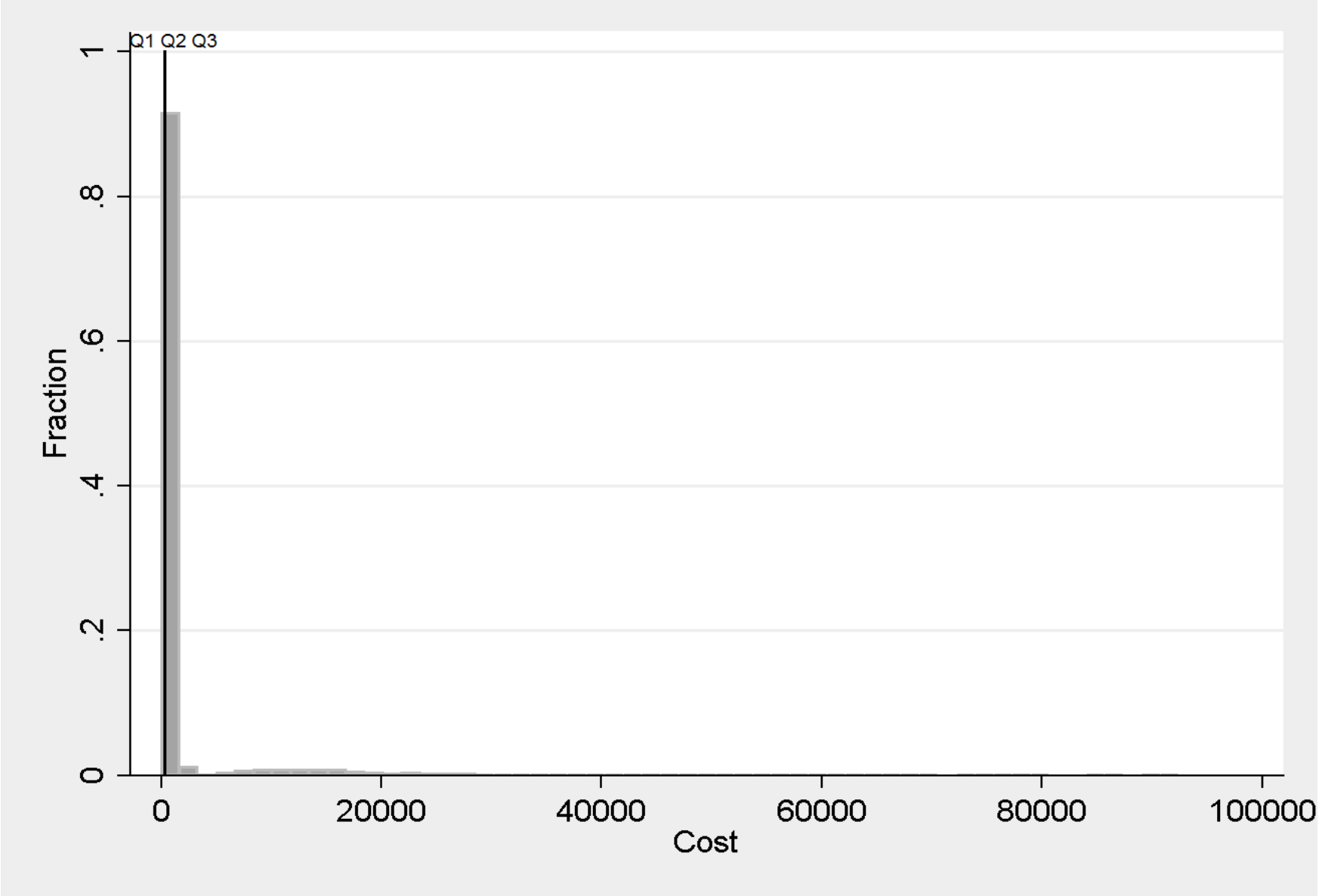

Figure 28: Colorectal cancer cost distribution, aggregate

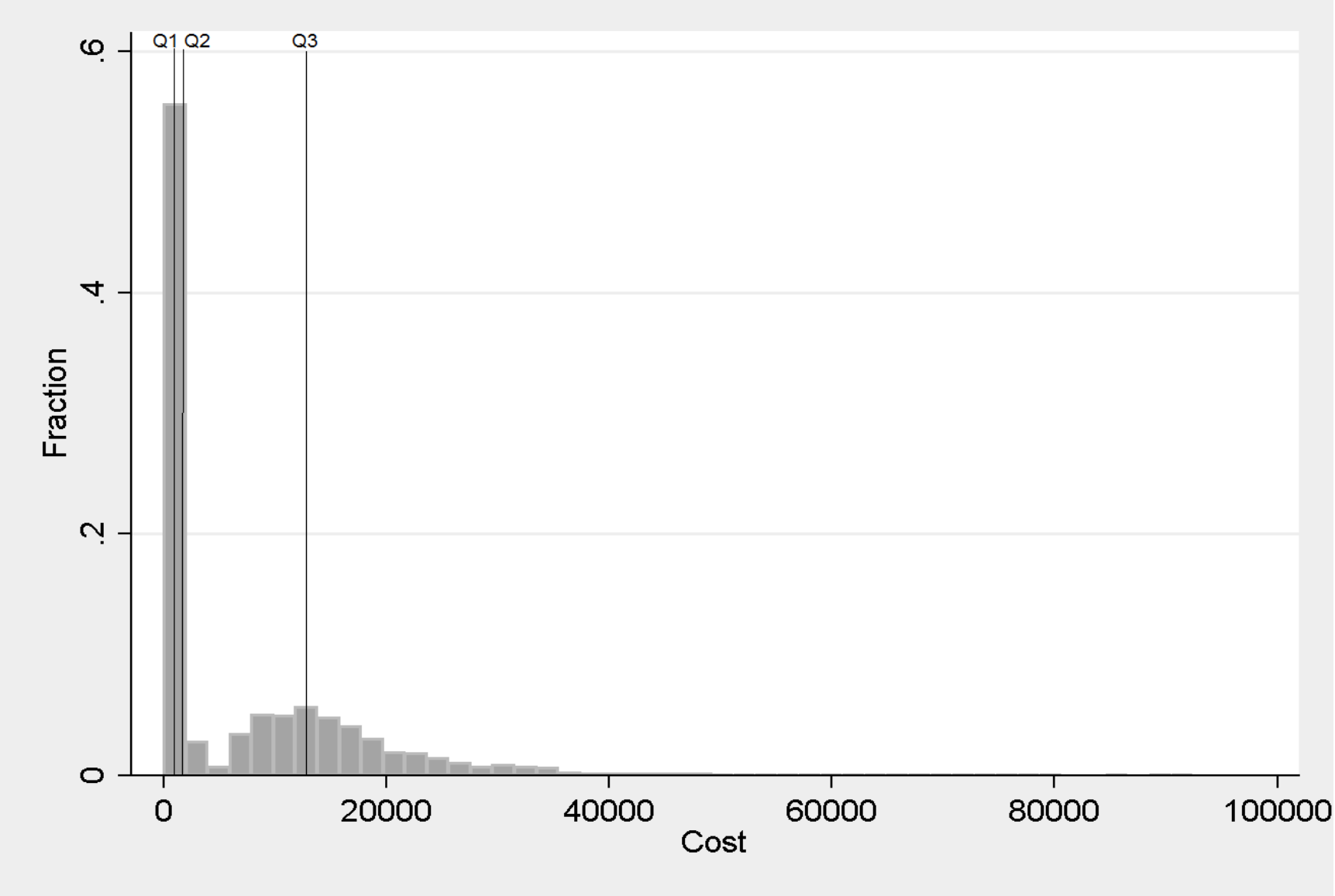

Figure 29: Colorectal cancer cost distribution, all individuals with cancer

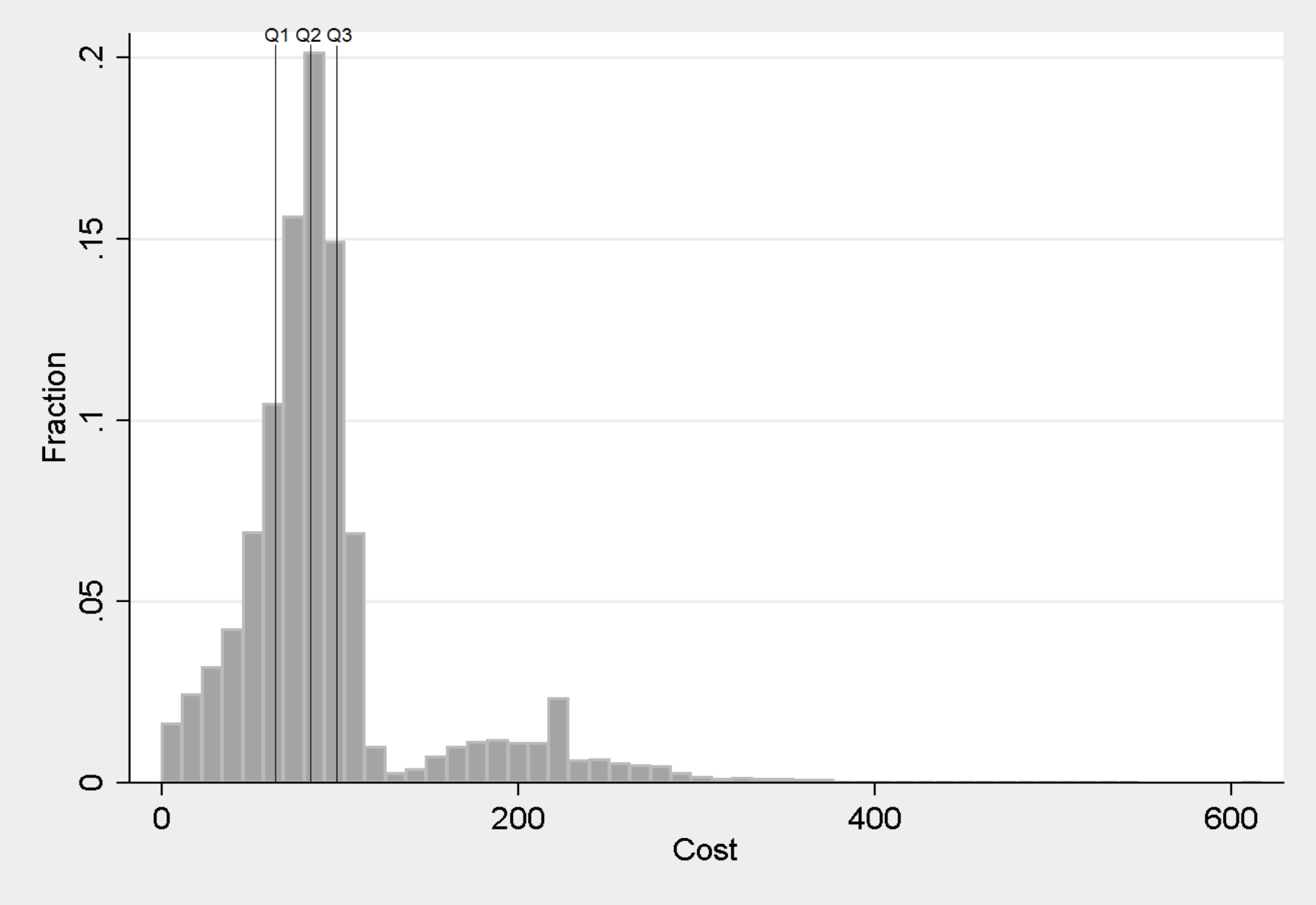

Figure 30: Colorectal cancer cost distribution, all individuals without cancer

The simulation recorded the number of cancer diagnoses received by individuals in the cohort over 25 years, broken down by stage of cancer. The program kept track of the highest level cancers diagnosed, so if an individual had stage 2 cancer, but then experienced a cancer recurrence, they were labelled as having stage 4 cancer. The distribution of the cancer stages was as follows:

Table 30: Colorectal cancer stages in the cohort

Health state	Percentage
No cancer	82.43
Stage 0	10.39
Stage 1	1.34
Stage 2	2.32
Stage 3	1.71
Stage 4	1.80

Given that the model used information from the CancerCare Manitoba report for the prevalence of colorectal cancer, and a study by Heitman et al. (2010), there is some degree of similarity expected in the simulated prevalence of cancer. Essentially, the simulation used the annual probability of developing cancer extrapolated from the reports (CancerCare Manitoba, 2010b, pp. 7, 42; Heitman et al., 2010, p. 4) for each year. For example, according to the CancerCare Manitoba report, about 0.8% of completed FOBTs resulted in an adenoma or advanced adenoma (considered stage 0 cancer in this study), and about 0.2% had invasive colorectal cancer. Over a 25-year time period, using the same yearly probability of developing any stage of cancer, one would expect that about 77.00% of the cohort would remain cancer-free. This is reasonably close to the 82.43% reported in the simulation.

As with the breast and cervical cancer models, the colorectal cancer model is likely to understate the prevalence of low stage cancer, and overstate the prevalence of high stage cancer. Once again, the difference could be explained by the fact that the simulation includes people in both their screening and non-screening years, where individuals in their non-screening years at risk of developing symptomatic cancer have a higher risk of a later stage of cancer. Another feature that could explain the difference is the fact that the simulation accounts for cancer recurrences over 25 years. For example, an individual could develop stage 1 cancer, but then experience a recurrence, labelling them as having stage 4 cancer instead of stage 1.

As mentioned in Section 2, when one introduces an outer loop to the Monte Carlo simulation, the program can generate a much more refined estimate of cost-effectiveness. Table 31 presents a number of results from the colorectal cancer simulations. In each case, it lists the cost per individual when there is no screening, versus the cost per individual when everyone follows the screening indicators associated with PIN. It then calculates the difference when switching from non-PIN to PIN screening, which will either represent an additional cost or cost avoidance per individual. Finally, it multiplies the additional or avoided cost per individual by the total number of individuals in the cohort (323,100) to calculate the total additional or avoided costs.

Table 31: Colorectal cancer cost-effectiveness results (no screening versus PIN screening)			
Description	**Original simulation**	**Refined cost-estimate simulation**	**Switch-point**
	Cost per individual	**Cost per individual**	**Cost per individual**
No cancer screening simulation over 25 years	$231	$1,524	$810
Full PIN screening simulation over 25 years	$395	$1,346	$810
Difference	$164	$178	$0
Count of simulated individuals	**Total estimated additional or avoided costs**	**Total estimated additional or avoided costs**	**Total estimated additional or avoided costs**
Simulation of 323,100 individuals	$52,988,400 additional cost	$57,511,800 avoided cost	$0

As in the sections above, the original simulation incorporates a limited number of costs taken from Manitoba. With these costs, the screening activity associated with PIN is not cost-effective compared to no screening whatsoever, leading to an increased cost of about $53.0 million. Under the refined cost-estimate structure, the screening behaviour associated with PIN is cost-effective compared to no screening whatsoever, generating a cost avoidance of about $57.5 million. The switch-point simulation results in average costs of $810 and was based on a 45% scaling of the difference between the original and refined simulation costs.

Table 32 presents the same information as Table 31, except instead of including a no cancer screening scenario, it includes current trend cancer screening versus PIN cancer screening.

Table 32: Colorectal cancer cost-effectiveness results (current trend screening versus PIN screening)			
Description	**Original simulation**	**Refined cost-estimate simulation**	**Switch-point**
	Cost per individual	**Cost per individual**	**Cost per individual**
Current trend cancer screening simulation over 25 years	$363	$1,379	$810
Full PIN screening simulation over 25 years	$395	$1,346	$810
Difference	$32	$33	$0
Count of simulated individuals	**Total estimated additional or avoided costs**	**Total estimated additional or avoided costs**	**Total estimated additional or avoided costs**
Simulation of 323,100 individuals	$10,339,200 additional cost	$10,662,300 avoided cost	$0

With the costs in the original simulation, PIN screening was not cost-effective compared to current trends, generating an extra cost of $10.3 million. With the costs in the refined simulation, PIN screening behaviour is cost-effective compared to current screening behaviour, generating a cost avoidance of about $10.7 million.

3.4 Diabetes

The diabetes model is guided by the following general assumptions. Each simulation begins with a cohort of 5,841 patients between the ages of 15 and 104, each of whom has been newly diagnosed with type 2 diabetes in the province of Manitoba, and follows their health outcomes and related health care costs for a pre-specified period.[7] The size and age distribution of the cohort was derived using recent data obtained from Manitoba Health and the National Diabetes Surveillance System.[8] It is important to distinguish between the *prevalence* of diabetes in Manitoba—that is, the number of people in the province who suffer from type 2 diabetes at any given time (73,467 in 2005)—from the *incidence* of diabetes, which refers to the number of new cases emerging in any given year. This research focused on newly diagnosed cases of type 2 diabetes because of the scarcity of data pertaining to the progression of diabetic complications among all Manitobans with the illness, which is likely to include patients who have had diabetes for many years and already suffer from one or more complications; imposing the assumption that patients have not experienced any diabetic complications prior to the first year of the simulation would not be credible. Because newly-diagnosed patients are expected to have experienced fewer complications on average than the general population of Manitobans with the disease, the models focused on this segment of the population.[9]

In each year, every patient has a probability of achieving or maintaining diabetic control, which is assumed to include appropriate management of levels of A1C, blood pressure, and lipids (i.e., high-density lipoprotein cholesterol [HDL-C], and total cholesterol), in line with the guidelines included in the 2010 Manitoba Diabetes Care Recommendations. The critical assumption underpinning the model is that relative to conventional diabetic control, intensive control will delay or prevent the progression of complications in patients with type 2 diabetes. Assumptions relating to diabetic control are discussed further in Section 3.4.1 below.

While all diabetes-related complications appear on the surface to be modelled as acute events, the model incorporates patients' histories of complications on outcomes in subsequent Markov cycles by using tracker variables, which change value when significant clinical events occur, and retain their value from one Markov cycle to the next. In the diabetes model, the severity of each diabetic complication is represented by a tracker variable that increases in value as the complication becomes more serious. The following assumptions guide the use of tracker variables in the diabetes model:

- The likelihood of acute events depends on the patient's current health state. For instance, the probability of mortality due to end-stage renal disease (ESRD) is assumed to be zero in the early stages of diabetic nephropathy. Thus, if the current value of the tracker variable for a particular patient is three (indicating ESRD), TreeAge—the software used

[7] Note that the length of the simulation can be varied, as appropriate.

[8] The steps involved in deriving the size and age distribution of the cohort are discussed in detail in Appendix B.

[9] The development of type 2 diabetes often precedes diagnosis by several years (Harris, Klein, Welborn, & Knuiman, 1992); therefore, some newly diagnosed patients already suffer from diabetic complications.

for the Markov modelling—assigns a positive probability of ESRD death in that Markov cycle; otherwise, the program assigns a probability of zero.[10]

- In any given Markov cycle, each tracker variable can either increase in value or remain constant; however, trackers are assumed never to decrease in value. In clinical terms, it is assumed that complications can only increase in severity over time.

The relatively "dense" structure of the decision tree means that patients can experience realistic combinations of diabetes-related health events within a single cycle. This is because, irrespective of the screening regimen received or the level of diabetic control attained, in each cycle, a patient is exposed to the risk of experiencing several types of acute events (e.g., cardiovascular or cerebrovascular events, lower extremity amputation (LEA), ESRD death), as well as potential progression of diabetic retinopathy and/or kidney disease. Thus, if a patient survives a myocardial infarction (MI), this does not preclude him or her from developing retinopathy in the same year of the simulation.[11]

3.4.1 Diabetic control

For an individual patient in the diabetes model, the progression of microvascular and macrovascular complications over time is assumed to be strongly influenced by his or her level of diabetic control, which refers to his or her management of levels of A1C, blood pressure, and lipids (i.e., HDL-C and total cholesterol). In any given Markov cycle, a patient is assumed to have some probability of achieving diabetic control. The critical assumption underlying the diabetes model is that relative to an uncontrolled state, patients achieving diabetic control face lower probabilities of experiencing diabetic complications; the nature of the relationship between diabetic control and the development and progress of complications is discussed more fully in Section 3.4.2 below.

The model defines controlled and uncontrolled diabetic states based on the distribution of 2010 Quarter 4 A1C test results from 4,902 diabetes patients being treated at a large clinic in Manitoba; these definitions are summarized in Table 33 below:

Table 33: Definitions of controlled and uncontrolled diabetic states in the diabetes model

Metric	Diabetic control	No diabetic control
A1C	6.6%	9.4%
Systolic blood pressure	122 mm Hg	170 mm Hg
Total cholesterol/HDL-C	3.8	5.9

[10] This approach enables health complications to interact in a myriad of ways. For example, there is a substantial literature arguing that diabetic nephropathy is associated with higher risks for cardiovascular conditions (Atthobari et al., 2006; Canadian Diabetes Association, 2008; Gross et al., 2005; Incerti, Zelmanovitz, Camargo, Gross, & de Azevedo, 2005). In future revisions, the model could be modified so that the probability of a myocardial infarction in a particular patient increases with the progression of diabetic kidney disease, by referencing the current value of the nephropathy tracker variable.

[11] This compares favourably, for example, with Grima, Thompson, and Sauriol (2007), who impose the assumption that diabetes patients cannot experience more than one diabetic complication in a single Markov cycle in order to simplify the structure of their model.

The values in the table were calculated by:

- Determining the average A1C values for patients with A1Cs below and above 8.0, which, according to the medical experts, constitutes a reasonable threshold for distinguishing between tight and less tight diabetic control

- Calculating the percentage difference between these A1C values and definitions and, respectively, the target value specified in current Manitoba diabetes treatment guidelines (Manitoba Health, 2010a) and a value from the literature typifying "conventional" diabetic control among Canadian patients with type 2 diabetes (S. B. Harris et al., 2006)[12]

- Applying the same percentage differences identified for A1C to corresponding values for systolic blood pressure and total cholesterol/high-density lipoprotein cholesterol listed in the above-mentioned sources

The following two assumptions are important for understanding how diabetic control affects model outcomes:

- The model assumes that a patient's probability of achieving diabetic control in any given Markov cycle is independent of his or her success in achieving diabetic control in the past; that is, knowing a patient's history of diabetic control does not help predict what level of control he or she will achieve in the future.

- The direct benefits of achieving control do not carry over into subsequent Markov cycles; that is, the lower probability of experiencing acute events and/or progression of diabetes-related complications applies only in this Markov cycle.

Please also note that according to the Manitoba A1C test result data, approximately 70% of diabetes patients achieve an A1C lower than 8.0%; for the purposes of the diabetes model, it is therefore assumed in the baseline scenario that on average, 70% of the patients run through the model will achieve diabetic control in a given Markov cycle.

[12] According to the *Manitoba Diabetes Care Recommendations*, diabetes patients should be treated to a target blood glucose level of 7.0% or lower. Harris et al. (2006) examine 549 patient charts provided by 56 family physicians in four Canadian cities and find an average A1C value of 7.7%.

3.4.2 Transition probabilities

Four types of probabilities drive the diabetes model. These include:

- The probability of achieving diabetic control in each Markov cycle, as defined in Section 3.4.1 above
- The probabilities associated with the progression of patients' diabetic complications as well as the likelihood of acute events, when they do not achieve diabetic control
- The probabilities associated with the progression of patients' diabetic complications as well as the likelihood of acute events, when the patient achieves diabetic control
- The probabilities associated with events, the outcomes of which are assumed not to depend on diabetic control

The likelihood of achieving diabetic control is a value between zero and one that is assumed to remain constant within each set of simulations; as discussed above, in the baseline scenario, it is assumed that in every given Markov cycle a patient has a 70% probability of achieving diabetic control. However, by varying this probability it is possible to assess how the likelihood of achieving intensive control affects costs accruing to the Manitoba health care system.

For macrovascular (i.e., cardiovascular and cerebrovascular) events, the model employs the equations underpinning the UK Prospective Diabetes Study (UKPDS) Risk Engine to estimate the likelihood of myocardial infarction (fatal or non-fatal) or sudden death or stroke, as well as the probability of death conditional on having experienced those events (Kothari, 2002; Stevens, Kothari, Adler, Stratton, & Holman, 2001; Stevens et al., 2004). Although a detailed discussion of the UKPDS Risk Engine and the calculation of probabilities for the model is provided in Appendix A, it is important to point out here that the various elements of diabetic control (i.e., A1C, blood pressure, and lipids) enter directly into the UKPDS Risk Engine equations, and so influence the probability of macrovascular outcomes. Effectively, these factors drive the chance of these events in the model.

For microvascular complications, probabilities associated with the controlled and uncontrolled states were derived primarily from the results of large clinical trials, including the UKPDS. Although this process is described in more detail in Appendix A, it is important to note that:

- Following an earlier model developed by Hoerger, Hicks, and Bethke (2004), PRA's model incorporates the assumption that A1C and blood pressure are the critical dimensions of diabetic control underpinning the progression of microvascular complications; that is, lipids are assumed to play a minimal role in the development and progression of retinopathy, nephropathy, and peripheral neuropathy.
- Where both A1C and blood pressure affect the progression of microvascular complications, only the factor with the largest impact on the likelihood of progression is incorporated into the model.

3.4.3 Complication costs

The diabetes model focuses solely on *complication costs*, which are the financial costs involved in managing the consequences of the progression of diabetes-related health complications and responding to acute events resulting from those complications. The model does *not* incorporate the costs of managing diabetic control, such as expenditures associated with physician care, screening, and pharmaceuticals.[13] This is discussed in more detail below in Section 6.3. Following O'Brien, Patrick, and Caro (2003), complication costs are assumed to include *event costs* and *state costs*:

- *Event costs* refer to "resource use specific to the defining clinical event [including] both acute care (initial management in an inpatient or outpatient setting) and event-related health care delivered subsequently in the first year."

- *State costs* refer to "the annual management costs for years subsequent to the event year and reflect the typical utilization of health care services for the ongoing management of the given health state." (O'Brien et al., 2003)

It is important to recognize the following assumptions underpinning the cost estimates provided in this section of the report:

- Following standard practice in economic evaluation, it is assumed that deferred costs are worth less in *present value terms* than costs payable today. This reflects the notion that a dollar payable one year from now could in principle be invested and earn its owner a positive return before he or she parts with it; if the dollar is instead payable today, the owner must forgo this return.[14] Therefore, even if (hypothetically) diabetic control served only to defer costly treatment, this in itself would have intrinsic value because those costs would be pushed into the future. In the diabetes model, future costs are converted into present value terms using a discount rate of 5%, as is typical in many current health studies.

- If a patient experiences a macrovascular or microvascular event, the health care system incurs the event cost in this Markov cycle; however, the system continues to incur the state cost associated with that event in each subsequent cycle, even if the patient experiences no additional events until either the simulation ends or the patient dies.

- If the patient dies as a result of a diabetes-related health complication, the health care system is assumed to incur half of the full event cost (assuming that, on average, patients would die halfway through the year), since any interventions that would have been required later in the year had the patient survived are no longer needed.

[13] The distinction between complication costs and management costs is attributable to Ray et al. (2005).

[14] The present value formula $PV = FV/(1+i)^T$ describes the relationship between present and future value. "T" is the number of years the cost or revenue is incurred and "i" is an appropriate discount rate.

Because the model does not incorporate any of the costs involved in carrying out interventions aimed at improving diabetic control, the interpretation of simulation results is slightly different than that applicable to the cancer models. To the extent that improved diabetic control delays or prevents the development and progression of microvascular and macrovascular complications, complication costs associated with diabetic control will usually be lower than the costs experienced in the uncontrolled state. Whether achieving diabetic control results in cost avoidance, however, requires an assessment of whether the present value of avoided costs resulting from the delay or prevention of diabetic complications is more or less than the present value of the cost increases needed to undertake the interventions required to achieve this level of control.

To simplify discussion of data sources for the diabetes model, the model is conceptually divided into three parts, including the model "roots," and the sub-trees modelling patients' ongoing exposure to risks associated with macrovascular and microvascular complications.

3.4.4 Diabetic control sub-tree

Figure 31 shows the "roots" of the diabetes model in which patients either achieve or fail to achieve diabetic control in each Markov cycle. A patient begins each Markov cycle in one of the three health states depicted in the figure, which include two diabetic control states and an absorbing state (i.e., death) containing all members of the cohort who have succumbed either to a diabetes-related complication or an unrelated malady in a previous cycle. At the beginning of the first Markov cycle, the population will consist of newly diagnosed type 2 diabetes patients who achieve or fail to achieve diabetic control.[15]

The green circles in Figure 31 denote chance nodes, where a patient's movement through the model depends on transition probabilities incorporated in the model; in Figure 31, the two chance nodes denoted by #4 and #5 reflect the chances that a patient achieving or failing to achieve diabetic control dies of non-diabetes-related causes. The two triangles situated to the right of these nodes denote terminal states representing situations where a patient dies as a result of a non-diabetes-related malady; in all subsequent cycles, this patient would "reside" in the absorbing (i.e., death) state represented by node #3.

The numbers in Figure 31 correspond to a row in Table 34, which reports an estimate of the probability and provides an interpretation of it. It is important to point out that the collection of branches shown in Figure 32 (the macrovascular complication sub-tree) appears in TreeAge at the ends of the two chance nodes at the right edge of Figure 31. Note that the [+] symbol indicates that a segment of the decision tree has been rolled up for illustrative purposes, and that the tree actually extends much further to the right.

[15] Note that no patients begin the simulation in the absorbing state.

After being sorted into the controlled or uncontrolled state, each patient faces a series of probabilities affecting his or her likelihood of experiencing both microvascular and macrovascular complications in this Markov cycle. The magnitude of those probabilities depends in large part on the diabetic control state to which the patient was assigned, as discussed below.

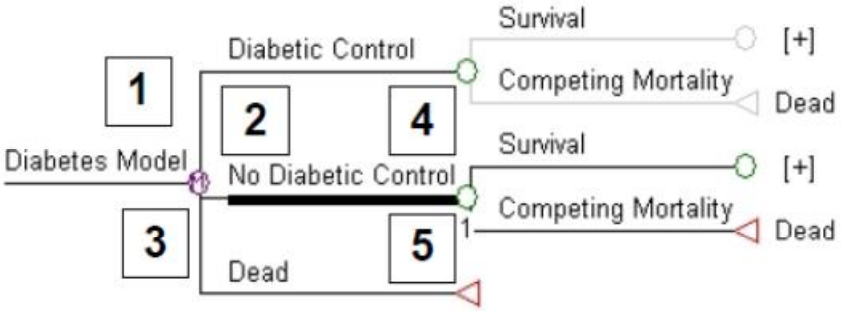

Figure 31: Diabetic control sub-tree

As noted, Table 34 reports estimates of transition probabilities and costs in the diabetic control sub-tree, where each number in Figure 31 corresponds to a row in the table.

Table 34: Transition probabilities and costs – "Diabetic control" sub-tree

Node # or Cost	Description	Estimate	Source
Transition probabilities			
1	Likelihood that an individual patient enters the simulation with diabetic control	0.70	Manitoba A1C test results
2	Likelihood that an individual patient enters the simulation without diabetic control	0.30	
3	Likelihood that an individual patient will begin each simulation in the absorbing state (i.e., death)	0	Assumption
4, 5	The probability of surviving death due to non-diabetes-related causes (assumed not to depend on level of diabetic control)	Age-dependent	Statistics Canada (2006); the probabilities associated with this outcome vary according to age. See Appendix A for the full list of estimates and the assumptions on which they are based.
Costs			
N/A	N/A	N/A	N/A

3.4.5 Macrovascular complications sub-tree

Figure 32 shows the segment of the diabetes model dealing specifically with macrovascular complications, namely cardiovascular (CVD) and cerebrovascular disease. As above, Table 35 presents the chance nodes associated with this part of the model, and describes the related probabilities. Again, the green circles represent chance nodes in the decision tree; the numbers in the figure correspond to a row in Table 35, which offers an interpretation of the associated probability as well as an estimate of its value. As already noted, in TreeAge, the macrovascular sub-tree appears at the ends of the two chance nodes at the right edge of Figure 31 above, while the tree segment depicted in Figure 33 (depicting the microvascular sub-tree) attaches to the right edge of Figure 32. The two red triangles denote terminal states representing situations where a patient dies as a result of a macrovascular event; in all subsequent cycles, this patient would "reside" in the absorbing (i.e., death) state in Figure 31.

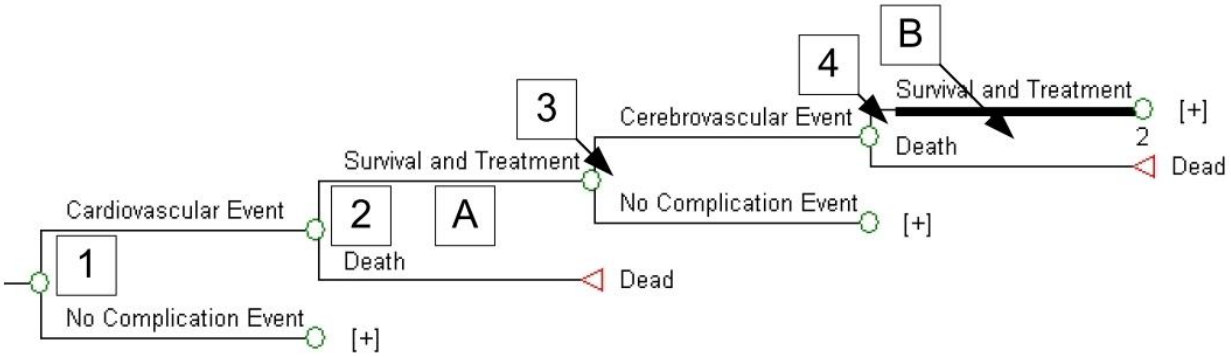

Figure 32: Macrovascular complications sub-tree

The [+] symbols underneath nodes #2 and #4 indicate segments of the decision tree that are duplicates of other parts of the tree. For example, if at decision node #2, a particular patient does not suffer a cardiovascular event, he or she would effectively "skip" decision node #2 (having not suffered an event, there is no need for treatment and no probability of death), and would then be exposed to the risk of a cerebrovascular event, the same as if he or she *had* suffered a cardiovascular event and survived. Put another way, when the decision tree is fully extended, the segment of Figure 32 from chance node #3 onward appears at the end of the "No Complication Event" branch at chance node #2. However, because the probabilities are defined in the same way, irrespective of where they appear in the model, they are only reported once in Table 35.

Since macrovascular events imply substantial financial costs for the health care system, letters "A" and "B" in Figure 32 show those points in the model where costs are incurred for cardiovascular and cerebrovascular events, respectively. It is important to emphasize that if a macrovascular event is experienced in this Markov cycle, the model would record a value for that patient equal to the full event cost if the patient survives, and half the event cost if the patient dies. If the patient survives, in all subsequent cycles (prior to the patient's death or the end of the simulation), the model records a value equal to the *state cost* for that type of macrovascular event unless the patient experiences another event.

Table 35 reports the transition probabilities and complication costs for the macrovascular sub-tree. Because it is assumed that chance node probabilities will differ in patients with diabetic control from other patients, Table 35 reports separate probabilities for each patient segment.

Table 35: Transition probabilities and costs – "Macrovascular complications" sub-tree

Node # or Cost	Description	Estimate		Source
		Diabetic control	No diabetic control	
Transition probabilities				
1	The probability of experiencing a CVD event (fatal or non-fatal MI or sudden death) during this Markov cycle	Varies with duration of diagnosed diabetes	Varies with duration of diagnosed diabetes	Stevens et al. (2001); Stevens et al. (2004); Kothari (2002) See Appendix A for the full list of estimates and the assumptions on which they are based.
2	The probability of a fatal MI, conditional on an MI occurring			
3	The probability of experiencing a stroke during this Markov cycle			
4	The probability of a fatal stroke, conditional on a stroke occurring	If no previous strokes: 0.0967; otherwise: 0.4939	If no previous strokes: 0.2618; otherwise: 0.7638	Stevens et al. (2004)
Costs				
A	Patient experiences a cardiovascular event	**If the patient survives:** - *Event costs:* $22,667 - *State costs:* $1,451 **If the patient dies:** - *Event costs:* $11,333 - *State costs:* $0		O'Brien et al. (2003) Assumption: If the patient dies within 12 months of the event, the health care system incurs half the cost that would be generated if the patient had survived.
B	Patient experiences a cerebrovascular event	**If the patient survives:** - *Event costs:* $40,451 - *State costs:* $10,666 **If the patient dies:** - *Event costs:* $20,226 - *State costs:* $0		O'Brien et al. (2003) Assumption: If the patient dies within 12 months of the event, the health care system incurs half the cost that would be generated if the patient had survived.

Note: All cost estimates have been converted to 2010 Canadian dollars.

It should be noted that the probability of mortality following a stroke depends in part on a patient's history of stroke; if he or she has not experienced a stroke in the past, his or her probability of survival is approximately 74–90%, while the probability of survival falls to about 24–51% for survivors of previous strokes. To enable the probability of survival to depend on a patient's history of stroke, the model incorporates a tracker variable that increments when he or she suffers his or her first stroke. In all subsequent Markov cycles for that patient, the model references the new value of the tracker variable in survival calculations.

3.4.6 Microvascular complications sub-tree

Figure 33 depicts the diabetes model sub-tree representing the development and progression of neuropathy, retinopathy, and nephropathy. As above, the green circles represent chance nodes in the decision tree; the numbers in the figure correspond to a row in Table 36, which offers an interpretation of the associated probability as well as an estimate of its value. In TreeAge, the microvascular sub-tree would appear at the ends of the chance nodes appearing at the right edge of Figure 32 (the macrovascular sub-tree); because of the recursive structure of the diabetes model, in fact, the full model contains many copies of the microvascular sub-tree. The two red triangles to the right of nodes #3 and #6 denote terminal states representing situations where a patient dies as a result of an LEA or ESRD, respectively.[16] In all subsequent cycles, this patient would "reside" in the absorbing (i.e., death) state in Figure 31. Each set of branches has been assigned a number that refers to a row in Table 36, and a letter is used to denote any place a cost is, or could potentially be, incurred by the health care system.

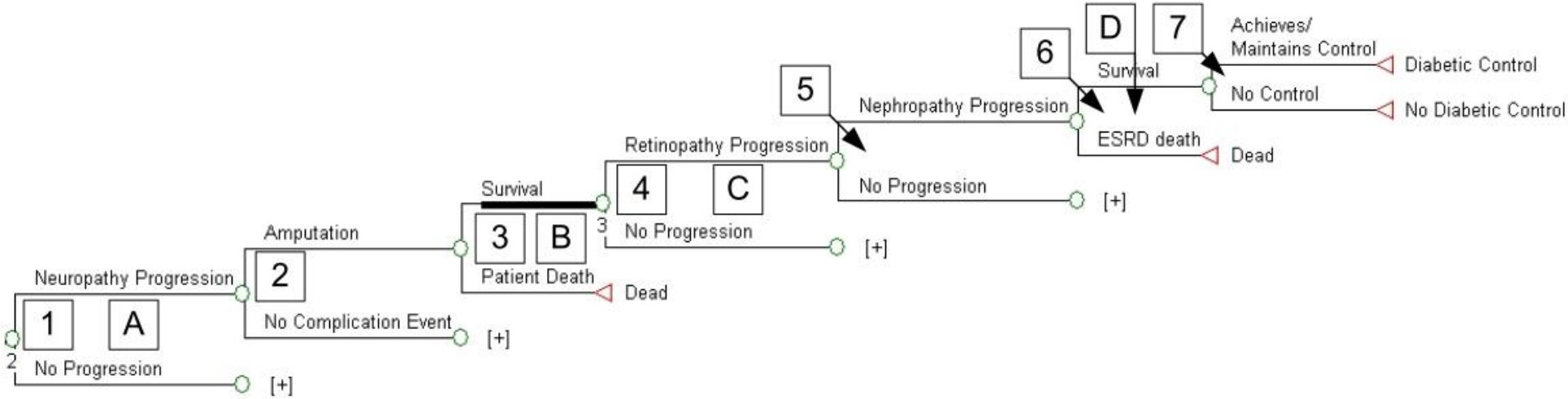

Figure 33: Microvascular complications sub-tree

[16] Though debilitating, the ultimate result of diabetic retinopathy (blindness) is not in itself fatal, and therefore retinopathy does not lead to the model's absorbing state.

It is important to recognize that the event-based orientation to the progression of microvascular complications not fully depicted in Figure 33 conceptually rests on top of a substructure of tracker variables representing discrete levels of severity associated with each of the three types of complications:

- *Neuropathy* is represented by a tracker variable with two values, reflecting the presence or absence of peripheral neuropathy. It is assumed that a patient will not experience an LEA unless he or she has first developed neuropathy.[17]

- *Retinopathy* is represented by a tracker variable with three values, reflecting the presence of either no/early retinopathy, severe retinopathy requiring photocoagulation, and blindness.

- *Nephropathy* is represented by a tracker variable with four values, reflecting the presence of either normoalbuminuria (no nephropathy), microalbuminuria, macroalbuminuria, and ESRD. It is assumed that a patient cannot die from nephropathy unless he or she has first reached ESRD.

It is important to emphasize that if a patient experiences progression of a microvascular complication during a given Markov cycle, TreeAge records a value for that patient equal to the full event cost if the patient survives, and half the event cost if the patient dies. If the patient survives, in all subsequent cycles (prior to the patient's death or the end of the simulation), the model records a value equal to the *state cost* associated with that level of severity of that microvascular complication unless the patient either experiences another event (in the case of LEA), or the complication increases in severity.

Table 36 reports both the cost and probability estimates for the microvascular sub-tree, and lists both the assumptions leading to those estimates as well as the sources used to derive them. Please note that the majority of the estimates included in the table do not appear directly in the literature, but were derived from various sources so as to align with the definitions of the controlled and uncontrolled states listed in Section 3.4.1 above. The derivation process is described in greater detail in Appendix A. Because it is assumed that chance node probabilities will differ in patients with diabetic control from other patients, Table 36 reports separate probabilities for each patient segment.

[17] The evidence suggests that 20% of foot ulcers develop in patients with no neuropathy (Reiber, Boyko, & Smith, 1995). Unfortunately, no estimate of the incidence of LEA in diabetic patients without neuropathy has been found to date.

Table 36: Transition probabilities and costs – "Microvascular complications" sub-tree				
Node # or Cost	**Description**	**Estimate**		**Source**
		Diabetic control	**No diabetic control**	
Transition probabilities				
1	The probability of developing peripheral neuropathy	0.0261	0.0459	UK Prospective Diabetes Study Group (1998a), adapted by Hoerger et al. (2004), p. 14
2	The probability of experiencing a lower extremity amputation, conditional on already having developed peripheral neuropathy	If no previous LEA: 0.0055; otherwise: 0.0392	If no previous LEA: 0.0277; otherwise: 0.1851	**Repeat LEA (no control):** Reiber et al. (1995), in Hoerger et al. (2004), p. 14 **Neuropathy to LEA (no control):** Humphrey et al. (1994), in Hoerger et al. (2004), p. 14 **Repeat LEA and neuropathy to LEA (control):** UK Prospective Diabetes Study Group (1998a), fig. 4; Adler et al. (2000), fig. 4 Assumption: LEA happens only in diabetes patients who have already experienced neuropathy.
3	Probability of a patient surviving a lower extremity amputation within 12 months of the procedure	0.9523	0.8332	**Mortality (no control):** Reiber et al. (1995), p. 419, adapted by Hoerger et al. (2004), p. 30 **Mortality (no control):** Stratton et al. (2000), p. 408; Adler et al. (2000), fig. 4
4	The probability that diabetic retinopathy will develop or progress to a more severe state	No/early retinopathy → photocoagulation:		UK Prospective Diabetes Study Group (1998a, 1998b), in CDC Diabetes Cost-Effectiveness Group (2002), pp. 2545–2546
		0.0065	0.0265	
		Photocoagulation → blindness:		UK Prospective Diabetes Study Group (1998b), fig. 5, in Hoerger et al. (2004), p. 15 Assumption: Glycemic and blood pressure control do not influence the transition from photocoagulation to blindness.
		0.1010	0.1010	
5	The probability that diabetic kidney disease (nephropathy) will develop or progress to a more severe state	No nephropathy → microalbuminuria:		**No nephropathy to microalbuminuria (no control):** CDC Diabetes Cost-Effectiveness Group (2002), pp. 2545–2546 **Microalbuminuria to macroalbuminuria (no control):** CDC Diabetes Cost-Effectiveness Group (2002), pp. 2545–2546 **Macroalbuminuria to ESRD (no control):** Eastman et al. (1997); Humphrey et al. (1989), as reported in Hoerger et al. (2004) **All nephropathy transitions (control):** ADVANCE Group (2008), p. 2567; de Galan et al. (2009), p. 886 Assumption: Blood pressure does not affect the likelihood of transition from macroalbuminuria to ESRD.
		0.0196	0.0813	
		Micro → Macroalbuminuria:		
		0.0758	0.1700	
		Macroalbuminuria → ESRD:		
		0.0077	0.0500	
6	The probability of surviving to the end of the current Markov cycle with or without diabetic nephropathy	If patient has ESRD: 0.9711 Otherwise: 1	If patient has ESRD: 0.8225 Otherwise: 1	**ESRD to death (no control):** Canadian Institute for Health Information (CIHI) (2010)* **ESRD to death (control):** CIHI (2010);* ADVANCE Group (2008), p. 2567 Assumption: 100% probability of surviving nephropathy, unless in ESRD. Assumption: Blood pressure level does not affect the probability of ESRD death.
7	The probability of achieving or maintaining diabetic control in the next Markov cycle	Variable		Determined through initial probabilities

Table 36: Transition probabilities and costs – "Microvascular complications" sub-tree				
Node # or Cost	**Description**	**Estimate**		**Source**
		Diabetic control	**No diabetic control**	
Costs				
A	Patient develops symptomatic neuropathy	*Event costs:* $180 *State costs:* $186		O'Brien et al. (2003); Singh, Armstrong, and Lipsky (2005)
B	Patient requires lower extremity amputation	**If the patient survives:** - *Event costs:* $29,902 for the first LEA; $31,179 for every subsequent LEA - *State costs:* $1,241 **If the patient dies:** - *Event costs:* $14,951 if patient dies after the first LEA; $15,590 thereafter - *State costs:* $0		O'Brien et al. (2003) Assumption: State cost is derived by multiplying the event cost of foot ulcers ($2,655) by their prevalence in the diabetic population (~7%), assuming most ulcers occur in patients who already suffer from neuropathy. Assumption: If the patient dies within 12 months of the event, the health care system incurs half the cost that would be generated if the patient had survived.
C	Patient has advanced diabetic retinopathy requiring photocoagulation	No retinopathy → photocoagulation: *Event costs:* $532 *State costs:* $49 Photocoagulation → blindness: *Event costs:* $0 *State costs:* $2,568		O'Brien et al. (2003); National Eye Institute (2010) Assumption: The cost of photocoagulation is the un-weighted average of the cost of proliferative diabetic retinopathy, and proliferative diabetic retinopathy with macular oedema.**
D	The probability that diabetic kidney disease (nephropathy) will develop or progress to a more severe state	No nephropathy → microalbuminuria: *Event costs:* $75 *State costs:* $12 Micro → Macroalbuminuria: *Event costs:* $66 *State costs:* $22 Macroalbuminuria → ESRD: **If the patient survives:** - *Event costs:* $38,343 - *State costs:* $76,685 **If the patient dies:** - *Event costs:* $38,343		O'Brien et al. (2003) Assumption: When a patient enters the ESRD state or dies of ESRD, the health care system incurs an amount equal to half the state cost for that year; this is done because the patient could in theory begin or cease dialysis treatment at any point during the year.

Note: All cost estimates have been converted to 2010 Canadian dollars.

* The baseline transition probability is derived from CIHI data in the following way. In 2008, approximately 37.5% of ESRD patients in Manitoba had transplants, while the remainder received dialysis. In Canada, for the same year, of 21,182 ESRD patients beginning the year with dialysis, 3,543 died (13.4%), compared with 201 deaths among the 14,147 patients with transplants (1.3%). The weighted average of mortality associated with the two treatment methods is therefore: (1-0.1340)* (0.625) + (1-0.0130)*(0.375) = 0.9114. This value is then calibrated to align with the controlled and uncontrolled states, as described in Appendix A.

** Please note that the prevalence of macular oedema without accompanying proliferative diabetic retinopathy is not known, and thus the costs do not incorporate expenditures associated with treatment for this condition alone.

3.4.7 Results

The cost-effectiveness analysis in this part of the study consists of a series of Monte Carlo simulations based on the diabetes model outlined above. Each simulation involves running 5,841 newly diagnosed type 2 diabetics between the ages of 15 and 104 through the model over a period of 40 Markov cycles, where each cycle represents one year. As noted in Appendix B below, the size of the cohort was determined using recent Manitoba diabetes incidence data, while the cohort's age distribution was established using age-specific Canadian diabetes incidence date from the National Diabetes Surveillance System (NDSS).[18]

Table 37 presents the results of an inner loop simulation with 5,841 individuals in the diabetes model, based on the assumption that each individual had a 70% chance of achieving diabetic control in each Markov cycle:

Table 37: Diabetes inner loop results

Statistic	Value
Mean cost per individual	$19,394
Standard deviation	$36,782
Minimum cost	$0
First quartile	$4,988
Second quartile (median)	$8,404
Third quartile	$22,067
Maximum cost	$857,738
Total cost*	**$113,280,354**

* Total cost is derived by multiplying the mean cost per individual by the size of the starting cohort.

The simulation provides some insight into the possible outcomes of the model. For example, the minimum cost of $0 would represent an individual who experienced no diabetic complications. The relatively low costs in the first, second, and third quartiles show that many cost observations will be low, since many individuals experienced few diabetic complications or did not reach late stages of progression during which costs of managing complications are relatively large. On the other hand, the maximum cost of $857,738 likely represents an individual who experienced multiple complications during the simulation, some or all of which reached an advanced stage.

Below is a histogram that depicts the outcomes of the simulation above. Figure 34 shows the cost distribution for the entire model cohort. As shown, the bulk of the simulations fall below approximately $100,000. However, there are a handful of diabetes patients with extremely high costs along the right "tail" of the distribution; these patients are so uncommon that they cannot be seen in the figure.

[18] Age-specific diabetes incidence data for Manitoba was not available from the NDSS.

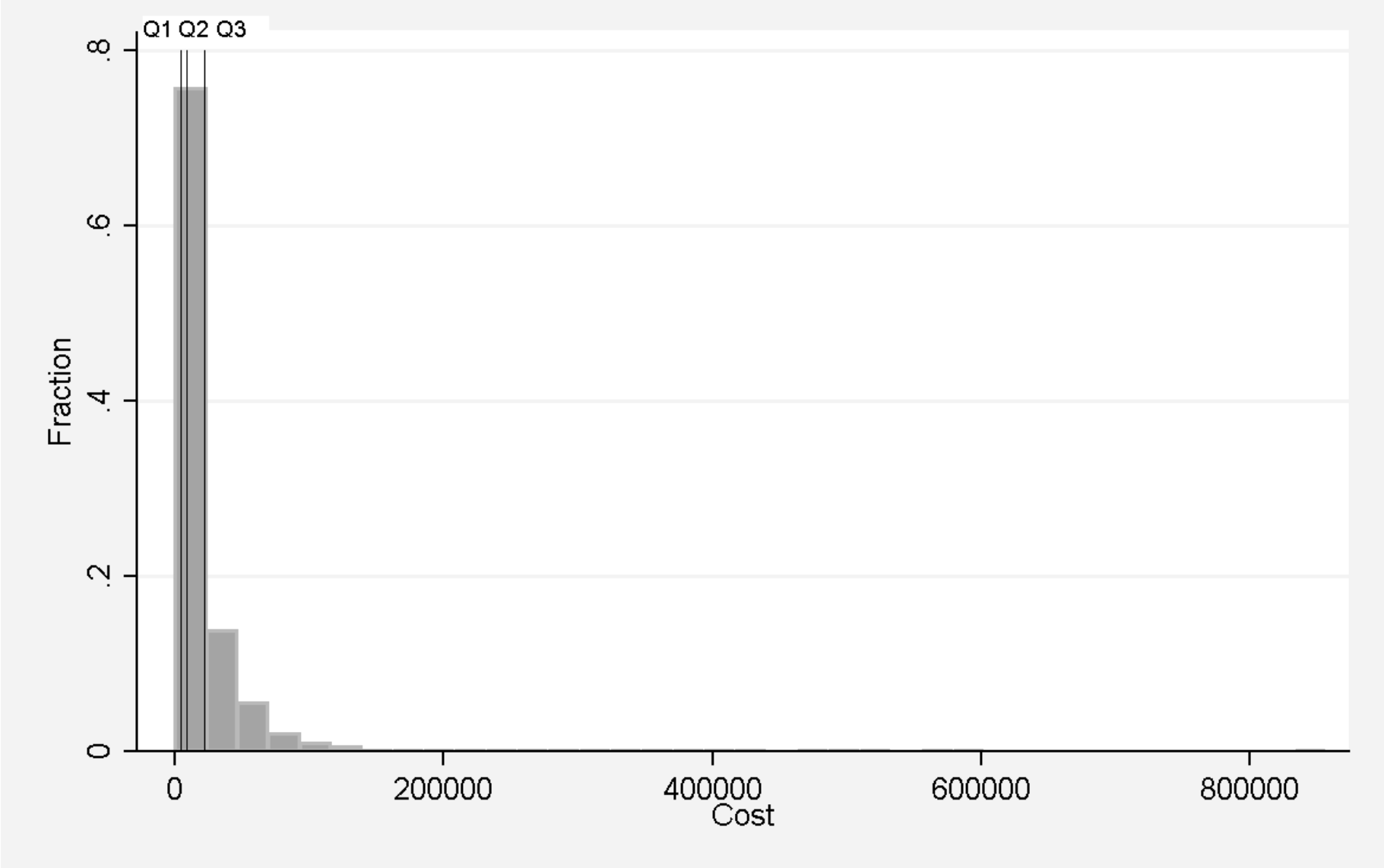

Figure 34: Diabetes Monte Carlo simulation: distribution of costs

As mentioned in Section 2, when an outer loop is introduced in the Monte Carlo simulation, the program can generate a much more refined estimate of cost-effectiveness. Table 38 presents results from two diabetes model simulations that include outer loops of 1,000 recalculations.[19] The first simulation assumes that each individual has a 70% chance of achieving diabetic control in each Markov cycle, consistent with the findings from Manitoba A1C test result data (see Section 3.4.1 above). By contrast, the second simulation assumes each individual has a 100% chance of achieving diabetic control in each Markov cycle; in other words, every member of the cohort achieves diabetic control and maintains it over his or her entire lifetime.

The table lists the cost per individual for each simulation, and then calculates the difference when switching to an intervention ensuring full diabetic control for all members of the cohort. Since the costs of administering this intervention are not included in the model (see Section 3.4.3 above) it will result in positive cost avoidance when averaged across individuals. Finally, the table reports avoided cost per individual by the total number of individuals in the cohort (5,841) to calculate cost avoidance from the perspective of the Manitoba health care system.

Table 38: Diabetes cost-effectiveness results (70% control versus 100% control)

Description	Original simulation Cost per individual
70% diabetic control simulation over 40 years	$20,003
100% diabetic control simulation over 40 years	$19,822
Difference	$181
Count of simulated individuals	**Total estimated cost avoidance**
Simulation of 5,841 individuals	$1,057,221 savings

As shown in the table, an intervention increasing an individual's likelihood of diabetic control in each Markov cycle from 70% to 100% generates present value avoided costs of $181 per individual, or $1,057,221 in total. However, it is critical to recognize that these results include only the financial costs involved in managing the consequences of the progression of diabetes-related health complications and responding to acute events resulting from those complications; that is, they do *not* include the financial costs involved in carrying out interventions aimed at managing diabetic control. As discussed in Section 3.4.3 above, to determine whether these interventions are ultimately cost-effective, it is necessary to also estimate the present value of any costs involved in increasing the level of diabetic control. If the present value of avoided costs resulting from a given increase in diabetic control exceeds the present value of increased expenditures required to carry out interventions generating that increase in control, it can be argued that the interventions contribute to net cost avoidance.

[19] To clarify, the results reflect the outcomes of 1,000 simulations, each incorporating a cohort of 5,841 individuals.

4.0 Conclusion

The micro-simulation process undertaken as part of this study represents an important tool in the estimation of primary care cost-effectiveness. Using information available in the medical literature, data from the province of Manitoba, and expert opinion, the models allow one to prospectively assess the cost implications of various primary care activities. In this case, these activities involve screening related to breast cancer, cervical cancer, colon cancer, and diabetes management as undertaken through alignment with CIHI evidence-based indicators currently monitored by PIN. This prospective approach has a considerable advantage over retrospective CEA in that it allows for primary care planning without the need to undertake a prolonged data collection and analysis period.

More broadly, CEA represents an important tool for health policy making. As this report acknowledges, a variety of factors require consideration when making decisions at the provincial level. Certainly, patient care, quality of life, and the social impact of policy decisions merit careful consideration. However, in the face of increasing costs of treatment and increasing demand for services, budgetary considerations loom large. The reality is that provinces face finite health budgets, and initiatives that potentially avoid downstream costs may free up resources for greater or improved care. To the extent that this represents a desirable health care system outcome, cost-effectiveness may also help inform practice.

All that said, the current approach to cost-effectiveness does have limitations. In particular, the findings of any analysis rest heavily on the availability of credible data to support modelling. In the case of the cancer modelling, information on provincially specific costs was limited. As a result, the analysis needed to assess the sensitivity of the models to changes in these costs. Specifically, the analysis needed to determine how higher model costs incorporating additional system costs—taken from other jurisdictions—would affect the estimated cost-effectiveness. In addition, developing transition probabilities required assumptions to make information from the literature fit with the details of the current analysis.

4.1 Cancer model results

All of the cancer models attempted to assess cost-effectiveness of primary care activity by comparing the alignment of primary care screening practice to PIN cancer screening to two alternative scenarios. The first involved a situation where no individuals underwent any cancer screening and the second involved screening practice currently prevalent in Manitoba. The first provides an indication of the value of screening generally, while the second suggests the incremental benefit of evidence-based primary care practice guidelines, as indicated in the PIN screening approach.

Manitoba cost information to support the modelling was limited. As a result, the comparisons noted above were undertaken using a number of cost structures. The first used Manitoba cost information available at the time of the analysis, exploring possible cost avoidance even in the face of low levels of treatment expenditure. The second used higher cost treatment estimates from other jurisdictions to demonstrate an upper bound on cost avoidance. A third cost structure examined the switch-point between the two structures where simulated costs per individuals were equivalent between scenarios.

In terms of the three cancers examined in the analysis, two most readily show the potential for avoided costs through the implementation of PIN screening practice. Under the refined cost model structure, the breast cancer modelling suggests a potential avoided cost of $2,581,200 over no screening, and a potential avoided cost of $717,000 over a 25-year period relative to current screening practice. The colorectal cancer modelling shows even greater avoided costs, with corresponding results for $57,511,800 and $10,662,300 over 25-year periods. By contrast, the cervical cancer modelling suggests increased costs through the implementation of PIN screening under all scenarios and assumptions. The switch-point analysis provides some confidence that even with lower treatment costs, breast cancer and colorectal cancer PIN screening will continue to result in avoided costs.

It is important to understand that two critical factors drive these results. The first is the incidence of the various types of cancer. Increased screening for low incidence cancers is less likely to show avoided costs. This is simply because there are fewer downstream treatment costs to avoid for a given population. The second is the population targeted for the screening. The more people targeted for screening, the higher overall costs. In the case of cervical cancer, both of these factors—a low cancer incidence and a broad screening program—contribute to increased overall costs as a result of moving from current screening practice to more intensive PIN practice.

4.2 Diabetes model results

As noted in Section 2 above, the diabetes model does not assess the cost-effectiveness of evidence-based primary care PIN activity in the same way as the cancer models. Unlike the cancer models, where the behaviour of patients is well known and may be modelled effectively, the relationship between diabetes treatment in Manitoba and patient health determinants is not well known. In addition, there is little information to assess the impact of PIN's maintenance activities on treatment, health determinants, and, most importantly, the underlying risk factors that affect diabetes complications. Thus, the diabetes modelling undertaken as part of the analysis attempted to assess the cost avoidance from moving individuals from a state of uncontrolled diabetes to one of diabetic control. The results suggest the potential avoided costs for Manitoba Health if PIN activity can support a similar movement of individuals.

As noted above, increasing an individual's likelihood of diabetic control from 70% to 100% avoids costs of approximately $1.1 million over a 40-year period. However, it is critical to recognize that these results include only the financial costs involved in managing the consequences of diabetes-related health complications. They do *not* include the financial costs involved in carrying out interventions aimed at managing diabetic control. Only if the cost avoidance resulting from a given increase in diabetic control exceeds the value of increased expenditures required to carry out these interventions can it be argued that these intervention avoid costs.

4.3 Future work

The CEA outlined in this report represents an important step in providing concrete evidence of the benefits of primary care beyond those commonly found in the literature. Several future steps are desirable.

1. Perhaps foremost, a fuller itemization of the costs related to cancer treatment and monitoring is very desirable. The current study faced challenges in calculating the full costs of treatment and monitoring of those diagnosed with cancer at various stages. This was because these costs are incurred in many different parts of the health care system or are incurred by individuals directly. While it is unlikely that a single data repository will exist in the near future to support a full costing of these aspects of the model, there are other avenues available for research. For example, a more extensive review of other jurisdictions may increase the precision of various elements of these costs. More usefully, a more detailed costing of treatment profiles using Manitoba data would be a useful exercise. Extracting specific benchmark patients and using their treatment patterns as a base would support the calculation of more accurate costs. Also important is a sub-provincial analysis that analyzes costs for various centres in Manitoba, since the current model implicitly assumes an average cost across the province.

2. The cancer modelling undertaken as part of this analysis would benefit from more detailed research on how cancer screening and diagnosis trends vary by patient attributes and cancer stage. The province gathers excellent information on overall trends and these are useful for calibrating the model at a general level. However, it is difficult to collect information of sufficient resolution to support complex modelling like that undertaken in the current analysis. While cancer diagnosis rates for the overall population of Manitoba may be well known, and provide important information, more detailed data on diagnoses within each cancer stage, for a variety of cancers, and for different patient groups would result in more precise modelling estimates.

3. It is important to collect data on and analyze the relationships between diabetes and its associated complications. The current analysis relied on information from the literature that commonly examined these relationships in isolation. More accurate information could be derived from an analysis of individual patient histories that associates the multiple underlying risk factors measured by the PIN indicators test procedures and diabetic complications. Again, this would likely require accessing information from a variety of data sources.

4. It is also important to understand the behavioural responses that can be expected with the management of diabetes. This would require monitoring of individual cases over time, possibly even creating an experimental design that would enrol patients into various levels of management to determine whether the costs of more active surveillance and management reduces the severity of complications. With regard to PIN, it is critical that the diabetes management activities are linked to changes in outcomes and considered in the context of other population characteristics and health determinants, which may affect complication risk factors.

5. The current work suggests that this type of Markov modelling is feasible in other areas. Under PIN, there are primary prevention activities that relate to other disease processes, such as cardiovascular diseases. With the two general approaches to modelling developed in this study, examining these diseases and the implications of their associated primary care activity is certainly a possibility. This represents an important means of assessing funding for primary care in these areas.

6. While cost avoidance determined under the controlled situations examined in this analysis provides important policy information, a variety of health determinants affect patient outcomes and costs. Socio-economic status is among the most commonly used proxies for a variety of influential factors. Its incorporation into analyses like this one, or other future work, could provide important insight into health policy making in Manitoba.

7. Finally, the other main social and economic costs not examined in this research are important to include in future analyses. The key is patient experience, and extensions of this research would gather information on the full costs experienced by patients. The extent that primary care mitigates all costs provides even more evidence to guide private and public health care investments.

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Only select studies to populate the models described above. However, numerous other studies contributed to the creation of the models. Many of them contained data sets that were incompatible with the type of modelling the cost-effectiveness analysis uses, but other aspects of the studies still contributed in meaningful ways.

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Appendix A – Estimation of probabilities for diabetes modelling

Estimation of transition probabilities: Macrovascular complications

The UK Prospective Diabetes Study (UKPDS) Risk Engine is essentially a system of equations enabling clinicians and researchers to calculate the absolute risks of macrovascular events for type 2 diabetics under a wide range of assumptions about individual patients' characteristics, such as age, gender, ethnicity, and current level of diabetic control; the equations are based on data from the UK Prospective Diabetes Study, a large randomized control trial that recruited 5,102 patients with type 2 diabetes, and followed them for an average of 10 years (Stevens, Kothari, Adler, Stratton, & Holman, 2001).

Risk equations for coronary heart disease

Risk equations for coronary heart disease (CHD) are provided by Stevens et al. (2001). The probability of a CHD event (fatal or non-fatal myocardial infarction [MI] or sudden death) over a one-year period is given by the following equation:

$$( ) = 1 - \quad (- \ * 1.078 \ )$$

Where *R(t)* is the probability of an event, *d* is the duration of diagnosed diabetes, and *q* is defined as follows:

$$= \quad . \quad (\quad .)/ \quad (\ ) \ .$$

The values of the parameters for the above equation are presented in Table 39 below:

Table 39: Parameters for the CHD risk equations

Parameter	Interpretation	Estimate	Range
q_0	Intercept	0.0112	0.082-0.14
$\hat{a}_1$	Risk ratio for additional year of age at diagnosis of diabetes	1.059	1.05-1.07
$\hat{a}_2$	Risk ratio for women	0.525	0.42-0.63
$\hat{a}_3$	Risk ratio for Afro-Caribbean ethnicity	0.390	0.19-0.59
$\hat{a}_4$	Risk ratio for smoking	1.350	1.11-1.59
$\hat{a}_5$	Risk ratio for 1% increase in A1C	1.183	1.11-1.25
$\hat{a}_6$	Risk ratio for 10 mmHg increase in systolic BP	1.088	1.04-1.14
$\hat{a}_7$	Risk ratio for unit increase in logarithm of lipid ratio	3.845	2.59-5.10
D	Risk ratio for additional year since diabetes diagnosis	1.078	1.05-1.11

Source: Stevens et al. (2001)

Conditional on the occurrence of an MI, the probability that an MI is fatal is given by Stevens et al. (2004) as follows:

$$= \frac{1}{1 + \quad 0.713 - 0.048 * (\quad - 55) - 0.178 \times (\ 1 \quad - 6.86) - 0.141 \times \frac{(\quad - 141)}{10} - 0.104 \times}$$

Where "age" is the patient's age at diagnosis of diabetes, A1C refers to the patient's level of blood sugar, SBP refers to systolic blood pressure, and "time to event" refers to time from diagnosis of diabetes until the event occurs.

Risk equations for stroke

The probability of a stroke over a one-year period is given by the following equation, provided by Kothari (2002):

$$( ) = 1 - \quad (- \ * 1.145 \ )$$

Where *R(t)* is the probability of a first stroke event during period *t*, *d* is duration of diagnosed diabetes, and *q* is defined as follows:

$$= \quad (\quad .)/ \quad (\ ) \ .$$

The values of the parameters for the above equation are presented in Table 40 below:

Table 40: Parameters for the stroke risk equations

Parameter	Interpretation	Estimate	Range
q0	Intercept	0.00186	0.001-0.003
â1	Risk ratio for additional year of age at diagnosis of diabetes	1.092	1.07-1.12
â2	Risk ratio for women	0.700	0.49-0.91
â3	Risk ratio for smoking	1.547	1.08-2.01
â4	Risk ratio for 10 mmHg increase in systolic BP	1.122	1.04-1.20
â5	Risk ratio for unit increase in logarithm of lipid ratio	1.138	1.03-1.24
â6	Risk ratio for atrial fibrillation	8.554	2.77-14.36
d	Risk ratio for additional year since diabetes diagnosis	1.145	1.09-1.20

Source: Kothari (2002)

Conditional on the occurrence of a stroke, the probability that a stroke is fatal is given by Stevens et al. (2004) as follows:

$$(\qquad) = \frac{1}{1 + \quad 1.684 - 0.249 \times \frac{(\quad - 144)}{10} - 2.210 \times}$$

Where SBP refers to systolic blood pressure, and "previous stroke" indicates a prior stroke in the patient in question.

Assumptions

As already noted, the UKPDS risk equations enable the estimation of probabilities of macrovascular events under a wide range of assumptions about individual patients' characteristics; however, it was necessary to introduce several key simplifying assumptions to employ the risk equations in estimating transition probabilities for the diabetes model. These assumptions are as follows:

1. At the outset of an individual trial, a patient's starting age is based on a distribution mirroring that of Canadian patients with newly diagnosed diabetes, according to data obtained from the National Diabetes Surveillance System (NDSS).[20]
2. The population is assumed to be divided equally across genders.
3. Following the finding from the Canadian Tobacco Use Monitoring Survey (CTUMS), it is assumed that about 20% of Canadians are current smokers (Health Canada, 2010).
4. Based on 2006 Census data, it is assumed that approximately 1.4% of the Manitoba population is of Afro-Caribbean ancestry (Statistics Canada, 2007).
5. Controlled and uncontrolled diabetic states are defined according to the levels of A1C, systolic blood pressure, and ratios of total cholesterol/high-density lipoprotein cholesterol (HDL-C) presented in Table 41 below:

Table 41: Definitions of controlled and uncontrolled states in the diabetes model

Metric	Controlled state	Uncontrolled state
A1C	6.6%	9.4%
Systolic blood pressure	122 mm Hg	170 mm Hg
Total cholesterol/HDL-C	3.8	5.9

6. Because the risk equation for stroke estimates only the likelihood of a patient's first stroke event, we are in effect assuming that the likelihood of stroke does not increase with subsequent strokes, which does not reflect clinical reality (although the likelihood of stroke-related mortality *is* assumed to increase after the first stroke).

Table 42 below reports the probability of a CVD event for a 55-year-old newly diagnosed type 2 diabetes patient characterized by the assumptions listed above, as well as the probability of mortality conditional on an event having occurred. Table 43, similarly, reports the probability of a stroke event for a newly diagnosed type 2 diabetes patient, as well as the likelihood the stroke will be fatal. Note that the tables presented here are included to illustrate the differences in the likelihood of macrovascular events and related mortality associated with differing levels of diabetic control, and do not include data for other ages in the cohort. To ensure that results account for the age distribution of Canadian patients newly diagnosed with diabetes, the diabetes model includes event probabilities for all ages between 15 and 104.

[20] This is discussed in further detail in Appendix B.

Table 42: Probability of CVD events and event-related mortality

Duration of diabetes (years)	Probability of CVD event*		Probability of mortality**	
	Diabetic control	No diabetic control	Diabetic control	No diabetic control
0	0.0052	0.0227	0.2634	0.5369
1	0.0057	0.0244	0.2840	0.5627
2	0.0061	0.0263	0.3056	0.5881
3	0.0066	0.0283	0.3281	0.6130
4	0.0071	0.0305	0.3515	0.6374
5	0.0076	0.0329	0.3755	0.6611
6	0.0082	0.0354	0.4002	0.6840
7	0.0089	0.0381	0.4254	0.7060
8	0.0096	0.0410	0.4510	0.7271
9	0.0103	0.0441	0.4769	0.7473
10	0.0111	0.0475	0.5029	0.7664
11	0.0120	0.0511	0.5288	0.7845
12	0.0129	0.0549	0.5546	0.8016
13	0.0139	0.0591	0.5802	0.8176
14	0.0150	0.0636	0.6053	0.8326
15	0.0161	0.0683	0.6298	0.8466
16	0.0174	0.0735	0.6537	0.8596
17	0.0187	0.0790	0.6769	0.8717
18	0.0201	0.0849	0.6992	0.8829
19	0.0217	0.0912	0.7206	0.8932
20	0.0234	0.0979	0.7410	0.9027
21	0.0252	0.1051	0.7605	0.9115
22	0.0271	0.1129	0.7789	0.9195
23	0.0292	0.1211	0.7963	0.9269
24	0.0314	0.1299	0.8127	0.9336
25	0.0338	0.1393	0.8280	0.9398
26	0.0364	0.1493	0.8423	0.9454
27	0.0392	0.1600	0.8556	0.9505
28	0.0422	0.1713	0.8680	0.9552
29	0.0454	0.1834	0.8795	0.9595
30	0.0489	0.1962	0.8901	0.9633
31	0.0526	0.2098	0.8998	0.9668
32	0.0566	0.2242	0.9088	0.9700
33	0.0608	0.2394	0.9171	0.9729
34	0.0654	0.2554	0.9247	0.9755
35	0.0703	0.2724	0.9316	0.9779
36	0.0756	0.2902	0.9379	0.9800
37	0.0813	0.3089	0.9437	0.9819
38	0.0873	0.3285	0.9490	0.9837
39	0.0938	0.3491	0.9538	0.9853
40	0.1007	0.3705	0.9582	0.9867

* This includes fatal or non-fatal MI or sudden death.

** Conditional on patient having experienced MI.

Table 43: Probability of stroke events and event-related mortality

Duration of diabetes (years)	Probability of stroke*		Probability of mortality**			
			Diabetic control		No diabetic control	
	Diabetic control	No diabetic control	No past stroke	Past stroke	No past stroke	Past stroke
0	0.0014	0.0032	0.0967	0.4939	0.2618	0.7638
1	0.0016	0.0036	0.0967	0.4939	0.2618	0.7638
2	0.0018	0.0042	0.0967	0.4939	0.2618	0.7638
3	0.0021	0.0048	0.0967	0.4939	0.2618	0.7638
4	0.0024	0.0055	0.0967	0.4939	0.2618	0.7638
5	0.0027	0.0062	0.0967	0.4939	0.2618	0.7638
6	0.0031	0.0071	0.0967	0.4939	0.2618	0.7638
7	0.0036	0.0082	0.0967	0.4939	0.2618	0.7638
8	0.0041	0.0094	0.0967	0.4939	0.2618	0.7638
9	0.0047	0.0107	0.0967	0.4939	0.2618	0.7638
10	0.0054	0.0122	0.0967	0.4939	0.2618	0.7638
11	0.0062	0.0140	0.0967	0.4939	0.2618	0.7638
12	0.0071	0.0160	0.0967	0.4939	0.2618	0.7638
13	0.0081	0.0183	0.0967	0.4939	0.2618	0.7638
14	0.0092	0.0210	0.0967	0.4939	0.2618	0.7638
15	0.0106	0.0240	0.0967	0.4939	0.2618	0.7638
16	0.0121	0.0274	0.0967	0.4939	0.2618	0.7638
17	0.0138	0.0313	0.0967	0.4939	0.2618	0.7638
18	0.0158	0.0358	0.0967	0.4939	0.2618	0.7638
19	0.0181	0.0408	0.0967	0.4939	0.2618	0.7638
20	0.0207	0.0466	0.0967	0.4939	0.2618	0.7638
21	0.0237	0.0532	0.0967	0.4939	0.2618	0.7638
22	0.0270	0.0607	0.0967	0.4939	0.2618	0.7638
23	0.0309	0.0691	0.0967	0.4939	0.2618	0.7638
24	0.0353	0.0788	0.0967	0.4939	0.2618	0.7638
25	0.0403	0.0897	0.0967	0.4939	0.2618	0.7638
26	0.0460	0.1020	0.0967	0.4939	0.2618	0.7638
27	0.0525	0.1159	0.0967	0.4939	0.2618	0.7638
28	0.0599	0.1315	0.0967	0.4939	0.2618	0.7638
29	0.0683	0.1491	0.0967	0.4939	0.2618	0.7638
30	0.0778	0.1688	0.0967	0.4939	0.2618	0.7638
31	0.0886	0.1908	0.0967	0.4939	0.2618	0.7638
32	0.1008	0.2152	0.0967	0.4939	0.2618	0.7638
33	0.1145	0.2423	0.0967	0.4939	0.2618	0.7638
34	0.1300	0.2722	0.0967	0.4939	0.2618	0.7638
35	0.1474	0.3050	0.0967	0.4939	0.2618	0.7638
36	0.1668	0.3407	0.0967	0.4939	0.2618	0.7638
37	0.1886	0.3794	0.0967	0.4939	0.2618	0.7638
38	0.2128	0.4208	0.0967	0.4939	0.2618	0.7638
39	0.2397	0.4649	0.0967	0.4939	0.2618	0.7638
40	0.2693	0.5113	0.0967	0.4939	0.2618	0.7638

* This refers to the probability a patient will experience his or her *first* stroke.

** Conditional on patient having experienced a stroke.

Estimation of transition probabilities: Microvascular complications

The estimation of transition probabilities associated with microvascular complications in the diabetes model was guided by the following considerations:

- Studies typically examine the impact of a single intervention on outcomes in type 2 diabetes, such as improved glycemic control or tight blood pressure; it is uncommon for a study to report on the net impact of several interventions. However, it is clear from the literature that intensive diabetic control implies management of several risk factors.

- Diabetic control is usually defined in terms of interventions applied to improve management of risk factors for macrovascular and microvascular complications, whereas the diabetes model defines it in terms of specific numerical values or targets for glycemic control, blood pressure, and lipids. As a consequence, levels of control reported in clinical trials tended not to align with the levels used to represent the controlled and uncontrolled states in the model. Therefore, it was necessary to calibrate baseline transition probabilities and risk reductions associated with health interventions to ensure alignment between the probabilities used in the macrovascular and microvascular sub-trees in the diabetes model.

It is important to recognize that the calculations needed to estimate the impact of diabetic control on health outcomes cannot be conducted using transition probabilities, but rather require *hazard rates*; for example, while hazard rates can be multiplied by factors representing the relative risk associated with a health intervention (e.g., intensive glycemic control), the same is not true of transition probabilities (Fleurence & Hollenbeak, 2007, p. 5).[21] Therefore, although they are conceptually similar, mistaking hazard rates and transition probabilities could potentially affect Markov simulation results.[22] A transition probability can be derived from a hazard rate using the equation below:[23]

(Equation #1) $= 1 -$

Where *r* is the hazard rate, *t* is time, *e* is the exponential function, and *p* is the transition probability being sought. Conversely, a hazard rate can be obtained from a transition probability using the following equation:

(Equation #2) $= - - \quad (1 - \quad)$

Where *p* is the probability, *t* is time, *ln* is the natural logarithm function, and *r* is the hazard rate being sought.

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21 Conversely, the last stage involved in all relative risk calculations is to convert hazard rates back into probabilities, as the latter and not the former are appropriate for use in economic modelling.

22 For detailed discussions of the distinction between rates and probabilities and the calculations necessary to convert between them, the reader is referred to Fleurence and Hollenbeak (2007), Briggs and Sculpher (1998), and Miller and Homan (1994).

23 Both this equation and the one produced below are drawn from Fleurence and Hollenbeak (2007, p. 5).

The approach used to derive a transition probability for a particular progression associated with one of the microvascular complications included in the diabetes model depends upon the data available in the medical literature.

In general, if multiple hazard rates are available and can be linked to particular A1C or systolic blood pressure (SBP) levels (as, for example, was the case for numerous studies undertaken through the United Kingdom Prospective Diabetes Study [UKPDS]), the chosen approach involves extrapolating from the available data to derive the hazard rates associated with the A1C/SBP levels corresponding to the controlled and uncontrolled states in the diabetes model; these are then converted into transition probabilities. It is important to recognize that this approach assumes a linear relationship between hazard rates and diabetic risk factors.

In other cases, only a single hazard rate was available or could be derived on the basis of the information provided in the medical literature. In these instances, transition probabilities were obtained by conducting relative risk calculations.

Estimation with multiple hazard rates

If the clinical evidence suggests that only a single factor (i.e., A1C or SBP) influences the transition between two health states (e.g., normal renal function to microalbuminuria), hazard rates for the levels of the risk factor corresponding to the controlled and uncontrolled diabetes states were estimated by extrapolating using the slope between the known points; the estimated hazard rates were then converted into transition probabilities using Equation #1 above.

If, however, both A1C and SBP were found to affect the likelihood of transition between health states, the estimation process was slightly more complicated. As noted above, the impacts associated with intensive glucose control and tight blood pressure control are generally examined separately.[24] The challenge is to impose credible assumptions about how the *combination* of changes in A1C and blood pressure affect the probability that patients will experience diabetic complications. For the purposes of the diabetes model, in such cases, transition probabilities were estimated by conducting separate calculations for A1C and SBP, and then selecting the larger of the two values.

The following example, which involves the estimation of the likelihood of transition from normoalbuminuria to microalbuminuria in patients with uncontrolled diabetes, illustrates the application of the above approach. Using data from the UKPDS (1998a), the CDC Diabetes Cost-Effectiveness Group (2002) estimates hazard rates associated with conventional and intensive glucose control of 0.0325 and 0.0237, respectively (p. 2545); in the original study, average A1C in the intensive group was 7.0%, compared with 7.9% in the conventional group. As shown in Figure 35 below, plotting these points yields a slope of 0.0098, which is interpreted here as the increase in the hazard rate associated with a 1.0% increase in A1C. On the basis of this information, an A1C of 9.4% (corresponding to the uncontrolled state) would produce a hazard rate of 0.0472, which, using Equation #1, is equivalent to a transition probability of 0.0461.

[24] For example, each of the two key UKPDS studies critical to the estimation of transition probabilities for the diabetes model focused specifically on an individual risk factor (1998a, 1998b).

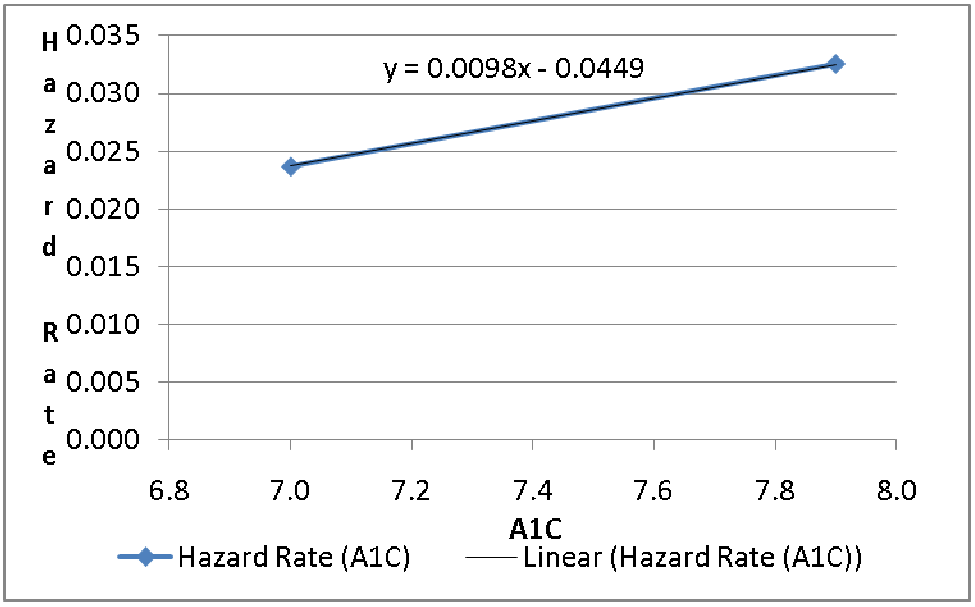

Figure 35: Relationship between A1C and the rate of transition from normal to microalbuminuria
Source: CDC Diabetes Cost-Effectiveness Group (2002, p. 2545)

The CDC Diabetes Cost-Effectiveness Group (2002) also estimates hazard rates associated with conventional and tight blood pressure control of 0.03773 and 0.05584, using data from the UKPDS (1998b); in the latter study, average SBP in the tight blood pressure group was 144 mm Hg, compared to 154 mm Hg in the less tight blood pressure group. As shown in Figure 36 below, plotting these points yields a slope of 0.0018, which is interpreted here as the increase in the hazard rate associated with a 1 mm Hg increase in SBP. On the basis of this information, an SBP of 170 mm Hg (corresponding to the uncontrolled state) would produce a hazard rate of 0.0848, which is equivalent to a transition probability of 0.0813.

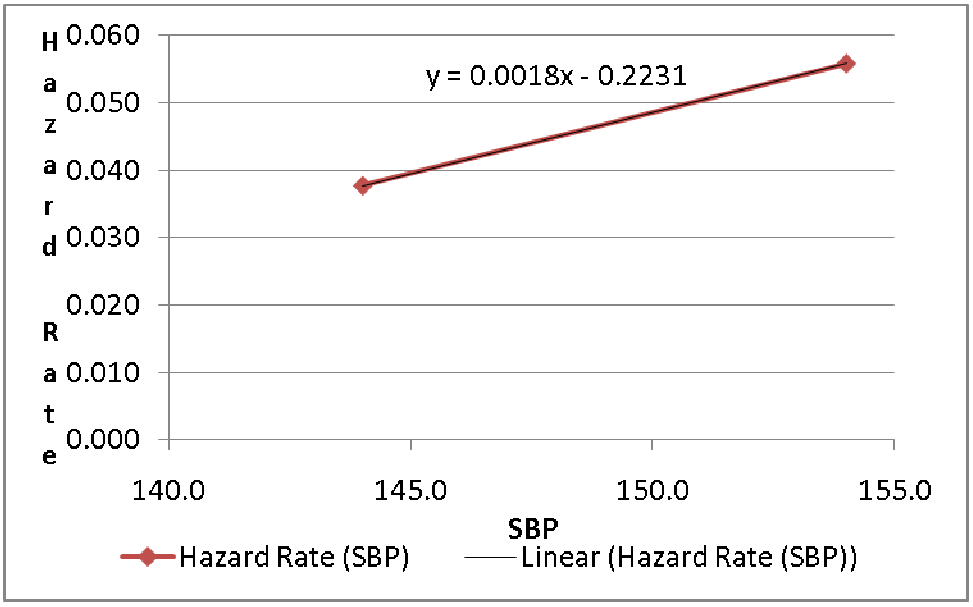

Figure 36: Relationship between SBP and the rate of transition from normal to microalbuminuria
Source: CDC Diabetes Cost-Effectiveness Group (2002, p. 2545)

As the transition probability associated with uncontrolled SBP is the largest of the two estimated values, this probability is used in the diabetes model to reflect the combined influence of uncontrolled A1C and blood pressure.

Estimation with a single hazard rate or hazard ratio

When only a single hazard rate was available from the literature, the estimation of transition probabilities for the microvascular sub-tree involved the following steps.[25] If the literature estimated the impact of a unit increase or decrease in risk factors, as, for example, is done for A1C in Stratton et al. (2000) and for SBP in Adler et al. (2000), the total impact of transitioning to diabetic control was determined by identifying the risk factor levels associated with the baseline hazard rate, calculating the difference in levels between the baseline and the diabetic control state, and multiplying by the unitary decrease in the hazard rate.[26] An analogous approach was used to estimate the impact of transition to the uncontrolled state. If the literature showed that both A1C and SBP affected the likelihood of microvascular complications, then the *largest* of the risk increases/decreases identified in the calculations was used to estimate the hazard rates for the controlled and uncontrolled states. In either case, at the end of the process, the hazard rates were converted into transition probabilities using Equation #1 above for use in the diabetes model.

The following example, which involves the estimation of the likelihood of transition from amputation to death in patients with uncontrolled diabetes, illustrates the application of the above approach. The probability of death following LEA is obtained from Reiber et al. (1995), as reported in Hoerger et al. (2004, p. 13); using Equation #2 above, this transition probability is converted into a hazard rate of 0.1109. Using UKPDS data, Stratton et al. (2000) find that a 1% decrease in A1C is associated with a 43% reduction in the risk of amputation or death from peripheral vascular disease; given a difference of 1.5% between A1C in the conventional glucose control group (7.9%) and the uncontrolled state in the diabetes model (9.4%), this implies an increase in the hazard rate of 64.5% (i.e., 43% x 1.5). Similarly, Adler et al. (2000, p. 4) determine that decreasing SBP by 10 mm Hg decreases the risk of amputation or death from peripheral vascular disease by 16%; given a difference of 26 mm Hg between SBP in the less tight blood pressure group in the UKPDS (154 mm Hg) and the uncontrolled state in the diabetes model (170 mm Hg), this implies an increase in the hazard rate of 25.6% (i.e., 16% x 1.6).

Because uncontrolled A1C is estimated to have a larger impact on the hazard rate than uncontrolled SBP, the risk increase associated with the former is used to represent the combined contribution of poor blood pressure and glycemic control; therefore, the hazard rate associated with the uncontrolled state is determined to be 0.1824 (i.e., 0.1109*[1 + 0.645]), which is converted into a transition probability of 0.1668 using Equation #1 above.

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[25] If the hazard rate was unavailable, the transition probability associated with a particular acute event or microvascular complication progression was converted into a hazard rate using Equation #2 above.

[26] If the risk factor levels associated with the baseline hazard rate were not explicitly identified, they were assumed equal to the levels of A1C and SBP associated with "conventional" diabetic control in the UKPDS studies. In the UK Prospective Diabetes Study Group (1998a) research related to glycemic control, the conventional control group had an A1C endpoint of 7.9; similarly, in the UK Prospective Diabetes Study Group (1998b) research pertaining to blood pressure control, the "less tight" blood pressure group had an SBP endpoint of 154 mm Hg.

In some instances, the literature reported the impact of improved glycemic or blood pressure control in terms of a *hazard ratio*, which in this context expresses the rate of progression from one clinical state to another under diabetic control, relative to the rate of progression in the absence of diabetic control.[27] In these cases, it was necessary to first convert the hazard ratio into a measure reflecting the percentage increase in the hazard rate associated with an increase in a particular risk factor.

For example, the ADVANCE Group (2008) reported a hazard ratio of 0.64 for intensive glucose control, as compared with standard glucose control with respect to transition to renal replacement therapy (ESRD) or death from renal causes (p. 2567), where these interventions resulted in median standardized glycated haemoglobin levels of 6.3 and 7.0, respectively, at the end of follow-up. For the purposes of the diabetes model, this suggests that a 0.7% increase in A1C is associated with a 56.3% increase in the hazard rate (i.e., 1/0.64). Using, for instance, an estimate of the rate of progression from macroalbuminuria to ESRD under standard glucose control of 0.2327,[28] and assuming a difference in A1C of 1.5% between the level of glucose control associated with this baseline and the uncontrolled state,[29] it is estimated that the rate of progression in the controlled state would be 0.0513 (i.e., 0.2327*[1 + (1.5/0.7)*(0.5625)]). Finally, using Equation #2 above, this is converted into a transition probability of 0.0500.

Calculation of competing mortality

To simulate mortality from non-diabetes-related causes, the model uses Statistics Canada's (2006) Manitoba life tables from 2000 to 2002 for the general provincial population. Two important assumptions underlie the use of this data in the diabetes model:

1. The probabilities employed in the model are simple averages of the probabilities reported for men and women; therefore, we are assuming that the prevalence of type 2 diabetes in Manitoba is split evenly between the genders.

2. The probability of mortality from causes unrelated to the diabetes complications incorporated elsewhere in the model is assumed to be the same as all-cause mortality for the general population.

[27] For a more formal definition and discussion of hazard ratios, please see Duerden (2009).
[28] This estimate is obtained from Hoerger et al. (2004, p. 11).
[29] Note that to conduct the required calculations, it is necessary to assume this hazard rate corresponds to an A1C of 7.9 (i.e., the level resulting from "conventional" glycemic control in the UK Prospective Diabetes Study Group (1998a)), as this is nowhere explicitly reported.

Table 44: Probability of survival, all-causes, for the population of Manitoba

below reports the likelihood of survival at each age for the population of Manitoba:

Table 44: Probability of survival, all-causes, for the population of Manitoba			
Age	**Men**	**Women**	**Combined**
15	0.9992	0.9997	0.9994
16	0.9990	0.9996	0.9993
17	0.9989	0.9996	0.9992
18	0.9988	0.9996	0.9992
19	0.9989	0.9995	0.9992
20	0.9989	0.9995	0.9992
21	0.9990	0.9995	0.9992
22	0.9990	0.9995	0.9992
23	0.9990	0.9995	0.9993
24	0.9991	0.9995	0.9993
25	0.9991	0.9995	0.9993
26	0.9991	0.9995	0.9993
27	0.9991	0.9995	0.9993
28	0.9991	0.9995	0.9993
29	0.9990	0.9995	0.9992
30	0.9989	0.9995	0.9992
31	0.9988	0.9995	0.9991
32	0.9987	0.9994	0.9991
33	0.9987	0.9994	0.9990
34	0.9987	0.9993	0.9990
35	0.9987	0.9992	0.9989
36	0.9987	0.9991	0.9989
37	0.9986	0.9990	0.9988
38	0.9986	0.9990	0.9988
39	0.9985	0.9989	0.9987
40	0.9984	0.9988	0.9986
41	0.9983	0.9988	0.9985
42	0.9981	0.9987	0.9984
43	0.9979	0.9986	0.9983
44	0.9977	0.9985	0.9981
45	0.9974	0.9984	0.9979
46	0.9971	0.9982	0.9977
47	0.9968	0.9980	0.9974
48	0.9965	0.9979	0.9972
49	0.9963	0.9976	0.9970
50	0.9960	0.9974	0.9967
51	0.9956	0.9971	0.9964
52	0.9951	0.9968	0.9960
53	0.9944	0.9965	0.9955
54	0.9936	0.9962	0.9949
55	0.9927	0.9958	0.9942
56	0.9917	0.9954	0.9936
57	0.9908	0.9949	0.9928
58	0.9900	0.9942	0.9921
59	0.9892	0.9934	0.9913
60	0.9884	0.9926	0.9905
61	0.9875	0.9917	0.9896

Table 44: Probability of survival, all-causes, for the population of Manitoba			
Age	**Men**	**Women**	**Combined**
62	0.9864	0.9909	0.9886
63	0.9850	0.9902	0.9876
64	0.9835	0.9895	0.9865
65	0.9819	0.9888	0.9853
66	0.9801	0.9881	0.9841
67	0.9782	0.9872	0.9827
68	0.9764	0.9864	0.9814
69	0.9745	0.9856	0.9800
70	0.9724	0.9847	0.9786
71	0.9701	0.9836	0.9768
72	0.9673	0.9820	0.9747
73	0.9642	0.9801	0.9722
74	0.9609	0.9780	0.9694
75	0.9571	0.9755	0.9663
76	0.9529	0.9726	0.9628
77	0.9481	0.9694	0.9587
78	0.9427	0.9659	0.9543
79	0.9369	0.9623	0.9496
80	0.9305	0.9582	0.9444
81	0.9234	0.9533	0.9384
82	0.9155	0.9474	0.9314
83	0.9067	0.9406	0.9236
84	0.8973	0.9331	0.9152
85	0.8871	0.9247	0.9059
86	0.8759	0.9150	0.8954
87	0.8636	0.9037	0.8836
88	0.8501	0.8937	0.8719
89	0.8360	0.8825	0.8593
90	0.8210	0.8704	0.8457
91	0.8050	0.8573	0.8312
92	0.7880	0.8432	0.8156
93	0.7700	0.8282	0.7991
94	0.7510	0.8121	0.7816
95	0.7310	0.7950	0.7630
96	0.7099	0.7769	0.7434
97	0.6879	0.7577	0.7228
98	0.6649	0.7375	0.7012
99	0.6410	0.7162	0.6786
100	0.6162	0.6940	0.6551
101	0.5906	0.6708	0.6307
102	0.5642	0.6467	0.6054
103	0.5370	0.6218	0.5794
104	0.5092	0.5960	0.5526
Source: Statistics Canada (2006)			

Appendix B – Derivation of diabetes cohort size for the Province of Manitoba

The cohort size used in the Monte Carlo simulations for the diabetes model was derived by:

1. *Establishing the incidence of diabetes in the Province of Manitoba.* This information was obtained from a recent Manitoba Health report finding that the average incidence of diabetes in the province between 2001/02 and 2005/06 was 6,390 (2009b, p. 16)

2. *Establishing the proportion of type 2 diabetes among new diabetics.* As the model focuses on type 2 diabetes, it was necessary to determine what proportion of new diabetics are typically diagnosed with type 2 versus type 1 diabetes. According to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), approximately 90–95% of new diabetics have type 2 diabetes (2011). For the purposes of this study, PRA assumed a type 2 diabetes "share" of 92.5% (i.e., the average between the upper and lower bound estimates provided by the NIDDK).

3. *Determining the proportion of new diabetics potentially affected by enhanced diabetes management.* To ascertain the number of Manitobans likely to benefit from improvements in diabetes management in primary care, it was necessary to first assess the age range to which each PIN indicator applies; for example, the indicator for blood pressure management (3.06) makes explicit reference to patients 18 years of age or older (Manitoba Health, 2010b, p. 9). It was decided that the cohort used in the simulations should include all patients 15 years of age or older, as this is the lowest age mentioned in the indicators.

4. *Estimating age-specific incidence of diabetes.* As data relating to the age-specific incidence does not appear to be available for Manitoba, countrywide 2005 data from the National Diabetes Surveillance System was used instead (Public Health Agency of Canada, 2009). Data from adolescents and children younger than 15 was excluded, as this segment of the population would not be included in the simulation cohorts.

5. *Calculating cohort size.* The size of each cohort was determined by multiplying incidence of type 1 and type 2 diabetes in Manitoba (i.e., 6,390) by the share of all new diabetes cases in persons 15 or older (i.e., about 98.8%),[30] and then multiplying by the proportion of new diabetics with type 2 diabetes (i.e., 92.5%). The total size of the cohort is therefore estimated to be 5,841 patients.

[30] Please note that this process implicitly assumes the distribution of new type 2 diabetes cases by age to be identical to the age distribution of new type 1 diabetes cases.

Table 45 below reports the distribution of new type 2 diabetes cases in Canada by age, estimated according to the procedure described above. This distribution has been incorporated into the diabetes model to enable each patient entering a simulation to be assigned a starting age consistent with actual age-related Canadian incidence data:

Table 45: Estimated distribution of new Canadian type 2 diabetes cases by age

Age	Proportion of cases	Age (continued)	Proportion of cases (continued)
15	0.0009	63	0.0241
16	0.0009	64	0.0241
17	0.0009	65	0.0215
18	0.0009	66	0.0215
19	0.0009	67	0.0215
20	0.0017	68	0.0215
21	0.0017	69	0.0215
22	0.0017	70	0.0187
23	0.0017	71	0.0187
24	0.0017	72	0.0187
25	0.0029	73	0.0187
26	0.0029	74	0.0187
27	0.0029	75	0.0149
28	0.0029	76	0.0149
29	0.0029	77	0.0149
30	0.0054	78	0.0149
31	0.0054	79	0.0149
32	0.0054	80	0.0100
33	0.0054	81	0.0100
34	0.0054	82	0.0100
35	0.0086	83	0.0100
36	0.0086	84	0.0100
37	0.0086	85	0.0047
38	0.0086	86	0.0047
39	0.0086	87	0.0047
40	0.0141	88	0.0047
41	0.0141	89	0.0047
42	0.0141	90	0.0020
43	0.0141	91	0.0020
44	0.0141	92	0.0020
45	0.0188	93	0.0020
46	0.0188	94	0.0020
47	0.0188	95	0.0006
48	0.0188	96	0.0006
49	0.0188	97	0.0006
50	0.0238	98	0.0006
51	0.0238	99	0.0006
52	0.0238	100	0.0001
53	0.0238	101	0.0001
54	0.0238	102	0.0001

Table 45: Estimated distribution of new Canadian type 2 diabetes cases by age

Age	Proportion of cases	Age (continued)	Proportion of cases (continued)
55	0.0272	103	0.0001
56	0.0272	104	0.0001
57	0.0272		
58	0.0272		
59	0.0272		
60	0.0241		
61	0.0241		
62	0.0241		

Source: See text.

Appendix C – Results from the scaled implementation of PIN cancer screening

The following table presents the average cost per individual, for various levels of PIN screening uptake, from each of the cancer screening simulations.

Comparison of cost-effectiveness results (comparing PIN-type screening with current screening trends), original versus refined costs		
PIN screener percentage	**Cost per individual (original costs)**	**Cost per individual (refined costs)**
Breast cancer		
0%	$380	$2,050
10%	$383	$2,048
20%	$386	$2,047
30%	$389	$2,053
40%	$392	$2,047
50%	$395	$2,048
60%	$397	$2,046
70%	$401	$2,046
80%	$404	$2,049
90%	$407	$2,048
100%	$410	$2,045
Cervical cancer		
0%	$195	$285
10%	$203	$295
20%	$210	$306
30%	$217	$315
40%	$224	$325
50%	$232	$335
60%	$239	$345
70%	$246	$355
80%	$254	$365
90%	$261	$375
100%	$268	$385
Colorectal cancer		
0%	$363	$1,379
10%	$367	$1,377
20%	$370	$1,372
30%	$373	$1,369
40%	$376	$1,367
50%	$379	$1,362
60%	$382	$1,359
70%	$386	$1,356
80%	$389	$1,352
90%	$392	$1,348
100%	$395	$1,346

Appendix D – Revised cancer cost estimates and discussion

The following table presents the refined costs used in the cancer model sensitivity analysis.

Description	Original estimate ($)	Revised estimate ($)	Percent increase	New source
Breast cancer costs				
Stage 0 treatment	280	14,661	5236%	Stout et. al, 2006
Stage 1 treatment	1913	22,384	1070%	Stout et. al, 2006
Stage 2 treatment	2568	33,050	1187%	Stout et. al, 2006
Stage 3 treatment	4027	40,976	918%	Stout et. al, 2006
Stage 4 treatment	5413	32,934	508%	Stout et. al, 2006
Stage 0 post-treatment	212	270	27%	Stout et. al, 2006
Stage 1 post-treatment	212	270	27%	Stout et. al, 2006
Stage 2 post-treatment	212	270	27%	Stout et. al, 2006
Stage 3 post-treatment	212	270	27%	Stout et. al, 2006
Stage 4 post-treatment	212	270	27%	Stout et. al, 2006
Cervical cancer costs				
CIN 1 treatment	64	938	1366%	Debicki et. al, 2008
CIN 2/3 treatment	143	1,094	665%	Debicki et. al, 2008
Stage 0 treatment	169	1,110	547%	Debicki et. al, 2008
Stage 1 treatment	547	13,029	2282%	Debicki et. al, 2008
Stage 2 treatment	1049	20,614	1865%	Debicki et. al, 2008
Stage 3 treatment	2541	20,614	711%	Debicki et. al, 2008
Stage 4 treatment	3897	28,168	623%	Debicki et. al, 2008
Stage 0 post-treatment*	96–188	96–188	0%	Unchanged
Stage 1 post-treatment	96–188	96–188	0%	Unchanged
Stage 2 post-treatment	96–188	96–188	0%	Unchanged
Stage 3 post-treatment	96–188	96–188	0%	Unchanged
Stage 4 post-treatment	96–188	96–188	0%	Unchanged
Colorectal cancer costs				
Stage 0 treatment	95	95	0%	Unchanged
Stage 1 treatment	772	15,673	1930%	Maroun et. al, 2003
Stage 2 treatment	1782	19,861	1015%	Maroun et. al, 2003
Stage 3 treatment	3186	26,729	739%	Maroun et. al, 2003
Stage 4 treatment	4952	38,215	671%	Maroun et. al, 2003
Stage 0 post-treatment*	144–699	144–1318	0%–89%	Heitman, 2008
Stage 1 post-treatment	144–699	144–1318	0%–89%	Heitman, 2008
Stage 2 post-treatment	144–699	144–1318	0%–89%	Heitman, 2008
Stage 3 post-treatment	144–699	144–1318	0%–89%	Heitman, 2008
Stage 4 post-treatment	144–699	144–1318	0%–89%	Heitman, 2008

*Note: the annual post-treatment costs for cervical and colorectal cancer vary from year to year, depending on the tests and procedures specified. This is why the costs are presented as ranges. In fact, there are specific costs for each year of post-treatment follow-up that fall within these ranges.

For breast cancer treatment (Stout et. al, 2006), the costs included the direct costs of treatment (such as surgery, chemotherapy, and radiation), materials and disposable goods, physician and other personnel salaries (nurses, pharmacists, radiologists, laboratory workers), and administrative overhead. The costs also included inpatient costs such as overnight stays in hospitals. The study did not include indirect costs such as travel and opportunity costs. In general, the costs are made up of initial treatments (surgery), ongoing treatment (radiation or

chemotherapy), and terminal care (calculated by multiplying the cost of terminal care by the 5 year mortality rate for each stage of cancer).

For cervical cancer treatment (Debicki et. al, 2008), costs included fee-for-service reimbursements for inpatient and outpatient claims. They included treatment costs (surgery, chemotherapy, radiation) as well as palliative care, medical staff costs (estimated using the mid-point of staff salaries), and laboratory and equipment costs.

For colorectal cancer treatment (Maroun et. al, 2003), costs included direct treatment costs (surgery, chemotherapy, radiotherapy), physician fees, laboratory tests, and hospitalization costs. These cover both inpatient and outpatient procedures. The costs were slightly higher for rectal cancer compared to colon cancer. Based on advice from a medical expert claiming that roughly 75% of colorectal patients have colon cancer while 25% have rectal cancer, the costs were weighted accordingly. Also, note that the cost for the treatment of stage 0 colorectal cancer (a polypectomy) is unchanged. This is because the cost listed is simply the physician's fee for conducting the polypectomy during a colonoscopy. The increase in the cost of treatment has already been reflected in the increased cost of a colonoscopy.

Readers should note that Will et al.'s 2000 study, *Estimates of the Lifetime Costs of Breast Cancer Treatment in Canada*, also presents alternative cost figures for the treatment of various stages of breast cancer. While appearing somewhat higher than those presented in the tables above, when corrected for inflation and the inclusion of post-treatment follow-up and recurrence costs, these figures are quite comparable to those presented above.