Evaluating the Cancer Risk Management Model (CRMM) – Colorectal Cancer Module

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1. Background and objectives

Cancer risk management model (CRMM) is a computer simulation model to inform policy and decision making in the Canadian context in various types of cancer currently including cervical, colorectal, and lung cancers. The objective of this activity was *to evaluate the colorectal cancer sub-model of the CRMM with regard to its capacity to evaluate decisions regarding colorectal cancer screening in Canada*. This is a methodological review of the CRMM from a health economics perspective. Given the nature of CRMM, evaluating the model structure, internal validity, and capacity to address stakeholders' and consumers' needs is different from evaluating data sources and input parameters. The latter component requires dedicated activity involving cancer epidemiology experts.

For this evaluation, the team had access to the CRMM Web interface (cancerview.ca) as well as the Colon Cancer Management Data workbook and supporting documents such as peer-reviewed publications based on CRMM. A recent peer-reviewed publication provided additional information about model performance and predictions(1).

2. The Canadian Cancer Risk Management Model (CRMM)

CRMM is a micro-simulation model developed by Statistics Canada; the parameters of the model are largely informed from the Canadian-based data sources such as Vital Statistics, Census data, Canadian Cancer registry, Canadian Community Health Survey (2), National Population Health Survey (3), General Society Survey (4), and Canadian Health Survey (5). Each patient in CRMM is followed over their life time and is at risk of developing any of the aforementioned types of cancer in a unified simulation platform. Consequently, costs and quality-adjusted life years (QALYs) and other epidemiological and clinical outcomes are calculated for each patient. This enables evaluation of strategies, programs, and interventions at all the levels (primary, secondary, tertiary) of prevention and treatment.

The CRMM is equipped with an advanced online interface facilitating model evaluation. This is a key advantage given complex simulation models can be seen as black boxes for the stakeholders. The interface allows the creation of customized scenarios and saving the scenarios in the interface for repeated use by the analyst or by other teams. Some of the key scenarios informing this evaluation have been saved in the online interface (Version 2.1) and are made available for the stakeholders of this review (all scenarios start with ‘ZZ’). In addition, the model is accompanied by a companion tool, a Microsoft Excel document 'The Colon Cancer Management Data workbook' with the specific aims of a) help with the transparency of methodology, data sources and documentation b) change/update treatment costs, and c) for ease of recalculating aggregated costs and probabilities. There is a one-to-one relation with highlighted cells in this workbook with many input parameter of the model, facilitating

informed updating of the model parameters based on changing the assumptions and 'upstream' calculations in the model. This seems to be mainly applicable to cost parameters and health state utility values. Specifically, it appears that the Data Workbook is mainly around cancer management and has not implemented screening. ***While screening parameters can be modified directly in the Web interface, companion documentation and input tables in the Data Workbook will be of value to end users.***

In evaluating CRMM, we have undertaken three broad steps of **1)** evaluating the model structure; **2)** evaluating the face validity of the model in terms of input-output relations, and **3)** evaluating the capacity of the model to perform high quality economic evaluations of colorectal cancer screening scenarios. The remainder of the report is structured around these three steps. Our concerns, suggestions, and recommendations are highlighted throughout the text.

2.1. Evaluation of model structure and settings

CRMM is a Discrete Event Simulation (DES). DES models the operation of a system as a discrete sequence of events, with individuals as the unit of simulation. Accordingly, we have followed the best practice guidelines in evaluating DES models (6). The choice of DES is valid given the complexity of the context such as multiple risk factors, future events' dependence on history, and interactions among multiple factors (7). Microsimulation models are generally data-intensive, requiring many parameters to be populated representing the natural course of the health condition, impact of screening/treatment, and variables representing the performance of the health care technologies and services. This is reflected in many input parameters in the Web interface and the Data Workbook. The evaluating team does not see this as a drawback, rather as the consequence of the complexity of the landscape underlying the evaluation objectives and the capacity of CRMM to capture such complexity. However, models of this level of complexity require dedicated calibration and validation attempts. An example is the rigorous efforts undertaken to validate the lung cancer screening module of CRMM (8). ***We are currently unaware of any such efforts for the colorectal cancer screening module and strongly recommend the completion of this task before the model is used to inform policies***.

For evaluation of the CRMM model structure we applied the relevant (methods and results) sections of the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist (9). ***Table 1*** summarizes the results of the implementation this checklist on CRMM model. An itemized description is provided below.

Table 1. Evaluation of the model structure

Model component	Component	Assessment
Target population	Should represent the Canadian population	✓

Setting		✓
Study perspective	Preference: societal perspective	?
Comparators	All relevant comparators should be evaluated (or the capacity for their evaluation should exist)	✓
Time horizon	Preference: life time	✓
Discount rate	Should be based on Canadian guidelines	✓
Currency and price index	Should use a reference costing year	✓
Model structure	Should be logical, plausible, and valid	✓
Analytic methods	Sound statistical analyses and assumption	✓
Programming codes*	N/A	?
Study parameters		
Disease progression		✓
Resources and costs		✓
Health outcomes		✓
Incremental cost and effectiveness	The model should generate estimates of both costs and effectiveness	✓
Characterizing uncertainty and probabilistic model	Full incorporation of uncertainty in the evaluation	✘
Characterizing heterogeneity	Full representation of the entire subgroups of populations and variables that might affect the result	✓

*: We did not have access to the programming codes.

2.1.1. Target population

Unlike conventional cost-effectiveness models that only follow a cohort of patients with a specific health condition, in CRMM a representative sample of Canadians is followed over time regardless of their health complications. This choice of target population is more informative and comprehensive than following only cases, as with this target population not only a broader picture of the impact of treatment strategies is given, but also trajectories of both at risk and cancer patients can be modeled. This is a fundamental strength of this platform for evaluation of screening strategies.

2.1.2. Setting

The CRMM is built for the Canadian context. Parameters of this model were constructed using Canadian data. We have not evaluated the validity and relevance of specific input parameters.

However, the development team's access to a multitude of highly representative Canadian survey data as well as population-based and health administrative data are reassuring that the CRMM results will have high external validity.

2.1.3. Study perspective

The perspective of the evaluations is not made fully clear. The current CRMM model seems to be from a third-party payer perspective and only direct costs are included in the cost-effectiveness analysis. Considering only direct cost in the cost-effectiveness analyses is recommended by the US Health Panel on Cost-Effectiveness (10). However, as it is postulated, cancer has a substantial impact on productivity loss from the societal perspective; thus ***the incorporation of 'indirect' costs in the model could have added to the utility of CRMM***.

2.1.4. Comparators

Cost-effectiveness analyses of different screening scenarios for colorectal cancer, cervical cancer, and lung cancer can be compared through the CRMM. We have not considered any particular screening strategies as valid 'usual care' comparators. Nevertheless, CRMM can clearly incorporate a wide range of screening (or lack thereof) scenarios at various uptake levels.

2.1.5. Time horizon

Time horizon of the CRMM model is life time by default, which is the most informative choice of time frame in any cost-effectiveness analysis. ***Currently, it does not appear that CRMM can accommodate other time-horizons.*** This can potentially be a drawback as there might be instances that stakeholders will require setting a specific time-horizon (e.g., comparison with different prediction models or for model calibration).

2.1.6. Discount rate

Different discount rates can be accommodated in CRMM. We have been able to run the evaluations using a wide range (0% to 10%) of discounting values. Within a single run, the CRMM can accommodate multiple discount rates. While this is not a standard practice in economic evaluations, it provides users with additional flexibility to investigate the outcomes of interest at different discount rates.

2.1.7. Currency and price index

Costs are based on appropriate Canadian sources. By default, costs are calculated annually and started from year 2005 in the model. The model appropriately adjusts costs for a given reference year and discounting is implemented. Detailed cost calculations are made possible in the companion Data Workbook.

2.1.8. Model structure

CRMM is a DES model, in which simulated entities (individuals) enter the model, are followed over time, and eventually die. Due to complexity of the context, and extensive number of parameters and their interaction, DES is the best simulation tool for modeling the natural history of the disease. The use of DES comes at the cost of lack of familiarity among stakeholders, lack of standardized software, and computational challenges. The choice of modeling platform as well as the implementation of a Web interface (and a Data Workbook) overcomes many of these. Overall, the colorectal cancer sub-model of CRMM seems to be based on a detailed, robust, and valid model structure. The pathways of care seem to have been modeled with a reasonable accuracy. A recent peer-reviewed publication on the colorectal cancer module provides additional recognition and additional face validity for the module to be the backbone of further evaluations (1); however, as stated earlier, there is a lack of rigorous and documented model calibration and validation attempt.

2.1.9. Analytic methods

In a DES model, the causal relation between entities and events is a key component of model structure. These relationships eventually determine time to events and how events further affect entities and subsequent events. In CRMM, events associated with cancer are modeled properly, and the submitted documents indicate that sound analytical methods have been used to determine the structure and extent of associations. A key component of the model, for example, is disease progression (time to next stage of cancer). Rigorous approaches and justifiable assumptions are made in this regard. The use of a Weibull distribution, for example, that accommodates a non-constant hazard is a valid and well justified choice.

2.1.10. Study parameters

Study parameters generally fall into four groups: screening, disease progression, resource use and costs, and measures of health, which are described below.

Screening: The model can properly accommodate a range of parameters characterizing a screening strategy. These include the sensitivity and specificity of the test, test costs, and uptake of screening. ***However, it is not clear how readily the model can accommodate more complicated features such as customized screening*** (e.g., targeted screening strategies based on risk profiles or other characteristics of individuals) or time-dependent uptake. It currently appears incorporating these features will require further efforts by CRMM developer team.

Disease progression: Disease progression in CRMM is simulated based on parametric survival models (resulting in time-dependent Weibull distribution for time to event), which are fitted to survival curves. Parameters of these distributions are explicitly mentioned in the model, and can be changed to any user-defined values.

Resources and costs: Resource use and costs for all different screening scenarios, treatments, and events are derived from Canadian data and implemented fully in the model. In general, there is quite an amount of flexibility in modeling the cost profile of screening strategies. Although implementing some complicated scenarios (e.g., time-dependent cost profile) will require 'tweaking' by model developers, it seems the model in general is flexible enough on this dimension.

The CRMM makes a tradeoff between the aggregate and detailed cost calculations: The model inputs aggregate cost parameters grouped by types (e.g., diagnostics, drugs, hospitalization). Detailed calculation of these costs is performed in the accompanying Data Workbook. This enables the developer team to work with a manageable number of parameters while the end-user has the flexibility of modifying very specific cost values (e.g., unit cost of bone scan). This is a clever tradeoff and a commendable feature of CRMM.

Health outcomes: Health outcomes are expressed in terms of quality-adjusted life years (QALYs) and are calculated based on utility values derived from Classification and Measurement System of Functional Health (CLAMES) (11,12). The choice of QALYs is a positive aspect of CRMM but we have not reviewed the robustness of the CLAMES-based utility values. Appropriate modification can generate alternative health outcomes (e.g., setting all utility values to 1) will generate estimates of life years gained from screening as a secondary output of the model. The Data Workbook provides an interface that enables modification of the input utility values.

Incremental cost and effectiveness: CRMM provides a platform to compare easily the cost and effectiveness of different user-defined screening scenarios and calculate their incremental cost-effectiveness ratio.

Characterizing parameter uncertainty: In general, random variation and uncertainty in a simulation model can be categorized into three broad terms(13). Stochastic uncertainty refers to the inevitable uncertainty in outcomes even within a single individual. Stochastic uncertainty should be removed from the analysis in population-based evaluations. Heterogeneity (or first-order uncertainty) refers to the variation in outcomes due to differences in causal factors (e.g., difference in age resulting in difference in time to metastasis). When making decisions for the whole population is concerned, the effect of heterogeneity also needs to be removed, but decisions can be made more efficient by stratification of decisions across identifiable subgroups(14). Finally, parameter uncertainty (or second-order uncertainty) refers to the uncertainty in our knowledge of the parameters governing the nature of the disease condition and the context in which it occurs (e.g., our uncertainty about the sensitivity of the screening test). Incorporating uncertainty in decision models requires the capacity for probabilistic analysis. Probabilistic analysis entails assigning probability distribution to all uncertain model

parameters, and creating multiple runs of the model such that within each iteration, the results are generated based on a set of random draws from the model inputs.

By simulating the outcomes across many (multiple millions) of individuals and averaging the results, CRMM removes the effect of stochastic uncertainty and heterogeneity. By incorporating the capacity to run the simulation is customized fashion for different subgroups of individuals, CRMM enables stratified decision making. However, and unfortunately, ***CRMM is not a probabilistic model and does not capture uncertainty in decision-making for different screening scenarios.*** This is a fundamental drawback of CRMM. Full incorporation and reporting of second-order uncertainty in decision analysis is a requirement and a recommendation by major guidelines and best practice standards(15).

Characterizing heterogeneity: As described above, heterogeneity is well captured in CRMM through generating a representative sample of Canadian population in terms of their sex, age, province of residence, income quintile, and health-related quality of life. However, the model cannot fully incorporate heterogeneity in other aspects. For example, it does not seem that the model is capable of modeling conditional sensitivity and specificity as a function of individual's characteristics. This, nonetheless, seems achievable through further involvement of the development team.

2.2. Face validity of the colorectal cancer model

We appraised the **face validity** of the CRMM model concentrating on colorectal cancer by manipulating the key input parameters and investigating if the direction of outcome changes stays in line with our expectation. This part of a validation assures us that there is a rational relationship between inputs and outputs of the model(16). Unexpected results can indicate programming error or implausible assumptions. Summary of this face validity can be found in ***Table 2.*** Brief description of the face validity tests are provided below. All simulated scenarios are based on Monte Carlo simulation of size 1,000,000

Table 2. Face validity: Impact of changes to key model parameters

Key parameters	Expected outcome
Incidence and prevalence	✓
Cost	✓
Sensitivity and specificity	✓
Cancer progression	✓

Changing cancer incidence and prevalence

We created a scenario (ZZ_incidence_1), in which we increased the incidence rate of colorectal cancer through changing its regression coefficients (*path: Cancer parameters/Colorectal cancer/Incidence/Natural History Approach/Polyp incidence/Colorectal adenomas incidence rates coefficients/Disappearance rate of 40*). This resulted in an expected increase in the prevalence of the disease in life time, while reduced the prevalence and incidence of other competing diseases (e.g., lung cancer and cervical cancer). This was in line with our expectation as colorectal cancer-specific mortality rate increases by ascending its incidence, which consequently results in decreased prevalence for other cancers that act as competing risks. All other outputs also changed in the expected direction. In a second analysis, we evaluated a scenario (ZZ_incidence_3(very low)) to reduce the incidence rate of colorectal cancer. We manipulated the incidence rate coefficients (*path: Cancer parameters/Colorectal cancer/Incidence/Natural History Approach/Polyp incidence/Colorectal adenomas incidence rates coefficients/Disappearance rate of 40*).

Costs

We created a scenario (ZZ_screeningCost_0), in which we changed the cost of colorectal cancer screening and its follow-up to 0 (path: Cancer parameters/Colorectal cancer/Screening/National/Screening costs). This resulted in life time cost of colorectal cancer screening being 0 (as expected) and all other costs at their default values as in the base case analysis (as expected). In addition, the ICER for screening versus not screening became smaller (as expected).

Of note, screening cost parameters in the outcome table consists of both actual screening cost and the follow-up colonoscopy costs. From an economic evaluation perspective, these two costs need to be separated, such that it could be more explicit for a policy maker at which cost of screening implementation the program becomes cost-effective.

Changing sensitivity and specificity of screening

First, we created two scenarios: 1) no screening with sensitivity and specificity of the follow-up colonoscopy set to their default values, and 2) no screening with sensitivity and specificity of the follow-up colonoscopy, only in distal model (represents location of Polyp/tumor), set to 0, and 1, respectively (path: Cancer parameters/Colorectal cancer/Screening/Sensitivity and Specificity of screening test). Literally, we expect worse health outcomes in scenario (2) as sensitivity of 0 and specificity of 1 result in no cancer diagnosis out of screening test. Our expectation was endorsed with worse number of

health-adjusted person-years and colorectal cancer-specific deaths in scenario (2) compared with scenario (1).

Second, we created two other scenarios: 1) no screening with sensitivity and specificity of the follow-up colonoscopy set to their default values, and 2) no screening with sensitivity and specificity of the follow-up colonoscopy, in both distal and proximal model, set to 0, and 1, respectively (path: Cancer parameters/Colorectal cancer/Screening/Sensitivity and Specificity of screening test). Similar to first part, health-adjusted person-years and number of colorectal cancer deaths in scenario (2) was worse than scenario (1), which was in concordance with our expectation.

Cancer progression

We created a scenario (`ZZ_progression_high`), in which we lowered the progression rate of colorectal cancer (path: Cancer parameters/Colorectal cancer/Progression/Colon cancer survival parameters) through changing the parameters of Weibull distributions fitted (lambda2 increased) to the survival curves of different stages of the disease. This resulted in the higher health-adjusted person-years as well as the lower number of colorectal cancer deaths, which was in line with our expectation.

2.3. Capability of the CRMM to address different types of screening programs or treatment strategies in colorectal cancer

The current CRMM model is generally capable of addressing the impact of a new screening scenario with updated specifications such as costs, sensitivity, and specificity as long as a time interval between two consecutive screenings is more than a year. The Data Workbook, however, does not seem to provide any functionality on this aspect, leaving the end user to directly input screening parameters in the Web interface.

Brief review of screening parameters in CRMM: Based on our understanding of the CRMM (version 2.1), the platform can in general accommodate the following features

1. Assessment of national or provincial screening programs
2. A recruitment program with explicit start and end date (calendar years), age bands, as well as 'real world' features of screening such as incomplete recruitment and additional recruitment attempts.
3. Multiple screening modalities (different screening tests for different age groups)
4. Detailed cost inputs

5. Sensitivity and specificity of screening tests conditional on various stages of the condition (currently: polyp size <5mm, 6-9mm, and >10mm, and presence of cancer). Specificity is modeled separately for first or subsequent rounds.
6. Flexible follow-up scheduling and incomplete compliance to follow-up recommendation

Overall, these are critical parameters in evaluation of cancer screening programs. However, we anticipate that additional parameters will have to be defined based on future specific screening recommendations as well as the availability of evidence. For example, specificity of a cancer screening test might be varied, or

To test the capacity of CRMM for evaluation of basic screening program (a list of which was supplied by the stakeholders), we have implemented a series of face validity tests. ***Table 3*** shows a list of different screening scenarios that can be addressed through the CRMM model.

Table 3. Different screening scenarios and capability of the CRMM model to address such scenarios are assessed in this table.

Screening scenario	**Is model capable of addressing this scenario?**	**Are outcomes of this scenario in line with our expectation (face validity)?**
Base Case (no screening)	✓	✓
Biennial FOBT, ages 50-59	✓	✓
Biennial FOBT, ages 60-74	✓	✓
Annual FOBT, ages 50-59	✓	✓
Annual FOBT, ages 60-74	✓	✓
Biennial FIT, ages 50-59	✓	✓
Biennial FIT, ages 60-74	✓	✓
Annual FIT, ages 50-59	✓	✓
Annual FIT, ages 60-74	✓	✓
Every 5 years Flex Sig, ages 50-59	✓	✓
Every 5 years Flex Sig, ages 60-74	✓	✓
Every 10 years Flex Sig, ages 50-59	✓	✓
Every 10 years Flex Sig, ages 60-74	✓	✓
Once per lifetime Flex Sig, ages 50-59	✓	✓
Once per lifetime Flex Sig, ages 60-74	✓	✓
Every 10 years Colonoscopy, ages 50-59	✓	✓
Every 10 years Colonoscopy, ages 60-74	✓	✓

CRMM: cancer risk management model.

Overall, CRMM seems to be capable of detailed evaluation of real world implementation of colorectal screening programs. In addition, implementing the impact of a new treatment or strategy in CRMM seems to be doable, as it deals with disease progression parameters than can be easily changed to any value in the corresponding Weibull distributions in the model.

Nevertheless, it is quite likely that the 'production-level' evaluation of screening programs will require the developer team to implement specific features of the screening program. We are unsure of the extent of work required from the developer team in this aspect.

Beyond screening: CRMM is a complex model importing many features of the Whole Disease Models (WDMs)(17). WMDs are emerging evaluation paradigms emerged from the UK's National Institute of Clinical Excellence out of the need for consistent evaluation of decisions along the entire pathway of care during clinical guideline development(17). WDMs are systematic attempts in objective decision making by enforcing the following three characteristics: **1)** modeling the complete natural history of the disease including pre-clinical stages, thus enabling the evaluation of the interventions in primary, secondary, and tertiary prevention; **2)** capturing multiple subgroups representing the population and pathways of care in a single framework (heterogeneity in care and population); and **3)** enabling the evaluation of interventions using various decision rules, such as conventional cost-effectiveness analysis, disinvestments given a constrained budget(18), and disease-specific program budgeting and marginal analysis(19). The feasibility of developing WDMs was successfully demonstrated in two recent examples for atrial filtration(20) and colorectal cancer(17,21). It appears that CRMM incorporates these features in principle (although further work is needed to fully incorporate WDM capacity), and we believe it has the capacity to become a reference platform for decision making in cancer.

Long-term support: The complexity of CRMM comes at the cost of the requirement for long-term (and perhaps perpetual) support from the development team. The long-term investment of the developer institution (Statistics Canada) in the ModGen platform(22) hosting CRMM is reassuring that support will be available.

Interactive Web interface: Another prominent feature of the CRMM model is its user-friendly and interactive Web interface. This web application increases the transparency of the model by allowing users to the change different model parameters as they wish and investigate the corresponding results of the model subsequently.

Isolated technical challenges: The simulation was not successfully accomplished for some input parameters. For example, with the following parameters the simulation ended in error: intercept= -6.6, age coefficient= 0.001, age^2 coefficients= -1E-05. This has been communicated to the development team.

3. Conclusion

We commend all the CRMM team members for the development of a state-of-the-art evaluation platform. It is very evident that considerable time and energy has been spent on this work. Appropriately, CRMM is a micro-simulation model of colorectal cancer (and other cancers), enabling robust and valid modeling of the complex natural history of cancer, multiple factors affecting the history, and multitude of outcomes that will be of interest to both epidemiologists and decision makers. CRMM can not only enable evaluation of the colorectal cancer screening strategies, it can also act as a reference platform for evaluation of other interventions in the pathway of cancer prevention and treatment.

CRMM is equipped with an advanced Web interface that provides detailed outputs of the analyses, enabling the user to explore not only the basic results informing a cost-effective analysis, but also myriad of additional outputs regarding the epidemiology of the disease as well as indices of health services use. This is also useful to test face validity, sensitivity to assumption and inputs. The companion document (Data Workbook) provides critically important additional information outlining the model structure and detailed calculation of costs and utility values and probabilities. Despite this, CRMM is inevitably a black box in terms of model structure and assumptions, and the complex inner workings of the platform and the input-output structure will require constant and long-term involvement of Statistics Canada in maintenance and upgrading the platform. This should be of little concern given the commitment and support from the agency for this type of work.

Currently, a major drawback of this platform for economic evaluation of colorectal screening strategies is lack of consideration of parameter uncertainty and consequently, lack of capacity for probabilistic analysis. This means the platform will not be able to generate measures of uncertainty (e.g., credible intervals around the outcomes and the incremental cost-effectiveness ratio [ICER], cost-effectiveness plane and acceptability curves) and value of information metrics. Contemporary economic evaluation guidelines strongly require incorporation of probabilistic analysis in evaluations(13). Indeed, in models that the relation between input and output is non-linear, even the calculation of the point estimates of outcomes and ICERs needs to be based on probabilistic analysis(15). Typically, a probabilistic microsimulation model will require a nested Monte Carlo simulation design in which in the outer loop, variables representing parameter uncertainty are sampled from their respective distributions, and in the inner loop the simulation is run, conditional on the parameter values from the outer loop(13). This might require extensive modification of the design and also might impose long computation times for evaluations. An alternative method is to combine parameter uncertainty and stochastic uncertainty/heterogeneity in a single Monte Carlo run. This will generate valid estimates of the expected values of the outcomes (and ICER), and with

the help of meta-modeling techniques, can enables approximate generation of the outcomes of a typical probabilistic analysis at a fraction of computational costs(23).

This was an evaluation of the CRMM from a methodological perspective, evaluating its structure/setting, face/internal validity, and its capacity to inform Canadian guidelines of colorectal cancer screening. This evaluation was not meant to assess the validity of model parameters or the quantitative outcomes of CRMM. This will require a dedicated effort by content experts and will most likely demand well-planned and detailed model calibration and validation.

Table 4 summarizes the key components of this evaluation.

Table 4. Summary of key issues and suggestions.

Issue	Suggestions
Lack of detailed documentation about screening parameter values and sources of evidence	Update the Data workbook
Lack of capacity for probabilistic analysis	Further development of the platform to accommodate parameter uncertainty. Use of statistical techniques to reduce computational time and need for nested simulations (see Conclusions)
Insufficient information on model validation	Dedicated effort (perhaps resulting in peer-reviewed publication) demonstrating internal, external, and predictive validity of the colorectal cancer module
Inability to perform evaluation from the societal perspective	Incorporating indirect costs (productivity loss)
Requirement for changing the model structure to explore other scenarios, especially customized screening strategies based on, for example, risk or patient characteristics	Continuous cooperation between the developer team and stakeholders.

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