Informing colorectal cancer screening in northern Canada using participatory simulation modeling

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To the people of northern Canada,
May this work improve your access to equitable healthcare.

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LIST OF ACCRONYMS

CRC	Colorectal cancer
FIT	Fecal immunohistochemical test
NWT	Northwest Territories
GRADE EtD	Grading of Recommendations Assessment, Development, and Evaluation Evidence to Decision framework
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-analysis
ISPOR-SMDM	International Society for Pharmacoeconomics and Outcomes Research-Society for Medical Decision Making
FOBT	Fecal Occult Blood Test
MISCAN-Colon	MIcrosimulation SCreening ANalysis Colorectal Cancer
LRA	Low risk adenoma
HRA	High risk adenoma
AA	Advanced adenoma
AN	Advanced neoplasia
RR	Relative risk
OR	Odds ratio
CI	Confidence interval
Parti-Sim	Participative Simulation
CoP	Communities of Practice

ABSTRACT

Background: Mortality from colorectal cancer (CRC) in the Northwest Territories (NWT), a northern region of Canada, is nearly double the national rate. While mortality could be reduced with greater adherence to CRC screening, this requires colonoscopy access which is limited, and difficult to predict in a complex remote health system. Simulation modeling has been used to plan CRC screening but the impact on decision-making and utility in complex remote health system is unclear.

Aim: This thesis aims to estimate the colonoscopy requirements and outcomes of CRC screening in the NWT using simulation modeling in a way that will inform feasible patient-centered strategies to enhance screening.

Methods: We conducted a systematic review of the validity and utility of simulation modeling in CRC screening delivery (Chapter 1, 2). Next, a retrospective cohort study of CRC screening participation and outcomes between 2014-2019 was conducted (Chapter 3). We used this data and the findings of the systematic review to inform our participatory simulation modeling approach (Chapter 4). With end-users of the simulation model (clinicians, administrators, and patients), we revised an existing simulation model, OncoSim-CRC, to estimate the resource requirements and outcomes of various strategies to deliver a CRC screening program in the NWT. Each scenario model was run for 500 million cases and model validity was assessed. To enhance ongoing collaboration, we shared the concepts of a Communities of Practice (CoP) framework with stakeholders and assisted in generating consensus on priorities for a CoP to address (Chapter 5).

Results: The systematic review showed that simulation models have been used to generate evidence critical to informing decision making for a broad range of decisions related to CRC screening delivery. However, the impact of these models on decision making, end-user engagement, and model validity were rarely described. In the retrospective cohort study, we observed that fecal immunohistochemical test(FIT)-based CRC screening did not appear to prevent CRC or provide earlier detection, but did result in more frequent positive pathology results than anticipated for average risk screening. Factors associated with this include long wait times for colonoscopy, over 1 in 3 FIT positive individuals had clinical signs and symptoms of CRC, and higher relative risk of advanced neoplasia among indigenous individuals. These findings and the involvement of end-users, informed the simulation model study. Under the parameters of the model, we estimate that colonoscopy demand with a CRC screening program would surpass capacity within 1-2 years, and continue to increase over the next 10-15 years due to adenoma surveillance. If this colonoscopy demand is met, we estimate screen detected cancers would increase by 110%, and clinically detected cases reduce by 26%. Increasing the phase-in period or revising adenoma follow-up guidelines would reduce demand and still improve cancer detection and prevention. A framework for a CoP, and consensus on priorities among stakeholders were established.

Conclusion: Participatory simulation modeling was a useful method of informing CRC screening delivery in a remote northern population. The simulated scenarios provide decision-makers with strategies to enhance programmatic screening while conserving colonoscopy resources. The findings

of this thesis helps to characterize the current outcomes of CRC screening in the NWT, and identifies opportunities to improve CRC screening effectiveness for a remote and, largely indigenous population.

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Thank you to my partner and family for supporting me in this endeavor.

PREFACE

INTRODUCTION

Colorectal cancer(CRC) is the second leading cause of cancer related mortality[1]. Significant variation in incidence and mortality exist between populations. Remote and indigenous populations have been shown to be disproportionately affected by a higher incidence[2] and mortality[3] from CRC. These inequities have been attributed to number of different factors related to the individual patient, health system, and environment[4]. There is strong evidence demonstrating that CRC screening can reduce mortality by facilitating earlier detection and treatment [5,6]. However, a critical resource for CRC screening is colonoscopy which is limited in remote regions and where access is complicated by multiple social, geographic, and cultural barriers [7]. Simulation modeling has increasingly been used to inform CRC screening delivery[8] and may be useful as a method of enabling evidence-informed screening planning and resource allocation in remote communities.

Simulation models are computer-generated representations of real-world systems developed using population statistics and probability estimates to demonstrate the evolving behaviour of systems over time and predict results of various "what if" scenarios. They have been used to predict outcomes, resource requirements, feasibility, and costs of proposed interventions in CRC screening [8–13]. However, the validity and impact of these models in the context of CRC screening delivery remains poorly understood and their application in remote regions has been limited.

The Northwest Territories (NWT) is a northern region of Canada where projections of CRC screening resource requirements would be particularly beneficial. In the NWT, the rate of death from CRC is nearly double that of the rest of the country[14]. Screening guidelines in the NWT involve screening average risk individuals between the age of 50-74 with fecal immunochemical testing (FIT) every two years and, if positive, conducting a colonoscopy within 60 days to diagnose a possible colon cancer[15–17]. Despite efforts in the NWT to improve opportunistic CRC screening, participation rates remain low (at 20% in 2014)[18]. These rates are even lower in small communities, where less than 16% of eligible individuals participated in screening in 2014[18]. Furthermore, among individuals who have undergone FIT, 8-16% are expected to have a positive result and require a diagnostic colonoscopy within 60 days[17,19]. Currently, FIT positive patients appear to wait much longer than the recommended 60 days; clinicians have estimated the wait-time to be up to 2-3 years[7]. Plans are underway to increase FIT screening through implementing a CRC screening program in the region. However, to increase FIT screening with appropriate follow-up, the region will require additional access to colonoscopy to provide screening in accordance with current guidelines. Further research regarding current screening patterns, and opportunities to optimize colonoscopy resources are needed to inform an effective CRC screening program.

AIM

This project aims to estimate the colonoscopy requirements and outcomes of CRC screening in the NWT using simulation modeling in a way that will inform feasible patient-centered strategies to enhance screening.

OBJECTIVES

Research objectives include:

1. Identify if simulation modeling employed in CRC screening research supports informed decision-making in CRC screening planning by conducting a systematic review of the literature.
2. Develop simulated projections of CRC screening colonoscopy demand and outcomes using an approach informed by objective 1.
   - 2.1. Formulate a conceptual flow diagram of the CRC screening process from FIT positive result to colonoscopy.
   - 2.2. Conduct a descriptive analysis of current trends in participation, and outcomes of FIT-based CRC screening in the NWT.
   - 2.3. Adjust the parameters of the OncoSim model to reflect the NWT context.
   - 2.4. Conduct preliminary verification and validation of the model.
   - 2.5. Generate and simulate alternative scenarios that would enable the NWT to deliver feasible CRC screening.
3. Develop a foundational aspects for a Communities of Practice to support long-term sustainable health systems changes proposed in this research project.

GENERAL METHODS

To address objective 1, a systematic review was conducted to assess if the use of simulation modeling in CRC screening research supports informed decision-making in CRC screening planning (Chapter 1 and 2). Recognizing that an impact on decision-making may not be directly discussed in the article, we compared the study results to the GRADE EtD framework to determine if they could potentially inform decision-making[20]. This framework was developed in collaboration with researchers in health systems and public health internationally to provide health care leaders with a structured and transparent approach for using research to support policy-making decisions in public health and health systems. It has been validated for use in a diversity of settings and outlines a set of criteria that are important to address with research evidence when seeking to inform a decision. These include resource utilization of the intervention, cost of the intervention, cost effectiveness of the intervention, impact of the intervention on healthcare equity, acceptability of the changes to stakeholders, feasibility of the intervention, and sustainability of the intervention[20].

The systematic review was conducted in accordance with the Cochrane Library systematic reviews guide and the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA). Details regarding the methods and results are outlined in Chapter 1 and 2.

In order to better understand the current status of CRC screening in the NWT prior to developing simulated projections, a retrospective cohort study was conducted as outlined in Chapter 3. Residents age 50-74 who underwent colorectal cancer screening by FIT between January 1, 2014-March 30, 2019 were included. For individuals with a positive result who underwent a colonoscopy, results were reviewed and compared to clinically detected colorectal cancer cases diagnosed between January 1, 2014-December 31, 2016. The primary endpoint was colonoscopy demand which included both the colonoscopy after positive FIT and ongoing surveillance based on the colonoscopy results.

Drawing upon the results of the systematic review in Chapter 2, and results of Chapter 3, we sought to use simulation modeling to inform decision-making in CRC delivery in the NWT (Chapter 4). To enhance success, we used a participatory approach by engaging end-users in the research question development, model conceptualization, and model validation process[21]. Clinicians, healthcare administrators, epidemiologists, and patients were recruited to join the research team as collaborators. The team met iteratively to develop research questions and objectives, contribute to the model development and validation, and to interpret the results of the retrospective review.

Using the data from the descriptive analysis and secondary sources, the OncoSim model was recalibrated to replicate the population of the NWT. The OncoSim model is a Monte Carlo microsimulation model developed by the Canadian Partners Against Cancer to project resource requirements, outcomes, and costs of CRC screening in Canada[13]. The preliminary face validity of the model was assessed by collaborators to confirm if the model structure, data sources, problem formulation, and results were consistent with CRC screening in the NWT. Internal validity was assessed using sensitivity analysis. External validity of the model was assessed using results from the descriptive analysis. The model outputs were disseminated to collaborators who suggested solutions to meet the demand. These solutions were integrated into additional model scenarios which were then compared to determine the impact on colonoscopy demand and cancer outcomes. Final evaluation of scenarios and face validity of the model outputs are pending due to COVID-19 restrictions.

Finally, to enhance the sustainability of health system changes proposed in this research, the foundations for a communities of practice (CoP) for CRC screening in the NWT were developed. A CoP is a social learning platform of practitioners engaged in a shared topic who meet on a regular basis to share knowledge and experiences[22]. The initial developments of this group are outlined in Chapter 5.

Approval for this work was obtained from the Northwest Territories Health and Social Services Association, Aurora College (protocol 20190404), University of Ottawa (S-03-19-3459), and Ottawa Hospital Research institute (20190073-01H).

CHAPTER 1: USE OF SIMULATION MODELING TO INFORM DECISION MAKING FOR HEALTH CARE SYSTEMS AND POLICY IN COLORECTAL CANCER SCREENING: PROTOCOL FOR A SYSTEMATIC REVIEW

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ABSTRACT

Background: Simulation modeling has frequently been used to assess interventions in complex aspects of health care, such as colorectal cancer (CRC) screening, where clinical trials are not feasible. Simulation models provide estimates of outcomes, unintended consequences, and costs of an intervention; thus offering an invaluable decision aid for policy makers and health care leaders. However, the contribution that simulation models have made to policy and health system decisions is unknown.

Objective: This study aims to assess if simulation modeling has supported evidence-informed decision making in CRC screening.

Methods: A preliminary literature search and pilot screening of 100 references were conducted by three independent reviewers to define and refine the inclusion criteria of this systematic review. Using the developed inclusion criteria, a search of the academic and gray literature published between January 1, 2008, and March 1, 2019, will be conducted to identify studies that developed a simulation model focusing on the delivery of CRC screening of average-risk individuals. The three independent reviewers will assess the validation process and the extent to which the study contributed evidence toward informed decision making (both reported and potential). Validation will be assessed based on adherence to the best practice recommendations described by the International Society for Pharmacoeconomics and Outcomes Research-Society for Medical Decision Making (ISPOR-SMDM). Criteria for potential contribution to decision making will be defined as outlined in the internationally recognized Grading of Recommendations Assessment, Development and Evaluation Evidence to Decision (GRADE EtD) framework. These criteria outline information that the health system and policy decision makers should consider when making an evidence-informed decision including an intervention's resource utilization, cost-effectiveness, impact on health equity, and feasibility. Subgroup analysis of articles based on their GRADE EtD criteria will be conducted to identify methods associated with decision support capacity (ie, participatory, quantitative, or mixed methods).

Results: A database search of the literature yielded 484 references to screen for inclusion in the systematic review. We anticipate that this systematic review will provide an insight into the contribution of simulation modeling methods to informed decision making in CRC screening delivery and discuss methods that may be associated with a stronger impact on decision making. The project was funded in

May 2019. Data collection took place from January 2008 to March 2019. Data analysis was completed in November 2019, and are expected to be published in the spring of 2020.
Conclusions: Our findings will help guide researchers and health care leaders to mobilize the potential for simulation modeling to inform evidence-informed decisions in CRC screening delivery. The methods of this study may also be replicated to assess the utility of simulation modeling in other areas of complex health care decision making.

INTRODUCTION

The benefits of colorectal cancer (CRC) screening have been well cited including: a reduced incidence of CRC, earlier stage of presentation, improved outcomes of patients with detected malignancy and reduced CRC associated mortality[23–26]. Screening uses fecal tests, diagnostic imaging, and/or endoscopic examination to assess for possible CRC among asymptomatic individuals at increased risk of developing CRC. Participation of eligible individuals is voluntary and remains low in many regions across our country[4]. Determining the best screening modality, delivery method, resource allocation, and follow-up for screening is complex because health policy and system decision-makers must weigh the cost and the benefits of screening, taking into account the sensitivity, specificity and accessibility of various screening modalities. Furthermore, such interventions often cannot be tested in clinical trials because of multiple environmental, sociocultural and health system factors that negate the feasibility and safety of a trial [27]. Researchers and decision-makers have increasingly relied on simulation models to evaluate interventions in CRC screening [13,28].

A simulation model is a computer generated representation of a real-world system or process that can be used to analyze the evolving behaviour of a system over time, or modified to predict results of a variety of "what if" scenarios[29]. Simulation models have been applied to a broad range of areas in healthcare to predict outcomes, unintended consequences, and costs of proposed interventions; therefore offering an invaluable decision aid for policy-makers and healthcare leaders [10–12,28]. The purpose of simulation models is well defined: to provide decision-makers with evidence to facilitate decision-making, however, the extent to which simulation modeling has fulfilled this purpose in CRC screening is unknown [30]. Simulation modeling has the potential to provide strong evidence for multiple aspects of informed decision-making at the policy and health system level including a proposed intervention's resource utilization, cost effectiveness, feasibility, sustainability, potential impact and acceptance among stakeholders [31,32]. For instance, by simulating what-if scenarios informed by clinical trials and observational data, the model can help to identify the appropriate age to initiate screening, superiority of one screening modality over another, or most cost-effective frequency of screening a particular population in the long-term. However, the extent to which simulation modeling has realized this potential impact in CRC screening is unknown.

For simulation models to be useful for decision makers, models must be sufficiently accurate and valid for application [30]. There have been concerns with model credibility in healthcare and reporting of model conceptualization, parameterization, and validation is not consistent in the literature [33–35]. For this reason, in this systematic review, each study will be assessed for adherence to best practice recommendations in model validation as detailed in the methods section of this proposal [33].

From our review of the literature, we identified two gaps in the literature we plan to address with this systematic review: 1. no systematic review has looked at the application of simulation in CRC screening within last ten years, 2. no systematic review specifically addressed the impact of simulation modeling on decision-making in healthcare. The most recent systematic review looking at CRC screening, only

included articles until 2007 inclusively [8]. Since that time, systematic reviews have been conducted looking at the quality and cost-effectiveness of simulation modeling in breast cancer screening but none in CRC screening [36,37]. A systematic review by Sobolev and colleagues looked at the reported "utility" of simulation models in surgical patient flow and reinforced the need for evaluating the impact of models on decision-making but did not formally evaluate this in their review[38]. Our described study aims to address these knowledge gaps by assessing the validity and impact of simulation modeling on health system and policy decision-making in CRC screening delivery. Publication of this protocol will allow for critical peer review of the aims and methods outlined for the intended study. This will strengthen the rigor by which it will be conducted and validate its utility.

METHODS

Protocol and registration

This systematic review will be conducted in accordance with the Cochrane Library systematic reviews guide and the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) [39,40]. This protocol is reported in accordance with the PRISMA-Protocols checklist. The protocol has been submitted for registration in PROSPERO, and any amendments will be filed with PROSPERO (no.130823).

Search strategy and eligibility criteria

Studies will be selected from a search of the academic and grey literature published between Jan 1, 2008-Mar 1,2019 conducted to identify articles that include both 1) simulation modeling methods and 2) a focus on CRC screening. Only full-text articles available in English will be included. Studies will be identified from academic databases (Medline, Embase, Cochrane Central, Scopus, Web of Science, IEEEXplore, ACM Digital Library, Econolit, National Health Service Economic Evaluation Database, Health Assessment Database, and Cost-Effective Analysis Registry) using controlled vocabulary (MeSH) and text word search terms selected by author HS and an experienced librarian, AD (Table 1, and appendix A table 1).

Table 1 Preliminary search strategies

Database: Ovid MEDLINE(R) ALL <January 1, 2008 to March 1, 2019>
Search Strategy:

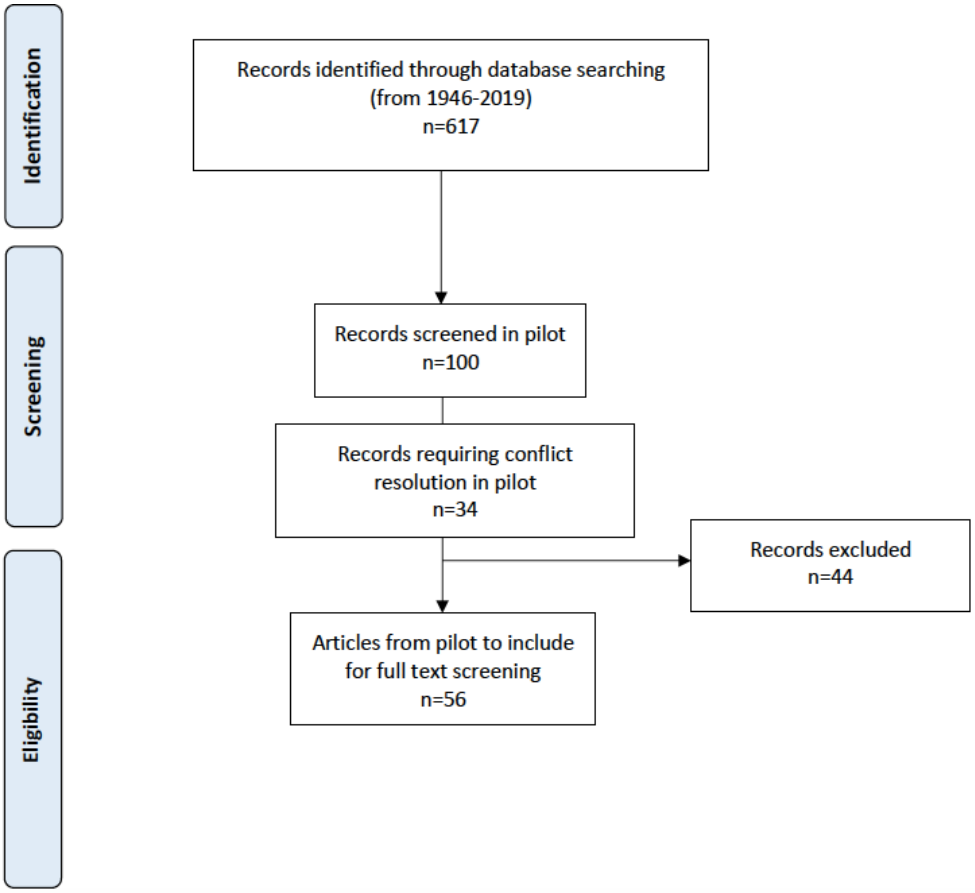
1	Systems Analysis/
2	systems thinking.tw,kw.
3	systems science.tw,kw.
4	systems approach.tw,kw.
5	systems theory.tw,kw.
6	systems analysis.tw,kw.
7	system* model*.tw,kw.
8	simulation model*.tw,kw.
9	monte carlo method/ or Markov Chains/
10	(markov or monte carlo).tw,kw.

11	discrete event.tw,kw.
12	agent based model*.tw,kw.
13	or/1-12
14	(system* dynamics or dynamic systems).tw,kw.
15	colonoscopy/ or sigmoidoscopy/
16	(colonoscop* or sigmoidoscop*).tw,kw.
17	FECES/ch or (f?ecal occult blood test or f?ecal immunochemical test or FOBT or stool DNA or stool test).tw,kw.
18	or/15-17
19	Mass Screening/ or "Early Detection of Cancer"/
20	(screening or "early detection").tw,kw.
21	19 or 20
22	exp Colorectal Neoplasms/
23	((colorectal or colo-rectal or colon* or rectal) adj2 (cancer or neoplasm*)).tw.
24	22 or 23
25	21 and 24
26	CRC screen*.tw,kw.
27	18 or 25 or 26
28	**13 and 27**

Terms were selected to capture the most commonly used types of simulation models in healthcare (discrete event simulation, Markov chain model, Monte-Carlo simulation, agent-based model and system dynamics model) [11]. This will be supplemented by hand searching of the grey literature and conference proceedings as well as citation searches of selected articles.

Simulation modeling can be used in a broad scope of applications in cancer screening. To help refine the appropriate inclusion criteria and feasibility of this review, a preliminary search of the literature was conducted. A search of articles published between Jan 1, 1946-Mar 1, 2019 was conducted and a pilot screen of 100 abstracts completed by three independent reviewers (HS, PV and CK) using inclusion criteria of 1) simulation model use and 2) colorectal cancer screening. This yielded 56/100 included abstracts after 24 conflicts were resolved through extensive discussion among all authors (figure 1). To reduce conflicts, the inclusion and exclusion criteria were further refined to only include original articles describing a simulation model derived from clinical data focused on the delivery of colorectal cancer screening to average risk individuals using one or all of the following modalities of screening recommended by Canadian guidelines within the last ten years: Fecal Occult Blood Test (FOBT), Fecal Immunohistochemical Testing (FIT), flexible sigmoidoscopy, colonoscopy [41–43]. Excluded articles were those describing other screening modalities not recommended in Canadian screening guidelines as identified above, commentary or review articles, or simulation models that include screening of other cancers, or no mention of screening delivery. The timeframe was also further restricted to only include articles after 2008 because a systematic review on the use of simulation modeling in healthcare, including colorectal cancer screening, was identified and had included articles until the end of 2007 [8]. A second pilot screen was conducted using the revised criteria which yielded fewer conflicts and the revised inclusion and exclusion criteria were adopted for this systematic review.

Figure 1. PRISMA flow diagram of pilot search and reference screening



Selection of studies for review

All article titles and abstracts will be screened by three independent reviewers using Abstrakr abstract screening program by HS, PV and CK followed by screening of selected full-text studies for compliance with the eligibility criteria as mentioned above using DistillerSR, version 2019 [44,45]. Articles or reports of the same study will be linked together. Authors of the articles will be contacted to clarify study eligibility where appropriate. Conflicts will be resolved through discussion between reviewers or consultation of author (RB) as needed.

Data extraction

All included studies will be reviewed by three independent reviewers (HS, CK, PV). Using DistillerSR version 2019**,** data will be extracted regarding the study and model description, and model validation as outlined in Table 2 [30]. Discrepancies will be identified and resolved through discussion and missing data will be requested from the study authors as needed.

Table 2 Model Characteristics and Validation

Characteristics	Description
Country	Location of intended application.
Year	Year of publication.
Simulation model type	Type of approach (i.e., system dynamics, Monte Carlo, Markov chain model, agent-based model, discrete-event).
Intended application(s)	Area of application (i.e., forecasting of cost, resource utilization).
Funding sources	Source of financial support of the project, if applicable.
Stakeholders	Identify model users/decision makers and their role in the modeling.
Conceptualization	
Parameters defined	Define the model parameters: values used to either define the characteristics of the model or calculate the performance indicators.
Structure	Demonstration of variables and their relationships (i.e., in graphical formation).
Operationalization	
Model duration	Length of time simulated, number of runs, and if the model was terminating or steady-state.
Inputs	List inputs of model.
Simulated Outputs	List outputs of model.
Observed results	Observed outcomes, if available.
Data sources	Type of data sources (i.e., primary or secondary).
Limitations	Assumptions and limitations of the model.
Software	Type of software used to develop the model.
Validation Methods[30]	
Face validation	Model structure, data sources, problem formulation and results are evaluated by people who have clinical expertise.
Verification/Internal validation	Examination of the extent to which the mathematical calculations are performed correctly and are consistent with the model's specifications.
Cross validation	Examination of the different models that address the same problem and comparing their results.
External validation	Comparison of model's results with actual event data.
Predictive validation	Comparison of model's simulated outcomes to similar clinical trial or cohort study.

The validation of a simulation model is an important determinant of the risk of bias and applicability of a simulation model. All models will be assessed in accordance with the guidelines of the International Society for Pharmacoeconomics and Outcomes Research-Society for Medical Decision Making (ISPOR-SMDM) report [30]. In reviewing the literature, several tools were identified to assist model developers and users with model validation [30,33,34,46–49]. The ISPOR-SMDM Taskforce has developed good practice guidelines for modeling in health care including recommendations on conceptualization,

parameterization and validation. Of the validation tools identified in the literature, the taskforce report had the broadest scope and most rigorous development process therefore, it was selected to guide validation assessment in this review[33]. Authors HS, CK and PV will individually assess whether or not authors report and/or conduct face validity (wherein experts evaluate model structure, data sources, assumptions, and results), verification or internal validity (check accuracy of coding), cross validity (comparison of results with other models analyzing the same problem), external validity (comparing model results with real-world results), and predictive validity (comparing model results with prospectively observed events) as outlined in Table 2 [30].

Studies will then be assessed for the extent to which the study has and/or could potentially have contributed evidence towards informed decision-making. For reported contribution, each article will be searched in its entirety for statements referring to the simulation model results informing decision-making. If not clearly stated in the publication, the information will be requested from study authors.

Recognizing that the impact of a simulation model on specific decision may not be communicated at the time of publication, we plan to also assess the potential contribution a simulation model could have made to evidence-informed decision-making based on whether the results align with important factors for making an informed decision[50]. The authors will assess articles to determine whether or not they include evidence considered to be important for decisions, as outlined in the internationally recognized Grading of Recommendations Assessment, Development and Evaluation Evidence to Decision framework (GRADE EtD)[31]. The GRADE EtD framework has been developed as part of the DECIDE project in collaboration with researchers in health system and public health internationally. It outlines a set of important factors that decision-makers should consider and address with research evidence to guide their decisions in health policy or systems [20]. These criteria include information on an intervention's resource utilization, cost-effectiveness, impact on health equity, and feasibility (Table 3). We will assess whether the study results apply to the GRADE EtD criteria. Subgroup analysis of articles based on their GRADE EtD criteria will be conducted to identify methods associated with decision support capacity (i.e., quantitative or mixed-methods).

Table 3 GRADE EtD Criteria of Decision-making for health system and public health decisions [31]

Criteria	Detailed questions
Is the problem a priority?	Are the consequences of the problem serious (i.e., severe or important in terms of the potential benefits or savings)? Is the problem urgent? [not relevant for coverage decisions] Is it a recognized priority (e.g. based on a political or policy decision)? [Not relevant when an individual patient perspective is taken]
How substantial are the desirable anticipated effects?	Judgments for each outcome for which there is a desirable effect.

How substantial are the undesirable anticipated effects?	Judgments for each outcome for which there is an undesirable effect.
What is the overall certainty of the evidence of effects?	See GRADE guidance regarding detailed judgments about the quality of evidence or certainty in estimates of effects.
Is there important uncertainty about or variability in how much people value the main outcome?	Is there important uncertainty about how much people value each of the main outcomes? Is there important variability in how much people value each of the main outcomes? [not relevant for coverage decisions]
Do the desirable effects outweigh the undesirable effects?	To what extent do the following considerations influence the balance between the desirable and undesirable effects: -How much less people value outcomes that are in the future compared to outcomes that occur now (their discount rates) - People's attitudes towards desirable effects (how risk seeking they are) - People's attitudes towards undesirable effects (how risk averse they are)
How large are the resource requirements?	How large is the difference in each item of resource use for which fewer resources are required? How large is the difference in each item of resource use for which more resources are required?
What is the certainty of the evidence of resource requirements?	Have all-important items of resource use that may differ between the options being considered been identified? How certain is the evidence of differences in resource use between the options being considered? (see GRADE guidance regarding detailed judgments about the quality of evidence or certainty in estimates) How certain is the cost of the items of resource use that differ between the options being considered? Is there important variability in the cost of the items of resource use that differ between the options being considered?
Are the net benefits worth the incremental cost?	Judgments regarding each of the six preceding criteria: - Is the cost-effectiveness ratio sensitive to one-way sensitivity analyses? - Is the cost-effectiveness ratio sensitive to multi-variable sensitivity analyses? - Is the economic evaluation on which the cost-effectiveness estimate is based reliable? - Is the economic evaluation on which the cost-effectiveness estimate is based applicable to the setting(s) of interest?
What would be the impact on health equity?	Are there groups or settings that might be disadvantaged in relation to the problem or options that are considered? Are there plausible reasons for anticipating differences in the relative effectiveness of the option for disadvantaged groups or settings? Are there different baseline conditions across groups or settings that

	affect the absolute effectiveness of the intervention or the importance of the problem for disadvantaged groups or settings? Are there important considerations that should be made when implementing the intervention in order to ensure that inequities are reduced, if possible, and that they are not increased?
Is the intervention acceptable to key stakeholders?	Are there key stakeholders that would not accept the distribution of the benefits, harms and costs? Are there key stakeholders that would not accept the costs or undesirable effects in the short term for desirable effects (benefits) in the future? Are there key stakeholders that would not agree with the values attached to the desirable or undesirable effects (because of how they might be affected personally or because of their perceptions of the relative importance of the effects for others)? Would the intervention adversely affect people's autonomy? Are there key stakeholders that would disapprove of the intervention morally, for reasons other than its effects on people's autonomy (e.g. in relation to ethical principles such as no maleficence, beneficence or justice)?
Is the intervention feasible to implement?	For decisions other than coverage decisions: - Is the intervention or option sustainable? - Are there important barriers that are likely to limit the feasibility of implementing the intervention (option) or require consideration when implementing it? For coverage decisions: - Is coverage of the intervention sustainable? - Is it feasible to ensure appropriate use for approved indications? - Is inappropriate use (indications that are not approved) an important concern? - Is there capacity to meet increased demand if covered? - Are there important legal or bureaucratic or ethical constraints that make it difficult or impossible to cover the intervention?

RESULTS

A preliminary search of the literature published between Jan 1, 1946-Mar 1, 2019 was conducted yielding 617 references and a pilot screen of 100 randomly selected abstracts was completed by three independent reviewers (HS, PV and CK) using inclusion criteria of 1) simulation model use and 2) colorectal cancer screening (figure 1). This resulted in 56 of 100 (56%) abstracts to be included after 24 conflicts were resolved through extensive discussion among all authors leading to revision and clarification of the inclusion criteria as described in "Methods". The revised search yielded 484 references to review. A repeated pilot screening resulted in 8 of 100 (8%) abstracts to be included after 16 conflicts resolved with minimal discussion.

DISCUSSION

The purpose of simulation modeling in healthcare is generally to inform a decision [30,49,51]. The extent to which simulation modeling has fulfilled this purpose has not been assessed. We anticipate that this systematic review will help to address this knowledge gap by assessing the contribution simulation modeling has made to informed decision-making in an area of healthcare where it has been frequently used: CRC screening delivery. We will use the GRADE EtD framework to structure our analysis of potential decision impact of the models. This includes the model's contribution to determining the feasibility of screening, acceptability of proposed screening strategies by stakeholders, and sustainability of screening over the long-term. This analysis will help guide researchers by identifying methods in simulation modeling that have been associated with a greater success in decision support such as mixed methods, participatory simulation model development or group model building which has been reported as beneficial in other applications of simulation modeling in healthcare [52,53]. It will assist decision-makers and model users to identify areas where simulation modeling has proven to be useful such as identifying resource requirements or conducting cost-benefit analysis.

The dataset search yielded 484 references which suggests the body of literature on this topic is fairly robust. We anticipate there will be an adequate number of relevant models to conduct an informative systematic review on this topic.

We foresee several potential limitations to this study. The heterogeneity of articles may make it challenging to evaluate studies using a uniform framework from validation and decision-making criteria. Furthermore, the question of impact and decision-support that a study provides are difficult to quantify and therefore will be subject to both authors' and reviewers' bias. We aim to mitigate this by using the GRADE EtD framework and by having reviewers with clinical (HS), health informatics (CK) and simulation (PV) expertise reviewing each included study. Finally, our assessment of model validity will be limited by a lack of validation standards in the literature, and by limited reporting by authors on their validation process and outcomes [35].

In conclusion, the proposed systematic review will provide insight into the contribution and validity of simulation modeling in CRC screening. The results have the potential to inform researchers, healthcare leaders and policy makers looking to develop valid, informative simulation models that will support decision-making. This analysis could be expanded to assess the use of simulation modeling in other areas of healthcare.

CHAPTER 2: SIMULATION MODELING VALIDITY AND UTILITY IN COLORECTAL CANCER SCREENING DELIVERY: A SYSTEMATIC REVIEW

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ABSTRACT

Objective: To assess the impact and validity of simulation modeling in informing decision-making in a complex area of healthcare delivery: colorectal cancer(CRC) screening.

Materials and Methods: We searched 10 electronic databases for English language articles published between Jan. 1, 2008-Mar. 1, 2019 which described the development of a simulation model with a focus on average-risk CRC screening delivery. Included articles were reviewed for evidence that the model was validated, and provided real or potential contribution to informed decision-making using the GRADE EtD.

Results: 43 studies met criteria. The majority used Markov modeling (31, 72%), and sought to determine cost-effectiveness, compare screening modalities, or assess effectiveness of screening. No study reported full model validation and only (58%) reported conducting any validation. Majority of models were developed to address a specific health systems or policy question; few articles report the model's impact on this decision (39, 91% vs. 5, 12%). Overall, models provided evidence relevant to every element important to decision-makers as outlined in the GRADE EtD framework.

Discussion and Conclusion: Simulation modeling contributes evidence which is considered valuable to decision-making in CRC screening delivery, particularly in assessing cost-effectiveness and comparing screening modalities. However, the actual impact on decisions and validity of models is lacking in the literature. Greater validity testing, impact assessment, and standardized reporting of both is needed to understand and demonstrate the reliability and utility of simulation modeling.

BACKGROUND AND SIGNIFICANCE

A simulation model is a computer-generated representation of a real-world system or process used to analyze the evolving behaviour of a system over time or to predict results of various "what if" scenarios. Using trial data, population statistics, and probability estimates, simulation models have been developed in a broad range of areas in healthcare. They have been used to predict outcomes, resource requirements, feasibility, and costs of proposed interventions. Simulation models offer an invaluable decision aid for policy-makers and healthcare leaders in a variety of healthcare applications, including colorectal cancer (CRC) screening [8–13]. CRC screening uses fecal tests, diagnostic imaging, and/or endoscopic examination to assess for possible CRC among asymptomatic individuals at increased risk of developing CRC. Screening has been shown to be effective at detecting CRC earlier, as well as at reducing CRC incidence, morbidity, and mortality [23,25,26,54]. There are many variations for CRC screening protocols with different modalities (i.e. fecal testing vs colonoscopy) and delivery methods (i.e. testing kit mailed to individual vs in person at a clinic visit). Determining the optimal modality, delivery method, and interval follow-up between tests in a population of a particular geographic region or jurisdiction can be complex and difficult to assess [7]. Simulation modeling offers an opportunity to address this gap by providing a method to test interventions in a simulated environment to inform decision making by health leaders, policy-makers and other end-users.

From our review of the literature, we identified two gaps in the literature we aim to address with this systematic review: 1. no systematic review has looked at the application of simulation in CRC screening within the last ten years as the most recent review included articles until 2007 inclusively [8]; 2. multiple systematic reviews have looked at the utility, strengths and opportunities for simulation modeling in healthcare, but have not evaluated the impact of models on health system and policy decision-making [9,38,55,56].

Therefore, we aim to address these knowledge gaps by assessing the validity and impact of simulation modeling in health system and policy decision-making for CRC screening delivery as reported in the literature. Recognizing the risk of under-reported impact, we also aim to assess the potential impact of a model on a healthcare or policy decision by assessing the utility of the evidence generated by the simulation model using the Grading of Recommendations Assessment, Development and Evaluation Evidence to Decision framework (GRADE EtD): an internationally recognized set of criteria for evidence-informed decisions in health systems and policy[31].

OBJECTIVE

This study aims to assess the validity and impact of simulation modeling in health system and policy decision making where it has been frequently applied in healthcare: CRC screening delivery.

MATERIALS AND METHODS

Protocol and registration

This systematic review was conducted in accordance with the Cochrane Handbook for Systematic Reviews and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA), and was registered in PROSPERO (no. 130823) [39,40]. A detailed description of the study protocol including the development process and rationale has been published elsewhere (Chapter 1 of thesis)[57]. Here we provide a summary of the methods and minor adjustments from the published protocol.

Search strategy and eligibility criteria

We searched for articles published between Jan 1, 2008-Mar 1, 2019 from ten electronic databases (Medline ®, Embase®, Cochrane Central, Scopus®, National Health Service Economic Evaluation Database, ACM Digital Library, Econolit, Health Technology Assessment Database, IEEEXplore®, and Cost-Effective Analysis Registry™) using controlled vocabulary (MeSH) supplemented by citation searches of all included articles. The final inclusion and exclusion criteria used to select articles are outlined in Table 4.

Table 4. Inclusion and exclusion criteria

Inclusion criteria	Full text articles published in English which meet all three criteria: 1. developed a simulation model derived from clinical data, 2. focused on the delivery of colorectal cancer screening to average risk individuals, 3. simulated screening using only the following modalities of screening recommended by Canadian guidelines within the last ten years: o fecal occult blood test (FOBT), o fecal immunohistochemical testing (FIT), o flexible sigmoidoscopy, o colonoscopy.
Exclusion criteria	Excluded if any of the following four criteria are met: 1. used other screening modalities not recommended in Canadian screening guidelines as identified above, 2. commentary or review articles, 3. simulation model that include screening of other cancers, 4. no mention of CRC screening delivery.

Selection of studies for review

All article titles and abstracts were screened by three independent reviewers (HS, PV and CK) using the Abstrackr abstract screening program followed by a screening of selected full-text studies. All were reviewed by HS, and 50% were each reviewed by CK and PV to assess for compliance with the eligibility criteria as mentioned in table 4 using DistillerSR, version 2019 [44,45]. Conflicts were resolved by discussion among all four authors until a consensus was reached.

Data extraction

All included studies were reviewed by HS. CK and PV each reviewed 50% of the included studies. Using DistillerSR version 2019**,** data was extracted regarding the model description, validation, and impact as outlined in table 1 and 2 of the published research protocol[57]. Discrepancies were identified and conflicts resolved through discussion to obtain consensus among the authors. Missing or incomplete data was requested from the study authors.

To assess model accuracy, all models were assessed in accordance with the guidelines of the International Society for Pharmacoeconomics and Outcomes Research-Society for Medical Decision Making (ISPOR-SMDM) good practice guidelines for modeling in health care including recommendations on model validation. We also assessed for the involvement of "end-users": decision-makers, clinicians, and administrators who would use the model for decision-making.

Studies were then assessed for the extent to which the study has and/or could potentially have contributed evidence towards informed decision-making. For contribution, each article was searched in its entirety for statements referring to the simulation model results informing decision-making. Recognizing that the impact on decision-making is often not communicated at the time of publication, we also assessed the potential contribution a simulation model could have made to evidence-informed decision-making based on whether the results align with important factors for making informed decisions as outlined in the Grading of Recommendations Assessment, Development and Evaluation Evidence to Decision framework (GRADE EtD) [31,50].

Corresponding authors of each study were also contacted to provide further information on model validation, end-user involvement, and impact of the simulation model. Results were analyzed using Microsoft Excel and RStudio version1.1463. In contrast to the protocol report, no subgroup analysis was conducted due to the heterogeneity of included articles [57].

RESULTS

A total of 492 relevant articles were identified through database and reference searching. Of these, 43 met inclusion criteria for data extraction (figure 2, table 5). Cohen Kappa interrater reliability was 0.82 for title and abstract screening and 0.93 for full text screening. Modeling methods were identified in all articles. Several used multiple modeling methods 9/43 (20%) and the most frequently encountered combination of techniques was Monte Carlos Simulation with Markov modeling (6 of 9 studies, 67%) (table 5). The most frequently used methods, including when they were used in combination with other techniques, were Markov modeling (in 31 of 43 studies, 72%), Monte Carlo simulation (in 7 of 43 studies, 16%), and microsimulation (in 6 of 43 studies, 14%) (figure 3). 33% were based on pre-existing models with MISCAN-colon the most frequently cited as the base model. A majority of models had multiple applications (39 of 43 studies, 90%). The most common applications were to assess cost-effectiveness of screening (in 32 of 43 studies, 74%), compare screening modalities (in 18 of 43 studies, 42%), and/or assess resource utilization of screening (in 15 of 43 studies, 35%) (table 5). Models often included multiple screening modalities, with colonoscopy being the most frequently

included (26, 63%). Inputs were mostly generated from published trials, registries, and population statistics databases within the 5 years of publication (figure 4). Occasionally authors conducted primary data collection to populate the model (6, 14% of models). Model outcomes most often included cost-effectiveness (30, 70% of included articles), mortality (19, 44%), cancer detection (13, 30%), resource utilization (6, 14%) and/or screening participation (7, 16%).

Figure 2. **PRISMA flow diagram**

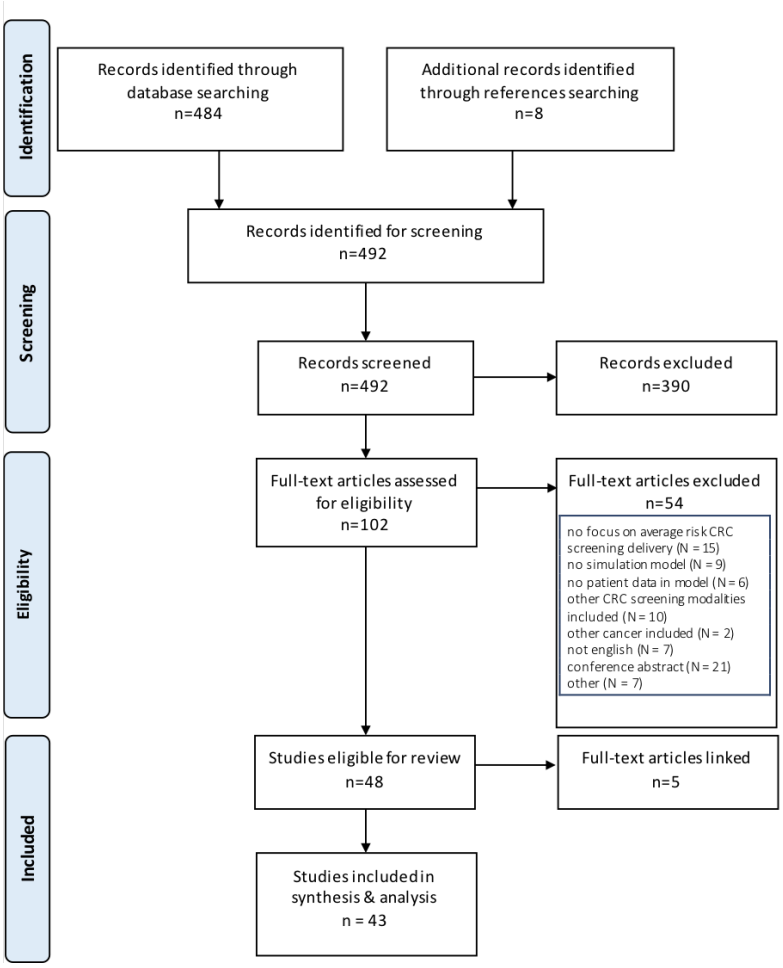


Table 5. Included article summary

			Model Type							Model Aim							Validation						GRADE-ETD criteria met									
Author	Country	Year	Markov Model	Monte Carlo Simulation	System Dynamics	Agent-based Model	Discrete Event Simulation	Microsimulation	Other	Cost-effectiveness	Intervention to increase screening	Compare modalities	Resource use	Specific population	Screening interval	Age of initiation	Face Validation	Internal Validation	External Validation	Cross Validation	Predictive Validation	Impact of simulation model on decision making	Priority of problem	Desireable outcome	Undesireable outcome	Attitudes towards outcomes	Resource requirements	Cost-effectiveness	Health equity	Stakeholder acceptance	Feasibility
Tsoi et al.	China	2008																		X	X	Actual									
Rodriguez-Moranta et al.	Spain	2008																X	X	X	X	Potential									
Macafee et al.	UK	2008															X					Potential									
Berg et al.	US	2009																				Actual									
Subramanian et al.	US	2009																		X	X	Potential									
Lejeune et al.	France	2010																				Potential									
Ventura et al.	Italy	2011																X	X	X	X	Potential									
Van Rossum et al.	Netherlands	2011																X			X	Potential									
Tran et al.	Australia	2011																X		X		Potential									
Whyte et al.	England	2011																				None									
Wang et al.	China	2012																X		X		Potential									
Sharp et al.	Ireland	2012																		X		Potential									
Sharp et al.	Ireland	2013																				Potential									
Sharaf et al.	US	2013																		X		Potential									
Hosking et al.	US	2013																	X			Potential									
Dinh et al.	US	2013																		X		Potential									
Cronin et al.	Australia	2013															X			X	X	Actual									
van Hees et al.	US	2014																X		X		Potential									
Wilson et al.	US	2014																X	X	X	X	Potential									
Li et al.	US	2014																X	X		X	Actual									
Chauvin et al.	France	2014																		X	X	Actual									
Cenin et al.	Australia	2014																X				Potential									
Sekiguchi et al.	Japan	2015																X		X		Potential									
Goede et al.	US	2015																				Potential									
Fitch et al.	US	2015																X				Potential									
Coldman et al.	Canada	2015															X	X				Potential									
Brenner et al.	Germany	2015																				Potential									
Wong et al.	China	2016																		X		Actual									
Song et al.	China	2016																				Potential									
Pil et al.	Belgium	2016																X		X	X	Potential									
Comas et al.	Spain	2016																		X	X	Potential									
McLeod et al.	New Zealand	2017																X		X	X	Potential									
Hassmiller Lich et al.	US	2017																				Potential									
Chiu et al.	Finland	2017																		X	X	Actual									
Aronsson et al.	Sweden	2017																			X	None									
Idigoras et al.	Spain	2017																		X	X	Potential									
Rice et al.	US	2018															X	X		X		Potential									

In Validation section: “x” denotes authors’ descriptions suggest the validation technique was performed but this was not explicitly reported and filled colour indicates the authors reported that they performed the validation technique. The selected colours do not have any significance. References:[58–100]

Figure 3. Popularity of simulation model methods

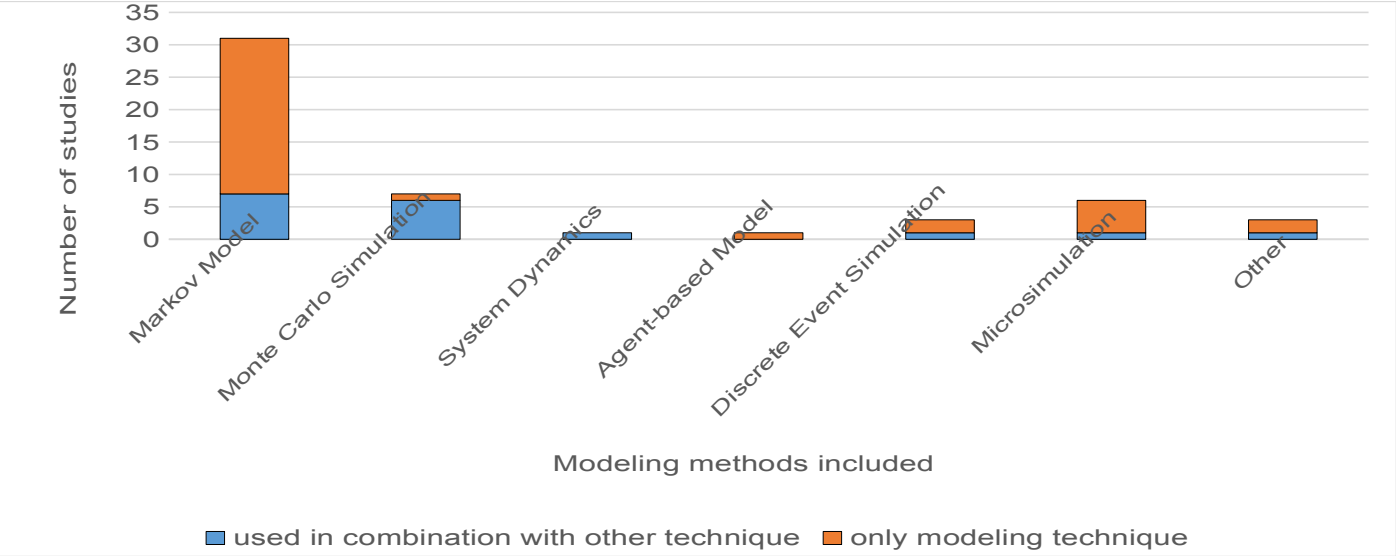
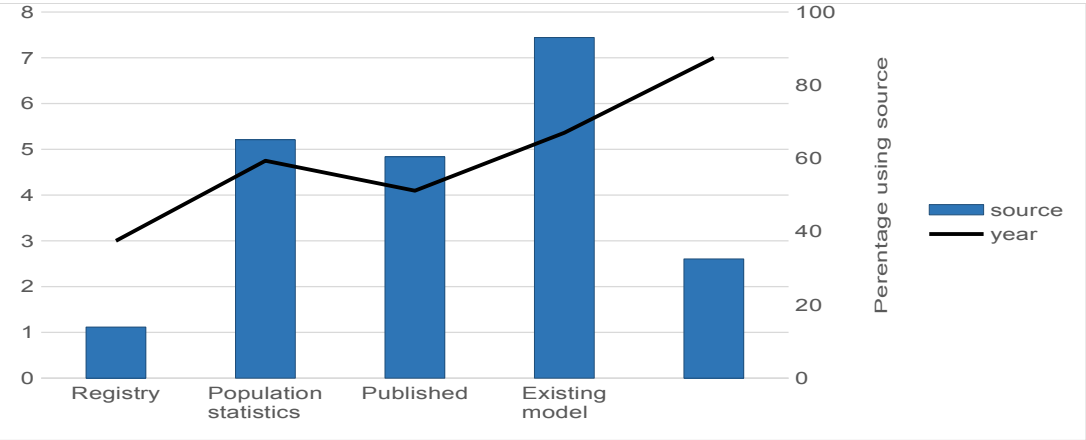


Figure 4. Data sources and year to publication

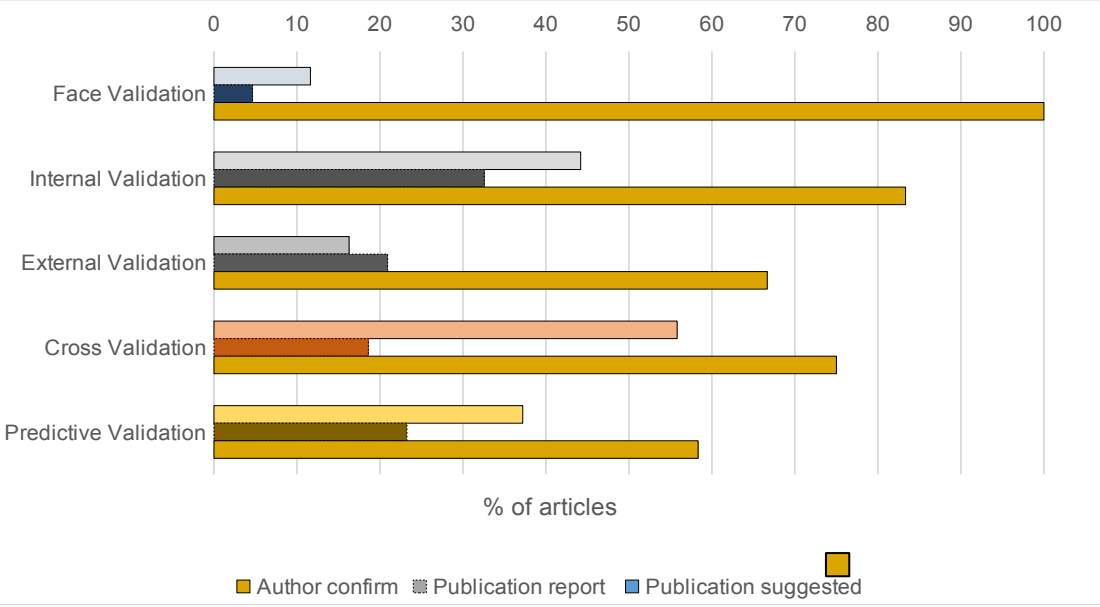


Details of the simulation models were not consistently described. The model entities, attributes, and variables were often identified; in contrast, 29(67%) of articles included a figure of the conceptual model, and 23(54%) identified the software program used to generate the model. Of those that mentioned a software program, TreeAgePro and Microsoft Excel were most frequently used (48% and 26%). Few articles described the role of end-users in developing or evaluating the simulation model (4, 9%). We contacted all authors for further information and among the 12 who responded, 11(92%)

reported end user involvement in both model conceptualization and development, 8(67%) in model validation.

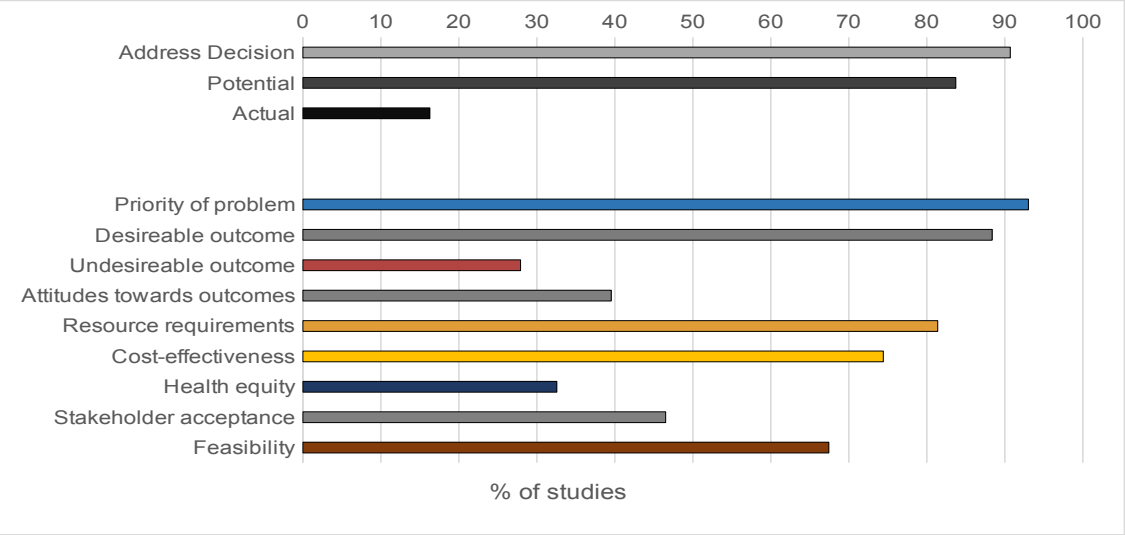
Model validation was not consistently reported (figure 5). A majority of authors mentioned steps in their methods which suggest model validation (42, 98%), in contrast to 25(58%) reported performing any form of model validation, and no article addressed all four aspects of model validation recommended by ISPOR-SMDM. Internal and predictive validation were most often reported whereas face validation was rarely reported (34% and 37% vs 7%). All 12 authors who responded to our correspondence reported conducting face validation and 4(33%) reported conducting all types of validation recommended by ISPOR-SMDM.

Figure 5. Model Validation



A majority of simulation models were developed to address a particular health system or policy decision in colorectal cancer screening delivery (91%) and all articles contributed some evidence important to informed decision-making as outlined in the GRADE EtD framework (figure 6). 12% of articles describe the study as having an impact on decision-making, whereas, 7 of the 12 authors (58%) who provided feedback reported that the model did have an impact on health system or policy decision making. All seven of these “impactful articles” also described having end-users involved in the research question formulation and model conceptualization. Articles with a reported impact on decision-making showed no significant difference in the relative contribution to the GRADE EtD framework (research protocol, Chapter 1, table 2)[57].

Figure 6. Model GRADE EtD framework contribution



DISCUSSION

Simulation modeling informing decision-making

This review demonstrates that simulation modeling is a valuable tool for informed decision-making in colorectal cancer screening delivery by providing evidence that meets all 9 criteria for informed health system and policy decisions outlined by the GRADE EtD framework. In particular, simulation models were found to be useful for estimating the long-term outcomes and cost-effectiveness of different screening strategies in a specific population or geographic region which is consistent with its application in other areas of healthcare [8,36]. However, the translation of these models to evidence-informed decisions appears to be lacking and/or under-reported. Studies rarely describe an impact on decision-making in contrast to the majority of the 12 authors who responded to our correspondence (16.3 vs 58.1%). The generalizability of these 12 responses are limited given that they only represent 28% of all contacted authors and may have been more inclined to respond given their impact on decision-making. Nonetheless, this gap in reporting of impact has been identified in multiple reviews and appears to be an issue unique to simulation modeling in health care unlike other sectors [8,28,101,102]. Reasons for this may include the journal focus, word count limitations, and/or timing between publication and policy decision. While we cannot confirm the actual impact of models in the context of these limitations, we find the potential for impact is very strong based on the GRADE EtD criteria. As clinicians and experts in health systems research, we find this represents a critical gap. The fact that a majority of models were developed to address a specific decision in colorectal cancer screening delivery further supports the argument that these models may be impactful, but their impact remains under-reported. Other studies, not included in this review, suggest that simulation modeling is very useful in decision-making as demonstrated by the use of multiple iterations MISCAN-Colon in the Netherlands [50,58]. If the purpose

of simulation modeling is to inform decision-makers, then this needs to be reported. Only then can we understand how to enhance methods of developing impactful simulation models in CRC screening.

End-user engagement is critical to the success of impactful simulation modeling [21]. A majority of authors with whom we corresponded indicate that end-users were involved in the study and that the model influenced their decision-making, but did not report this in publication. Only one included article provided a thorough description of end-user involvement in model development and evaluation [59]. Various articles, outside the inclusion criteria of this review, have advocated for greater end-user participation, termed "participatory simulation modeling" whereby end-users collaborate with researchers in all phases from conceptualization to validation of the model [50]. The extent to which similar collaborations actually occur in the development, analysis, and validation of "non-participatory" simulation models of colorectal cancer screening delivery remains unknown. If our correspondence with authors is representative of all articles included in this review, then end-users are frequently involved but their participation is not reported in the published article. The goal of simulation modeling is to serve as a decision support technique for end-users. Therefore, it is important to report on the methods used to engage with end-users and the extent to which the model supports their decisions, recognizing their importance and that they may vary between projects [51].

Model validation and reporting

For simulation models to be useful for decision makers, models must be accurate and valid for application [30]. Few articles in this systematic review describe model validation. This concern has been raised by many other reviews of simulation modeling in healthcare (37–39). In further discussion with the authors, we found that validation was often conducted but not reported. The validation process is not an isolated set of procedures, but rather an integral part of model development. It provides the model with higher levels of credibility and ensures that the model's behavior is close enough to that of the actual system so that the model can be a good substitute (41). Reporting the validation process is highly important in model development. There are methods available for testing the validation of simulation models using both subjective comparisons and statistical procedures (41). Multiple guidelines for validation have been developed but are not consistently adopted. A potential next step to address this issue is to require model registration, as is done with clinical trials to reinforce standardization of model validation, promote collaboration, and minimize redundancy of one-off model building [105].

Model components and model conceptualization were also not consistently reported. Only 28(68%) articles included a figure of the conceptual model. To provide a verifiable simulation model, the model entities, attributes, states, activities involved, and the events a system will encounter should be identified to be able to develop a verified simulation model. Providing a conceptual model allows readers to understand the simulation model functions, and see that it mimics the actual system in a way that is accessible to both modelers and end-users. Reporting the model components and the conceptual model are also important for assessing the credibility and reproducibility of a model.

Templates such as those presented by Banks can be used to categorize the model components and to construct an efficient conceptual model [29].

An initial aim of this study was to assess the validity and utility of simulation modeling in CRC screening delivery. However, our final observations are limited due to potentially incomplete reporting by authors at the time of publication. Few studies reported the validity and utility of the simulation model. However, the majority of the 12 authors who responded to our correspondence indicated that their simulation models had been validated and were impactful for end-user decisions. Further research with a larger cohort of author responses is needed to conclude that these authors are representative of all included studies.

CONCLUSION

In this study, we found simulation models can be a powerful adjunct to empirical research in understanding optimal CRC screening delivery and have been used to generate evidence critical to informing decision making for a broad range of health system and policy decisions in average-risk CRC screening delivery. However, reports of impact on decision making and the validity of simulation models are limited in the literature. Greater validity testing, impact assessment, and standardized reporting of both is needed to understand and demonstrate the validity and utility of simulation modeling.

CHAPTER 3: THE EFFECTIVENESS OF COLORECTAL CANCER SCREENING IN REMOTE NORTHERN CANADA

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ABSTRACT

Background: Screening provides earlier colorectal cancer detection and improves outcomes. It remains unknown if these benefits are realized by screening guidelines in remote populations.

Objective: We aim to evaluate colorectal cancer screening in a remote northern population.

Design: A retrospective cohort study.

Setting: Northwest Territories, a northern territory of Canada.

Patients: Residents age 50-74 who underwent colorectal cancer screening by a fecal immunohistochemical test between January 1, 2014-March 30, 2019. For individuals with a positive result who underwent a colonoscopy, results were reviewed and compared to clinically detected colorectal cancer cases.

Main outcome measures: Primary outcomes were diagnosis of advanced neoplasia after positive fecal test, and the stage of cancers compared with clinically detected cases.

Results: Between 2014-2019, 6,817 fecal tests were completed, translating to an annual average screening rate of 25.04%. 843(12.37%) were positive. 629 underwent a follow-up colonoscopy, of which, 24.48% had advanced neoplasia. There were no significant differences in stage, pathology, or location between screen detected cancers and clinically detected cancers. Individuals who were more likely to have advanced neoplasia were those with signs and symptoms of cancer at the time of screening, who waited over 180 days for colonoscopy, and those who were indigenous (respectively, estimated relative risk (RR) 1.18 (95% confidence interval(CI) of RR 0.89-1.59); RR1.523; (CI 1.035, 2.240); RR 1.722 (CI 1.165, 2.547)).

Limitations: This study was limited by retrospective data and chart accessibility.

Conclusion: The incidence of advanced neoplasia in this population was higher than anticipated for average risk screening. Long colonoscopy wait times, clinical signs and symptoms of CRC at the time of FIT screening, and a higher relative risk of colorectal cancer among indigenous individuals contributed to this. Further research is needed to guide effective screening when colonoscopy access is limited, and to discern if indigenous individuals should undergo high-risk screening.

INTRODUCTION

The benefits of colorectal cancer (CRC) screening have been well established in multiple prospective studies, including earlier detection, removal of pre-cancerous lesions, and reduction in CRC associated mortality (RR 0.84, CI 0.78-0.90) [6,106]. While guidelines for CRC screening have been widely adopted, the extent to which the desired benefits of screening have been realized among remote northern populations remains poorly understood[107]. Remote northern populations experience multiple geographic and systemic barriers to health care which may impact CRC screening guideline implementation and adherance[7,108]. This is particularly important for indigenous populations who represent a high proportion of northern residents and are known to experience important sociocultural barriers to healthcare[109]. Significant disparities in CRC outcomes have been observed among remote and indigenous residents[109–112]. Therefore, it is imperative to evaluate if the benefits of CRC screening are realized in these regions in order to optimize CRC detection and outcomes.

The Northwest Territories (NWT) is a northern region of Canada with 44 900 residents living in remote and isolated communities dispersed across 1.1 million km^2, of which, 50.7% of residents identify as indigenous. The incidence of CRC in the NWT has been consistently higher than the national rate. Screening guidelines have been established in this region since 2009 and recommend screening of average risk individuals between the age of 50-74 with fecal immunochemical testing (FIT) every 1-2 years [15–17]. Guidelines recommend that if the FIT is positive, the patient should receive a colonoscopy within 60 days. Higher risk individuals are advised to undergo regular screening colonoscopy (i.e., those with a family history of CRC, relevant genetic syndrome, or inflammatory bowel disease). Semi-structured Interviews with clinicians in the territory indicate that implementation of these guidelines has been challenging particularly with regards to recruiting of participants, determining their eligibility for FIT, and arranging timely colonoscopy access for residents[7]. This study assesses the participation and outcomes of CRC screening in the NWT to better understand the effectiveness of colorectal cancer screening in a remote northern population.

MATERIALS & METHODS

This study was approved by the Aurora College Research Ethics Committee (protocol no. 20190404).

A population-based, retrospective cohort study was conducted of individuals who underwent CRC screening by fecal immunohistochemical test (FIT) in the NWT between January 1, 2014-March 30, 2019. Individuals were identified in the prospectively collected Public Health Registries maintained by the Northwest Territories Department of Health and Social Services Association. We included all individuals who, at the time of testing, were between the ages of 50-74 and had a valid NWT health card.

Individuals with a positive FIT result were included in further analysis of FIT follow-up, excluding individuals without accessible health records, or who moved out of territory during the observation period. The following variables were extracted: (1) participant demographics, (2) FIT eligibility, and (3) colonoscopy details. FIT-eligibility was derived from the patient's chart and defined as per the NWT

screening guidelines: individuals age 50-74 who are average risk and asymptomatic. This definition of FIT-eligible excludes individuals with signs and symptoms concerning for CRC, first degree relative with a history of colorectal cancer, genetic syndromes, inflammatory bowel disease, and/or indications for surveillance colonoscopy (i.e., a history of colonic polyps without a normal follow-up colonoscopy, or history of colorectal cancer) [113]. Signs and symptoms considered concerning for CRC included: rectal bleeding, melena, anemia, abdominal pain, change in bowel habits, and/or unexplained weight loss[113].

For pathology results, participants were classified by the highest-risk pathology on colonoscopy. Low risk adenoma (LRA) refers to 1-3 tubular adenomas or sessile serrated adenomas that are each <10 mm diameter. High risk adenoma (HRA) refers to 3 or more tubular adenomas or an advanced adenoma (AA) described as having at least one of the following features: size >10mm diameter, villous or tubulovillous histology, and/or high-grade dysplasia. Advanced neoplasia (AN) referred to either an AA or cancer. These definitions are in keeping with the US Multi-Society Task Force CRC guidelines for colonoscopy surveillance after screening and polypectomy [114,115].

Clinically detected cases of CRC were identified using the NWT Cancer Registry. Individuals who were between the ages of 50-75 years at the time of diagnosis and were diagnosed between January 1, 2014-Dec 31, 2016 were included. We collected data regarding the patient demographics, cancer pathology, stage, and location.

Statistical Analysis

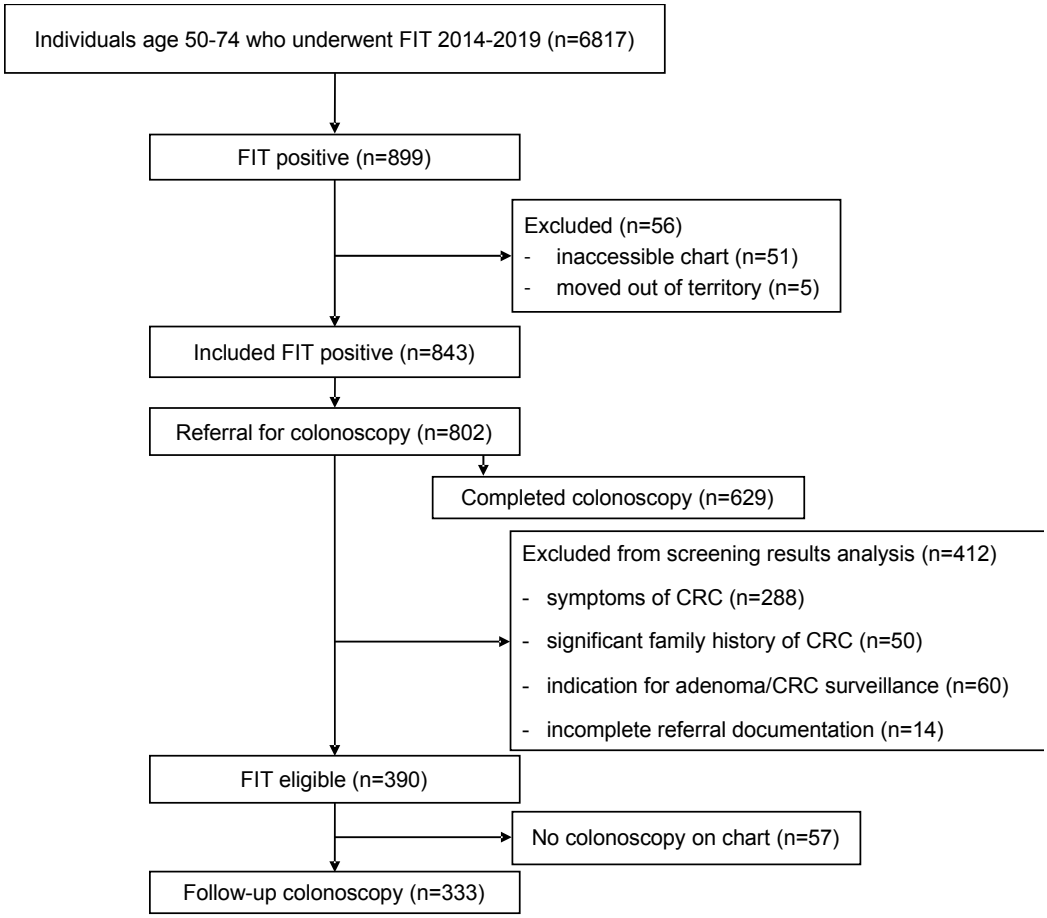
The screening participation rate was calculated using the Canadian Partnership Against Cancer definitions and the estimated cohort of screen eligible individuals age 50-75 based on the NWT Bureau of Statistics[116,117]. We compared screen detected cases of CRC to clinically detected cases. We conducted several subgroup analyses of FIT positive individuals to explore the relationship between different patient factors, wait times for colonoscopy, and screening outcomes. We compared individual with signs and symptoms of CRC to FIT eligible individuals, as well as indigenous to non-indigenous individuals, and finally FIT eligible individuals with AN to FIT eligible without AN. Statistical analysis were conducted using Microsoft Excel (version 16.16.19) and RStudio (version 1.1463). The following tests were used to discern relationships between variables: two sample Welch t-test was used for normally distributed continuous variables, Kruskal-Wallis Rank Sum Test for data without normal distribution, and Chi-Square Goodness of Fit Test for categorical variables. Relative risk (RR) was calculated using the “epitools” package in RStudio. A p-value of <0.05 was considered to be statistically significant.

RESULTS

Between 2014-2019, 6,817 FITs were completed by individuals between the 50-74 years, translating to an estimated biannual screening rate of 25.04% on average (appendix A figure 22). 843 (12.37%) FITs were positive after 56 were excluded due to incomplete records or moving out of territory (figure 7). We compared included and excluded individuals and observed a higher number of excluded individuals

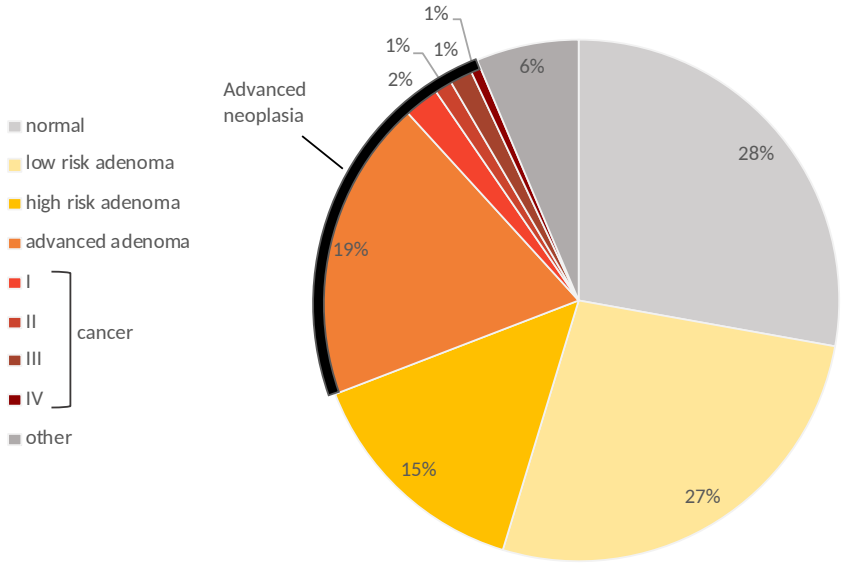
identified as Inuit (18 vs expected 5.17), and/or were from the Beaufort Delta region (22 vs expected 7.41). Fewer excluded patients were from Yellowknife (11 vs expected 27.26) (appendix A table 15). There was no significant difference in mean age or sex of individuals of included and excluded individuals.

Figure 7. Inclusion of individuals in the study analysis



Of the 843 FIT positive individuals included in our analysis, 629 (74.61%) underwent a colonoscopy after waiting a median of 133.00 days (SD 236.40; mean 207.20). On colonoscopy exam, 380(60.41%) were found to have adenomas, of which, 120 were AA(s) (figure 8). 34 individuals were found to have a cancer. This translated to PPV for FIT of 24.48% for AN.

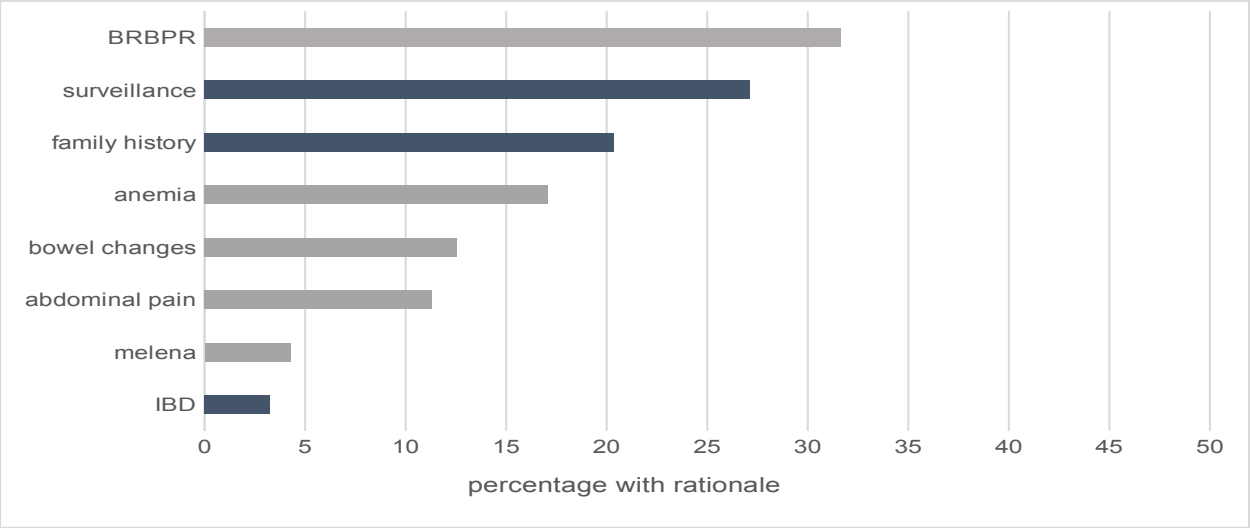
Figure 8. Colonoscopy findings after FIT positive result



We observed no differences in age, sex, or indigenous status of individuals with screen detected cancer compared to those with clinically detected cancer (appendix A table 16). In comparing the differences in histology, location, and stage, we did not observe any statistically significant differences between the screen detected and the clinically detected cancers.

At the time of referral for colonoscopy, 802 individuals were referred for a colonoscopy, of which, 398 (49.62%) met at least one exclusion criteria for FIT screening. Among these individuals, we identified 288 (35.91%) with signs or symptoms concerning for CRC, 50(6.23%) with a significant family history of CRC, and 60 (7.48%) with other indications for colonoscopic surveillance (figure 9).

Figure 9. Reason for FIT ineligibility



When we compared the symptomatic individuals to FIT eligible individuals, we identified no statistically significant differences in sex, but observed symptomatic individuals were, on average, older than FIT eligible individuals at the time of FIT (61.18 vs 60.15 years, p=0.047; 95% CI of difference (0.01, 2.06)) (table 6). Indigenous patients were approximately 49.04% more likely to have symptoms at the time of referral than non-indigenous patients (95% CI of RR: (1.25, 1.78)). When comparing by the region of residence, we observed that the region of residence was not independent of FIT eligibility (p<0.01): more patients than expected were referred from Fort Smith with symptoms, and fewer patients than expected from Yellowknife, but neither observation was statistically significant (appendix A figure 23). Similar proportions of individuals underwent a colonoscopy however, patients who were symptomatic waited, on average, significantly longer than patients who were asymptomatic (199.5 vs 149.0 days, p < 0.05; 95% CI of difference: (5.07, 41.92)). Symptomatic individuals were at least 22.8% more likely to have cancer identified on colonoscopy than screen eligible individuals (95% CI of RR: (1.228, 4.754)) (figure 10).

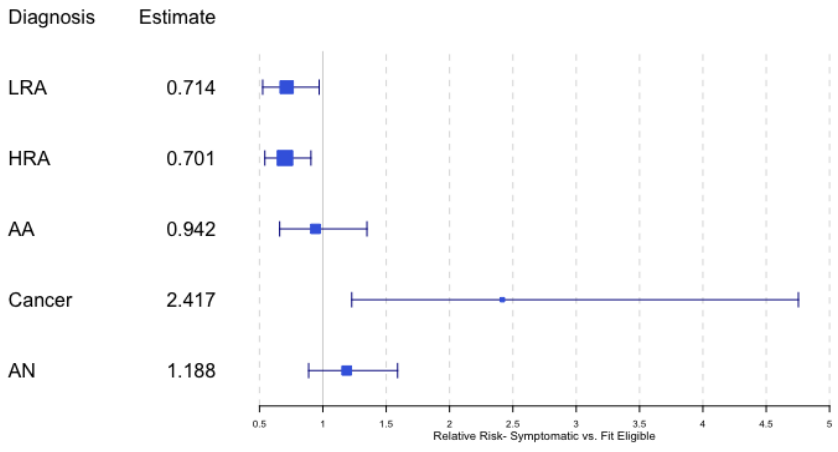
Table 6. Demographics and outcomes of screen eligible vs symptomatic individuals

Baseline characteristics	FIT Eligible (n=390)	Symptomatic (n=288)	P-value
Age, mean years (SD)	60.15 (6.55)	61.18 (6.82)	0.0474[+]
Sex, female, n(%; Std. Res)	157 (40.26; -0.52)	127 (44.10; 0.58)	0.316
Indigenous, n(%; Std. Res)	152 (38.97; -2.15)	162 (56.25; 2.49)	0.000008
Region of residence, n(%; Std. Res)			0.009
Beaufort Delta	42 (10.77; -0.26)	34 (11.81; 0.30)	non-specific to region
Dehcho	17 (4.36; -0.58)	17 (5.90; 0.67)	
Fort Smith	26 (6.67; -1.62)	36 (12.50; 1.88)	
Hay River	39 (10.00; -0.80)	38 (13.19; 0.93)	
Sahtu	21 (5.38; 0.06)	15 (5.21; -0.08)	
Tilcho	18 (4.62; -0.94)	21 (7.29; 1.09)	
Yellowknife	227 (58.20; 1.64)	127 (44.10; -1.91)	

Size of health centre, n(%; Std. Res)			0.0002
Yellowknife	219 (56.15; 1.94)	115(39.93; -2.26)	
Regional			
○ Fort Smith	26 (6.67; -1.62)	36 (12.50; 1.88)	
○ Hay River	36 (9.23; -0.84)	36 (12.50; 0.98)	
○ Inuvik	21(5.38; 0.60)	11(3.82; -0.70)	
Small community	88 (22.56; -1.42)	90 (31.25; 1.66)	
Colonoscopy, n(%)	333 (85.38)	212 (74.65)	0.29
Completed, n(%; Std. Res)	318 (95.50; 0.15)	198 (93.40; -0.19)	
Incomplete, n(%; Std. Res)	15 (4.50; -0.65)	14 (6.60; 0.81)	
FIT to colonoscopy, days			
Mean	159.9	183.4	0.01+
Median	149.0	199.5	0.02
<60 days, n(%; Std. Res)	79 (23.87; 0.88)	38 (18.10; -1.10)	
60-180 days, n(%; Std. Res)	111 (33.53; 0.69)	59 (28.10; -0.86)	0.04
>180 days, n(%; Std. Res)	141 (42.60; -1.16)	113 (53.80; 1.45)	
Findings, n(%; Std. Res)			
Low risk adenoma	99 (29.73; 1.17)	45 (21.23; -1.47)	0.03
High risk adenoma	130 (39.03; 1.41)	58 (27.36; -1.77)	0.005
Advanced adenoma	65 (19.52; 0.18)	39 (18.40; -0.23)	0.75
Cancer	13 (3.90; -1.60)	20 (9.43; 2.00)	0.008
Advanced neoplasia	78 (23.42; -0.62)	59 (27.83; 0.78)	0.25

+ Welch two sample t-test, Std. Res = Standardized Residual, SD=standard deviation

Figure 10. Relative risk of diagnosis for symptomatic patients vs. eligible patients



When looking at the outcomes of FIT eligible individuals who underwent a colonoscopy, 229 of 333 were found to have adenomas, of which, 99 were LRAs, and 130 were HRAs. The most frequent contributing factor to the classification of adenomas as HRA was a count of 3 or more adenomas. We identified 13 screen eligible individuals who were diagnosed with CRC, the majority of which were early

stage (stage I or II) (63.1%). The PPV for FIT among asymptomatic eligible individuals was 42.9% for HRA and AN combined, 23.4% for AN and 3.9% for cancer.

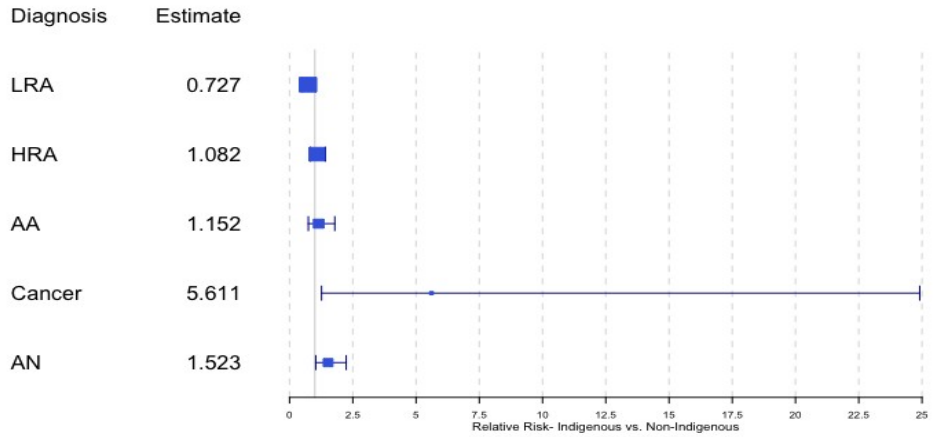
We conducted a subgroup analysis of screen eligible individuals comparing those with AN to those without (table 7). We observed no significant difference in sex (p = 0.30), or in the mean age at the time of FIT (59.69 years with AN vs 59.96 years without; p=0.746). However, we did observe that indigenous patients experienced an estimated 52.3% higher relative risk of AN relative to non-indigenous patients (95% CI of RR: (1.0354, 2.239)). To assess this further, we looked at the relative risk for indigenous patients of having advanced pathology. Indigenous residents experienced a higher relative risk of CRC compared to non-indigenous individuals both overall and when excluding individuals with signs and symptoms of CRC (estimated RR 2.60, (95% CI of RR: (1.26-5.34)) and 5.6 when excluding symptomatic individuals (95% CI of RR:(1.26, 24.91))(figure 11). Screen-eligible indigenous patients were older than non-indigenous screen-eligible patients (61.23 vs. 59.03 years, p<0.01; 95% CI of difference: (0.76, 3.63)). However, they did not experience any statistically significant difference in wait time for colonoscopy (median wait time 153.5 days for indigenous vs 146.0 days for non-indigenous, p=0.79; mean 161.77 vs 158.70, CI of difference: (-20.32, 26.47), p=0.80). We also observed that those with AN, on average, experienced a longer wait time for colonoscopy than those without AN (194.54 versus 148.09 days; 95% CI of difference: (20.04, 72.85), p=0.0007). We found that that the relative risk of having an AN for FIT eligible patients who wait more than 180 days is estimated to be 72.24% more than those who wait less than 180 days (95% CI: (1.17, 2.55)). The availability of colonoscopy services within the patients' community of residence was not associated with a diagnosis of AN.

Table 7. FIT eligible with advanced neoplasia vs without advanced neoplasia

Baseline characteristics	With AN (n=78)	Without AN (n=255)	P value
Age, mean years (SD)	59.69 (6.50)	59.96 (6.41)	0.75
Sex, female (%; Std. Res)	27(34.62; -0.71)	105 (41.18; 0.39)	0.30
Indigenous (%; Std. Res)	39 (50.00; 1.45)	93 (36.47; -0.80)	0.03
Region of residence, n(%; Std. Res)			0.20
Beaufort Delta	14 (17.95; 1.92)	22 (8.63; -1.06)	
Dehcho	6 (67.69; 1.33)	9 (3.53; -0.73)	
Fort Smith	5 (6.41; -0.44)	21 (8.24; 0.24)	
Hay River	7 (8.98; -0.01)	23 (9.02; 0.01)	
Sahtu	4 (5.13; -0.11)	14 (5.49; 0.06)	
Tilcho	3 (3.85; -0.39)	13 (5.10; 0.21)	
Yellowknife	39 (50.00; -0.89)	153 (60.00; 0.49)	
Endoscopy in community, n(%; Std. Res)			0.86
yes	53 (23.14; -0.09)	176 (76.86; 0.05)	
no	25 (24.04; 0.13)	79 (75.96; -0.07)	

FIT to colonoscopy, days			
mean	194.54	148.09	0.0007
median	201.5	130	0.004
<180 days, n(%; Std. Res)	34 (43.59; -1.58)	155 (61.26; 0.88)	0.006
>180 days n(%; Std. Res)	44 (56.41; 1.82)	98 (38.74; -1.01)	

Figure 11. Relative Risk of diagnosis for FIT eligible indigenous vs. FIT eligible non-indigenous



DISCUSSION

In this retrospective cohort study of CRC screening in a remote northern population, FIT based CRC screening did not facilitate earlier CRC detection. This may be due to the limited participation of only 25% of eligible individuals[118]. Nonetheless, CRC screening appears to have effectively facilitated adenoma detection. 61% of FIT positive individuals had adenomas identified at colonoscopy, a majority of which were amenable to removal at index colonoscopy and therefore, may reduce that individual's risk of CRC in the long term[119].

Interestingly, the positivity rate and PPV of FIT were higher than observed in recent studies. A recent prospective trial by Liles et al. (2018) assessed the performance of FIT using the same brand and threshold for 2761 individuals undergoing screening and observed a FIT positivity rate of 8.1%, and PPV for HRA or AN of 21.9-24.8% whereas in this study we observed a positivity rate of 12.3% and PPV of 43.8%[120]. The population of the NWT has been shown to have a higher age-standardized incidence rate of CRC than other areas of Canada; however, the reasons for this have not been explored[121]. We observed three factors associated with AN and CRC in this population which warrant further discussion: (1) individuals with signs and symptoms of CRC frequently participated in screening and were more likely to be diagnosed with CRC, (2) longer wait times for colonoscopy were associated with a higher risk of AN, and (3) indigenous individuals experienced a higher burden of CRC than non-indigenous.

Over 1 in 3 FIT positive individuals had signs or symptoms of colorectal cancer at the time of screening, despite the recommendations for their exclusion from FIT screening. Several studies have similarly evaluated the symptoms of FIT positive individuals and observed even higher rates among participants of 47-78% [122–124]. The frequency of these symptoms among participants may have important implications for CRC screening positivity and definition of "asymptomatic" screen detected cancer[125]. We observed higher rates of AN and CRC among individuals with reported signs or symptoms than FIT eligible individuals. However, other studies have identified the predictive value of red flag symptoms to be variable for colorectal pathology [122–124]. De Klerk and colleagues (2018) reviewed 527 FIT positive patients and the 41% of individuals who had symptoms had a higher odds of CRC but the results were not statistically significant (OR 1.64 (CI 0.86-3.13). In their analysis by individual symptoms, only a change in bowel habits or blood in the stool were associated with CRC detection at colonoscopy (OR 2.86, CI 1.23-6.62 and OR 8.65, CI 2.35-32.0)[124]. Previous systematic reviews summarizing the predictive value of red flag signs and symptoms, independent of FIT, have found rectal bleeding has diagnostic value, but other signs and symptoms only provide modest diagnostic value[126,127]. The inconsistency of symptom detection and definitions between studies also limits the generalizability of these results. Further research is needed to discern if a clear relationship exists, particularly in the context of FIT use, in order to guide screening and endoscopy protocols. The reason for symptomatic individuals to undergo FIT in the territory is not clear, but may be attributed to its use as a tool to reduce patient's wait time for colonoscopy, as identified in previous interviews with clinicians in the territory[7]. This strategy does not appear to be effective, as we observed that patients with symptoms wait significantly longer for colonoscopy than FIT eligible individuals (p=0.036), despite the recommendations for symptomatic individuals to be triaged as a higher priority for colonoscopy[17]. Further research is needed to discern the reason for individuals with concerning signs and symptoms to undergo screening and the impact of their screening participation on the diagnostic yield of FIT.

Patients in this study experienced long wait times for colonoscopy following a positive FIT result. Longer wait times were associated with more advanced pathology at colonoscopy. National screening quality guidelines in Canada recommend a follow-up colonoscopy be completed within 60 days of a positive FIT and define a follow-up colonoscopy as one completed within 180 days of FIT[117]. We found that only 23.87% of FIT eligible individuals met the benchmark of 60 days, and 42.60% were completed within 180 days. Individuals who waited more than 180 days were 72.24% more likely to have AN than those waited 180 days or less (95% CI of RR: (1.165, 2.547)). Other studies have similarly observed wait time for colonoscopy after fecal screening test to be associated with more advanced pathology at colonoscopy[128,129]. Corley and colleagues found wait times of 10-12 months associated with a higher odds of CRC (OR 1.49 (95% CI 1.05-2.08)[128]. Flugelman and colleagues identified a significant relationship between increasing wait time interval and stage of disease at presentation, as well as an association between wait times more than 12 months and a higher risk of CRC mortality (adjusted hazard ratio 1.53(1.13-2.12))[129]. Both studies were also retrospective and therefore unmeasured confounders remain a possible explanation for these observations. Nonetheless, our findings reinforce

the expert recommendations for prompt colonoscopy follow-up after FIT to enhance the quality of screening, and potentially, detect AN earlier.

Finally, we observed significantly higher rates of AN and cancer among indigenous individuals compared to non-indigenous residents in the territory. Indigenous individuals were also more likely to present with symptoms, however, even when restricting our analysis to FIT eligible individuals, we observed a 5.6 relative risk of cancer (95% CI of RR: (1.264, 24.911)). The reason for this difference is not discernable with this study and research on this topic is sparse. We were unable to identify any study which has specifically looked at CRC rates among indigenous residents in northern Canada. Research of Alaskan indigenous populations observed that they experienced a higher CRC incidence than other ethnic groups in the United States[130]. Boardman and colleagues assessed this further by comparing the tumour genetics among Alaskans but found no significant differences, and concluded that the cause of the higher incidence of CRC is likely multifactorial and attributable to recent diet changes, namely higher intake in fat, refined carbohydrates, and animal protein; lifestyle factors; and smoking[2]. These factors may be generalizable to the NWT, however further research is needed. Cancer is increasingly a public health concern among northern indigenous populations and our study is the first demonstrate this in CRC screening results[131]. The higher incidence of malignancy we observed requires further investigation and advocates for a reconsideration of the current average-risk CRC screening protocol for this population. Individuals with a first degree relative with a history of CRC have a 1.9-4.4 relative risk of CRC compared to average risk individual and are recommended to undergo colonoscopy screening every 5-10 years in Canada [132]. As such, our findings would suggest that indigenous individuals should also be considered for enhanced screening to optimize CRC detection and control given their relative risk of CRC.

The generalizability of our results is limited to the retrospective data collected in the health records and small sample size. FIT eligibility was derived from clinicians notes and therefore dependent on the consistency of provider documentation. We excluded 51 individuals due to inaccessible records. A higher than anticipated proportion of these individuals were from Beaufort Delta region and/or were Inuit. This is not surprising as we experienced difficulty in accessing paper records in this region. However, the included Inuit and Beaufort Delta residents did not experience any significant difference in colonoscopy outcomes than the remainder of the cohort.

CONCLUSION

In this study of a northern remote population, FIT-based CRC screening did not appear to prevent CRC or provide earlier detection, but did result in more frequent positive pathology results than anticipated for average risk screening. Individuals were more likely to have positive results (defined as AN on colonoscopy), if they experienced long wait times for colonoscopy, had clinical signs and symptoms of CRC, and/or were indigenous. Increasing access to colonoscopy, and effective triaging of FIT eligible individuals could enhance CRC screening effectiveness. Further research is needed to understand how

to increase colonoscopy access in this remote region, and to discern if colonoscopy screening should be adopted among indigenous individuals given their relative risk of CRC.

ACKNOWLEDGEMENTS

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CHAPTER 4: ENHANCED SCREENING WOULD REDUCE THE BURDEN OF COLORECTAL CANCER IN NORTHERN CANADA: PROJECTIONS OF PARTICIPATORY SIMULATION MODELING

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ABSTRACT

Background: Mortality from colorectal cancer (CRC) in the Northwest Territories (NWT), a northern region of Canada, is nearly double the national rate. While mortality could be reduced with greater adherence to CRC screening, this requires colonoscopy access which is limited, and demand is difficult to predict. We use participatory simulation modeling to estimate colonoscopy demand and CRC outcomes with enhanced screening in the NWT.

Methods: Using a participatory approach, a conceptual model of CRC screening was developed with local collaborators and used to inform input parameter calibration of an existing simulation model OncoSim-CRC version 3.3.6.0 to reflect the NWT population. The model was run for 500 million cases with an anticipated increase in screening participation (from 30 to 60%) and validity assessed.

Results: The participatory approach informed simulation model parameters. Using the adjusted version of OncoSim-CRC, we estimate that colonoscopy demand with a CRC screening program would surpass capacity within 1-2 years, and continue to increase over the next 10-15 years due to adenoma surveillance. If this colonoscopy demand is met, we estimate screen detected cancers would increase by 110%, and clinically detected cases reduce by 26%. Alternatively, increasing the phase-in period or revising adenoma follow-up guidelines would reduce demand and still improve cancer detection.

Interpretation: The anticipated increase in FIT screening participation will quickly surpass current capacity for colonoscopy follow-up in the territory. If the demand is met, this could reduce the burden of CRC. Strategies to phase-in screening and to reduce adenoma follow-up could enhance the feasibility and effectiveness of screening in the NWT.

INTRODUCTION

Colorectal cancer is the third the most common malignancy worldwide, and the second leading cause of cancer related death in Canada [133]. The widespread uptake of organized CRC screening in many countries, including Canada, has been associated with a reduction in the incidence and mortality of CRC [5,6,134]. However, rural and indigenous populations experience significant disparities in access to CRC screening and cancer care[135]. For instance, in Canada, none of the three northern territories currently have an organized screening program in place. In northern and remote regions, screening is difficult to optimize within the constraints of resource-limited health systems providing care to a diverse and widely distributed population [7,136].

Simulation modeling has increasingly been used to assist in planning efficient CRC screening, and could inform decision-makers in rural and remote regions [57]. Simulation models are mathematical models derived from clinical, epidemiologic, and economic data, and can be manipulated and recalibrated to assess the long-term outcomes of a screening intervention or proposed program in a target population [137]. In Canada, OncoSim-CRC was developed to inform CRC screening recommendations and could be used to evaluate screening strategies for Canada's remote communities in the territories [138].

A region of Canada where participatory simulation model would be useful to inform CRC screening is the Northwest Territories (NWT), one of the three northern regions of Canada. The NWT encompasses 1.1 million^2 kilometers[139] and has a population of 44 900 people living in 33 communities, of which 50.7% identify as indigenous[116].The mortality rate from colorectal cancer (CRC) in the NWT is nearly double the national rate[140]. Screening guidelines recommend that average risk individuals between the age of 50-74 receive a fecal immunochemical testing (FIT) every two years to identify cases of suspected cancer. If the FIT is positive, a colonoscopy should be completed within 60 days to establish a diagnosis[15–17]. In 2018, only 23.9% of eligible individuals participated in FIT screening, and of those who tested positive, only 18.7% received a follow-up colonoscopy within the recommended 60 days. Plans for programmatic screening to increase FIT participation are underway. However, the benefits of this would be limited without adequate colonoscopy access to diagnose CRC and remove adenomas. Developing accurate projections of colonoscopy demand, and strategies to allocate endoscopy resources to meet the demand in the territory are needed.

However, screening delivery in the territories is complex. For instance, Champion and colleagues found screening delivery in the Northwest Territories was influenced by multiple geographic, cultural, social, and environmental factors. These contributed to unclear accountability for testing, limited colonoscopy resource access, poor information technology communication, and redundant system processes [7]. Therefore, to develop valid and useful projections for rural and remote end-users, integrating the complex health system factors would be important. This could be done by using a participatory simulation modeling approach whereby, end-users are included in the modeling process from conceptualization to validation [141]. This has been previously described as an effective method to

enhance the validity of model projections and facilitate translation of model outputs to feasible interventions[50].

This study applies a participatory simulation modeling approach to estimate future colonoscopy demand in the NWT using an adjusted version the OncoSim-CRC model, and end-user participation.

METHODS

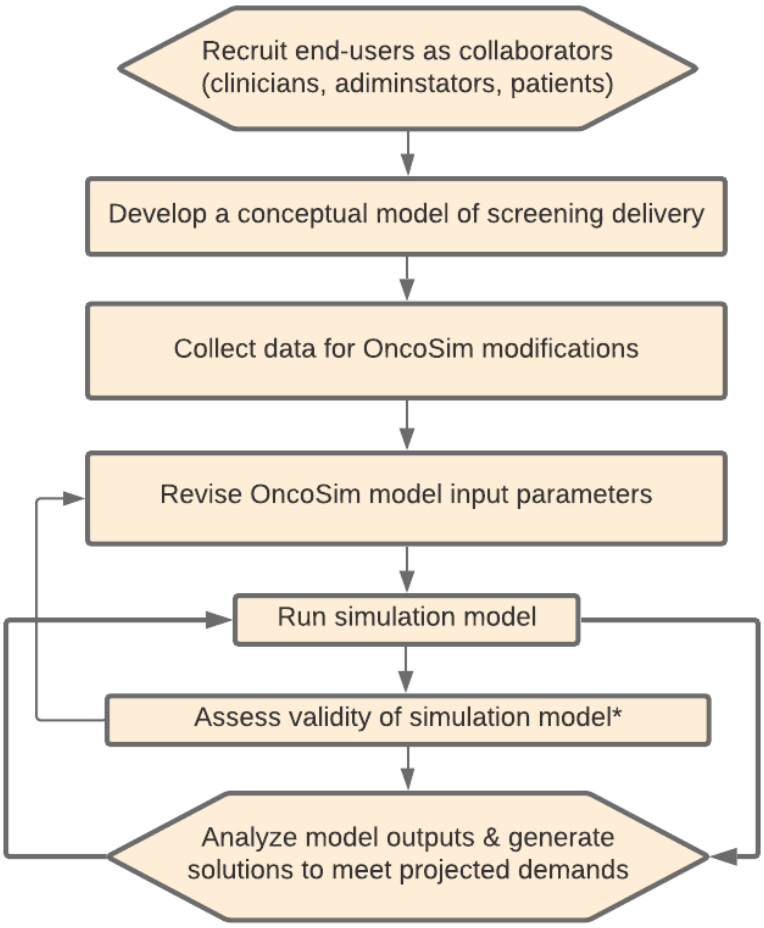
Setting

CRC screening guidelines in the NWT were introduced in 2009 which recommend FIT screening of average risk individuals age 50-74 every 1-2 years and colonoscopy screening for higher risk individuals with a family history of CRC, relevant genetic syndrome, or inflammatory bowel disease. Colonoscopy is available in 3 communities: Yellowknife, Hay River and Inuvik.

Participatory simulation approach

This study was approved by the Aurora College Research Ethics Committee (protocol no. 20190404). We adapted the participatory approach of PartiSim to engage end-users in model conceptualization, development, assessment, and validation (figure 12)[21].

Figure 12. Overview of adapted participatory modeling process



**Collaborators assessed face validity of the model.*

End-users involved in CRC screening planning and delivery were identified and recruited to participate as collaborators including chief public health officers, epidemiologists, managers, clinicians, and patients. Invitations were sent to the Office of the Chief Public Health Officer and snowball sampling was used to recruit additional collaborators with expertise in colorectal cancer screening. Two patients, who were familiar with the process of CRC screening, were recruited through social media to participate as patient collaborators. The research question of this study was refined with collaborators and a conceptual model of CRC screening in the NWT was developed through iterative collaborator meetings. This conceptual model was used to identify key parameters of the OncoSim-CRC model to adjust and inform data collection.

Model

OncoSim-CRC version 3.3.6.0 was developed by the Canadian Partners Against Cancer to evaluate the outcomes and cost-effectiveness of cancer control strategies.[138] It was derived using Canadian demographic and risk exposure data, as well as the results of published trials. Both its internal and external validity have been previously assessed.[83,142] A complete description of the model including the

sources used for input parameters and the validation assessments conducted has been previously published.[143]

The parameters of OncoSim-CRC version 3.3.6.0 were iteratively adjusted based on data from a retrospective review of CRC screening results between 2014-2019, NWT population statistics, published systematic reviews, and expert opinion of collaborators (Table 8). A detailed description of model adjustments and their results are included in appendix B.

Table 8. Summary of parameter adjustments

Parameter(s)	Value	Source
Recruitment and Participation	**Average risk:** FIT screening: 2009-2013: 20% 2014-2051 current: 30% 2021-2051 FIT Program: 60% 2021-2051 CS Program: 60%	2009-2013, performance report[144] 2014-2019, NWT Public Health Registries 2020-2051, expert opinion
	High risk: 1990-2051: 60%	Expert opinion
Screening modality	FIT if average risk* Colonoscopy if high risk **Except for CS Program, colonoscopy every 10 years if average risk*	NWT CRC screening guidelines Expert opinion
FIT performance±		
Sensitivity	Adenoma: ≤5mm, 0.04 6-10mm, 0.10 ≥10mm, 0.40 CRC: 0.82	Systematic review [145,146], prospective trial[120], expert opinion.
Specificity	Advanced neoplasia: 0.96	Systematic review [145,146], prospective trial[120]
Colonoscopy		
Sensitivity	Adenoma ≤ 5mm, 0.75 6-10mm, 0.85 ≥10mm, 0.95 CRC: 0.93	Systematic review [146]
Specificity	Advanced neoplasia: 0.96	Systematic review [146]
Proportion of FIT positive patients undergoing colonoscopy ≤180 days+ after	Current+:37% Program: 85%	Retrospective cohort study 2014-2019, CPAC quality indicator guidelines[117] Program: expert opinion
Adenoma incidence (NWT vs national rate)	Female: 1.71 Male: 1.82	Statistics Canada[121]

Population (Ratio of NWT/NU which are from NWT)	0.75	NWT vital statistics [116] NU population statistics[147]

±adjusted to OC-Auto by Polymedco at the threshold of 75ng/ml (15ug/g). + Using CPAC quality indicator definition of a follow-up colonoscopy after FIT defined as within 180 days, 37% would undergo colonoscopy as per retrospective cohort study.

The model was adjusted to simulate a screening program using FIT phased in over 5 years (from 2021-2025) in the NWT. As recommended by collaborators, we estimate that 50-60% of eligible individuals would participate in this program, and that 85% of individuals with a positive FIT would undergo colonoscopy within 180 days . Three comparator scenarios were developed to simulate CRC screening participation continuing as currently practiced based on a retrospective cohort study employing the CPAC quality indicator definition of colonoscopy follow-up as one within 180 days after FIT.[117] Given the higher rate of CRC observed in this population when compared to the general Canadian population, two additional programs were simulated: one where all average risk individuals undergo colonoscopy every 10 years, and one where all average risk individuals undergo annual colonoscopy. All scenarios were run for 500 million individuals eligible for screening between the years of 2005-2051.

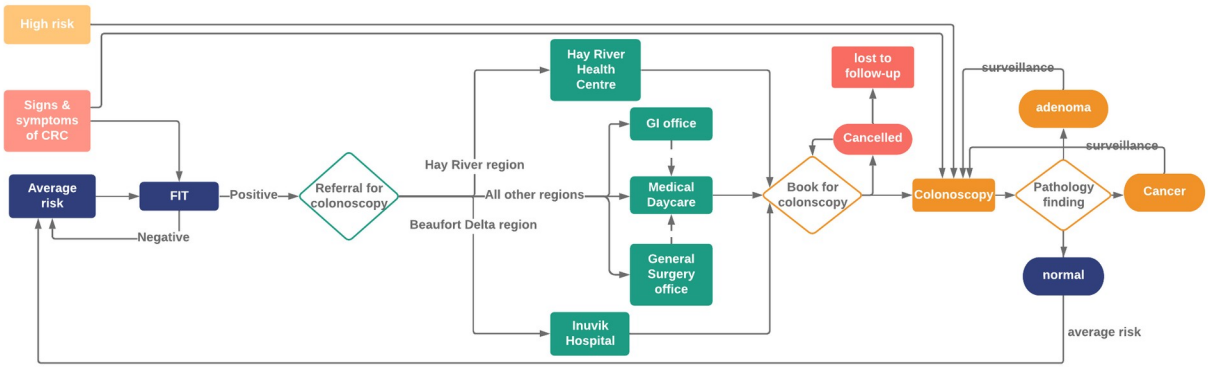
Model validity

The validity of OncoSim-CRC has been previously assessed.[138] To gauge the credibility of the adjusted model, we conducted targeted assessments of the face validity, internal validity, and external validity of the revised model using practices outlined by the International Society for Pharmacoeconomics and Outcomes Research-Society for Medical Decision Making Taskforce for Modeling Good Research Practices.[30] To assess face validity of the model, the final input parameters, model structure, and outputs were presented to collaborators who evaluated the model's completeness, credibility, and plausibility. To assess internal validity, one-way sensitivity analysis of all modified parameters was conducted. To assess the external validity, model outputs of interest were compared to CRC screening outcomes between 2014-2018. Cross validity and predictive validity have been previously assessed for OncoSim-CRC and were not repeated in this study because relevant comparators for a northern rural context were not identified.

RESULTS

For the participatory approach, 12 end-users were recruited as collaborators. With these collaborators, a conceptual model of CRC screening in the NWT was developed (figure 13). This proved to be an effective tool to identify appropriate parameter adjustments and data sources for OncoSim calibration. Knowledge gaps identified through this process included colonoscopy wait-times after FIT, and current colonoscopy capacity in the territory.

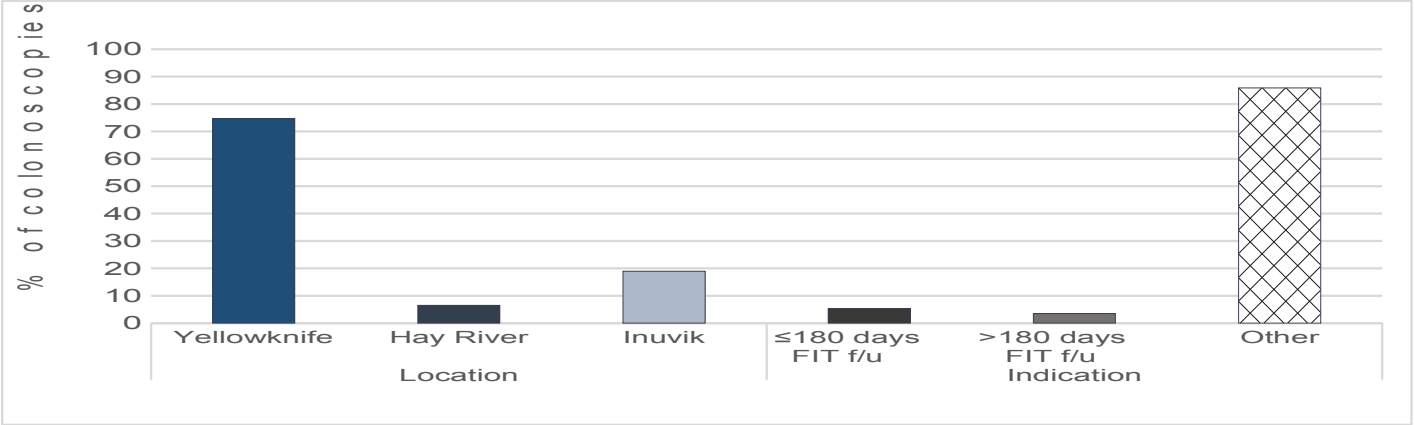
Figure 13. Conceptual diagram of CRC screening in the NWT



Colonoscopy capacity

We assessed colonoscopy capacity using collected data on the number of colonoscopies conducted in the NWT, and observed that between Jan 1, 2014-Dec 31, 2018, approximately 6630 colonoscopies were conducted in the NWT, of which 538(8.8%) were follow-up to positive FIT results. A majority of the colonoscopies (74.6%) were conducted at Stanton Territorial Health Authority in Yellowknife (figure 14).

Figure 14. Colonoscopies conducted in the NWT 2014-2018

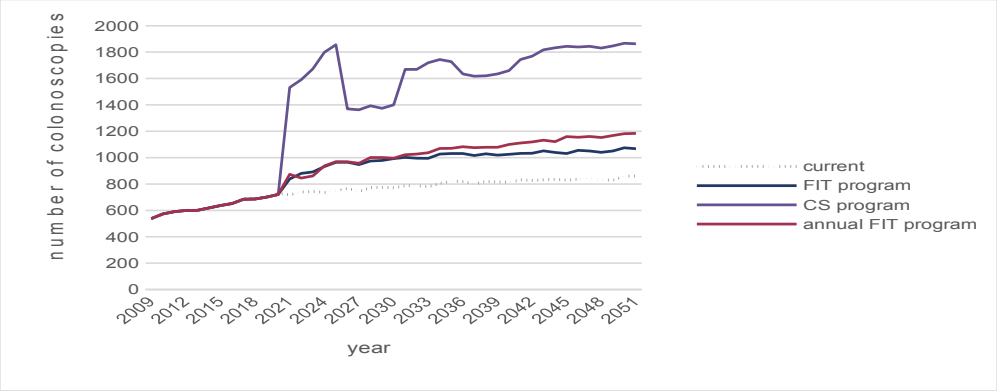


Simulation model outcomes

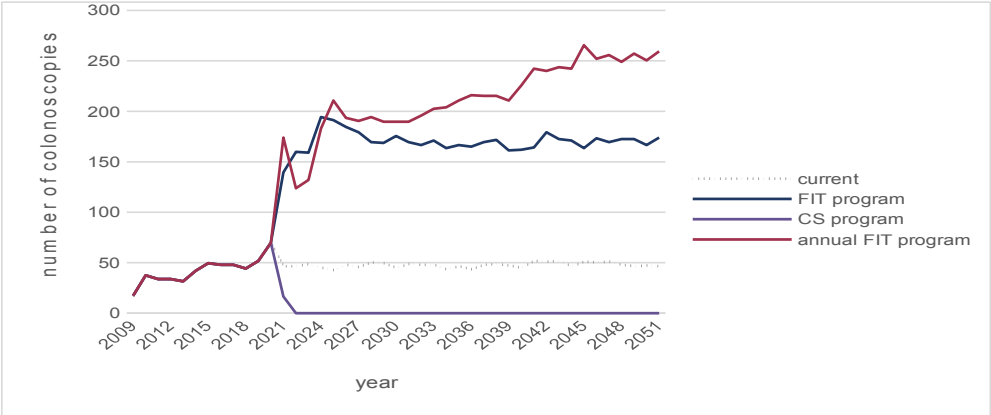
Integrating input from collaborators, and recent data sources, the OncoSim-CRC model was revised and run to compare current screening with programmatic screening in the NWT (table 8). Under the simulation model assumptions, we estimate that implementation of a FIT-based CRC screening program would increase total colonoscopy demand by 25.3% compared to current screening (figure 15a). A colonoscopy screening program would increase demand for colonoscopy by 110.2%, and annual FIT screening program by 31.9% (figure 15a). With implementing a FIT screening program, initially, the greatest increase in demand would be for follow-up colonoscopy from FIT positive results, surpassing current capacity within the first 2 years of implementation, and generating an increase in demand over the long term of 256.6% compared to current screening (figure 15b).

Figure 15.Colonoscopy demand for screening program implementation

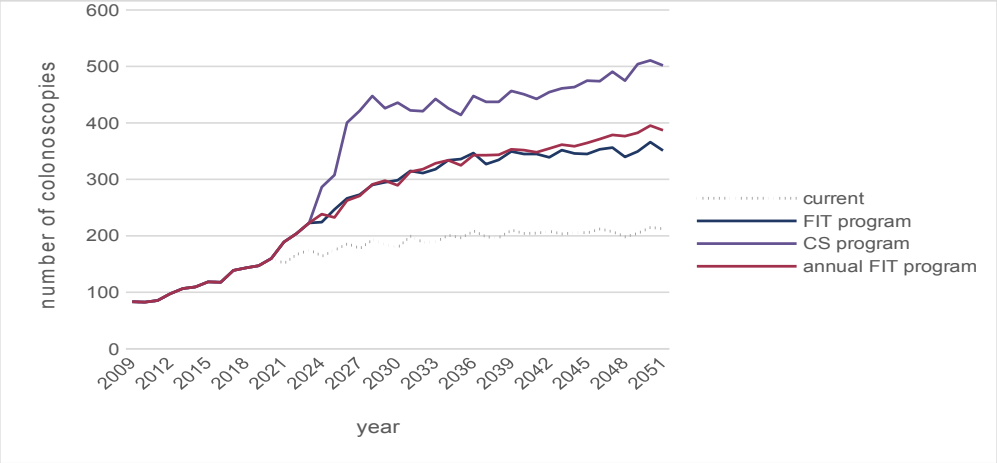
a. Total colonoscopy



b. Colonoscopy for FIT follow-up



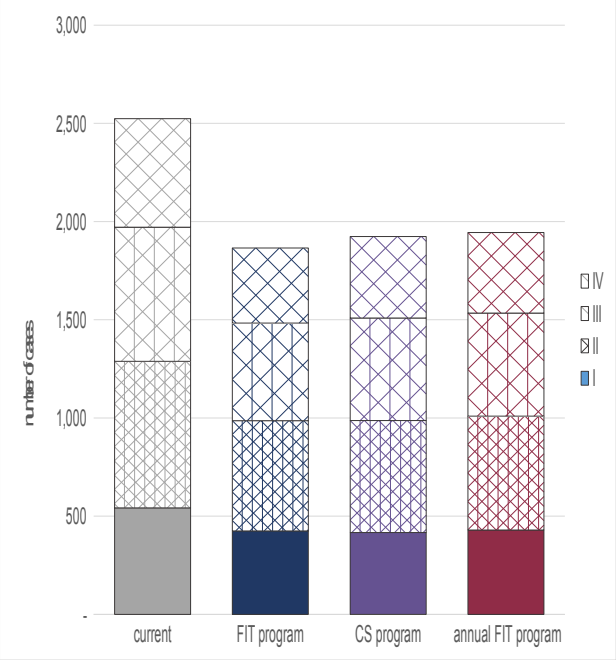
c. Colonoscopy for adenoma surveillance



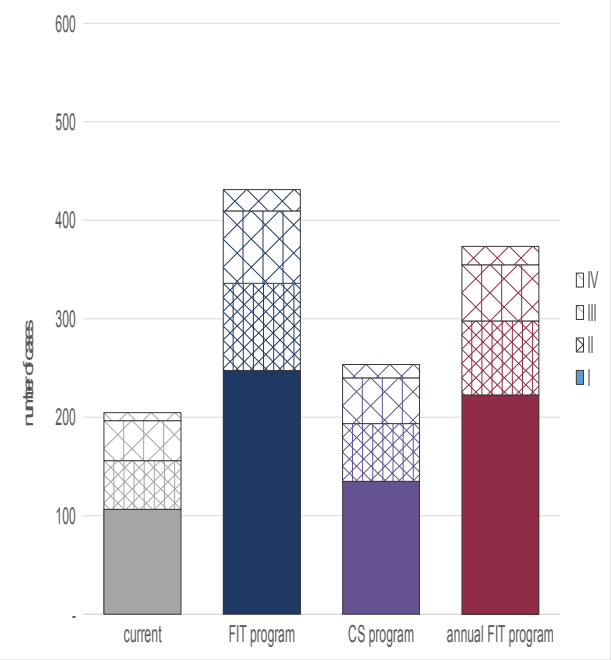
In the long-term, adenoma follow-up would account for the highest number of additional colonoscopies (9,668 colonoscopies from 2021-2051 for FIT program screening) (figure 15c). If this colonoscopy demand could be met, we predict that implementing a FIT screening program would lead to a reduction in clinically detected CRC (-26.1% for a FIT program compared to current screening), and facilitate earlier detection of CRC (110.6% increase for a FIT program compared to current screening) (figure 16 a and b).

Figure 16. CRC detection 2021-2051

a. Clinically detected CRC



b. Screen detected CRC



Alternative scenarios

In presenting these results to collaborators, the following alternative scenarios were developed as potential strategies to reduce the initial colonoscopy demand: A) 7-year phase in period B) 10-year phase in period C) no low risk adenoma colonoscopy follow-up, and D) lower program participation of 40% (table 2).

Table 9. Simulated scenarios to reduce colonoscopy demand

	Parameter adjusted	Target	Description
A	Phase-in period	7 years	Introduce the screening program over 7 years to reduce the initial impact on colonoscopy demand.
B	Phase-in period	10 years	Introduce the screening program over 10 years to reduce the initial impact on colonoscopy demand.
C	Low risk adenoma (LRA) follow-up	No further colonoscopy, return to FIT	Individuals identified to have a LRA would return to FIT in 5 years without a repeat colonoscopy as per Ontario guidelines and recent evidence suggesting individuals with LRA have lower risk of CRC than average risk individuals [148].
D	FIT screening invitation	40% participate	Reduce the number of individuals invited to FIT screening to lower participation to approximately 40%

As outlined in table 10, we observed that these scenarios all reduced colonoscopy demand compared to program screening with Scenario C (no LRA follow-up) requiring the lowest number of colonoscopies (figure 17a). When comparing CRC incidence, we found that all alternative scenarios resulted in a decrease in clinically detected CRC incidence compared to current screening (mean annual incidence of 74.08-79.91 in scenarios vs 84.1 with current screening) (figure 18a). All scenarios increased screen detected cancer incidence compared to current screening, particularly in the number of early stage CRC cases (mean annual incidence of stage I/II screen detected cancer of 8.2-10.8 with the program or alternative scenarios vs 5.2 with current screening)(figure 18b).

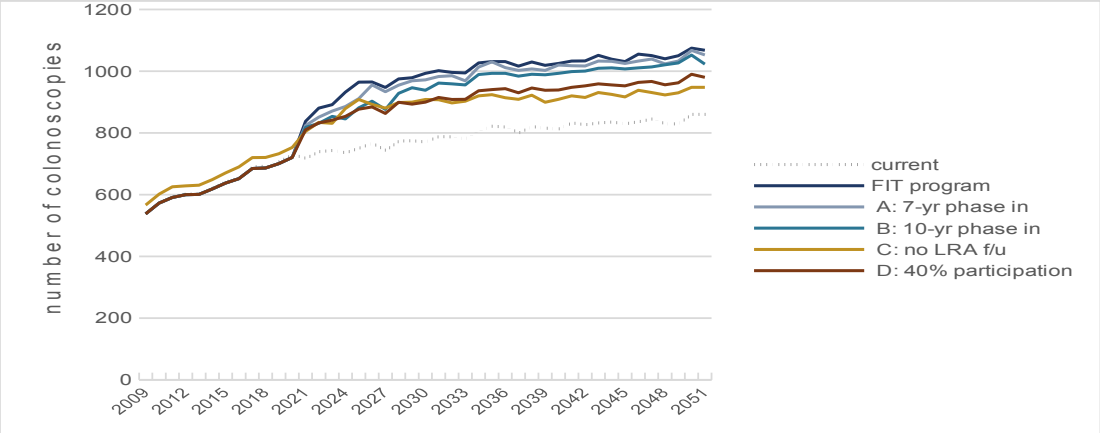
Table 10. Screening participation and resource requirements, annually* between 2021-2051

			alternative scenario			
	current	**FIT program**	**A: 7-yr phase in**	**B: 10-yr phase in**	**C: no LRA f/u**	**D: 40% participation**
Age 50-75	12,211	12,233	12,231	12,227	12,233	12,224
FIT						
Eligible, n	8,808	6,942	7,198	7,546	6,892	7,972
Mean participation, % (SD)	32.2 (0.27)	57.5 (4.51)	53.1 (4.68)	47.2 (4.34)	58.3 (4.70)	40.4 (1.58)
Positive, n(%)	133.5 (7.7)	198.0 (7.0)	185.9 (7.1)	169.1 (7.1)	202.2 (7.1)	142.3 (6.9)
Colonoscopy						
Total	826.15	1,035.50	1,017.58	993.45	935.60	951.58
Screening	242.58	242.58	242.58	242.58	278.08	242.58
Positive FIT	49.23	175.55		149.85	179.00	126.00
Adenoma Surveillance	200.78	322.28	312.18	298.75	173.78	272.13
Cancer surveillance	249.48	233.03	234.60	236.80	237.93	239.05
Symptoms of CRC	84.05	62.23	63.45	65.35	66.95	71.73

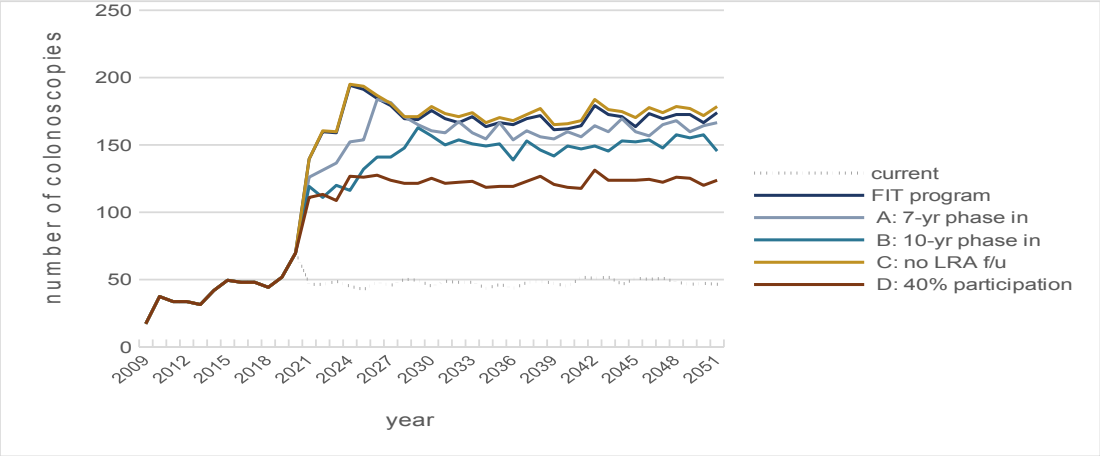
**indicates the mean annual number of individuals for 2021-2051*

Figure 17. Colonoscopy demand for colorectal cancer

a. Total colonoscopy



b. Colonoscopy demand to follow-up positive FIT



c. Colonoscopy demand to follow-up detected adenoma

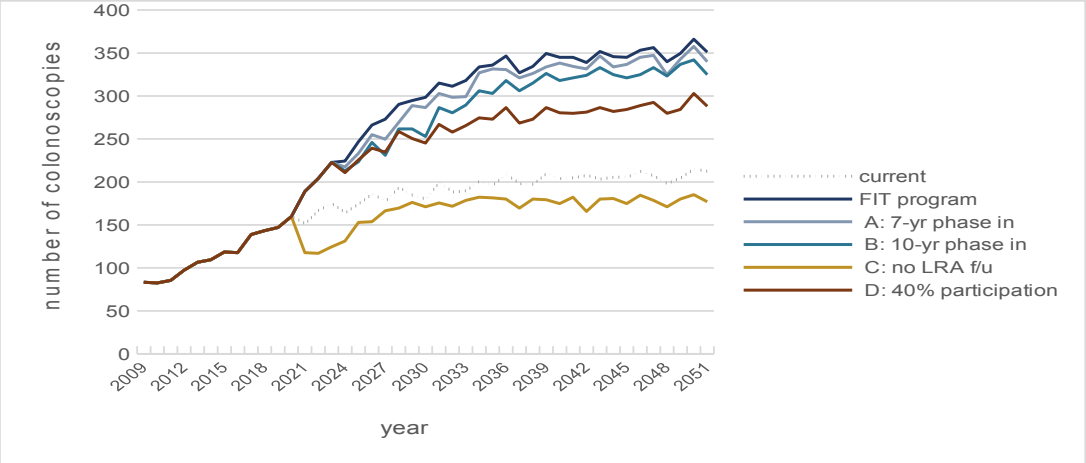
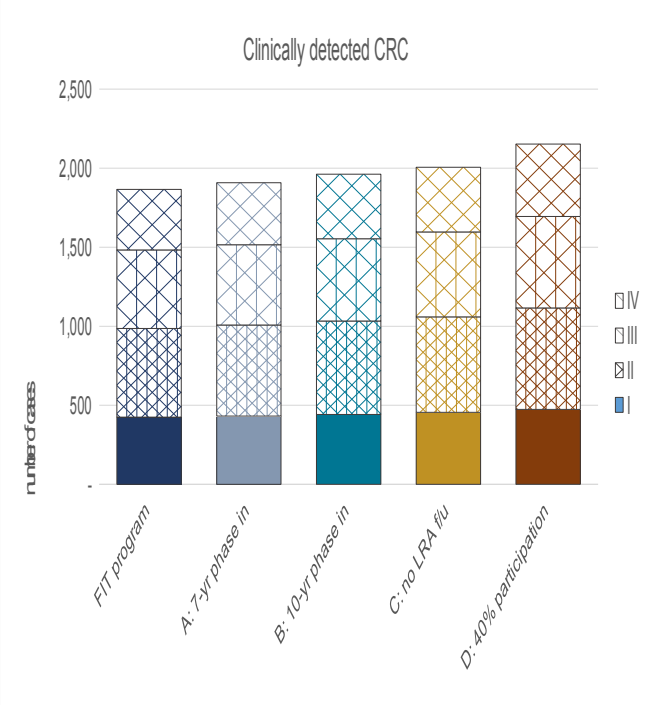
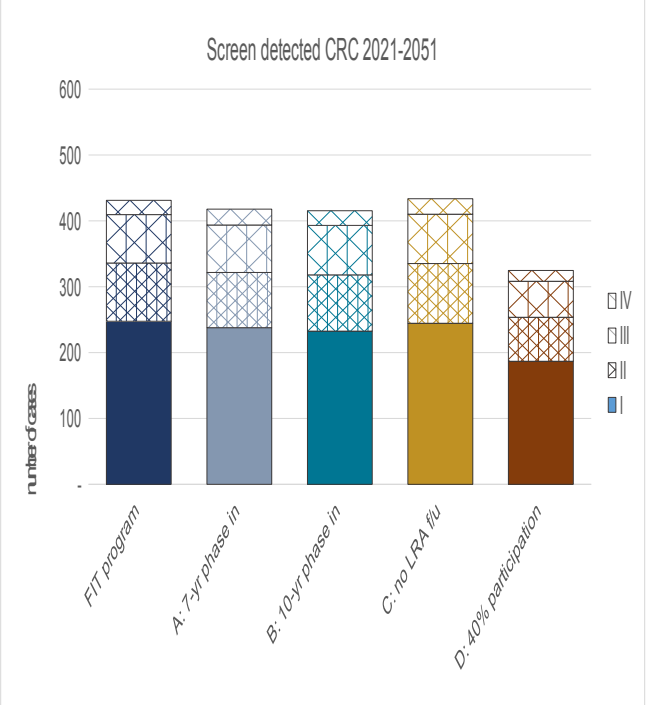


Figure 18. Detected cancer for 2021-2051

a. Clinically detected CRC



b. Screen detected CRC



We compared adenoma detection between the FIT program, and alternative scenarios (table 11). We observed that LRA detection was highest for FIT program implementation and alternatively, a 10 year program phase in period in Scenario A (mean number of individuals identified with LRA annually between 2021-2051 of 376.8 and 361.1 respectively). In Scenario C, no LRA follow-up reduced LRA detection compared to current screening (mean incidence of 301.7 in scenario C vs 304.3 with current screening annually). In comparing the incidence of a high risk adenoma (HRA), we found that all alternative scenarios, including Scenario C, increased the detection of HRA compared to current screening (mean incidence of HRA annually between 2021-2051 of 63.0-70.3 in FIT program and alternative scenarios vs 33.1 with current screening).

Table 11. Total detected adenoma and colorectal cancer for 2021-2051

			alternative scenario			
	current	FIT program	A: 7-yr phase in	B: 10-yr phase in	C: no LRA f/u	D: 40% participation
ADENOMA						
Screen detected						
LRA	9,130	11,672	11,455	11,180	9,343	10,628
HRA	992	2,168	2,084	1,952	2,155	1,667
CANCER						
Screen detected						
I	107	248	238	233	245	187
II	50	89	84	86	91	67
III	41	74	72	75	75	55
IV	8	22	24	23	23	17
Clinically detected						
I	542	425	432	442	455	474
II	746	562	576	592	604	642
III	683	497	508	521	538	578
IV	553	383	392	408	409	458

Model validity

In assessing face validity, collaborators observed that the model included all aspects of CRC screening considered to be important in colonoscopy demand; the model flow was consistent with CRC screening delivery in the NWT; the most accurate data sources were used; the population, region, interventions, outcomes, assumptions, and time horizons correspond with those of interest. Sensitivity analysis of all adjusted parameters showed appropriate directional correlation between the parameter adjustments and outputs of interest (appendix B) In assessing external validity, we observed that the model under-estimated the positivity rate of FIT compared to the retrospective cohort study (6-7% simulated vs 11.9% in retrospective cohort study). We also observed that the model underestimated the proportion of individuals identified to have LRA on colonoscopy after positive FIT (14.96% simulated vs 27.20% actual) but accurately represented the proportion with HRA and CRC (37.57% simulated vs 33.78% actual with HRA, and 7.30 vs 5.41% with cancer)(appendix B).

DISCUSSION

Under the simulation model assumptions, we anticipate that a CRC screening program would reduce the burden of CRC in the NWT by reducing the incidence of CRC and facilitating earlier detection. Despite the higher incidence of CRC in the NWT compared to the general Canadian population, we observed more intensive screening protocols such as colonoscopy screening and annual FIT greatly increased the demand for colonoscopy, however, neither conferred a benefit in CRC detection or prevention compared to a FIT program. Organized FIT screening will require additional colonoscopy resources in the territory; however, the demand on the health system could be decreased by applying several strategies to reduce the demand for colonoscopy while still providing greater CRC detection and prevention compared to current screening.

Much of the decline of CRC incidence seen in developed countries has been attributed to the introduction of programmatic screening [144,149,150]. In a large community-based study, initiation of an organized CRC screening program was associated with a 25.5% reduction in annual CRC incidence, and a 52% reduction in cancer mortality[151]. Similarly, in Canada, between 2008 and 2015 all provinces, except Quebec, have adopted programmatic screening. During this time, incidence of CRC has steadily declined and is projected to continue to decrease [152]. In contrast, the age standardized incidence of CRC in the NWT has been consistently higher than the national rate and continues to increase

(incidence in the NWT increased from 82.7 to 105.7 per 100,000 vs 60.7 to 52.6 in Canada, excluding Quebec, between 2014-16)[121]. In this study, we observed that an organized screening program in the NWT would reduce the incidence of CRC. This creates a strong argument that programmatic screening could help reduce the disparity in colorectal cancer experienced by the NWT population.

The mechanism by which screening reduces the incidence of CRC is postulated to be by polypectomy: the removal of adenomas, and therefore, arrest of the adenoma to carcinoma transformation sequence[119]. When compared the simulation model to actual adenoma rates, the model under-predicted the number of individuals with adenomas. Therefore, although we also observed programmatic screening to increase adenoma detection and prevent CRC, the magnitude of this impact may be underestimated in this model. Further research regarding the incidence of adenomas in this population could assist with developing more accurate projections.

To confer the benefits of CRC prevention and early detection, the NWT will require additional colonoscopy resources. However, increasing access to colonoscopy in the NWT may be challenging. Access to colonoscopy is particularly complex in the NWT, as 50% of residents will need to travel out of their community, sometimes thousands of kilometers to access an endoscopy centre. While addressing some of the barriers to colonoscopy could improve access, also identifying strategies to reduce the demand for screening can help to improve access to those who need it most [7].

In discussion with collaborators, we identified four strategies, all of which effectively reduced initial colonoscopy demand for CRC screening. Reducing the anticipated participation rate to 40% (scenario D), offered the greatest reduction in colonoscopy demand (920.88 vs 1002.10 annually with programmatic screening), however, this also reduced the observed impact of programmatic screening on CRC, demonstrated by the higher incidence of clinically detected CRC (69.44 annually vs 60.17 annually with programmatic screening), and the lower incidence of early stage screen detected CRC (8.18 vs 10.84 annually with programmatic screening). In contrast, prolonging the phase-in period of CRC screening (Scenario A and B) only modestly decreased the demand for colonoscopy overall (961.40 and 984.75 vs 1002.10 with programmatic screening). Both Scenarios A and B alleviated the initial influx in demand for colonoscopy to follow-up positive FITs (figure 6A), however, in the long-term, the greatest demand for colonoscopy was surveillance and both Scenarios A and B had only modest effects on this (figure 17B). This is where reducing LRA colonoscopy follow-up showed the greatest impact (Scenario C). When individuals with LRA(s) return to FIT screening, the demand for colonoscopy to follow-up adenomas would decrease by 46.08% (168.17 annually vs 311.88 with programmatic screening). This reduced the adenoma detection but appeared to have minimal impact on cancer detection and prevention. These findings align with the systematic review by Dubé et al, which found that individuals with LRA had a higher risk of adenomas but a lower risk of CRC than average risk individuals [153].

Overall, the findings of these scenarios illustrate the value of the participatory simulation model approach. Local collaborators directed the focus of this study to colonoscopy resource requirements and screening outcomes. They were instrumental in identifying feasible strategies reducing colonoscopy demand in the NWT, and will be critical in translating the model results to practice.

Limitations

The results of this study are limited to the data available for input parameters and assumptions of the simulation model. We were limited by the small population of the NWT and restricted availability of local data which may reduce the accuracy of the model. Additionally, we did not re-examine the assumptions of the OncoSim-CRC model concerning risk factors, or treatment interventions which may influence the model outputs. The ISPOR-SMDM recommends that face validation be conducted by external reviewers. However, in our case, few individuals have the unique expertise required to critically evaluate the model. Therefore we had collaborators validate the model who may also have a vested interest in the model and therefore introduce bias. Furthermore, formal evaluation of the utility and credibility of model outputs is pending due to restrictions imposed by the COVID19 pandemic. Finally, despite our efforts to calibrate the adenoma incidence multiplier, the model appeared to underestimate the relative risk of adenomas and FIT positivity in this population. There may be important differences in CRC risk for subgroups of this population that are not being captured by Onco-Sim thereby underestimating the colonoscopy demand.

CONCLUSION

This study illustrates the impact of programmatic CRC screening on CRC incidence and colonoscopy access in a remote northern population. We anticipate programmatic screening to reduce the burden of CRC in the NWT; however, achieving this would require additional colonoscopy access. Strategies to reduce the initial strain on the health system include prolonging the phase-in period of screening, and restricting colonoscopy follow-up of individuals with LRA which would enhance the feasibility of screening without compromising the oncologic benefits. The participatory simulation modeling approach in this study provided decision-makers with evidence-informed strategies to implement programmatic screening, and may be useful to inform CRC screening strategies in other rural and remote populations.

ACKNOWLEDGEMENTS

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CHAPTER 5: APPLYING A COMMUNITIES OF PRACTICE FRAMEWORK TO IMPROVE COLORECTAL CANCER SCREENING IN NORTHERN CANADA

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ABSTRACT

Improving colorectal cancer screening in northern Canada is challenging where the small diverse population is spread across a large geographical area. Efforts may be improved by enhancing collaboration across health departments and regions through a Communities of Practice (CoP): a social learning platform that facilitates iterative group learning and innovation. Establishing a CoP requires its members understand its framework and have reached consensus on priorities.

METHODS: A workshop to teach CoP concepts and develop priorities was designed and implemented by the authors in collaboration with stakeholders in the Northwest Territories, Canada. Nominal group technique was used to conduct an analysis of gaps in process, practice, and evidence for the CoP to focus on. An anonymous polling system was used to prioritize areas of focus for the CoP and obtain participants' feedback to the workshop.

RESULTS: The workshop cultivated interest to develop a CoP. The gap analysis identified 23 areas for the CoP to potentially focus on. The two areas ranked as highest priority were: communication between clinicians and identification of screening eligibility in the electronic medical record. All participants found the workshop to be useful, educational, and interesting. There was unanimous interest in moving forward with the development of a CoP.

CONCLUSION: This workshop was successful in fueling interest in developing a CoP for colorectal cancer screening in the NWT, and in developing consensus on the group's priorities. Similar workshops could be used in other sectors to generate collaborative learning and lay the foundation for establishing a CoP.

KEYWORDS: communities of practice, collaboration, colorectal cancer screening, rural and remote health

BACKGROUND

Delivering colorectal cancer screening to northern regions of Canada, such as the Northwest Territories (NWT), requires cooperation across health sectors and departments. A structured platform to facilitate collaboration and co-learning, such as a Communities of Practice (CoP), could enhance the current efforts, improve innovation, and strengthen continuity of care.

Colorectal cancer screening in northern Canada: the need for a collaborative network

Mortality from colorectal cancer (CRC) in the NWT is double that of the rest of the country [14]. A contributing factor to this is low CRC screening uptake among average risk individuals. Screening has been shown to facilitate earlier cancer detection and treatment [5,6]. In the NWT, screening involves Fecal Immunohistochemical Testing (FIT) followed by a colonoscopy if the FIT is positive. Currently, only 22% of eligible individuals in the NWT participate in screening in contrast to other regions of Canada where screening rates average 40-68% [18,154]. Furthermore, access to colonoscopy after a positive screening test is limited in the territory. Work is underway to increase screening uptake, and to accelerate appropriate follow-up but these initiatives are challenging to integrate across health sectors in the territory[18].

A recent study by Champion et al suggests that efforts to improve screening are limited by the health system complexity in the NWT: unclear accountability for testing, limited colonoscopy resource access, poor information technology communication, and redundant system processes in a complex geographic, cultural, and social environment[7]. Research to further quantify and address these factors has led to partnerships between researchers at the University of Ottawa, patients, and local health leaders who bring experience and expertise in multiple aspects of screening: primary care, public health, and endoscopy to study the trends and potential system gaps in CRC screening in the territory. These stakeholders have expressed an interest to act on the identified gaps and align with initiatives to establish a CRC screening program. However, this would require a platform to support collaboration and engagement of an even broader multidisciplinary team of stakeholders which could be provided by a CoP[155].

Opportunity for a Communities of Practice

A CoP is a social learning platform which brings together groups of people who share a concern, set of problems, or passion for a topic, and who deepen their knowledge and expertise in an area by interacting on an ongoing basis[156]. It draws upon the concepts of a learning health system to bring together a collaborative network of stakeholders to share their unique knowledge and skills to mobilize sustainable, evidence-based change[155,157]. This approach has been successfully implemented across a broad range of sectors in business and government. Dr. Fung Kee Fung and colleagues at the University of Ottawa have designed a model to implement a CoP in healthcare, which has stimulated improvements in healthcare across multiple health sectors and regions[22,158,159].

Stakeholders in the NWT, have identified that a CoP could enhance current efforts to improve colorectal cancer screening. To start this, further training is needed for stakeholders to understand the concepts of a CoP, determine interest in collaborating, and set priorities. This may be done in the form of a workshop to provide this training and expand on the existing partnerships between the NWT and the University of Ottawa to initiate a collaborative network of stakeholders well-positioned to adopt a CoP.

WORKSHOP PROCESS/METHODS

Workshop sessions were co-designed with stakeholders in the NWT to allow for discussion of the CoP concepts and framework, data sharing, and an informed gap analysis. At a research meeting in February of 2020, we introduced the basic concepts of a CoP to stakeholders involved in CRC screening and there was unanimous interest. Eleven stakeholders were recruited as collaborators to assist in co-design of the workshop including representatives from public health, primary care, surgery, endoscopy, management, and administration. At the initial meeting, the primary author (HS) presented a preliminary agenda for the workshop. This was iteratively revised with collaborators over the course of three in-person meetings and via email correspondence.

Participants

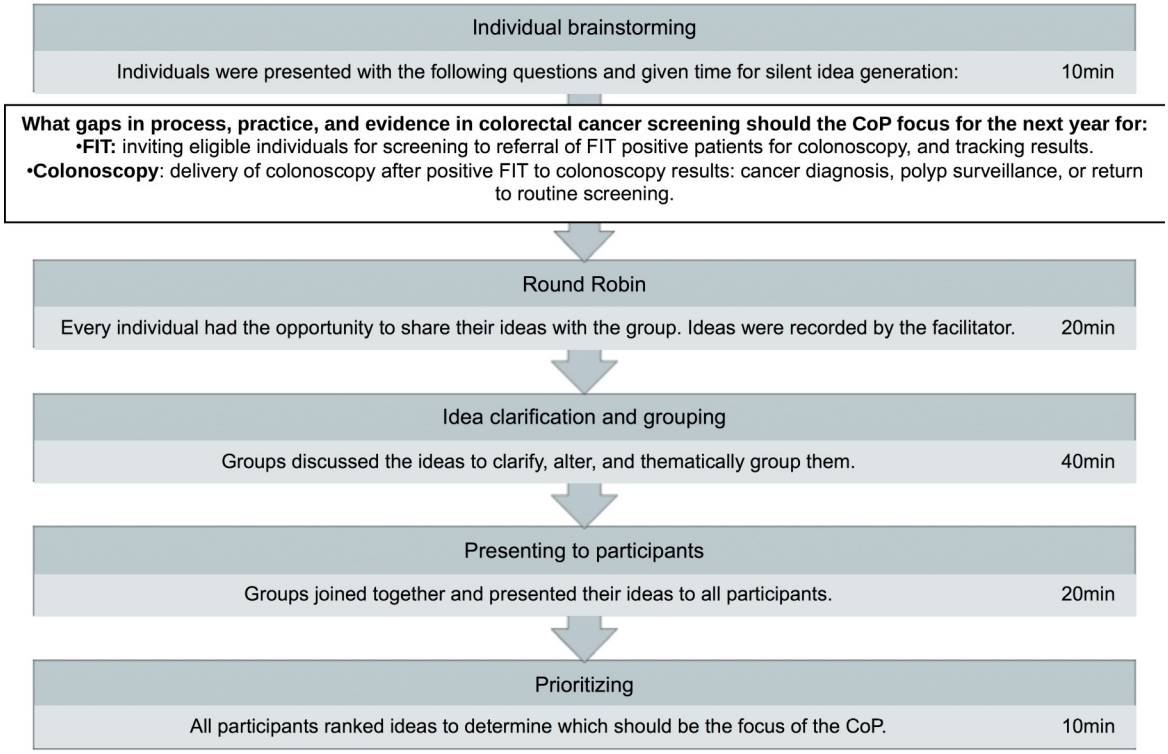
Representatives from public health, primary care, surgery/endoscopy, management, administration, epidemiology, and patient transport were invited to the meeting by email or in-person discussion.

Nominal Group Technique

Nominal Group Technique (NGT) was used to identify priorities for the CoP. NGT is a method of enhancing participation, generating ideas, and obtaining group consensus. The technique is particularly useful for situations which require consensus on a plan, and multidisciplinary input to discover or generate a solution to a complex problem. It has been shown to produce more unique and higher quality ideas than those arising from general discussion by accommodating both personal and interactive learning, reducing hierarchy, and promoting interaction from all group members[160–162].

At this workshop, NGT was implemented as a multistep process (figure 19). Participants self-allocated to one of two breakout groups to discuss either the FIT or colonoscopy aspects of screening. The FIT group focused on the recruitment of eligible individuals for screening, follow-up of positive results, and tracking of screening participation rates. The colonoscopy group focused on the delivery of colonoscopy to patients with a positive FIT, follow-up on colonoscopy results, and return to routine screening when appropriate. The breakout groups started with silent individual idea generation followed by an opportunity for each group member to share those ideas in a round-robin sequence. Next, the groups evaluated, clarified, and thematically clustered the ideas. The groups then joined together and presented their ideas to all participants who then had the opportunity to ask questions to explore and clarify the ideas. All participants ranked the ideas using an anonymized interactive presentation software, Mentimeter Version 2.0.7[163].

Figure 19. Nominal Group Technique



Participant feedback

All participants were invited to participate in an anonymized survey using Mentimeter Version 2.0.7 to provide their initial perceptions of the workshop, interest in pursuing a CoP, and suggestions for additional participants[163].

RESULTS: WORKSHOP SUMMARY

The workshop sessions were developed through iterative meetings between the authors, clinicians, administrators, and epidemiologists. The final agenda included four interactive talks in the morning to provide an overview of the CoP concepts and their application, and to provide an update on CRC screening trends in the NWT. The afternoon was dedicated to small group brainstorming and consensus generation using the NGT. This section provides an overview of the results of these sessions.

CoP framework: **Ottawa Model**

Dr. Fung Kee Fung summarized the development and implementation of the Ottawa Model: a framework for developing a CoP in healthcare. A CoP is a social learning platform characterized by a group of people who share a concern or passion for a topic who deepen their knowledge or expertise in that area by interacting on an ongoing basis [156]. The idea of a CoP is not new; a CoP structure has been used extensively to support knowledge-based social structures for centuries. But, what is new, is the value of systematically and intentionally implementing these social structures in a hybrid model with

the support of organizations to manage knowledge in our era of rapidly advancing technology and system complexity. CoPs are particularly useful in capturing tacit knowledge: the "deep understanding of complex, interdependent systems that enable dynamic responses to context specific problems"[156]. This knowledge is inherent to patient care and healthcare planning. It is challenging to codify and can only be shared with interaction and informal learning processes. A CoP promotes co-learning and translation of tacit knowledge to explicit knowledge through active participation of all members . Fung Kee Fung and colleagues have integrated the concepts of a CoP with quality improvement in healthcare to develop the Ottawa Model which focuses on a bottom up (practitioner), top (administrative) enabled strategy to foster quality improvement and innovation across a region. It also identifies tools for CoP success: access to data, access to evidence, education credits, project management, and communication strategies[22,158]. Using the Ottawa Model, multiple interdisciplinary CoPs have successfully initiated interventions to improve patient care. One example where CoPs enabled an intervention is the complex regional redesign of the lung cancer care processes from diagnosis to initial treatment in the Ottawa region which reduced patient wait times by 48%[166]. In this project, the CoP was foundational to generating innovative ideas, obtaining consensus and reducing the time to implementation on plans moving forward.

Use of a Communities of Practice to facilitate quality improvement initiatives in colorectal cancer

From his experience in leading the Colorectal CoP for the Ottawa region over the last decade, Dr. Boushey provided an overview of some of the initial challenges that groups may face in the early years of forming a CoP in health care. The Colorectal CoP was initiated in response to alarming statistics noted by clinicians and administrators which showed a significant variation in wait-times, and patient outcomes for rectal surgery in the region. In an effort to stimulate discussion on current practices and obtain consensus on standards and processes of care, a CoP was formed. Multidisciplinary stakeholder engagement was initially challenging. Regular face-to-face meetings, a commitment to learning as a group, a focus on building trust across disciplines and institutions, and a clear framework for implementing the CoP helped foster engagement. In addition, providing members with Canadian Medical Education credits incentivized participation. Once the CoP was successfully developed, members conducted an environmental scan of patient care across the regions to identify gaps in evidence, practice, and process. Data access was initially difficult and obtained through manual chart review at individual centres. The ideas generated from the CoP led to multiple successful interventions including the centralization of rectal surgery to high volume centres with specialized teams which improved patient outcomes.

FIT to colonoscopy: review of the last five years

To provide an overview of current colorectal cancer screening patterns and inform discussion, Dr. Smith presented preliminary results from a retrospective cohort study of FIT positive individuals in the territory from 2014-2019 (analysis currently in progress). This review found the estimated screening rate among average risk individuals to be 22%. This rate was lower than anticipated, because a

number of FIT positive patients had undergone FIT as a diagnostic tool for gastrointestinal symptoms rather than average risk screening. A majority of FIT positive individuals had received a follow-up colonoscopy (85%). The median wait-time for colonoscopy after referral was 186 days. Of those who underwent a colonoscopy, only 4% were identified to have a cancer and a majority of patients were found to have polyps (70%) which would require removal and ongoing surveillance to reduce the risk of a cancer.

Colorectal cancer screening NWT update

The Northwest Territories Health and Social Services Association has initiated plans for an organized territorial colorectal cancer screening program. This presentation highlighted the progress and potential future challenges include patient engagement, developing a centralized territory database, and ensuring downstream capacity in endoscopy, and pathology reconciliation.

Nominal Group Technique Sessions

For the breakout sessions, all participants self-allocated to participate in either the FIT group or colonoscopy group for discussion (7 in FIT and 5 in colonoscopy group). The discussions were facilitated by Kuziemsky and Champion.

FIT group discussion

Participants all shared ideas during the round robin phase. In the second phase, participants identified an overarching theme related to understanding and defining the information needed to support an effective FIT-based screening program (table 12).

Table 12. FIT Screening ideas and top five priorities

Ideas	Top priorities
Map information flows and responsibilities Use EMR best practices to drive outcomes Use EMR to identify FIT use and eligibility Maintain autonomous decision making of patients Enhance primary care system EMR education for locum clinicians Patient-centred CRC screening Reduce FIT use for ineligible patients Cross-reference vital statistics with FIT data Target communities with low FIT uptake A centralized data repository Determine and track FIT eligibility Assess cost-effectiveness of different FIT invitation interventions (i.e. mailing kit vs calling) Optimize FIT access	1. Use EMR to identify FIT use and eligibility 2. Map data and information flows 3. Determine and track FIT eligibility 4. Enhance primary care systems for screening 5. Patient-centred CRC screening

Many of the initial ideas or problems during the roundtable session were specific examples of problematic information flows related to FIT screening. These issues included: the need to map FIT information flows and processes, to identify dedicated responsibility for results, to identify and communicate FIT eligibility, and to ensure a patient-driven system.

Determining eligibility for FIT screening is a challenge if it is not readily tracked or apparent in a patient's chart. Using EMR data, cross-referencing with vital statistic registries, and/or developing a central data repository to guide FIT testing were suggested as possible ways to systematically determine eligibility. It was also emphasized that FIT testing had to be patient centered and patient autonomy respected. Some patients may not want to do a FIT test and that decision needs to be respected. The different models of distributing FIT kits to patients may have different impacts on a patients' level of autonomy in their decision of whether or not to participate. These included mailing of FIT kits directly to patients' homes, providing information cards and/or having a health professional call the patient directly. The ease of participation and cost efficiencies of each process would also need to be considered.

It was agreed that the EMR will have to be a key driver of an enhanced FIT screening system. The EMR can help identify FIT eligible people and track the FIT process. However, ensuring that all providers use the EMR to its maximum value is a challenge, especially in the context of the frequency of locum providers in some regions.

Colonoscopy group discussion

Participants all shared ideas during the round robin phase of issues and opportunities to improve colonoscopy follow-up after a positive FIT. In the second phase, participants identified five overarching priorities to address (table 13).

Table 13. Colonoscopy related ideas and top five priorities

Ideas	Top priorities
Transparent communication between endoscopy and primary care providers Trust in communication between providers Need for screening data extraction and reporting of endoscopy service delivery (if paper charts, will require human resources for manual extraction; and if electronic charts, will require software and/or IT expertise to extract) Collect and present endoscopy quality metrics Address regional differences in communication and resources by focusing on territory wide	1. Communication between providers and with patients 2. Collect and present endoscopy quality metrics 3. Human resource supports to the endoscopy programs 4. Support healthcare administration and

services Centralize endoscopy waitlist Patient experience when traveling for procedures including housing to complete preparation Patient education and communication of appointment Interventions for patient education which could include handouts, videos, group consultation Support healthcare administration and leadership Human resource support to endoscopy programs	leadership 5. Address territory-wide service delivery

Participants expressed a need for prospective data collection to understand endoscopy capacity and potential gaps currently and in the future. A shared understanding of endoscopy resource requirements across all system stakeholders may be difficult to achieve. Collecting and presenting data to administrative decision makers could provide an opportunity for more comprehensive system planning discussions and stimulate change where needed.

The quality of data available to endoscopists was also identified as an important area for CRC screening. An endoscopy capture software could be cost-effective at providing this because it facilitates easier data extraction than paper charting. Paper charts require manual data collection and analysis, which requires greater human resources for extraction and are likely be less complete. A potential project for the COP could be to develop a business case for endoscopy capture software.

To facilitate colonoscopy provision, primary care providers must be confident that their sent referral is communicated to the endoscopist and that the recall requirements will be communicated back to them. Without consistent closed-loop communication, primary care providers may lose trust in the system. In addition, informing patients of their scheduled appointments, and pre-endoscopy education sessions needs to be standardized and communicated more consistently. Participants identified several potential interventions to address these issues including developing a more transparent waitlist management approach, and protocols for direct communication between endoscopy unit staff and patients at the time of the appointment booking instead of at the time of travel arrangements. This may be a crucial opportunity to minimize no-show appointments at the time of colonoscopy.

Patient education was also identified as a key communication area, with opportunities including the development of educational handouts and/or video overviews or group education session for colonoscopy consults and preparation. These would need to be developed in multiple languages and be culturally appropriate; a potential avenue could be in collaboration with community health representatives who assist with health promotion in communities.

Enhancing central administrative support may help with the area of waitlist management and patient education support. Within the Beaufort Delta region, an initiative to have nursing staff perform booking and patient outreach/education for endoscopy has been beneficial in reducing no-shows and may be beneficial to expand to other centres in the territory. In addition, developing consistently shared waitlist management resources across physician specialties could support the development of standardized communication for patient booking and endoscopy preparation.

Engagement of stakeholders in administration and leadership is important for project management and implementation of widespread changes for endoscopy services. This is especially the case when considering territory-wide strategies for endoscopy services. Local variation in some initiatives would likely be required. Nonetheless, an opportunity for the CoP would be to discuss and develop standards for waitlist management, pathology review protocols, and patient education to help support equitable access to endoscopy for patients across the territory.

Priority setting

The ideas identified by the small groups were presented to all participants; twelve participants ranked the priorities. Two participants did not rank as they were unable to attend the final session due to scheduling conflicts. The highest priority issues were standardizing EMR screening documentation of FIT and improving communication around colonoscopy delivery (figure 20 and 21).

Figure 20. FIT related priorities

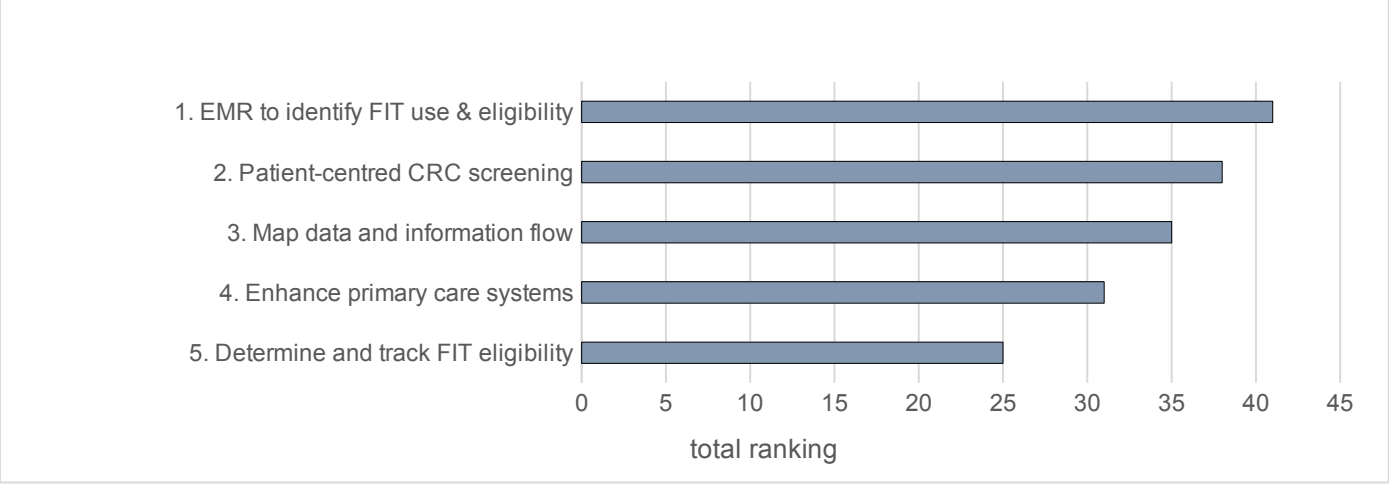
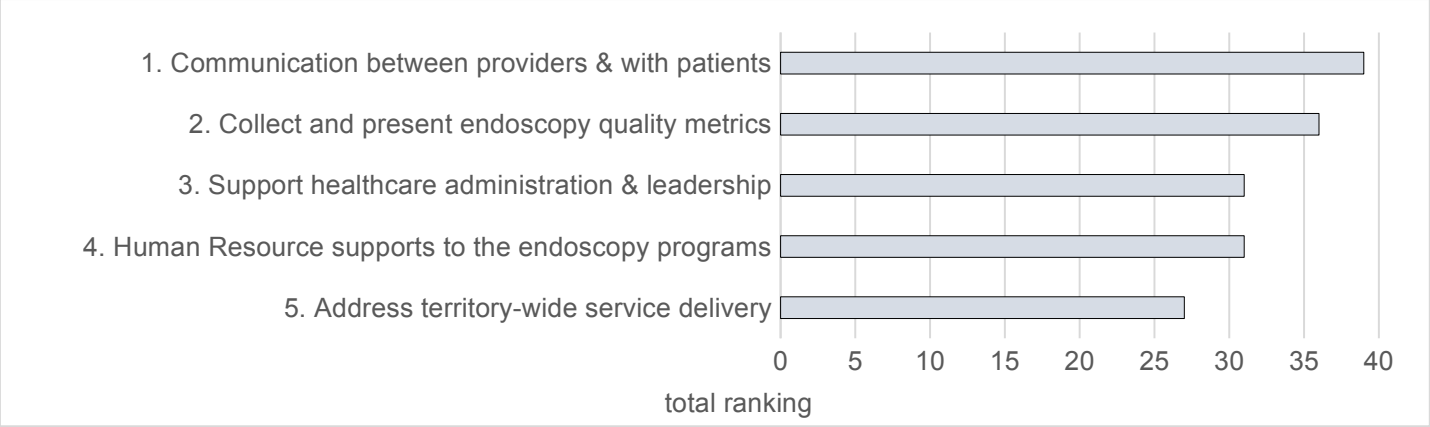


Figure 21. Colonoscopy related priorities



Workshop feedback

All twelve participants who participated in the poll strongly agreed that the workshop was useful, educational, and interesting (mean response of 4.5/5, 4.7/5, 4.7/5 for 12 respondents). There was unanimous interest in establishing a CoP (12 of 12 respondents, 100%). Individuals suggested by participants to be invited to future CoP meetings included hospital and territorial leaders, managers, community health representatives, administrative staff, and additional patients.

DISCUSSION

This process of co-designing and conducting a one-day workshop with stakeholders, addressed some of the foundational aspects to develop a CoP to improve colorectal cancer screening in the NWT. The series of workshop planning with stakeholders and interactive workshop cultivated a group of engaged and informed stakeholders who were able to obtain consensus on key priorities to address in CRC screening.

The participants found the workshop to be useful, interesting, and educational. There are two factors which potentially contributed to this. The first was the co-design of the interactive workshop. When the authors initially met with stakeholders on June 5, 2019 to discuss the agenda, there was apprehension expressed on the utility of the workshop because of the high proportion of didactic education sessions in the proposed agenda. Over the course of iterative evaluations and meetings, the agenda was refined. This not only refined the workshop to one that was useful for stakeholders but also empowered stakeholders to feel invested in the workshop and develop important relationships even before the workshop. Secondly, the Ottawa Model CoP framework is well suited to address some of the current issues faced by stakeholders in CRC screening. Delivery of CRC screening in the NWT is a complex process and planning an organized program requires extensive tacit knowledge of how to best deliver screening to the population. A CoP provides a platform to cultivate and share this tacit knowledge through regular interaction of informed participants in an emergent network without hierarchical barriers. The Ottawa Model is particularly relevant, because it identifies aspects critical to CoP success

in healthcare which might otherwise be overlooked including access to data, project management support, communication strategies, and leadership/organizational sponsorship. This model resonated with stakeholders' impressions of essential aspects to improve screening in the territory as reflected in the priorities for the CoP identified by stakeholders: enhancing communication and generating data.

Priorities for the CoP were identified using the NGT. In relation to FIT, the group identified the need for standardized EMR reporting of FIT participation and result. Standardized reporting is an essential component of an organized screening program to enable follow-up of positive results[167]. As a multidisciplinary group, the CoP could provide valuable insight into how to integrate EMR reporting of screening into providers' workflow while also ensuring data can be reliably extracted for public health reporting. In relation to colonoscopy, the group identified communication between providers and with patients to be the highest priority issues. This aligns well with the priority of EMR reporting which may be seen as a form of communication between providers.

This project has several important limitations due to the small number of participants, the short-term view of the "success" for the CoP in the NWT, and risk of bias in the interpretation of the results. Only 14 of 40 invitees (35%) participated in the workshop which limits the generalizability of the results of the workshop to the larger group of invitees. We recognize as researchers and clinicians with an interest to improve CRC screening, there is a risk for moderator and social acceptance bias in participants' responses. To minimize this risk we used an anonymized polling system to conceal participants' identity with their responses. Furthermore, we generally recruited professionals involved in organizing CRC screening and did not explicitly recruit indigenous participants who may therefore be underrepresented in the group of invitees.

CONCLUSIONS

The co-designed workshop outlined in this report has helped bring together a group of engaged stakeholders and obtain consensus on priorities for a CoP. These aspects are foundational for a establishing CoP. Our approach may be useful when working to establish a CoP in other sectors of healthcare where stakeholders are unfamiliar with the CoP concepts.

To move forward with a CoP in the NWT, workshop participants will be meeting with hospital administrators and territorial health leaders to express their interests and generate additional support in standardizing EMR reporting of FIT, enhancing communication, and improving access to colonoscopy data.

DISCUSSION

This chapter summarizes the key findings, limitations, and conclusions of this work. This is followed by suggestions for next steps to advance research in this area.

RESEARCH OBJECTIVES

1. Identify if simulation modeling employed in CRC screening research supports informed decision-making in CRC screening planning by conducting a systematic review of the literature.
2. Develop simulated projections of CRC screening colonoscopy demand and outcomes using an approach informed by objective 1.
    2.1. Formulate a conceptual flow diagram of the CRC screening process from FIT positive result to colonoscopy.
    2.2. Conduct a descriptive analysis of current trends in participation, and outcomes of FIT-based CRC screening in the NWT.
    2.3. Adjust the parameters of the OncoSim model to reflect the NWT.
    2.4. Conduct preliminary verification and validation of the model.
    2.5. Generate and simulate alternative scenarios that would enable the NWT to deliver feasible CRC screening.
3. Initiate aspects of a Communities of Practice to support long-term sustainable health systems changes proposed in this research project.

KEY FINDINGS

Screening provides an opportunity to reduce the burden of colorectal cancer (CRC) experienced by remote and indigenous populations. However, developing effective strategies to deliver screening to a diverse and distributed population is challenging. In this thesis we demonstrate the utility of participatory simulation modeling in generating evidence-based strategies to optimize CRC screening in a remote northern population, where 50% of residents identify as indigenous. To enhance the sustainability of this research, we have also laid the groundwork for a Communities of Practice (CoP) which would enable ongoing collaboration between stakeholders. This work provides both clinical and academic contributions to health systems research. It contributes to an increased understanding of the resource requirements and outcomes of CRC screening in a remote northern population. It also illustrates the utility of participatory simulation modeling in developing targeted strategies for CRC screening.

Simulation modeling is a powerful adjunct to empirical research in understanding CRC screening delivery. Our systematic review was the first to assess the reported impact of these models on decision-making. We observed that simulation models have been used to generate evidence critical to informing decision making for a broad range of health system and policy decisions for average-risk CRC screening delivery. Despite this, the impact of these models on decision making and their validity

were rarely described in the included studies. This is concerning, given that the majority of simulation models were developed with the purpose of informing decision-makers. Furthermore, to develop models which are valid and useful, we know that end-user engagement is critical. However, we observed that only 9% of the articles mention end-user involvement. In summary, the findings of this review emphasize the need for greater standardized reporting, validation assessment, and end user engagement to enhance the impact of simulation modeling.

To enhance end-user engagement, we applied a participatory simulation modeling approach. To our knowledge, this is the first study to use participatory simulation modeling in a remote northern population. We adapted the participatory approach developed by Tako and colleagues to a case where projections are needed to inform delivery: colorectal cancer screening in the Northwest Territories (NWT)[168]. We found this to be useful in engaging end-users as collaborators in this research. Collaborators directed the focus of this thesis work to an aspect of screening where projections were needed: colonoscopy resources. Throughout these studies, their input provided a valuable understanding of the complex contextual factors that influence screening.

In the initial phase of our work with collaborators, we developed a conceptual diagram of CRC screening in the NWT. Through this process, we identified the need for a retrospective cohort study of FIT positive individuals in the NWT to inform current trends in screening participation and outcomes.

In our retrospective cohort study, we observed that current FIT-based CRC screening did not appear to prevent CRC or provide earlier detection, but did result in more frequent positive pathology results than anticipated for average risk screening. Individuals were more likely to have positive results (defined as AN on colonoscopy), if they experienced long wait times for colonoscopy, had clinical signs and symptoms of CRC, and/or were indigenous. Wait-times for colonoscopy after positive FIT were beyond the current guidelines in the NWT. Only 18.7% received a follow-up colonoscopy within the recommended 60 days. This is the first known study to provide a detailed description of CRC screening in a remote region. Our observations suggest that individuals' screening eligibility, indigenous status, and wait time for colonoscopy have important implications on CRC detection. CRC risk among indigenous individuals has not previously been described in Canada but in Alaska,USA has similarly been described as higher than among indigenous individuals than non-indigenous individuals[2,130]. These findings emphasize the importance of timely colonoscopy to optimize screening, and the need for ongoing research to elucidate if indigenous individuals should be considered for a high risk screening protocol.

These results and additional references informed our modifications to the OncoSim-CRC model. In collaboration with local stakeholders in the NWT, we adjusted the OncoSim-CRC model to estimate future resource requirements and outcomes of CRC in the territory. According to projections, we anticipate programmatic FIT screening to reduce the burden of CRC in the NWT by reducing the incidence of CRC and facilitating earlier detection. This is in contrast to the retrospective cohort study of

current screening and likely attributable to the presumed higher participation rate among eligible individuals and earlier colonoscopy follow-up. However, achieving this would require additional colonoscopy resources. With collaborators we identified several strategies to reduce the initial resource demand and strain on the health system. These included prolonging the phase-in period of screening, and restricting colonoscopy follow-up of individuals with low risk adenomas. Both would enhance the feasibility of screening by reducing colonoscopy demand while still improving CRC detection. Nonethless, in both strategies access to colonoscopy resources would still need increase in the NWT and without meeting that colonoscopy demand, the benefits of CRC screening may be limited. This study illustrates the value of participatory simulation modeling to inform strategies of improving the feasibility of CRC screening delivery in a remote region.

Translating these findings into practice would require long-term collaborative efforts and knowledge sharing; however no knowledge management system for CRC screening in the NWT is in place. Our workshop, co-designed with collaborators, was gathered a network of some of the key stakeholders in the NWT and disseminated the concepts of a Communities of Practice (CoP), a social learning platform well suited to capture and generate the tacit knowledge of CRC screening. Furthermore, by using Nominal Group Technique (NGT), we were able to obtain consensus on priorities to address with the CoP. This demonstrates the utility of NGT and stakeholder engagement in establishing some of the foundational aspects for ongoing collaboration.

LIMITATIONS

The results of this thesis should be interpreted in consideration of its limitations, namely data availability, population size, simulation model estimates, and interests of collaborators. The observations of our systematic review were limited to authors' reporting of the validity and utility of the simulation models at the time of publication. While the majority of the 12 authors who responded to our correspondence indicated that their simulation models had been validated and were impactful for end-user decisions, a minority of authors describe model validation and impact in their article.

The generalizability of our findings from the cohort study are limited to the retrospective data identified in health records and to the NWT population. Furthermore, we did not capture details of patients' comorbidities and risk factors for CRC which may have confounding effects on our observations.

The findings generated from the simulation model are limited to the model assumptions and its inputs. For several input parameters, we relied on the expert opinion of collaborators due to the scarce availability of local data. In recruiting collaborators, we focused on their role in CRC screening and did not priorities any particular ethnicity which may have led to under-representation of indigenous individuals. Additionally, we did not re-examine the assumptions of the OncoSim-CRC model concerning risk factors, or treatment interventions which may influence the model outputs. For instance, despite our efforts to calibrate the adenoma incidence multiplier, the model appeared to underestimate the relative risk of adenomas and FIT positivity in this population. As observed in the retrospective

cohort study, there may be important differences in CRC risk in this population that are not being captured by Onco-Sim and therefore lead to the model underestimating the colonoscopy demand. Finally, the intent of this thesis was to inform CRC screening delivery in the NWT. A presentation of these results had been planned for April of 2020 to evaluate the findings with decision-makers. However, this has been postponed due to COVID-19. Therefore, submission of this thesis precedes formal evaluation of the perceived credibility, accuracy, and utility of the model output and should be interpreted within those limitations.

FUTURE DIRECTIONS

We anticipate the simulation model developed in this thesis will be useful in guiding feasible and effective CRC screening in the NWT by outlining strategies to enhance screening while conserving limited colonoscopy resources. Furthermore, this model could be useful to develop ongoing predictions and recommendations for CRC screening in the NWT by adapting the model to suit the complex evolving environment. For instance, as a result of the current COVID-19 pandemic, all cancer screening in the NWT was temporarily put on hold. The simulation model developed in this thesis could be used to project the impact of COVID-19 on screening resource requirements and CRC outcomes, as well as generate strategies to re-introduce screening. We anticipate a CoP would help facilitate translation of these thesis results into action, and ongoing knowledge translation in the long-term. Furthermore, this thesis focused on the colonoscopy resource requirements for a CRC screening program. Using simulation modeling to assess the cost-effectiveness of CRC screening, would be an important next step, given the high cost of specialty care and long distances for patient travel which would impact the cost-effectiveness of screening.

This work illustrates the utility of participatory simulation modeling, and to our knowledge, this is the first study to use simulation modeling CRC screening in a remote region. Long-term evaluation and application of participatory simulation modeling to other rural and remote populations will help to understand the predictive validity of these projections and generalizability of our results. Furthermore, additional case studies using a participatory approach in complex health systems will enhance our understanding of its value as a method of end-user engagement.

Finally, in our retrospective cohort study, indigenous individuals had a higher risk of CRC at the time of screening. Limited research has been conducted on this topic and is desperately needed to understand the generalizability of the trends we observed and discern why this vulnerable population experiences an inequitable burden of CRC. If indigenous status is associated with a high risk of CRC, OncoSim-CRC could be used to estimate the benefit and system trade-offs of high-risk screening strategies.

CONCLUSION

This thesis illustrates participatory simulation modeling as a useful method of informing CRC screening delivery in a remote northern population. Colonoscopy access in the NWT is limited. The simulated scenarios provide decision-makers with strategies to enhance programmatic screening while

conserving colonoscopy resources. Implementation would require ongoing collaboration to enable ongoing adjustments and projections to adapt to the changing environment. We have provided stakeholders with the some of the foundational elements to develop a CoP. The findings of this thesis helps to characterize the burden of CRC in the NWT, and identifies opportunities to use screening to improve CRC outcomes for a remote and, largely indigenous population.

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APPENDIX A: ADDITIONAL FIGURES & TABLES

Table 14. Systematic Review Search Terms

Database: Ovid MEDLINE(R) ALL <1946 to November 21, 2018>
Search Strategy:

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1 Systems Analysis/ (5194)
2 systems thinking.tw,kw. (666)
3 systems science.tw,kw. (301)
4 systems approach.tw,kw. (3067)
5 systems theory.tw,kw. (1893)
6 systems analysis.tw,kw. (1745)
7 system* model*.tw,kw. (5160)
8 simulation model*.tw,kw. (8994)
9 monte carlo method/ or Markov Chains/ (36676)
10 (markov or monte carlo).tw,kw. (58741)
11 discrete event.tw,kw. (912)
12 agent based model*.tw,kw. (1477)
13 or/1-12 (94979)
14 (system* dynamics or dynamic systems).tw,kw. (3235)
15 colonoscopy/ or sigmoidoscopy/ (27752)
16 (colonoscop* or sigmoidoscop*).tw,kw. (29810)
17 FECES/ch or (f?ecal occult blood test or f?ecal immunochemical test or FOBT or stool DNA or stool test).tw,kw. (16068)
18 or/15-17 (55393)
19 Mass Screening/ or "Early Detection of Cancer"/ (110732)
20 (screening or "early detection").tw,kw. (507726)
21 19 or 20 (542365)
22 exp Colorectal Neoplasms/ (184862)
23 ((colorectal or colo-rectal or colon* or rectal) adj2 (cancer or neoplasm*)).tw. (137027)
24 22 or 23 (222367)
25 21 and 24 (20868)
26 CRC screen*.tw,kw. (2357)
27 18 or 25 or 26 (66935)
28 13 and 27 (302)
29 14 and 27 (1)
30 28 or 29 (302)

Database: Embase Classic+Embase <1947 to 2018 November 21>
Search Strategy:

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1 system analysis/ (21159)
2 systems thinking.tw. (703)
3 systems science.tw. (280)
4 systems approach.tw. (3837)
5 systems theory.tw. (2068)
6 systems analysis.tw. (2155)
7 system* model*.tw. (5836)
8 Monte Carlo method/ (34610)
9 Markov chain/ (3250)
10 (markov or monte carlo).tw. (61185)
11 discrete event.tw. (1294)
12 agent based model*.tw. (1370)
13 or/1-12 (103673)
14 (system* dynamics or dynamic systems).tw. (3130)
15 colonoscopy/ (70289)
16 sigmoidoscopy/ (12280)
17 (colonoscop* or sigmoidoscop*).tw. (55475)
18 occult blood test/ or *feces analysis/ (7561)
19 (f?ecal occult blood test or f?ecal immunochemical test or FOBT or stool DNA or stool test).tw. (5415)
20 or/15-19 (91958)
21 cancer screening/ (70351)
22 (screening or "early detection").tw. (714399)
23 21 or 22 (733083)
24 exp colorectal cancer/ or colorectal tumor/ or colorectal adenoma/ or *colon cancer/ or *rectum cancer/ (217671)
25 ((colorectal or colo-rectal or colon* or rectal) adj2 (cancer or neoplasm*)).tw. (203501)
26 24 or 25 (272469)
27 23 and 26 (32127)
28 CRC screen*.tw. (4016)
29 20 or 27 or 28 (108321)
30 13 and 29 (347)
31 14 and 29 (4)
32 30 or 31 (351)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <October 2018>
Search Strategy:

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1 Systems Analysis/ (15)

2 systems thinking.tw,kw. (10)
3 systems science.tw,kw. (3)
4 systems approach.tw,kw. (61)
5 systems theory.tw,kw. (33)
6 systems analysis.tw,kw. (18)
7 system* model*.tw,kw. (144)
8 simulation model*.tw,kw. (294)
9 monte carlo method/ or Markov Chains/ (408)
10 (markov or monte carlo).tw,kw. (1397)
11 discrete event.tw,kw. (37)
12 agent based model*.tw,kw. (11)
13 or/1-12 (2058)
14 (system* dynamics or dynamic systems).tw,kw. (23)
15 colonoscopy/ or sigmoidoscopy/ (1819)
16 (colonoscop* or sigmoidoscop*).tw,kw. (4728)
17 FECES/ch or (f?ecal occult blood test or f?ecal immunochemical test or FOBT or stool DNA or stool test).tw,kw. (578)
18 or/15-17 (5274)
19 Mass Screening/ or "Early Detection of Cancer"/ (3564)
20 (screening or "early detection").tw,kw. (31410)
21 19 or 20 (31999)
22 exp Colorectal Neoplasms/ (6797)
23 ((colorectal or colo-rectal or colon* or rectal) adj2 (cancer or neoplasm*)).tw. (11911)
24 22 or 23 (13625)
25 21 and 24 (2105)
26 CRC screen*.tw,kw. (529)
27 18 or 25 or 26 (6109)
28 13 and 27 (25)
29 14 and 27 (0)
30 28 or 29 (25)

Scopus

(TITLE-ABS-KEY (*"systems analysis"* OR *"systems thinking"* OR *"systems science"* OR *"systems approach"* OR *"systems theory"* OR *"systems analysis"* OR *"system* model*"* OR *"simulation model*"* OR *markov* OR *"monte carlo"* OR *"discrete event"* OR *"agent based model*"* OR *"system* dynamics"* OR *"dynamic systems"*)) AND ((TITLE-ABS-KEY (*colonoscop** OR *sigmoidoscop** OR *"f?ecal occult blood test"* OR *"f?ecal immunochemical test"* OR *fobt* OR *"stool DNA"* OR *"stool test"*)) OR ((TITLE-ABS-KEY (*screening* OR *"early detection"*)) AND (TITLE-ABS-KEY ((*colorectal* OR *colo-rectal* OR *colon** OR *rectal*) AND (*cancer* OR *neoplasm**)))) OR (TITLE-ABS-KEY (*crc* AND *screen**))) = **432 references**

Table 15. Included vs excluded cohort of FIT positive individuals

Baseline characteristics	Included (n=843)	Excluded (n=56)	P-value
Age, mean years (SD)	60.8 (6.7)	61.2 (6.6)	0.663
Sex, female, n(%; Std. Res)	349 (41.4; -0.09)	25 (44.6; 0.35)	0.633
Indigenous status Indigenous, n(%; Std. Res)	411 (48.8; -0.22)	32 (57.1; 0.84)	0.224
Region of residence, n(%; Std. Res)			<0.001
Beaufort Delta	99 (11.74; -1.37)	22(39.29; 5.36)	
Dehcho	50 (5.93; -0.23)	5 (8.93; 0.89)	
Fort Smith	77 (9.13; 0.11)	4 (7.14; -0.43)	
Hay River	83 (9.85; -0.16)	7 (12.50; 0.63)	
Sahtu	44 (5.22; -0.30)	5 (8.93; 1.15)	
Tilcho	56 (6.64; 0.34)	1 (1.79; -1.33)	
Yellowknife	434 (51.48; 0.80)	11*(19.64; -3.11)	

Table 16. Screen detected vs clinically detected cancer, 2014-16

Baseline characteristics	Screen detected (n=19)	Clinically detected (n=34)	P value
Age, mean years (SD)	63.2 (7.47)	59.1 (7.27)	0.06$^{\phi}$
Sex, female (%; Std. Res)	6 (31.58; -0.56)	15 (68.42; 0.45)	0.37
Indigenous (%; Std. Res)	11 (33.33; -0.24)	22 (66.66; 0.18)	0.62
Region of residence (%; Std. Res)			0.78
Beaufort Delta	<5 (21.05; -0.31)	9 (26.47; 0.23)	
Dehcho	N/A	N/A	
Fort Smith	<5 (5.26; -0.59)	<5 (11.76; 0.44)	
Hay River	<5 (15.79; 0.31)	<5 (11.76; -0.23)	
Sahtu	<5 (0; -0.85)	<5 (5.88; 0.63)	
Tilcho	<5 (10.53; 0.16)	<5 (8.82; -0.12)	
Yellowknife	9 (47.37; 0.54)	12 (35.29; -0.40)	
Histology type, n(%; Std. Res)			0.15
adenocarcinoma	18 (94.74; 0.37)	28 (82.35; -0.28)	
carcinoid	<5 (5.26; 1.07)	<5 (0; -0.80)	
mucinous	<5 (0; -0.85)	<5 (5.88; 0.63)	
other	<5 (0; -1.20)	<5 (11.76; 0.90)	
Location, n(%; Std. Res)			0.08
proximal	<5 (10.53; -1.23)	11 (32.35; 0.92)	
distal	17 (89.47; 0.70)	23 (67.65; -0.53)	
Stage, n(%; Std. Res)			0.18
early	12 (63.16; 0.75)	15 (44.12; -0.56)	

late	7 (36.83; -0.76)	19 (55.88; 0.57)	

ϕKruskal-Wallis rank sum test

Table 17. Relative Risk of Diagnosis of Indigenous Patients vs. Non-Indigenous Patients

Diagnosis	Relative Risk for Indigenous Patients Estimate	95% CI (LB, UB)
Low Risk Adenoma	0.735	(0.549, 0.983)
High Risk Adenoma	1.002	(0.795, 1.264)
Advanced Adenoma	1.144	(0.810, 1.616)
Cancer	3.17	(1.501, 6.693)
Advanced Neoplasia	1.438	(1.075, 1.924)

Table 18. Relative Risk of Diagnosis of Indigenous Patients vs. Non-Indigenous Patients of FIT eligible only

Diagnosis	Relative Risk for Indigenous Patients Estimate	95% CI (LB, UB)
Low Risk Adenoma	0.727	(0.508, 1.042)
High Risk Adenoma	1.082	(0.825, 1.419)
Advanced Adenoma	1.152	(0.743, 1.788)
Cancer	5.611	(1.264, 24.911)
Advanced Neoplasia	1.523	(1.035, 2.239)

Figure 22. Biannual FIT screening rate 2014-2018

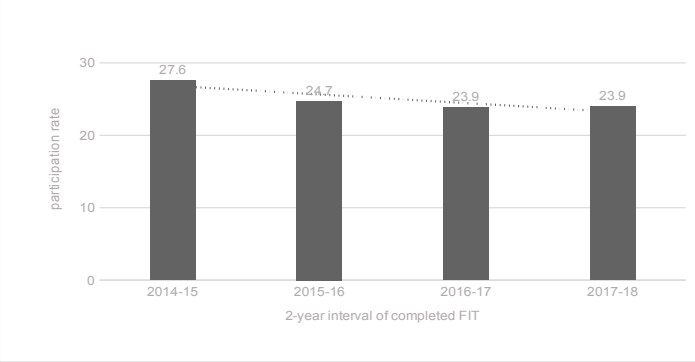
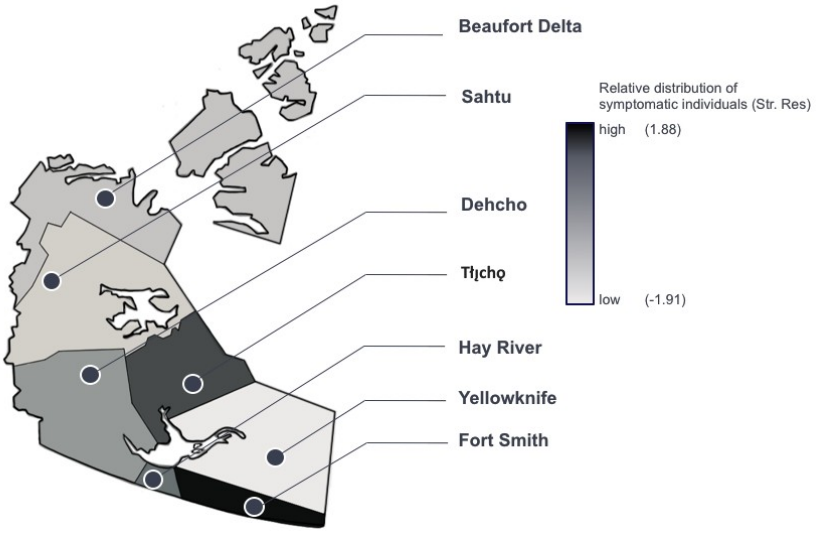


Figure 23. FIT positive individuals signs and symptoms of CRC by region



APPENDIX B: DETAILED METHODOLOGY DESCRIPTION USING ONCOSIM TO EXAMINE THE IMPACTS OF COLORECTAL SCREENING IN NWT

OVERVIEW

This document outlines the analysis for projecting the impact of colorectal cancer (CRC) screening in the Northwest Territories (NWT) using OncoSim Version 3.3.6.0.

Primary study objective: to project the impact of implementing a colorectal cancer screening on colonoscopy demand in the NWT.

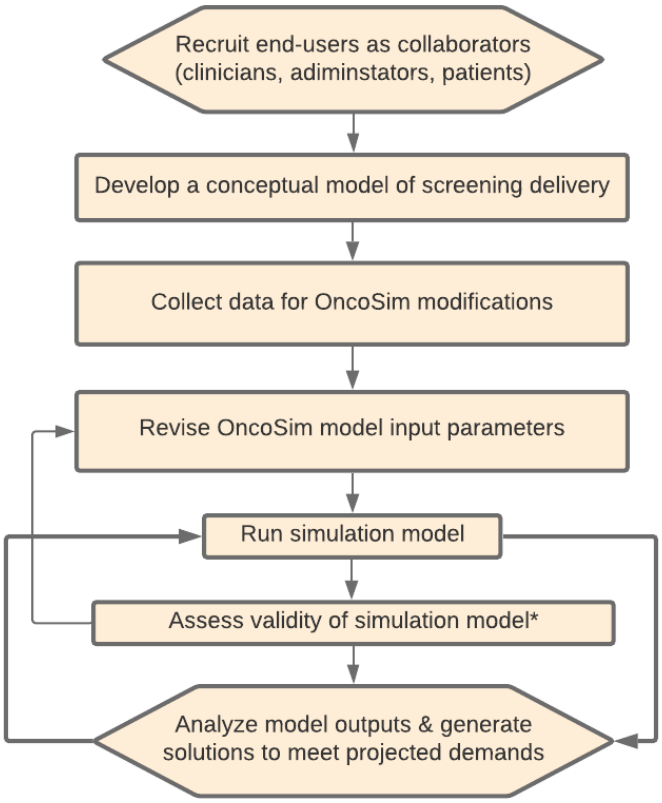
Secondary objective(s):

1. To project the impact of program implementation on CRC incidence, stage, and outcomes in the NWT.
2. To simulate alternative scenarios which provide effective screening with reduced colonoscopy demand.

METHODS

The analysis was conducted in OncoSim version 3.3.6.0. For the model to more accurately reflect the NWT, changes were made to the program specifications, FIT sensitivity/specificity, colonoscopy wait-time, polyp natural history, and population immigration. This study uses a participatory approach, with end-users of the model engaged in all phases of the study (Figure 1).

Figure 1. Participatory simulation modeling approach



B.

The OncoSim parameters were revised based on data from a retrospective chart review of individuals who had undergone FIT-based colorectal cancer screening between 2014-2019; expert opinion of healthcare providers and administrators in the NWT; a review of the academic literature; and publicly available population databases. Parameter revisions are detailed as follows:

MODEL ADJUSTMENTS

Adjusting Program Specifications: recruitment, participation, and modality

Recruitment and participation: National level parameters for recruitment, participation, and screening modality were modified to reflect the participation of the population of NWT in opportunistic FIT screening since its introduction in 2009 as well as colonoscopy screening for high risk individuals since 1990:

- Starting in 1990 we estimate high risk screening of individuals with a first degree relative (FDR) family history (Parameter 0,1) was started using colonoscopy every 5 years (Modality C). Participation is estimated to be 60% and adherence 80%.
- Starting in 2009 average risk screening of individuals aged 50-74 was conducted (Parameter 3,4,5,6) using FIT every 2 years (Modality A)[144]. Participation was adjusted to obtain the following targets:
    - 20% phased in over 2 years between 2009-2013 (Parameter 3,4)[144].
    - 30% in 2014-2020, phased in over 2 years to reflect the data from the retrospective chart review.
    - 60% in 2021, phased in over 5 years to represent the CRC program implementation based on discussion with collaborators.

To estimate participation, we adjusted visibility and adherence to follow-up. We assumed an adherence rate of 80%. Visibility was incrementally adjusted (table 1) to obtain a participation rate that matched the targets outlined above.

Table 1: Visibility calibration

Visibility	**0.25**	**0.3**	**0.35**	**0.4**	**0.45**	**0.5**	**0.55**	**0.6**	**0.65**	**0.7**	**0.75**	**0.8**	**0.85**
Mean participation (%)	19.52	22.08	25.42	28.39	31.80	35.69	38.84	43.06	46.99	51.60	56.36	61.66	67.30

Participation rate was calculated using the following equation:

Participation rate 2020: $\frac{\text{(number of FIT participants 2019+number of FIT participants 2020)}}{\text{(mean population age 50-75 between 2019-2020)*0.89 – number of individuals with an adenoma identified in the past 10 years)}}$

This equation is derived from the CPAC definition of number of individuals who have undergone FIT within the last 2 years / average number of eligible individuals in those two years. The number of

eligible individuals excluded those who were high risk of CRC (history of IBD, genetic syndrome, family history of CRC), and those who had adenomas identified within the last 10 years. OncoSim 3.3.6.3 estimates 11% of the population to be high risk. Based on a systematic review in 2015, prevalence of atleast one FDR with CRC is 3.1-10% of the population[132]. The prevalence of IBD in Canada is estimated to be 0.5% of the overall population[169].

After iterative evaluation, the visibility was adjusted to 0.42 to estimate status quo screening and to 0.80 for program participation (figure 2). This simulated an average annual FIT screening participation rate of 20% between 2009-2013, 31% between 2014-2020, and 57% between 2021-2051.

Figure 2: Recruitment and Participation adjustments

A) Status quo screening

Parameter: Recruitment and Participation

Screening program element / Overall program controls	0	1	2	3	4	5	6	7	8	9
Visibility (prob visible)	0.8	0.8	1	0.27	0.27	0.42	1	1	1	1
Recruitment start year	1990	1991	0	2009	2010	2014	0	0	0	0
Recruitment end year	1990	9999	0	2009	2013	9999	0	0	0	0
Recruitment start age	40	40	0	50	50	50	0	0	0	0
Recruitment end age	74	74	0	74	74	74	0	0	0	0
First degree relative with CRC : One (1), Multiple (2), None (3)	12	12	0	123	123	123	0	0	0	0
Participation to first invitation (probability)	1	1	0	1	1	1	0	0	0	0
Phase-in of first invitation (years)	5	1	0	2	1	2	0	0	0	0
Additional recruitment attempts	0	0	0	0	0	0	0	0	0	0
Years between recruitment attempts	99	99	0	99	99	99	0	0	0	0
Participation at subsequent recruitment attempts (probability)	0	0	0	0	0	0	0	0	0	0

B) Program screening

Parameter: Recruitment and Participation

Screening program element / Overall program controls	0	1	2	3	4	5	6	7	8	9
Visibility (prob visible)	0.8	0.8	1	0.27	0.27	0.42	0.8	1	1	1
Recruitment start year	1990	1991	0	2009	2010	2014	2021	0	0	0
Recruitment end year	1990	9999	0	2009	2013	2020	9999	0	0	0
Recruitment start age	40	40	0	50	50	50	50	0	0	0
Recruitment end age	74	74	0	74	74	74	74	0	0	0
First degree relative with CRC : One (1), Multiple...	12	12	0	123	123	123	123	0	0	0
Participation to first invitation (probability)	1	1	0	1	1	1	1	0	0	0
Phase-in of first invitation (years)	5	1	0	2	1	2	5	0	0	0
Additional recruitment attempts	0	0	0	0	0	0	0	0	0	0
Years between recruitment attempts	99	99	0	99	99	99	99	0	0	0
Participation at subsequent recruitment attempts (...	0	0	0	0	0	0	0	0	0	0

Screening modality: modality selection was adjusted to accommodate the additional screening program element columns for FIT screening (modality A) and colonoscopy screening (modality C).

Figure 3: Modality selection

Parameter: Modality selection

Screening modality plan / Screening program element	Modality	Age start	Age end	Year start	Year end	Element recruited under	First degree relative with CRC : One (1), Multiple (2), None (3)	Adherence (probability)	Y ne
A	2	50	74	0	9999	3456	0	0.8	
B	0	0	0	0	0	0	0	0	
C	4	40	74	0	9999	10	0	0.8	
D	0	0	0	0	0	0	0	0	
E	0	0	0	0	0	0	0	0	
F	0	0	0	0	0	0	0	0	
G	0	0	0	0	0	0	0	0	
H	0	0	0	0	0	0	0	0	

Adjusting Sensitivity and Specificity

FIT: The NWT guidelines recommend OC-Auto by Polymedco at the threshold of 75ng/ml (15ug/g). We reviewed the recent literature on performance of this FIT. Sensitivity and specificity for CRC varied from 75.0% to 100% and 92.3% to 93.4% respectively. For advanced adenoma sensitivity and specificity varied from 22.2% to 44.1% and 89.8% to 97.4%, respectively[146]. In these studies, the prevalence of advanced adenoma was much lower than in our retrospective review (6.9-7.9% vs. 39.03%). This may be due to the frequency of symptomatic patients presenting for FIT testing who have been shown to have a higher incidence of advanced adenomas and CRC however, the impact on sensitivity cannot be calculated as the false negative rate in this population is unknown. For the purpose of this study, we assumed a FIT sensitivity for polyps >1cm of 0.3 and for CRC of 0.87.

Figure 4: FIT sensitivity parameter adjustments

Parameter: Sensitivity of the screening test

Distal or Proximal colon - Proximal (cecum, ascending, transvers)

Primary screening modality / Polyp or Cancer state	FOBT guaiac	FIT immunoch	Flexible sigmoidos	Colonosco	CT colonogra
Polyp less or equal to 5mm in size	0.03	0.04	0	0.75	0
Polyp between 6 and 9mm in size	0.04	0.1	0	0.85	0.6
Polyp greater or equal to 10mm in size	0.1	0.4	0	0.95	0.938
Cancer	0.5	0.87	0	0.95	0.967

The specificity was not changed, given that it was also found to be 96% in a recent prospective study by Liles et al for presence of tumour or advanced adenoma at the same threshold used in the NWT [120].

Colonoscopy: Recent systematic review found 3 good quality prospective trials that assessed the sensitivity and specificity of colonoscopy. These studies describe the lesion sensitivity for adenoma >6mm to be 75.8-90.4; for adenoma >10mm 89.8-97.6; for CRC 17.9-100.[146] Therefore the parameters for colonoscopy were left unchanged.

Adjusting Colonoscopy compliance and wait-time.

Compliance to follow-up colonoscopy after positive FIT screen: adjusted to achieve close to the 74.61% adherence rate seen in the retrospective chart review. With the program implementation, we aim for a 85% adherence as per the CPAC quality indicator target [117].

We conducted iterative scenario series of the simulation model run at 2,000,000 cases with a kill factor of 80 (table 2). As a result, adherence without status quo screening was at two different rates for "status quo" set to 0.80 and for "status quo <180 days FIT follow-up" set to 0.37 to reflect the retrospective cohort study adherence rate, and programmatic adherence set to 0.91 (figure 5).

Table 2. Colonoscopy compliance scenario analysis

Parameter	**0.87**	**0.89**	**0.91**	**0.93**	**0.95**	**0.97**
Colonoscopy adherence after FIT	80.9%	82.5%	84.0%	86.0%	87.2%	93.9%

Figure 5. Colonosocpy compliance parameter adjustment

A) Status quo screening

Parameter: Compliance to follow-up by colonoscopy for positive screens

Primary screening modality / Province	FOBT guaiac	FIT immunoch	Flexible sigmoidos	Colonosco	CT colonogra
Newfoundland and Labrador	0.85	0.85	0.77	1	1
Prince Edward Island	0.85	0.85	0.77	1	1
Nova Scotia	0.85	0.85	0.77	1	1
New Brunswick	0.85	0.85	0.77	1	1
Quebec	0.85	0.85	0.77	1	1
Ontario	0.85	0.85	0.77	1	1
Manitoba	0.85	0.85	0.77	1	1
Saskatchewan	0.85	0.85	0.77	1	1
Alberta	0.85	0.85	0.77	1	1
British Columbia	0.85	0.85	0.77	1	1
Yukon	0.85	0.85	0.77	1	1
North West Territories and Nunavut	0.85	0.80	0.77	1	1

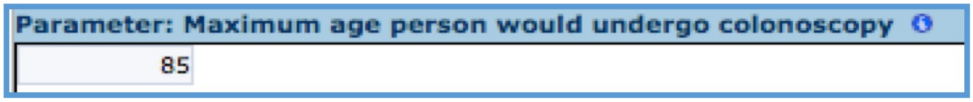
B) Programmatic screening

Parameter: Compliance to follow-up by colonoscopy for positive screens

Primary screening modality / Province	FOBT guaiac	FIT immunoch	Flexible sigmoidos	Colonosco	CT colonogra
Newfoundland and Labrador	0.85	0.85	0.77	1	1
Prince Edward Island	0.85	0.85	0.77	1	1
Nova Scotia	0.85	0.85	0.77	1	1
New Brunswick	0.85	0.85	0.77	1	1
Quebec	0.85	0.85	0.77	1	1
Ontario	0.85	0.85	0.77	1	1
Manitoba	0.85	0.85	0.77	1	1
Saskatchewan	0.85	0.85	0.77	1	1
Alberta	0.85	0.85	0.77	1	1
British Columbia	0.85	0.85	0.77	1	1
Yukon	0.85	0.85	0.77	1	1
North West Territories and Nunavut	0.85	0.91	0.77	1	1

Maximum age for undergoing a colonoscopy: was adjusted from 89 to 85 years based on expert opinion of collaborators in the NWT (figure 6).

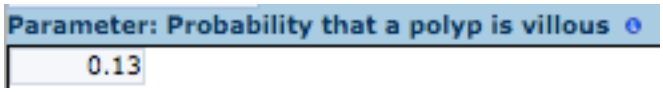
Figure 6. Maximum age to undergo screening



Adjusting adenoma characteristics

Proportion Villous: based in polyp characteristics after FIT the probability of villous pathology was increased from 0.09 to 0.13 based on retrospective review of NWT CRC screening outcomes between 2014-2019 (figure 7).

Figure 7. Probability of a polyp to be villous



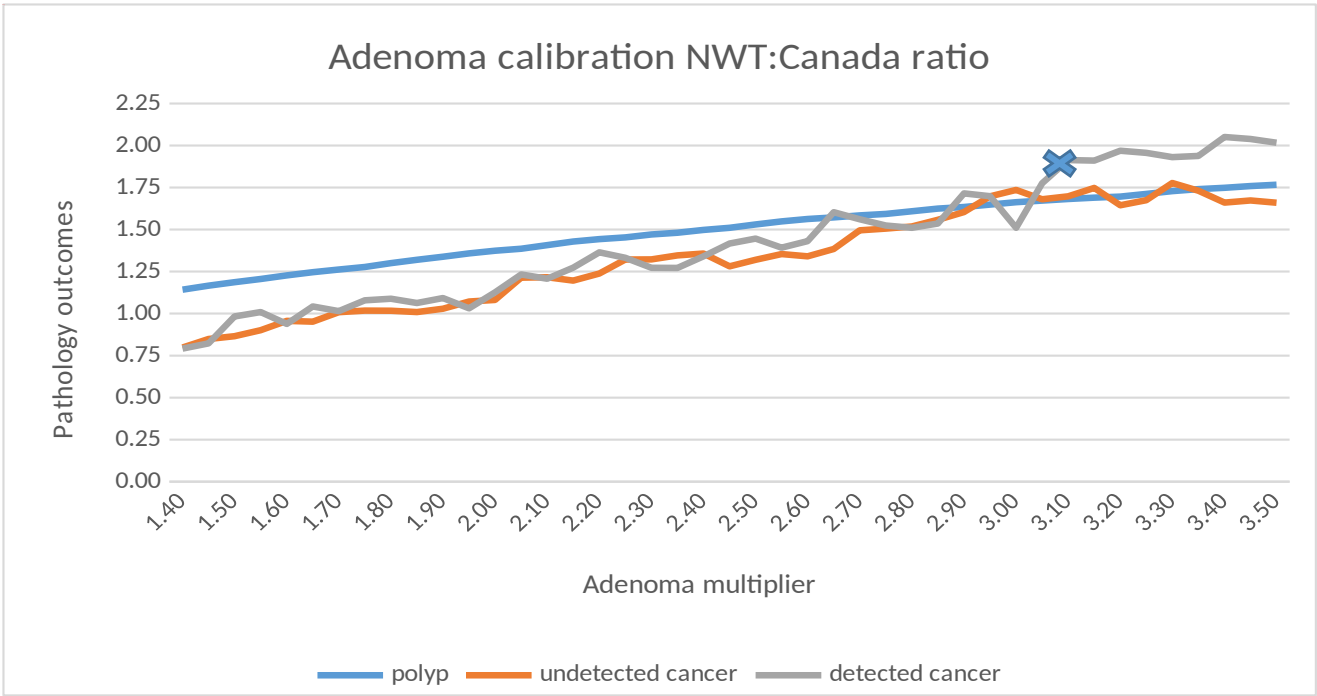
Adenoma and CRC incidence: the incidence of colorectal adenomas are estimated by the incidence of colorectal cancer available from Statistics Canada and adjusted by province/territory. To adjust the incidence of colorectal adenomas to the NWT population, we first compared the age standardized incidence of CRC between Canada and NWT from 2011-2016 (table 3). We found the mean incidence of CRC was higher in the NWT than Canada for both males and females (RR 1.82 and 1.70 respectively) (Table 3).

Table 3. Colorectal cancer rates per 100,000 population[121]

	2011	2012	2013	2014	2015	2016	Overall NWT: Canada ratio
	Males						
Canada excluding Quebec							1.824
Northwest Territories	159.7	76.7	88.2	131.5	78.1	170.1	
	Females						
Canada excluding Quebec							1.709
Northwest Territories	76.8	140.8	61.6	79.2	85	72.2	

We then incrementally adjusted the colorectal adenoma incidence rate age multiplier in the model by increments of 0.05 and assessed the ratio of detected CRC incidence in the NWT population compared to that of Canada (figure 8).

Figure 8. Adenoma incidence ratio NWT:Canada



To achieve an incidence of detected CRC in the NWT population that was approximately 1.70 for females and 1.82 for males the adenoma multiplier was adjusted to 2.97 for females and 3.03 for males (figure 9). This resulted in a RR of 1.69 for detected CRC among females and 2.03 among males.

Figure 9. CRC adenoma incidence adjustments

A) Age multiplier parameter

Parameter: Colorectal adenomas incidence rates age multiplier (alternative route or not)

Age group / Sex	[min,40[	[40,45[	[45,50[	[50,55[	[55,60[	[60,65[	[65,70[	[70,75[	[75,80[	[80,max]
Female	2.97	2.97	2.97	2.97	2.97	2.97	2.97	2.97	2.97	2.97
Male	3.03	3.03	3.03	3.03	3.03	3.03	3.03	3.03	3.03	3.03

B) Provincial multiplier

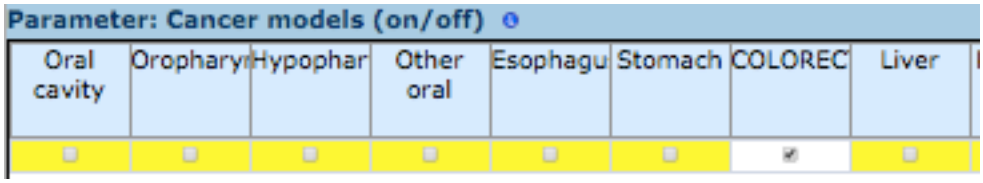
Parameter: Colorectal adenomas incidence rates provincial multiplier (alternative route or not)

Province / Sex	Newfoundland and Labrador	Prince Edward Island	Nova Scotia	New Brunswick	Quebec	Ontario	Manitoba	Saskatche	Alberta	British Columbia	Yukon	North West Territories and Nunavut
Female	1.104343	1.103300	1.129554	0.873320	1.081260	0.890894	0.967926	1.161911	0.772028	0.808282	0.80839	1
Male	1.094677	1.021272	1.028455	0.919528	1.055727	0.829928	0.892567	1.148611	0.787498	0.787904	0.84393	1

Master Controls: cancer models

All cancer models except colorectal were set to off (figure 10).

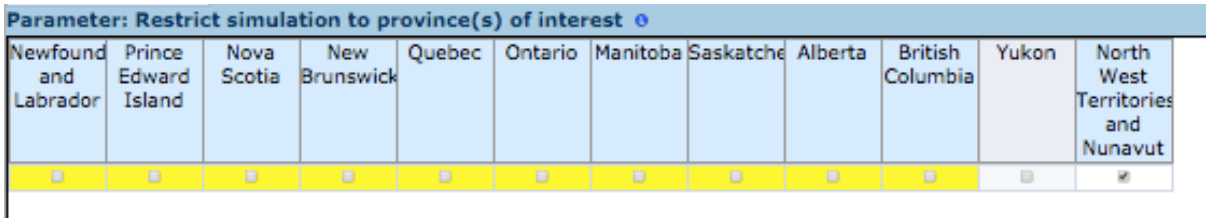
Figure 10. Cancer models parameter



Restricted simulation

The simulation was restricted to run for only NWT/NT (figure 11).

Figure 11. Provincial models

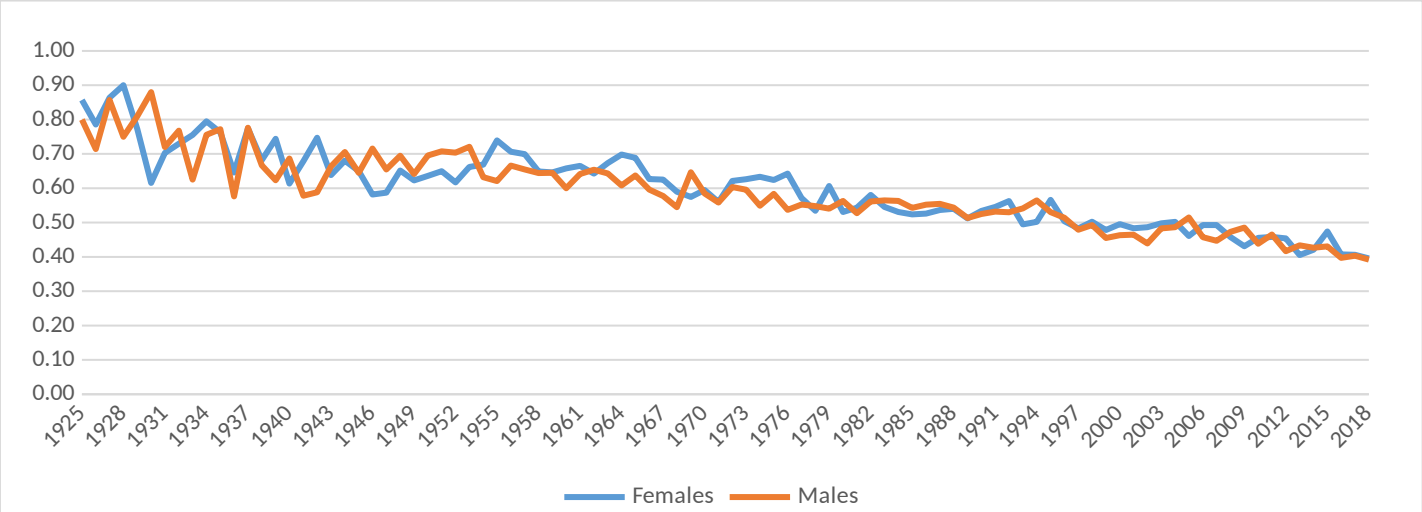


Adjusting to NWT population only

The OncoSim 3.3.6.0 model runs the cohort for NWT and Nunavut populations together to xx (rationale). This cohort is generated from birth based on combined birth rate of the two territories provided by Statistics Canada. To narrow our estimates to the NWT population alone we tried two methods:

1. **Comparing estimated birthrate:** using the most recent year of population estimates for the both territories available with Statistics Canada (2014) and counted back to identify the proportion of males and females from each territory born each year still alive in 2014 as demonstrated in figure 2. The proportion of births from NWT have gradually declined. Since the our population of interest are those at risk of colorectal cancer (age greater than 40 years), we used the average estimated proportion for those age 40-85 in 2014 (born between 1929-1974 which was 66.1% from all NWT/NT births per year. We then divided all model outputs by 66%.

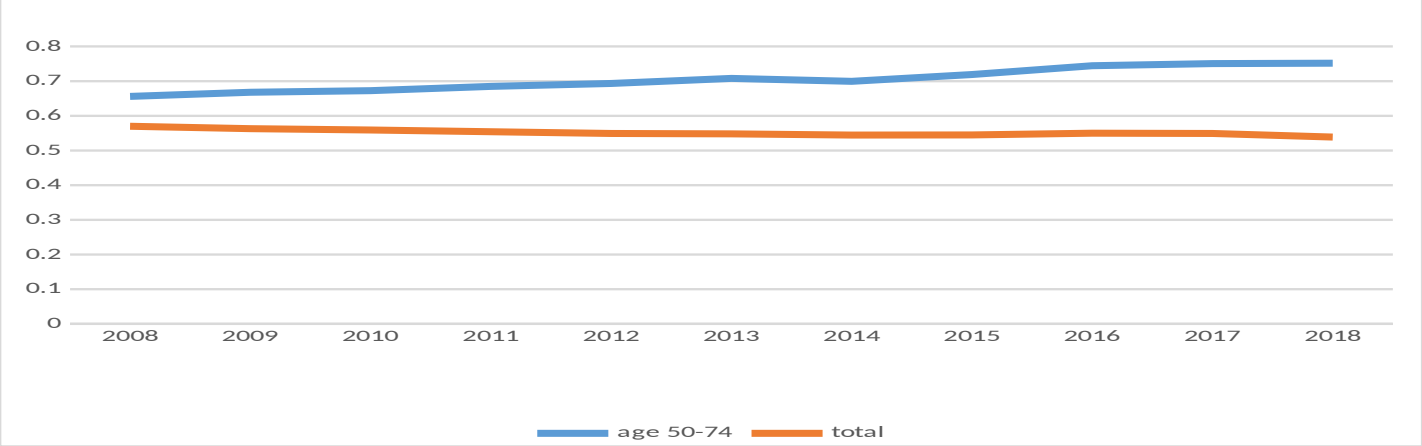
Figure 12. Proportion of births from NWT



2. **Comparing current proportions:** we compared proportions of the NWT/NT population who are from NWT. We see that the NWT population appears to be growing slower than NT overall

(demonstrated by a decrease in the proportion from NWT). But the population age 50-74 continues to increase in the NWT at a faster rate than NT. In 2016-18, 74.4-75.2**%** of the population age 50-74 were from NWT. Therefore a proportion of 0.75 was selected as an estimate of the population[116,147].

Figure 12 Proportion of the population which is from NWT



MODEL VALIDITY ASSESSMENT

OncoSim is a mathematical simulation model developed by the Canadian Partnership Against Cancer. It models the natural history and progression of adenomas and CRC in Canada. Its' validity has been previously assessed and it has been shown to reproduce the observed impact of CRC screening in randomized screening trials [138]. To enhance the end user confidence in the adjusted OncoSim model, we assessed if it is sufficiently valid and accurate by conducting the validation practices recommended by the ISPOR-SMDM Taskforce for Modeling Good Research Practices where possible (Table 4) [30].

Table 4. Validation method definitions

Validation Methods[30]	
Face validation	Model structure, data sources, problem formulation and results are evaluated by people who have clinical expertise.
Verification/Internal validation	Examination of the extent to which the mathematical calculations are performed correctly and are consistent with the model's specifications.
Cross validation	Examination of the different models that address the same problem and comparing their results.
External validation	Comparison of model's results with actual event data.
Predictive validation	Comparison of model's simulated outcomes to similar clinical trial or cohort study.

Face Validity

Definition: model structure, data sources, problem formulation and results are evaluated by people who have clinical expertise.

To enhance the face validity of the model, we used a participatory approach, meaning that end-users were involved as collaborators through the model development and evaluation process through iterative meetings during 2018-2020.

The research question and input parameters of OncoSim-CRC to adjust were identified with territorial collaborators (healthcare providers, administrators and patients) who have expertise in the system of colorectal cancer screening in the NWT. From these discussions it was identified that further data would be required to adjust the model and a retrospective chart review of FIT positive individuals and as well as collection from prospective territorial databases were conducted. On January 14, 2020, the proposed adjustments generated from the retrospective chart review data were presented to collaborators who confirmed they were valid.

The final model inputs, structure, and outputs were discussed with collaborators. They observed that the model included all aspects of CRC screening considered to be important in colonoscopy demand; the model flow was consistent with CRC screening delivery in the NWT; the most accurate data sources were used; the population, region, interventions, outcomes, assumptions, and time horizons correspond with those of interest; results are plausible. Overall, collaborators found the model to be credible and useful.

Model Verification/Internal Validity

Definition: Examination of the extent to which the mathematical calculations are performed correctly and are consistent with the model's specifications.

In this study the OncoSim model parameters were adjusted. The equations and coding were not modified and have been previously validated. To verify the model performance with the adjusted parameters, one-way sensitivity analysis was conducted to determine whether the direction and magnitude of the model outputs behave as expected. We adjusted the visibility of screening, sensitivity and specificity of FIT, wait-time for colonoscopy, and adenoma incidence multiplier. We assessed the directional impact on colonoscopy demand. For each adjustment, OncoSim V3.3.6.0 was run for 2,000,000 cases with a kill factor of 100.

Screening participation:

To assess directional change in participation, we compared a visibility of 0.1 to 1.0 with a compliance to follow-up colonoscopy to set to 1.0 (figure 13). In doing so we found that the change in total screens output changed in the appropriate direction.

Figure 13. Recruitment and participation parameters

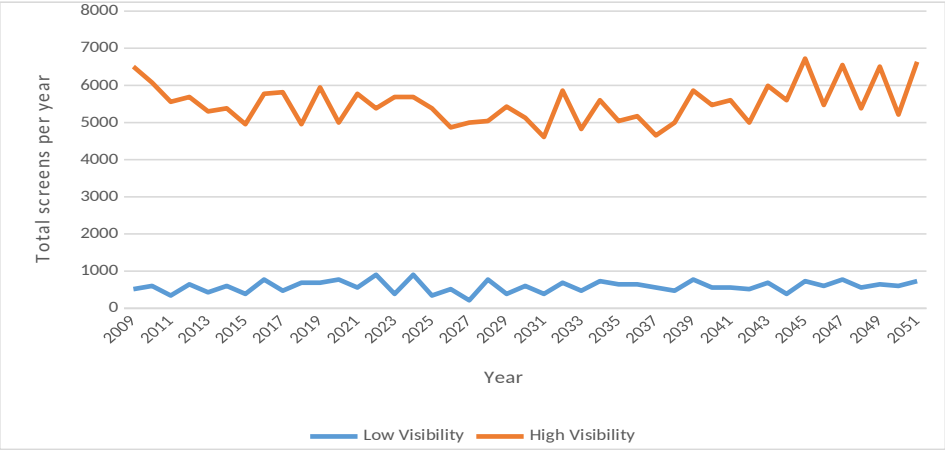
A) Low visibility

Parameter: Recruitment and Participation										
Screening program element / Overall program controls	0	1	2	3	4	5	6	7	8	9
Visibility (prob visible)	0.1	0.1	1	0.1	0.1	0.1	0.1	1	1	1
Recruitment start year	1990	1991	0	2009	2010	2014	2020	0	0	0
Recruitment end year	1990	9999	0	2009	2013	2019	9999	0	0	0
Recruitment start age	40	40	0	50	50	50	50	0	0	0
Recruitment end age	74	74	0	74	74	74	74	0	0	0
First degree relative with CRC : One (1), Multiple...	12	12	0	123	123	123	123	0	0	0
Participation to first invitation (probability)	1	1	0	1	1	1	1	0	0	0
Phase-in of first invitation (years)	5	1	0	2	1	2	5	0	0	0
Additional recruitment attempts	0	0	0	0	0	0	0	0	0	0
Years between recruitment attempts	99	99	0	99	99	99	99	0	0	0
Participation at subsequent recruitment attempts (...	0	0	0	0	0	0	0	0	0	0

B) High visibility

Parameter: Recruitment and Participation										
Screening program element / Overall program controls	0	1	2	3	4	5	6	7	8	9
Visibility (prob visible)	1	1	1	1	1	1	1	1	1	1
Recruitment start year	1990	1991	0	2009	2010	2014	2020	0	0	0
Recruitment end year	1990	9999	0	2009	2013	2019	9999	0	0	0
Recruitment start age	40	40	0	50	50	50	50	0	0	0
Recruitment end age	74	74	0	74	74	74	74	0	0	0
First degree relative with CRC : One (1), Multiple (2), None (3)	12	12	0	123	123	123	123	0	0	0
Participation to first invitation (probability)	1	1	0	1	1	1	1	0	0	0
Phase-in of first invitation (years)	5	1	0	2	1	2	5	0	0	0
Additional recruitment attempts	0	0	0	0	0	0	0	0	0	0
Years between recruitment attempts	99	99	0	99	99	99	99	0	0	0
Participation at subsequent recruitment attempts (probability)	0	0	0	0	0	0	0	0	0	0

Figure 14. Low vs high visibility FIT participation



Compliance to colonoscopy after positive screening:

we adjusted the adherence to colonoscopy after positive FIT to see the impact on the number of colonoscopies. We found with a low adherence the number of projected colonoscopies appropriately decreased both for follow-up after a positive FIT and for adenoma surveillance (Figure 15).

Figure 15. Colonoscopy compliance parameter

A) Low compliance after FIT

View as: Data Chart Edit

Parameter: Compliance to follow-up by colonoscopy for positive screens

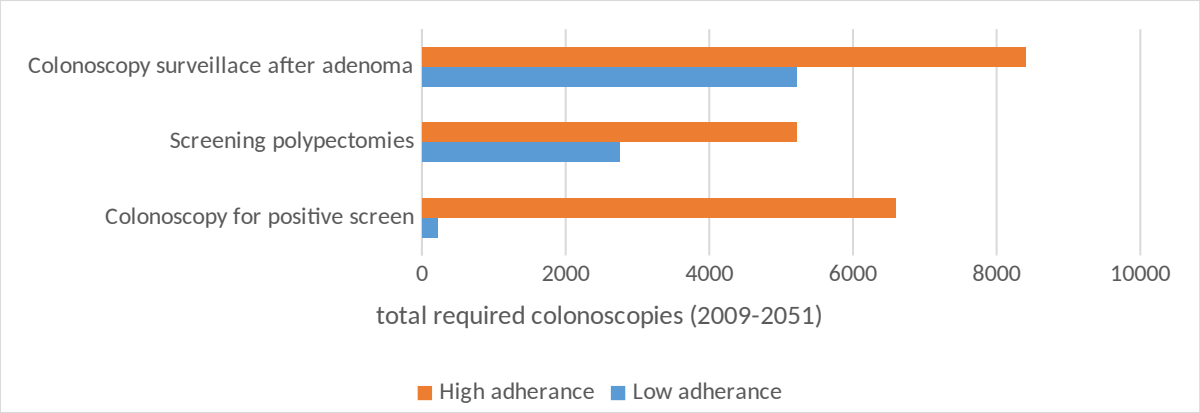
Primary screening modality / Province	FOBT guaiac	FIT immunoch	Flexible sigmoidos	Colonosco	CT colonogra
Newfoundland and Labrador	0.85	0.85	0.77	1	1
Prince Edward Island	0.85	0.85	0.77	1	1
Nova Scotia	0.85	0.85	0.77	1	1
New Brunswick	0.85	0.85	0.77	1	1
Quebec	0.85	0.85	0.77	1	1
Ontario	0.85	0.85	0.77	1	1
Manitoba	0.85	0.85	0.77	1	1
Saskatchewan	0.85	0.85	0.77	1	1
Alberta	0.85	0.85	0.77	1	1
British Columbia	0.85	0.85	0.77	1	1
Yukon	0.85	0.85	0.77	1	1
North West Territories and Nunavut	0.85	0.01	0.77	0.01	1

B) High compliance after FIT

Parameter: Compliance to follow-up by colonoscopy for positive screens

Primary screening modality / Province	FOBT guaiac	FIT immunoch	Flexible sigmoidos	Colonosco	CT colonogra
Newfoundland and Labrador	0.85	0.85	0.77	1	1
Prince Edward Island	0.85	0.85	0.77	1	1
Nova Scotia	0.85	0.85	0.77	1	1
New Brunswick	0.85	0.85	0.77	1	1
Quebec	0.85	0.85	0.77	1	1
Ontario	0.85	0.85	0.77	1	1
Manitoba	0.85	0.85	0.77	1	1
Saskatchewan	0.85	0.85	0.77	1	1
Alberta	0.85	0.85	0.77	1	1
British Columbia	0.85	0.85	0.77	1	1
Yukon	0.85	0.85	0.77	1	1
North West Territories and Nunavut	0.85	1	0.77	1	1

Figure 16. Colonoscopy demand with high vs low compliance after FIT



Sensitivity of Screening:

the sensitivity of FIT for distal adenomas and cancer were adjusted to a low value of 0.01 and then compared to a high value of 1 (figure 18). In doing so, the number of true positives and false negatives changed appropriately, as did the number of screen detected cancers and polypectomies (Table 5).

Figure 18. Sensitivity of FIT

A) Low sensitivity

Parameter: Sensitivity of the screening test

Distal or Proximal colon - Distal (descending, sigmoid, rectum)

Primary screening modality / Polyp or Cancer state	FOBT guaiac	FIT immunoch	Flexible sigmoidos	Colonosco	CT colonogra
Polyp less or equal to 5mm in size	0.03	0.01	0.75	0.75	0
Polyp between 6 and 9mm in size	0.04	0.01	0.85	0.85	0.6
Polyp greater or equal to 10mm in size	0.1	0.01	0.95	0.95	0.938
Cancer	0.5	0.01	0.95	0.95	0.967

B) High sensitivity

Parameter: Sensitivity of the screening test

Distal or Proximal colon - Distal (descending, sigmoid, rectum)

Primary screening modality / Polyp or Cancer state	FOBT guaiac	FIT immunochemical	Flexible sigmoidoscopy	Colonoscopy
Polyp less or equal to 5mm in size	0.03	1	0.75	0.75
Polyp between 6 and 9mm in size	0.04	1	0.85	0.85
Polyp greater or equal to 10mm in size	0.1	1	0.95	0.95
Cancer	0.5	1	0.95	0.95

Table 5 FIT performance

Measure	low sensitivity	high sensitivity
True Positives	172	6,504
False Positives	0	0
True Negatives	3,101	3,188
False Negatives	0	1,465
Positive rate	0.0526	0.583
Number of screens to detect one cancer	3,553	1,006
Number of screening polypectomies	2,800	9,132
Number of screen detected cancers	43	129

Adenoma incidence multiplier:

We adjusted the adenoma incidence provincial multiplier to a low value of 0.01 and high value of 3 (Figure 19). We observed that the number of surveillance colonoscopies were higher with a higher adenoma incidence (figure 20).

Figure 19. Adenoma incidence multiplier

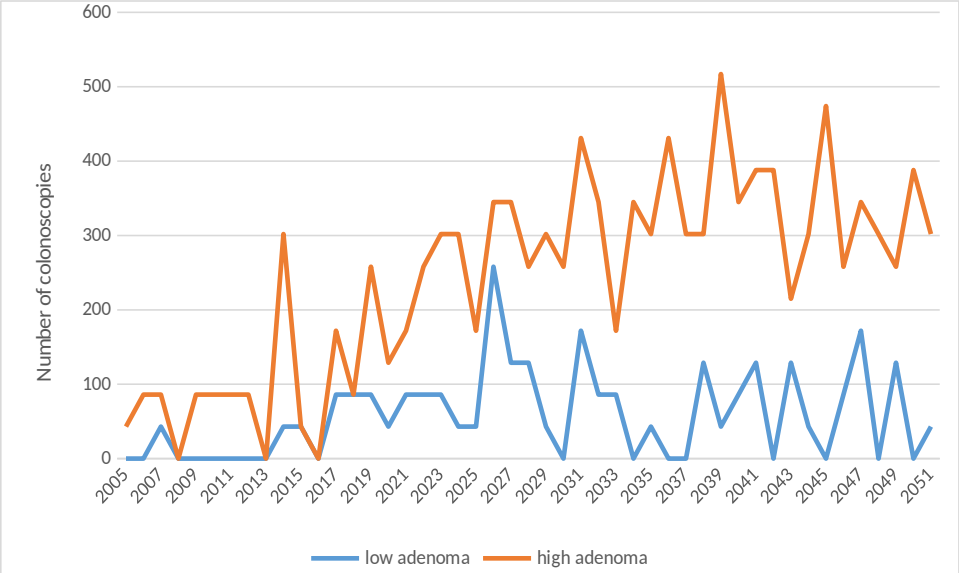
A) Low incidence

Parameter: Colorectal adenomas incidence rates provincial multiplier (alternative route or not)												
Province / Sex	Newfoundland and Labrador	Prince Edward Island	Nova Scotia	New Brunswick	Quebec	Ontario	Manitoba	Saskatchewan	Alberta	British Columbia	Yukon	North West Territories and Nunavut
Female	1.104343	1.103300	1.129554	0.873320	1.081260	0.890894	0.967926	1.161911	0.772028	0.808282	0.80839	0.01
Male	1.094677	1.021272	1.028455	0.919528	1.055727	0.829928	0.892567	1.148611	0.787498	0.787904	0.84393	0.01

B) High incidence

Parameter: Colorectal adenomas incidence rates provincial multiplier (alternative route or not)												
Province / Sex	Newfoundland and Labrador	Prince Edward Island	Nova Scotia	New Brunswick	Quebec	Ontario	Manitoba	Saskatchewan	Alberta	British Columbia	Yukon	North West Territories and Nunavut
Female	1.104343	1.103300	1.129554	0.873320	1.081260	0.890894	0.967926	1.161911	0.772028	0.808282	0.80839	3
Male	1.094677	1.021272	1.028455	0.919528	1.055727	0.829928	0.892567	1.148611	0.787498	0.787904	0.84393	3

Figure 20. Colonoscopy demand adenoma surveillance with low vs high adenoma incidence



Cross Validity

Definition: Examination of the different models that address the same problem and comparing their results.

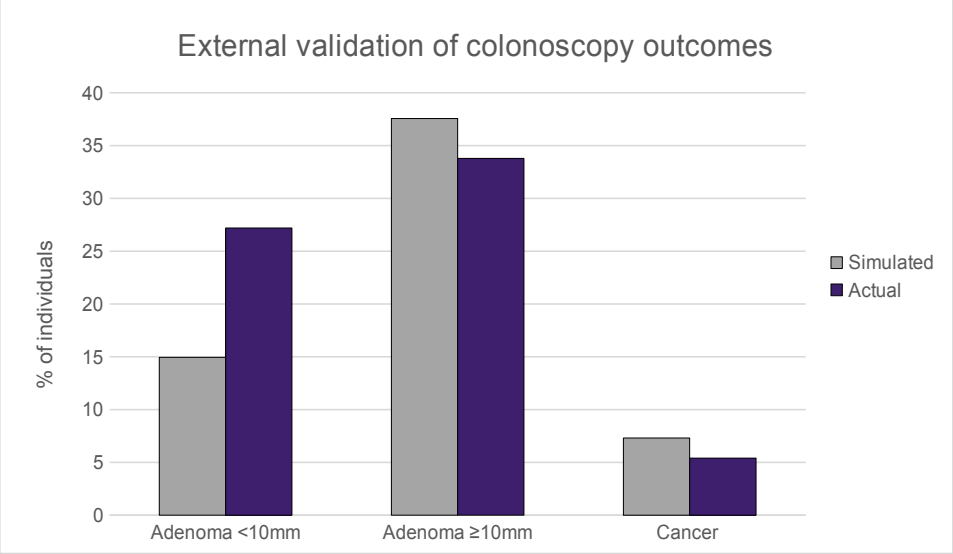
Deferred due to previous validation of the OncoSim model and lack of relevant direct comparators to strengthen the previous validation.

External Validation

Definition: Comparison of model's results with actual event data.

The model outputs for the years 2014-2018 were compared with results from the retrospective chart review to assess key model outputs: FIT participation, number of colonoscopies for positive screening, incidence of colorectal cancer, pathology results on colonoscopy. We assumed NWT population to be 75% of the NWT/NT population. We observed an estimate of 7088 would have participated in FIT CRC screening according to the model, compared to 6817 in actuality. The comparison of these screening results are summarized in the figures below compared to the actual NWT data to the simulated results (figure 21, 22). Margins of error were calculated assuming normal distribution. intervals were and to only those participants with no symptoms identified at the time of referral. The positivity of FIT was lower than actual (506/5774, 7.1%; vs 785/6817, 11.5%). The proportion of FIT positive individuals who underwent a diagnostic colonoscopy was higher (464, 91.7%; vs 592/783, 76% overall, and 313/356, 87.9% among screen eligible individuals). In terms of pathology, the burden of cancer was higher but few cases overall (5.3 vs 4.1% of FIT positive individuals), whereas the burden of polyps was similar for HRA and slightly low for LRA.

Figure 21. FIT participation and colonoscopy simulated vs actual



Predictive Validation

Definition: Comparison of model's simulated outcomes to similar clinical trial or cohort study.

This model was revised to forecast colonoscopy resource requirements for CRC screening after 2020. At this time, the predictive validation cannot be assessed until the anticipated changes to screening participation and delivery starting in 2020 are implemented.

SCENARIO COMPARISON

Additional scenarios were developed to compare alternative scenarios of CRC screening program implementation which may reduce the demand for colonoscopy. All developed scenarios were run for 5 million individuals with outputs for the years 2005-2051.

Figure 22. Screening program phase in 10 years

Parameter: Recruitment and Participation

Screening program element / Overall program controls	0	1	2	3	4	5	6	7	8	9
Visibility (prob visible)	0.8	0.8	1	0.27	0.27	0.42	0.8	1	1	1
Recruitment start year	1990	1991	0	2009	2010	2014	2021	0	0	0
Recruitment end year	1990	9999	0	2009	2013	2020	9999	0	0	0
Recruitment start age	40	40	0	50	50	50	50	0	0	0
Recruitment end age	74	74	0	74	74	74	74	0	0	0
First degree relative with CRC : One (1), Multiple...	12	12	0	123	123	123	123	0	0	0
Participation to first invitation (probability)	1	1	0	1	1	1	1	0	0	0
Phase-in of first invitation (years)	5	1	0	2	1	2	10	0	0	0
Additional recruitment attempts	0	0	0	0	0	0	0	0	0	0
Years between recruitment attempts	99	99	0	99	99	99	99	0	0	0
Participation at subsequent recruitment attempts (...	0	0	0	0	0	0	0	0	0	0

Figure 23. Screening program phase in 7 years

Parameter: Recruitment and Participation

Screening program element / Overall program controls	0	1	2	3	4	5	6	7	8	9
Visibility (prob visible)	0.8	0.8	1	0.27	0.27	0.42	0.8	1	1	1
Recruitment start year	1990	1991	0	2009	2010	2014	2021	0	0	0
Recruitment end year	1990	9999	0	2009	2013	2020	9999	0	0	0
Recruitment start age	40	40	0	50	50	50	50	0	0	0
Recruitment end age	74	74	0	74	74	74	74	0	0	0
First degree relative with CRC : One (1), Multiple (2), None (3)	12	12	0	123	123	123	123	0	0	0
Participation to first invitation (probability)	1	1	0	1	1	1	1	0	0	0
Phase-in of first invitation (years)	5	1	0	2	1	2	7	0	0	0
Additional recruitment attempts	0	0	0	0	0	0	0	0	0	0
Years between recruitment attempts	99	99	0	99	99	99	99	0	0	0
Participation at subsequent recruitment attempts (probability)	0	0	0	0	0	0	0	0	0	0

Figure 24. No LRA follow-up

Parameter: Colonoscopy follow-up schedule after abnormality detected

Follow-up controls / Risk Level for colorectal cancer	Years to first follow-up colonosco	Years between subsequer follow-up colonosco	Number of follow-up colonosco
Patients who had cancer detected	1	3	99
High risk patients (villous, large or many small tubular polyps)	3	5	2
Low risk patients (few small tubular polyps found <10mm)	0	0	0

Figure 25. Program participation of 40%

Parameter: Recruitment and Participation

Screening program element / Overall program controls	0	1	2	3	4	5	6	7	8	9
Visibility (prob visible)	0.8	0.8	1	0.27	0.27	0.42	0.58	1	1	1
Recruitment start year	1990	1991	0	2009	2010	2014	2021	0	0	0
Recruitment end year	1990	9999	0	2009	2013	2020	9999	0	0	0
Recruitment start age	40	40	0	50	50	50	50	0	0	0
Recruitment end age	74	74	0	74	74	74	74	0	0	0
First degree relative with CRC : One (1), Multiple (2), None (3)	12	12	0	123	123	123	123	0	0	0
Participation to first invitation (probability)	1	1	0	1	1	1	1	0	0	0
Phase-in of first invitation (years)	5	1	0	2	1	2	5	0	0	0
Additional recruitment attempts	0	0	0	0	0	0	0	0	0	0
Years between recruitment attempts	99	99	0	99	99	99	99	0	0	0
Participation at subsequent recruitment attempts (probability)	0	0	0	0	0	0	0	0	0	0

Figure 26. Colonoscopy screening for average risk

Parameter: Modality selection

Screening modality plan / Screening program element	Modality	Age start	Age end	Year start	Year end	Element recruited under	First degree relative with CRC : One (1), Multiple...	Adherence (probability)	Years to next screen
A	2	50	74	0	2020	345	0	0.8	2
B	0	0	0	0	0	0	0	0	0
C	4	40	74	0	9999	10	0	0.8	5
D	0	0	0	0	0	0	0	0	0
E	4	50	74	0	9999	6	0	0.8	10
F	0	0	0	0	0	0	0	0	0
G	0	0	0	0	0	0	0	0	0
H	0	0	0	0	0	0	0	0	0

Figure 27. Annual FIT

Parameter: Modality selection

Screening modality plan / Screening program element	Modality	Age start	Age end	Year start	Year end	Element recruited under	First degree relative with CRC : One (1), Multiple...	Adherence (probability)	Years to next screen
A	2	50	74	0	2021	3456	0	0.8	2
B	0	0	0	0	0	0	0	0	0
C	4	40	74	0	9999	10	0	0.8	5
D	0	0	0	0	0	0	0	0	0
E	2	50	74	0	9999	6	0	0.8	1
F	0	0	0	0	0	0	0	0	0
G	0	0	0	0	0	0	0	0	0
H	0	0	0	0	0	0	0	0	0