General Discussion

In this thesis, we have shown that microsimulation models are useful tools for investigating potential benefits, costs, and harms of colorectal cancer (CRC) screening. In order to inform screening recommendations, we used an established microsimulation model (MISCAN-Colon) estimating the impact of current screening policies, the potential benefits of specific health policies, and the optimal screening strategies in specific populations at higher risk of CRC. We reviewed the effectiveness of CRC screening in Europe, and we standardized MISCAN-Colon into an online user-friendly application. All the studies included in this thesis were finalized to provide tools and examples that may help researchers and policy-makers to reduce the burden of CRC in their countries.

In this chapter, we will use our results to answer the research questions formulated in Chapter 1. Then, we will discuss our results and we will suggest future research directions. Finally, we will provide conclusions and recommendations based on the work of this thesis.

ANSWERS TO SPECIFIC RESEARCH QUESTIONS

Part 1: The standardization of the MISCAN-Colon model for European countries: What is the effectiveness of CRC screening in Europe? How does reduction in CRC mortality due to screening vary according to screening settings and European regions?

The estimated effectiveness of gFOBT and FS screening appeared similar across different European regions. Compared to no screening, individuals invited to gFOBT screening have shown to have from 8% to 16% lower CRC mortality. Among those invited to FS screening, CRC mortality reductions varied from 21% to 30%. Evidence on effectiveness of FIT and colonoscopy screening was insufficient to permit a comparison across different European regions.

Since 2003, the European Union has recommended CRC screening with gFOBT for men and women within ages 50-74 years. At the time of that recommendation, effectiveness of other CRC screening modalities was not yet assessed by RCTs and, therefore, FIT, FS, and total colonoscopy were not indicated.[55] However, in the past decade, several studies showed that FIT, FS, and total colonoscopy can be considered reasonable alternatives to gFOBT screening.[56] Existing European organized programs differed in terms of target ages, screening interval, and primary test (**Table 1.3**).[57-61] We performed a systematic review to assess how mortality effects of CRC screening varied across European regions and screening settings. Six databases were searched for relevant studies investigating the effect of various screening tests. Our study suggests that the effect of FS and gFOBT on CRC mortality may be consistent across several European settings, indicating that FS screening is more effective than gFOBT. However, the most implemented stool test across Europe is FIT, which can achieve at least the same CRC mortality reduction as gFOBT (or potentially up to FS) with

participation rates higher than those reported by FS screening within organized screening programmes.

In improving CRC screening programmes, European policymakers and researchers should, therefore, give more attentions to national endoscopy resources and population preferences (such as expected participation in screening) rather than country-specific effectiveness of the implemented screening modality.

What is the reliability of MISCAN-Colon model parameters? How valid are the results of the MISCAN-Colon model?

MISCAN-Colon replicated consistently CRC incidence and mortality reduction of an FS screening trial (the Norwegian Colorectal Cancer Prevention; NORCCAP), which suggests that it can be considered a reliable tool to support decision making on CRC screening.

MISCAN-Colon has been calibrated and adapted to quantify CRC screening outcomes in several countries. In its development, MISCAN-Colon was calibrated using CRC incidence data, scientific evidence from autopsy studies (adenoma prevalence and multiplicity), and expert opinions. In an external validation carried out using the results of FS screening trial (UKFSS trial),[112] MISCAN-Colon underestimated CRC incidence reduction due to screening and overestimated the number of screen-detected adenomas and cancers in the intervention arm. As a consequence, MISCAN-Colon was re-calibrated, assuming a longer duration for the adenoma progression to symptomatic CRC. Thus, we performed a specific external and predictive validation using the result of another European FS screening trial (NORCCAP).[39] We found that MISCAN-Colon predictions were highly consistent to the NORCCAP trial results, suggesting that the re-calibrated MISCAN-Colon allows for accurate predictions of CRC incidence and mortality reduction of FS screening.

Is the reliability of the MISCAN-Colon model parameters affected by a different country population or screening setting?

Three European regional MISCAN-Colon model versions were developed varying only a minimum set of country-specific parameters (i.e. adenoma onset and CRC stage distribution at diagnosis) and assuming the same progression time from adenoma to symptomatic CRC. In quite diverse countries and screening settings, MISCAN-Colon accurately estimated CRC stage distributions, incidence, mortality rates, and cancer-specific mortality reduction due to screening.

Although the MISCAN-Colon model structure has been externally validated, it does not imply that the assumptions of the model are valid considering different populations or

different screening settings.[57-61] CRC incidence rates varied remarkably across countries (especially in Europe).[2] Several factors may be behind those variations (genetics, lifestyle, and socioeconomics).[4] However, it is unclear how these factors impact the natural history of disease. They might influence the adenoma prevalence (increasing or decreasing the number of adenomas that may occur at individual level) or impact the progression rate from adenoma to CRC.[177-180] To answer this question, we developed three new versions of the model for quite diverse European countries (Italy, Finland, and Slovenia) and screening settings (gFOBT, FIT, and FS) varying only a minimum set of country-specific parameters. We specifically tested the assumption that differences in CRC across European countries can solely be related by differences in adenoma prevalence and not progression from adenoma to CRC. In this modelling investigation, we found that our model versions accurately estimated CRC stage distributions, incidence, mortality rates, and mortality reduction due to screening in Europe.

Hence, our modelling results provide an important implication. The natural history of CRC may not vary substantially across Europe, increasing the reliability of our validated model structure and assumptions (at least among European countries). Moreover, it is essential that microsimulation models, such as MISCAN-Colon, are validated regularly to provide transparency regarding their performance. The validation results provided in this thesis (Chapters 3 and 4) are part of this regular process. In this thesis, we proved that the MISCAN-Colon model provided accurate estimates for CRC screening and may be considered a useful decision-making tool for public health organizations and governments involved in CRC screening in Europe.

How can models be used to inform policy decisions regarding CRC screening in Europe?

The EU-TOPIA consortium has developed an open, online, and user-friendly tool (the EU-TOPIA evaluation tool; https:\\miscan.eu-topia.org). It incorporates the validated structure of the MISCAN-Colon model. With this tool, European researchers and policymakers may upload and use their country-specific data (demographic, epidemiological, and cancer screening information) to simulate future benefits of CRC screening in their countries and the impact of changes and improvements to their screening programmes.

Many of the current microsimulation models for CRC screening are proprietary, limiting the capacity of policymakers to directly inform their decisions with modelling results. Moreover, only few of those models have been externally validated, providing, therefore, reliable estimates. Given this context, the EU-TOPIA project (EU-Framework Programme, Horizon 2020 – 634753)[279] decided to develop an open, user-friendly, and online tool based on MISCAN-Colon (The EU-TOPIA evaluation tool). The overall goal of the project was to share knowledge, create professional networks, and assist all European countries in moni-

toring, evaluating, and improving their CRC screening programme. This tool was presented in Malmö and Turin (EU-TOPIA workshops; in September 2018, Sweden, and in April 2019, Italy), where 120 researchers and policymakers from 26 European countries used their country-specific data to quantify future benefits of CRC screening in their countries.

It is essential for policymakers to assess favourable and unfavourable short- and long-term effects of their cancer screening programme. In Europe, several research groups worked and defined essential data indicators for monitoring screening programmes.[280] Those indicators were already standardized and included in periodical European reports.[59] The EU-TOPIA evaluation tool uses those standard indicators, giving additional functions to those monitoring data. Collecting those data, European policymakers can now also use them to quantify CRC screening long-term effects.

Part 2: The impacts and cost-effectiveness of colorectal cancer screening: What is the impact of waiving Medicare coinsurance for screening colonoscopy in US? Can it be cost-effective?

In US, waiving the Medicare coinsurance was estimated to reduce CRC mortality up to 13% and slightly increase CRC-related CMS costs (+0.6%; when the policy was assumed to increase colonoscopy screening rate from 60% to 70%). Consistent results were found also assuming FIT as primary screening modality. Assuming a willingness-to-pay threshold of US $50,000, waiving coinsurance would be cost-effective if screening adherence increased from 60% to 60.6%.

Despite the substantial evidence on effectiveness of CRC screening, several financial barriers are currently limiting the participation in screening worldwide. In the US, Medicare beneficiaries do not face any supplementary costs after a negative FIT or negative colonoscopy. However, a positive screening (or diagnostic) colonoscopy is subject to 20% coinsurance,[65] limiting potentially the participation among individuals with no supplementary insurance. Using our microsimulation model, we estimated that at least 36% of screening colonoscopies performed in the US were subjected to coinsurance requirements. Moreover, the model estimated that – simulating FIT as primary screening modality – waiving this coinsurance would be cost-effective if it increased the screening rate from 60.0 percent to 60.6 percent in Medicare beneficiaries (using a willingness-to-pay threshold of $50,000 per QALY gained). Assuming no effects on screening participation, waiving this coinsurance would increase the total costs for Medicare by only 1.5-1.9% (assuming that costs were discounted at the conventional 3% annual rate). It is important also to mention that the waiver would primarily affect the out-of-pocket costs of Medicare beneficiaries from low socioeconomic status background,[222] who more often lack Medigap and supplemental insurance.

Thus, waiving coinsurance is not only cost-effective, but it may also contribute to reducing CRC health disparities in the US.

Given the higher risk of developing CRC among individuals with Cystic Fibrosis (CF), is early CRC screening cost-effective? What is the optimal screening strategy in this population in US?

The colorectal cancer screening guidelines for the US average risk population are not optimal among individuals with CF. Up to 79% of CRC deaths may be averted recommending colonoscopy screening from age 40 years with a screening interval of 5 years. In patients with CF that underwent transplantation, optimal colonoscopy screening should start at an age of 30 or 35 years, depending on the patient's age at time of transplantation.

Gastrointestinal malignancies are an emerging health problem among individuals with CF.[11, 17] Although this group has a risk of developing CRC comparable or higher to that observed in people with family history of CRC or Lynch Syndrome, there are no specific recommendations for screening and surveillance for the CF population. In our model simulations, only 36% of individuals with CF survived until age 50, thereby meeting the age requirement to participate in the screening strategy for the average risk population (US Preventive Services Task Force guideline). Several premature deaths for CRC could have been avoided. Compared to absence of screening, our model predicted a reduction of 52% in CRC incidence and 79% for CRC mortality among non-transplant individuals with CF with colonoscopy screening starting at age 40 and repeated every 5 years (also at acceptable costs: $84,000 per LY gained). Up to 82% of CRC deaths may be prevented in those who underwent transplantation. For this group, optimal colonoscopy screening should commence at age 30 or 35, depending on age of transplantation. Annual FIT screening was also cost-effective. However, the lack of FIT data in the CF population is limiting the reliability of those last results.

In a context of limited available evidence, clinicians, researchers, and policymakers valued the findings of our model decision analysis. This study was formally requested by the CF Foundation and used by the Cystic Fibrosis CRC Screening Task Force in determining their CF CRC screening consensus recommendations.[241]

What is the optimal age to start colonoscopy screening among Childhood Cancer Survivors (CCS) in US?

In the US, colonoscopy every 10 years starting at age 35 may lead to substantial CRC health benefits among CCS treated with abdominopelvic radiation therapy at an acceptable cost (ICER of $92,000 per LYG). Commencing colonoscopy screening at age 45 years (and repeated every 10 years) was optimal for CCS not previously treated with radiation therapy (ICER of $57,000 per LYG)

CCS have shown to be at increased risk of developing a second malignancy and their risk is in large part related to their primary cancer treatment.[10, 260] Abdominal or pelvic radiation therapy (APRT), for example, increases risk of CRC up to 11-fold.[9, 10, 12] As consequence, some expert panels, such as the Children's Oncology Group (COG), have indicated a more frequent and early CRC screening among CCS with this exposure.[144, 261] COG in 2013 suggested to screen CCS treated with APRT (at higher doses, ≥ 30 Gray) with colonoscopy from age 35 and using a screening interval of 5 years. The same experts decided to update their previous recommendations in 2018, suggesting now 5-yearly colonoscopy from age 30 years in all CCS treated with APRT regardless of the radiation dosage.[52] However, several expert groups are debating, arguing that available evidence is insufficient to base those recommendations.[281, 282] According to our simulations, colonoscopy screening as suggested by COG could avert 84.8% of CRC deaths among CCS exposed to APRT (compared to absence of screening), but at high total costs ($8.4 Million per 1,000 CCS). With colonoscopy screening from age 35 to 65 years every 10 years, 82.3% of CRC deaths may be averted (97 colonoscopies needed per CRC death prevented) at overall costs of $6.3 Million per 1,000 CCS (ICER of $92,000/LYG). Shorter screening intervals (every 5 or 3 years) might be optimal depending on primary tumor location (Wilms Tumors) or radiation dosage (≥ 30 Gray).

Under most clinically plausible scenarios, commencing screening at age 35 would be the most cost-effective approach, supporting indirectly COG's previous colonoscopy screening recommendations.[261]

Modelling-based decision-making in colorectal cancer screening

With this thesis, we demonstrated that microsimulations models are useful tools to inform decision-making in CRC screening, providing several scientific contributions, and answering a variety of research questions. The chapters included in this thesis investigated two main points. The first concerned the steps that are necessary to standardize, simplify, and generalize the use of a complex microsimulation model across a quite diverse variety of countries, populations, and screening settings. This point was one of the core goals of the EU-TOPIA project: sharing knowledge, tools, and expertise to help European policymakers in their decisions.[279] The second point concerned the quantification of the potential costs and benefits of CRC screening, aiming to find ways by which CRC health effects and costs could be optimized in the US.

Part 1: The standardization of the MISCAN-Colon model for European countries

Microsimulation modeling is a complex method often used for studying the clinical course of a disease from prescreening stage to deaths. As it can take in consideration various health determinants, factors, states, and transition, modelling has been shown to be a reliable instrument in evaluating the natural history of CRC and inform decision-making in CRC screening.[71] Microsimulation models can provide accurate estimations on the impact on

CRC incidence and mortality of new intervention or policy changes.[69, 70, 160] However, if decision makers want to directly use one of these models, they must have sufficient statistical proficiency to understand the model structure, assumptions, equations (that are at the base of the model), stochastic uncertainty of the modeling results, uncertainty of the model inputs, and data sources.[71] In addition, many of these models are proprietary and not open to be used without the owners' authorization.

In this context, the online tool provided in Chapter 5 can be an important contribution for the policymakers working in cancer screening. The tool is user-friendly and open, but it is currently designed specifically for European policymakers requiring only an account registration. It allows users to upload their country-specific data (using standardized templates), adjust the model, identify the screening scenarios, simulate outcomes of CRC screening in their countries, and download the results. Instructions, model assumptions, and data inputs are provided in a detailed and ordered documentation (downloadable from the tool website). These online materials summarize the steps needed for developing the application, which constitute the first part of this thesis. In Chapter 3, the MISCAN-Colon structure was externally validated against the NORCCAP trial,[239] providing a reliable fundament for designing the architecture of this application. As CRC incidence and mortality differ substantially in Europe,[2, 4] it was necessary to evaluate robustness of the model-specific assumptions (i.e. duration time in each precursors lesions and progression rates from adenoma to CRC; the natural history of CRC) and screening model parameters. In Chapter 2, effectiveness of CRC screening was investigated across quite different countries and screening settings. The effectiveness of gFOBT and FS screening did not vary substantially across European regions. In Chapter 4, the MISCAN-Colon model structure was found robust across three different screening and population settings, indicating that the natural history of CRC (progression rates from adenoma to CRC) might be assumed similar across European countries. The findings provided in Chapters 2, 3, and 4 were essential components that structured the EU-TOPIA evaluation tool. However, lack of published evidence from Eastern European countries is currently limiting the full generalizability of our modelling findings.

Part 2: The impact and cost-effectiveness of colorectal cancer screening

In the US, CRC screening is carried out opportunistically and health care providers are fundamental in reminding patients to undergo screening. Screening participation has also been found strongly associated with health insurance status. This is one of the main health disparities and inequities of concern in the US. The Patient Protection and Affordable Care Act (ACA, Pub. L. 111-148, 2010) was introduced with the objective to improve access to quality health care for all Americans.[194] However, some financial barriers are still present in US for CRC screening. As colonoscopy is defined a diagnostic intervention (rather than preventive), individuals without supplementary insurance may face coinsurance and out-of-pockets costs and decide therefore to not participate in CRC screening.[65] Since 2011,

several bills were presented at the US Congress to remove this barrier (H.R. 4120, H.R. 1070 & S. 2348, and H.R. 1220 & S.624), but all were rejected as no specific economic studies investigated this issue. Chapter 6 of this thesis provided a valuable contribution to this debate. Waiving coinsurance payments may result in a likely favorable balance of health and costs for Medicare. Moreover, it would reduce health disparities across US, affecting directly the Medicare beneficiaries with low socioeconomic status who lack supplemental insurance. Furthermore, CRC screening can be improved for other groups of US citizens, such as those who were recently seen to be at higher risk of developing CRC. Up to 2018, no CRC screening recommendations were indicated in the CF population. Among CCS, screening was recommended only for those treated with APRT (by the US COG). However, in this last case, scientific evidence that supported those recommendations was limited and questioned by several non-US expert groups, such as the Scottish Intercollegiate Guidelines Network and the Swedish Working Group for Long-term Follow-up after Childhood Cancer.[281, 282] Although, the CRC risk in the CF and CCS population is comparable that of individuals with family history of CRC or even with Lynch Syndrome (groups with existing differential CRC screening recommendations),[53, 54] these existing screening recommendations cannot directly be extended to individuals CF and CCS. These groups not only have higher CRC risks, but also a considerably lower life-expectancy that might indirectly reduce potential benefits of screening (i.e. 70% of deaths in CF individuals are related to cardiorespiratory causes, early detection of CRC might not result in avoiding a premature CRC death but only in additional costs and unnecessary treatments).[283] The balance between high CRC risk and low life-expectancy can be taken into account by microsimulation models, as shown in Chapters 7 and 8. Among CCS, COG's current recommendation was unlikely to be the most cost-effective: commencing colonoscopy screening 5 years later can result in a better ratio between costs and benefits of screening. In patients with CF, colonoscopy screening should commence between age 30 and 40 years, depending on whether or not they received a transplantation. In both groups, the optimal age for beginning screening was far from that suggested for individuals with Lynch Syndrome (from age 20 or 25 years),[54] even though the CRC risk could be almost comparable.

METHODOLOGIC CONSIDERATIONS AND LIMITATIONS

In this thesis, MISCAN-Colon model has been used to answer several questions ranging from the natural history of the CRC to the cost-effectiveness and impacts of CRC screening. Microsimulation models (as MISCAN-Colon) are reliable tools, but it is important to realize that good models are only the reflection of the quality of their assumptions. In this thesis, we used several data sources for informing our model, including information from cancer registry, mortality databases, RCTs, and cohort studies. However, some spe-

cific model parameters are still surrounded by uncertainty because not directly observable (i.e. the parameters behind the duration time of the adenoma-carcinoma sequence). We assessed this uncertainty of our model in Chapters 3 and 4. We found that the core assumptions of the MISCAN-Colon model were robust in predicting effectiveness of CRC screening in the average risk population. Evaluating optimal screening among CCS and individuals with CF (population at high risk of developing CRC), we found that several other model inputs presented uncertainty because the data used for informing the model was limited. For instance, model predictions were sensitive to the limited data available on life-expectancy for those populations. This uncertainty affected directly the optimal age to stop screening. As consequence, a more prudent approach was introduced to suggest for stopping screening: it should not be indicated and performed for individuals with less than 10 years of life-expectancy.[66, 284] On the other hand, ages at commencing screening were not sensitive to this modelling input. Those were also robust considering the uncertainty behind the biology underpinning the higher CRC risk (Chapters 7 and 8). This is important for the reliability of the model, but it is also important to realize that additional assessments should be performed when more evidence becomes available. For instance, a recent study has shown that among CCS the prevalence of sessile serrated polyps may be higher than in the average risk population due to prior anticancer treatments.[18] Sessile serrated polyps are believed to be an alternative pathway that may cause the development of CRC. These lesions are often flat making them harder to detect with endoscopy.[22] Currently, MISCAN-Colon model incorporated only the adenoma-carcinoma sequence, believed to cause up to 90% of CRCs. As described in this thesis (Chapters 3, 4 and in Appendix), the model was reliable in predicting outcomes for CRC incidence and mortality considering different level of model validation: internal, external, predictive, and cross-validation (this latter within the Cancer Intervention and Surveillance Modelling Network).[26, 69, 164] As evidence regarding sessile serrated polyps is still limited, it is unclear how this alternative pathway would play a role in predicting the CRC outcomes at population level. It is also important to realize that sessile serrated lesions may also affect effectiveness of FIT screening because they are less likely to bleed and characterized by different molecular features than traditional adenomas. Those hypotheses are based on limited evidence.[22] A RCT is ongoing comparing colonoscopy and FIT screening (results probably available in the next decade)[47] and might provide useful results to assess the effectiveness of FIT screening in detecting sessile serrated polyps. With those future findings (as reported also in the next paragraph) it will be possible to incorporate and validate the sessile serrated pathway into the MISCAN-Colon structure.

FUTURE DIRECTIONS

In the last decades, CRC screening showed great scientific improvements, with many countries deciding to implement CRC screening programs. We expect that the following areas will be important future directions in the field of CRC screening.

Monitoring, evaluating, and improving of CRC screening in Europe

CRC screening was not implemented homogenously across Europe. Existing organized programs differ in terms of target ages, screening interval, and primary test (**Table 1.3.**).[57-61] Furthermore, several countries are facing organizational and financial barriers that limit the uptake of their CRC screening programme and, therefore, its beneficial impacts. In some European countries, population registries are incomplete or outdated, lacking important information for some individuals (i.e. address). In others, human, physical and/or financial resources are insufficient to conduct follow-up investigations for individuals that need it. Simulating future outcomes and costs of CRC screening might help policymakers to plan resources and identify possible changes. However, decision-making is a complex process that includes a careful analysis of the organizational barriers and stakeholders involved. Our future research (next step of the EU-TOPIA project) should investigate standardized protocols that can merge with the microsimulation tool provided in Chapter 5 and assist each policymakers to i) identify organizational barriers and stakeholders, ii) simulate and plan future outcomes and resources, and iii) design feasible country-specific road-maps to overcome the barriers in their CRC screening programmes.

Personalize CRC screening recommendations

In Chapter 7, CRC screening was evaluated for a specific population (recently seen to be at high risk of CRC). Those results informed new screening recommendations in US. Moreover, MISCAN-Colon has previously been used to investigate potential effects of personalizing CRC screening based on family history of CRC in Ontario, Canada (the ColonCancerCheck program).[285] Other risk factors, such as obesity, diabetes, low physical activity, smoking, alcohol, and red meat consumption can be combined for identifying reliable personal risk profiles and targeted CRC screening recommendations. We can use microsimulation models and machine-learning methods to determine how categorizing these risk profiles and which would be their corresponding optimal screening indication.

Effectiveness of FIT screening in CRC high risk groups

In Chapters 7 and 8, the optimal screening strategies were investigated for individuals with CF and CCS, using MISCAN-Colon and taking in consideration population-specific information (i.e. CRC risk and life-expectancy). Until now, only evidence for colonoscopy screening is available. However, this screening modality is invasive and could result in se-

vere complications. CF patients and CCS might benefit from using non-invasive stool-tests (of which FIT is currently the most accepted worldwide). As evidence on FIT performance is still lacking or limited,[286] clinicians could hardly recognize FIT as valid screening modality for these individuals. Our future research should, therefore, evaluate the effectiveness, the benefits, and the cost-effectiveness of stool-based screening for those CRC high risk populations.

Continued model validation

As previously described, model validation is a continue process. It is important to keep testing the structure and the assumptions of MISCAN-Colon against new evidence that becomes available. Two RCTs are ongoing assessing effectiveness of colonoscopy and stool-based screening.[46, 47] Those studies may provide useful information for further validate our model and check different assumptions for its core structure. For instance, MISCAN-Colon model can be tested and augmented assuming separate pathways (adenoma dysplasia, villous aspect, and sessile serrated lesions).

Conclusions and recommendations

Based on the results presented in this thesis we conclude that:

- Effectiveness of gFOBT screening does not vary substantially, across quite diverse European regions and populations (Chapter 2).
- FS screening was evaluated only in RCTs in Europe and its effectiveness appeared similar across different European regions (Chapter 2).
- The MISCAN-Colon was able to replicate CRC incidence and mortality outcomes of the NORCCAP trial (Chapter 3).
- The natural history of CRC (specifically the assumptions on progression rates from adenoma to CRC) might be assumed similar across quite diverse European populations and countries (Chapter 4).
- The MISCAN-Colon model is a reliable tool for informing decisions in CRC screening (Chapters 3 and 4).
- A standardized, open, and user-friendly version of the MISCAN-Colon model can be designed and provided for European policymakers and researchers (the EU-TOPIA evaluation tool; Chapter 5).
- In the US, waiving Medicare coinsurance payments for diagnostic and primary therapeutic colonoscopy is cost-effective, and may contribute to reducing CRC health disparities (Chapter 6).
- Considering the high risk of developing CRC, individuals with CF can benefit from an early initiation of CRC screening, especially those that underwent a transplantation. Moreover, CRC screening in this population is cost-effective (Chapter 7).

- In CCS, colonoscopy screening is cost-effective among those treated with abdominopelvic radiation therapy (≥ 30 Gray; Chapter 8).

Furthermore, our findings support the following recommendations:

- Validated microsimulation models may be useful tools for informing decisions in CRC screening.
- Medicare coinsurance payments should preferably be waived. This policy is expected to have favorable balance of health and cost impact.
- Individuals with CF should consider colonoscopy screening from age 40 years and repeat screening every 5 years.
- Individuals with CF that underwent an organ transplant should commence colonoscopy screening at age 30 or 35, depending on the age at transplantation.
- CCS treated with radiation therapy (≥ 30 Gray) should commence colonoscopy screening at age 35 years as indicated by the previous COG guidelines (released in 2013).