

**CREATING SIMULATED EQUIVALENTS TO PROJECT LONG-TERM POPULATION
HEALTH OUTCOMES OF UNDERSERVED PATIENTS: AN APPLICATION TO
COLORECTAL CANCER SCREENING**

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ABSTRACT

Simulation models can be used to project the impact of interventions on long-term population health outcomes. To project the value of an intervention in a specific population, the model must be able to simulate individuals with similar characteristics and pathways as the population receiving the intervention. We aimed to estimate the long-term colorectal cancer (CRC) outcomes (cancers and deaths averted, life-years gained) associated with receipt of a first CRC screening through the Colorectal Cancer Control Program (CRCCP) among low-income and underserved patients in the U.S. We recalibrate a simulation model previously calibrated based on a real-world mix of insurance and demographic factors for a particular state. We describe our strategy for developing simulated equivalents in terms of demographics, natural history, and CRC screening results for the CRCCP patients and matching these patients to their simulated equivalents. We then project lifetime CRC incidence and mortality with and without intervention.

1 INTRODUCTION

Simulation models can be used to project the long-term outcomes associated with implementing a public health intervention or program at the population level. These models can help to estimate the effectiveness of the specific program in improving health outcomes as compared to one or more control scenarios (e.g., the absence of interventions). This information about the value of the program in the target population can inform decision-making related to potential adaptation or sustainment of the program. However, while simulation can be a powerful tool for evaluating health programs, it is essential that the model be able to simulate individuals whose characteristics (e.g., demographics, level of risk, etc.) and health results (e.g., test results, diagnoses, etc.) reflect those of the actual population receiving the intervention to accurately project their outcomes.

In our case, we aimed to estimate the long-term impact, including cancer cases averted and cancer deaths averted, of a first-time colorectal cancer (CRC) screening provided to patients who are uninsured or underserved through the Colorectal Cancer Control Program (CRCCP), a Centers for Disease Control and Prevention (CDC)-funded program (Joseph and DeGroff 2019). However, our population simulation model was previously calibrated to the full population of a single state, reflecting a diverse mix of patient demographics and insurance status (Hassmiller Lich et al. 2019; Hassmiller Lich et al. 2017; Nambiar et al. 2018). Thus, our model was unlikely to generalize to the CRCCP patients, who are geographically diverse and often face increased barriers to accessing CRC screening due to being uninsured or underinsured. Since patients’ future health outcomes are a function of their demographics and past CRC screening history, we

needed to create simulated individuals with equivalent characteristics and experiences as those of the actual patient population. Another challenge with estimating the effectiveness of this first CRCCP screening in improving CRC outcomes was that we can only partially observe the health trajectories in this population. For example, while data are available on CRC test results, such as abnormal stool test results and detection of polyps during colonoscopy, the types of evidence-based interventions used to provide this screening varied substantially within the CRCCP and data were not available on these variations.

In this paper, we first describe how we addressed these methodological challenges for projecting the outcomes over time specifically within the CRCCP patient population. We explain how we created simulated equivalents that reflect the demographics, natural history, and CRC screening test results of the CRCCP patients, matched the CRCCP patients to their simulated equivalents, and then sampled their long-term CRC outcomes. We then report the effectiveness of the CRC screening provided through this program in averting CRC cases and CRC deaths and adding life-years over these patients’ lifetimes.

2 LITERATURE REVIEW

A digital twin is a virtual representation of a physical object, process, or system that can be used to assess its future outcomes through simulation (Tao et al. 2018; Bjornsson et al. 2020). By modeling the physical system, the digital twin allows for testing potential solutions and evaluating their expected impact in a way that may otherwise not be practically or economically feasible, thus informing decision-making (Bjornsson et al. 2020). Digital twins have been used in diverse fields, such as manufacturing (Tao et al. 2018; Shao and Helu 2020) and healthcare (Barat et al. 2021; Bjornsson et al. 2020; Corral-Acero et al. 2020). Within healthcare, for example, digital twins of individual patients are used to support personalized medicine through the virtual testing of pharmaceuticals and other clinical treatment options (Bjornsson et al. 2020; Corral-Acero et al. 2020), and digital twins of cities are informing public health approaches for addressing the COVID-19 pandemic (Barat et al. 2021).

Although the use of digital twins is becoming more common, there is not yet a standardized definition across fields. That said, the development of digital twins typically depends on having complete, detailed records for the physical objects being replicated which are updated in real-time. As examples, digital twins in warehouse logistics integrate real-time data about staffing and productivity (Shao and Helu 2020), and digital twins in healthcare include comprehensive patient-level data (Barat et al. 2021; Bjornsson et al. 2020).

Building on the concept of digital twins, in this analysis, we aimed to create simulated individuals who match those in our CRCCP patient population as a method to simulate and evaluate their future CRC outcomes which cannot yet be observed. However, our simulated individuals differ from other digital twins in two key ways. First, our goal was to create simulated individuals who match the CRCCP patients in one exact moment – when they decide to participate in the CRCCP by completing their first CRC screening – rather than serve as exact replicas across the lifespan. Second, and relatedly, our available data to create a type of digital twin was more limited. Instead of using complete patient records, we had data on the results of the CRCCP patients’ first CRC screening and limited information on their demographic characteristics and prior personal and family history of CRC. Therefore, we subsequently refer to matched individuals in our simulation model as *simulated equivalents*, rather than *digital twins*, of the CRCCP patients.

Multiple simulation models have been developed and widely used to inform CRC screening and care decisions (Rutter et al., 2016). These models seek to explore various what-if scenarios to inform decisions about how to best improve CRC outcomes. In this analysis, we use our simulation model previously developed to estimate the impact of evidence-based interventions and health policy scenarios on CRC screening, incidence, and mortality (Davis et al. 2019; Hassmiller Lich et al. 2019; Hassmiller Lich et al. 2017; Nambiar et al. 2018; Powell et al. 2020). To apply this model to the CRCCP intervention, we developed simulated equivalents for the patients in the CRCCP population.

3 METHODS

3.1 Simulated Interventions

The CDC’s Colorectal Cancer Control Program (CRCCP) aims to improve CRC screening among age-eligible adults, with the ultimate goal of reducing CRC incidence and mortality, by funding state and tribal organizations to provide and promote screening (Joseph and DeGroff 2019). Grantees partner with clinical providers to provide CRC screening tests to low-income, uninsured, and underinsured patients. In addition, they implement evidence-based interventions, such as client and provider reminders and small media, to promote population-level CRC screening awareness and uptake (Joseph and DeGroff 2019). In this analysis, we focused specifically on CRCCP grantees’ provision of a first-time CRC test to underserved patients as the intervention. We included two cohorts within the CRCCP population – 1) those who underwent a screening colonoscopy (“Screening Colonoscopy Cohort”), and 2) those who completed a stool test (e.g. fecal immunochemical test or FIT) and, after testing positive, underwent the recommended follow-up diagnostic colonoscopy (“Diagnostic Colonoscopy after Positive Stool Test Cohort”). For each cohort, we compared the CRCCP patients’ outcomes with and without this single CRC test. The CRCCP has been closely evaluated and monitored for its effectiveness in improving CRC screening since its inception (Hannon et al. 2019; Hannon et al. 2013; Nadel et al. 2019; Sharma et al. 2021); however, this is the first time that simulation is used to project the longer-term impacts of this program.

3.2 Target Population

Patients who are eligible to receive a CRC screening test through the CRCCP include those with an annual household income less than or equal to 250 percent of the federal poverty level (equivalent to \$66,250 for a family of 4 in 2021, for example) (U.S. Department of Health & Human Services 2021). In addition, patients are either uninsured or underinsured, meaning that their insurance did not cover preventive services or they were unable to afford co-pays or deductibles for their preventive services (Joseph and DeGroff 2019). As of February 2021, the CRCCP awards 35 grantees, including 20 states, 8 universities, 2 tribal organizations, and 5 other organizations, which are located across all regions of the U.S. (CDC 2021).

3.3 Simulated Cohorts

Between 2009 and 2020, a total of 82,973 unique patients received a CRC test as part of the CRCCP. For this analysis, we selected two cohorts of these patients based on testing modality (screening colonoscopy or stool test plus diagnostic colonoscopy) who were between ages 45 and 75 (i.e., recommended ages for CRC screening) (U.S. Preventive Services Task Force 2021) and at average risk for developing CRC (i.e., reported no personal history of polyps or CRC). We excluded patients with missing data (e.g. gender), those with history of CRC or polyps, and those who reported information indicating that the CRC test may not be due to screening (e.g. currently experience symptoms). Lastly, we excluded individuals with prior screening history, resulting in 62,682 individuals. Of these 22,880 screened with colonoscopy first and 39,802 with FIT/FOBT first.

3.3.1 Screening Colonoscopy Cohort

For our first cohort, we included patients who screened specifically by colonoscopy for their first CRC screening as part of the CRCCP. After excluding patients who did not have a final or conclusive diagnosis, our final cohort is comprised of 22,605 first-time colonoscopy screeners, with a median age of 54. Table 1 presents the demographic characteristics of this cohort.

3.3.2 Diagnostic Colonoscopy after Positive Stool Test Cohort

For our second cohort, we identified 39,802 CRCCP patients who screened for the first time using a stool test, such as FIT or fecal occult blood test (FOBT). We then focused specifically on the individuals within this group who had a positive FIT/FOBT result, underwent the recommended follow-up diagnostic colonoscopy, and had a final diagnosis available from their diagnostic colonoscopy, providing a final cohort size of 2,802 patients. The reason that we did not include patients who either received a negative FIT/FOBT test result or received a positive result but never completed their diagnostic colonoscopy is that these events do not directly impact their health trajectories. While these events may potentially affect these individuals’ future screening adherence, only the possible detection of polyps and CRC during the diagnostic colonoscopy will affect their natural history. This cohort of 2,802 individuals who completed a diagnostic colonoscopy after a first-time FIT/FOBT screening has a median age of 56. The demographic composition of this cohort is presented in Table 1.

Table 1: Demographic characteristics of the two simulated cohorts of CRCCP patients.

Characteristic		Screening Colonoscopy Cohort		Colonoscopy after Positive FIT/FOBT Cohort	
		N	%	N	%
Total		22,605	100.0	2,802	100.0
Sex	Female	14,718	65.1	1,858	66.3
	Male	7,887	34.9	944	33.7
Race	Black	4,637	20.5	339	12.1
	White	14,406	63.7	2,144	75.4
	Other	3,562	15.8	349	12.5
Ethnicity	Hispanic	6,410	28.4	1,180	42.1
	Non-Hispanic	16,195	71.6	1,622	57.9

3.4 Model Description

Our CRC simulation model is an individual-level microsimulation model run using Anylogic software, version 8.5.2. The model consists of three components: 1) polyp incidence and development, 2) individual health states, and 3) screening and surveillance. Figure 1 summarizes the different model components and highlights which parts of the model were modified specifically for this analysis. In our model, individuals are simulated from birth until death from either CRC or other non-CRC natural causes. During their lifespan, individuals can develop polyps, which may progress from non-cancerous to cancerous as the individuals transition within and across health states. The implementation of interventions, such as a colonoscopy screening provided through the CRCCP, can change individuals’ natural history by detecting and removing polyps before the individuals would have otherwise become symptomatic. Likewise, the completion of a diagnostic colonoscopy following an abnormal FIT/FOBT test provided through CRCCP can also alter individuals’ natural history. Details about the model structure, parameters, and assumptions have previously been reported (Davis et al. 2019; Hassmiller Lich et al. 2019; Hassmiller Lich et al. 2017; Nambiar et al. 2018; Powell et al. 2020). In this paper, we adapted the model as described in Figure 1. We

removed the statistical model previously used to determine how individuals screen (e.g., by which modality). We also did not model individuals’ type of and access to insurance. Instead, we focused specifically on the impact of their first CRC testing.

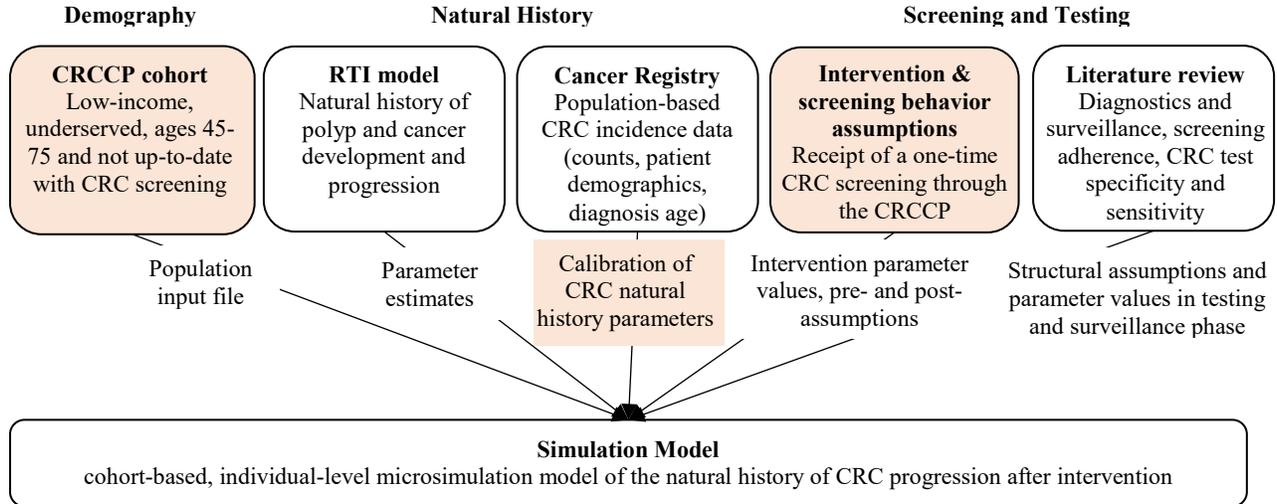


Figure 1: Components of the CRC simulation model. Shaded sections indicate those parts of the model that we changed specifically to be able to simulate the long-term outcomes of the one-time CRCCP intervention.

3.5 Model Calibration

To start the calibration process using our CRC simulation model, we first assessed how accurately our model was able to predict polyp detection and CRC incidence for our cohort of CRCCP colonoscopy screeners. Although individuals in both cohorts included in this analysis may have their natural history changed by undergoing a colonoscopy, we calibrated our model using only the *screening* colonoscopy cohort for two reasons. First, our diagnostic colonoscopy cohort is relatively small in size compared to the screening colonoscopy cohort (2,802 vs. 22,605 individuals, respectively). Second, there is a potential for bias in the data when a colonoscopy is triggered due to a positive FIT/FOBT test. For example, an abnormal FIT/FOBT may result in increased likelihood that polyps are detected during a diagnostic colonoscopy, as compared to a screening colonoscopy, due to providers’ awareness of the stool test result (Ebner and Kisiel 2020; Kligman et al. 2018). Thus, we calibrated our model to the colonoscopy results of the screening cohort in which providers have no prior knowledge of the potential presence of polyps or cancer.

For the screening colonoscopy cohort, our previous model (which adjusts for age, sex and race) well underestimated the actual proportion of polyps and cancers based on their CRCCP results. Specifically, the proportion of polyps and cancers among these CRCCP patients was about 0.4184 and 0.0050, respectively; however, our simulated results showed proportions of 0.1051 and 0.00329, respectively. Our model likely underestimated the colonoscopy outcomes in this cohort because it was previously calibrated to cancer incidence in the full state population of North Carolina using the North Carolina Central Cancer Registry (Hassmiller Lich et al. 2019). In contrast, the CRCCP patient population is a U.S.-wide low-income and underserved population with low CRC screening rates.

Due to the large differences between the actual and simulated results, our first step was to calibrate the model to the colonoscopy findings for our CRCCP screening colonoscopy cohort. We aimed to identify the best combination of multipliers to match the actual CRCCP data for three parameters - 1) individual risk factor, 2) incidence rate, and 3) transition rate from polyp to cancer. One multiplier is associated with each of these three parameters. We focused on these three specific parameters as they drive incidence and polyp progression toward cancer in the model. The risk factor is associated with how susceptible a person is to

ever developing polyps. The incidence rate is associated with the likelihood of developing a polyp based on a person’s age. Finally, the third parameter affects the rate at which non-cancerous polyps become cancerous. We focused on finding multipliers for the original parameters as extensive time-based clinical data about CRC incidence and progression is not available for this population, and this allowed us to maintain interactions between sex, age, and race that had been calibrated in the population-level model.

We used Latin hypercube sampling (LHS) to achieve our calibration objective. LHS is a sampling method (Mckay et al. 1979; Helton and Davis 2003) in which a grid of all possible variables is created and samples are selected from non-overlapping intervals across each dimension. In 2-dimensions, for example, this results in one sample in each row and column. This method allows for coverage of the entire parameter space with a smaller number of samples. We chose LHS as the simulation model runs are computationally expensive. The full calibration process is described in Figure 2. The main objective was to reduce the initial sample space after obtaining a batch of samples at each step by identifying the concentration of points giving us the lowest Sum of Squared Errors (SSE). The SSE was calculated as the sum of squared errors between the average proportion of polyp and cancer rates of the simulated versus true data. Our stopping criterion was to find a combination of multipliers that gave predicted proportions of polyps and cancers within +/- 1% of the actual values. To account for randomness in the simulation model, each LHS sample was run 30 times and average values were obtained. We selected a total of 30 replications due to computationally expensive runs and to also ensure a halfwidth of less than 0.005 and 0.0005 around the mean of the estimated proportions of polyps and cancers in the simulated population, respectively.

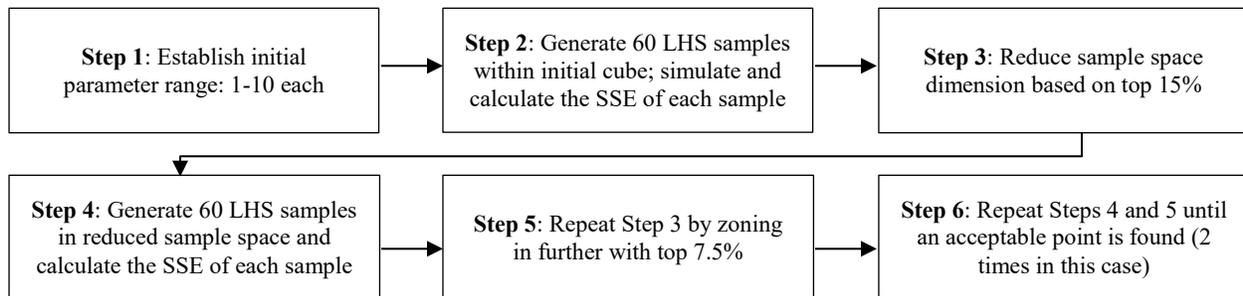


Figure 2: Model calibration process.

After calibration, our model successfully matched the CRCCP data for the screening colonoscopy cohort based on our criteria; simulated results now showed proportions of about 0.4171 and 0.0050 for both polyps and cancers, respectively. This is less than a one percent difference in both the simulated proportion of detected polyps and the simulated proportion of detected cancers compared to the actual results. Computationally, based on the point combination, 30 replications took between 1 and 10 minutes to run.

3.6 Simulated Equivalents and Matching Strategy

To assess the long-term impact of the first-time CRC testing intervention provided through the CRCCP in our two CRCCP cohorts and stay true to the individuals’ clinical results, we created simulated equivalents for each individual in the CRCCP cohort. The process of creating simulated equivalents is fully described here using the CRCCP screening colonoscopy cohort. However, we used the same process to create simulated equivalents for the diagnostic colonoscopy after positive FIT/FOBT cohort since we directly simulated the diagnostic colonoscopy, but not the stool test itself since stool tests do not alter natural history. Figure 3 presents the full process we used to create the simulated equivalents and then match the CRCCP screening colonoscopy patients to their simulated equivalents.

Our initial step in constructing simulated equivalents was to identify unique combinations of demographic characteristics for each cohort (see Steps 1 and 2 in Figure 3). We focused specifically on the race, gender, and age of the individuals at the time of receipt of their baseline CRCCP testing. Using these

three demographic factors for our screening colonoscopy cohort of 22,605 individuals, there were a total of $T=183$ combinations of individuals with unique demographic characteristics (e.g., white male screened at age 50) to simulate. Identifying these combinations allowed us to reduce both the number of individuals we needed to track and the number of simulations that we needed to run because we were able to pool simulated individuals to sample from who shared the same characteristics.

After creating the reduced cohort of T combinations of individuals (i.e., individual types) sharing the same demographic information as our CRCCP screening colonoscopy cohort, we simulated their lifetimes with and without receipt of the CRCCP screening colonoscopy numerous times as shown in Step 3 in Figure 3. We created up to $R = 1$ million replications of each individual type in the set T . Replications that did not reflect reality were discarded. For example, we removed replications where simulated individuals died before their age when they received the CRCCP intervention, or where they were diagnosed with cancer prior to receipt of the intervention. Then, in Step 4, we chose simulated equivalents – that is, simulated individuals who in addition to matching demographically shared the correct colonoscopy result as their real counterpart’s CRCCP colonoscopy result. We grouped the colonoscopy results into the following categories: normal with no polyps detected, polyps detected but not cancerous, and diagnosed cancer. We ran up to one million replications for each individual type in set T to ensure that we had enough to sample the desired number of simulated equivalents for each person in the original cohort.

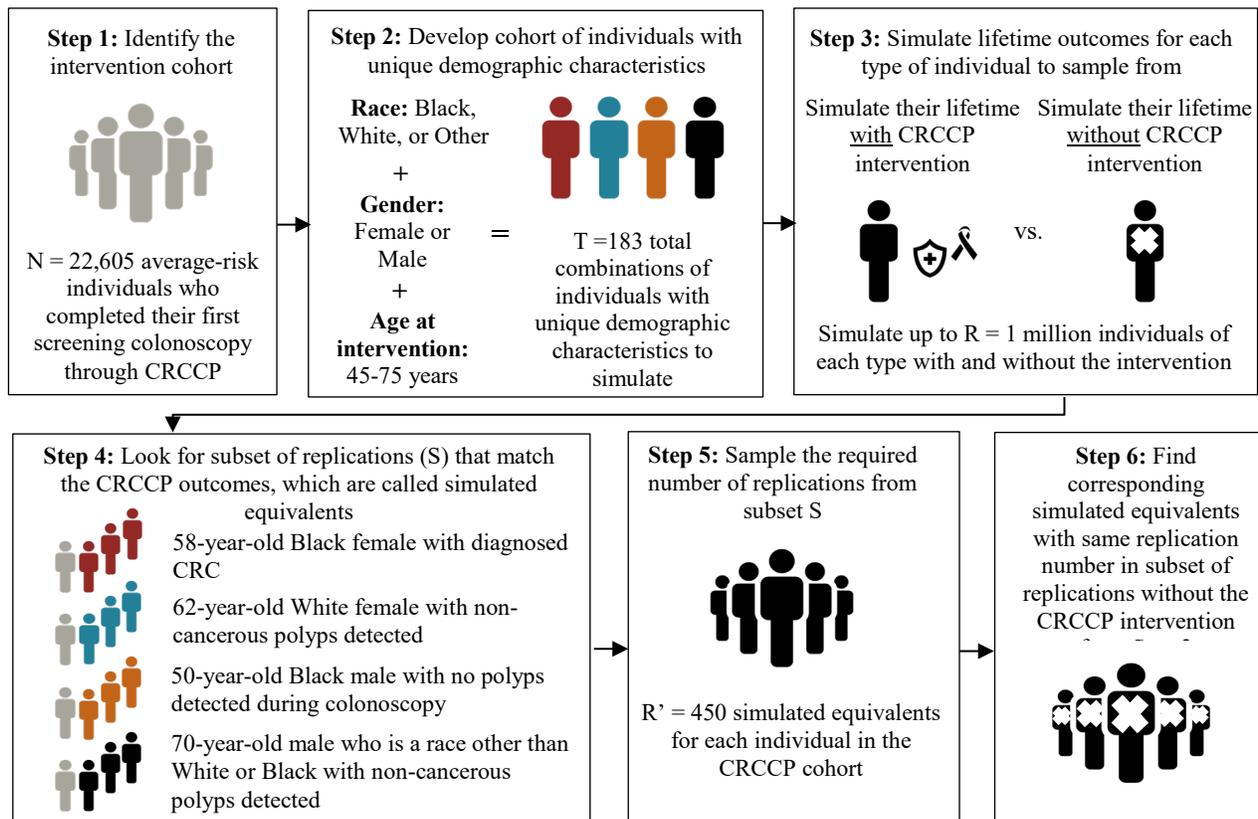


Figure 3: Process for creating simulated equivalents and matching CRCCP patients to their equivalent for our screening colonoscopy cohort. We used the same steps to simulate equivalents for our diagnostic colonoscopy after positive FIT/FOBT cohort.

To estimate this cohort’s long-term outcomes, we matched individuals in the CRCCP screening colonoscopy cohort to their simulated equivalents with the correct colonoscopy result in Step 4 and then sampled the required number of replications in Step 5. The number of replications for the CRCCP screening

colonoscopy cohort (n = 450 simulated equivalents per cohort individual) was established to produce results that were within 1% of the total number of cancers in the population. To estimate the impact of the CRCCP screening colonoscopy intervention compared to no intervention, we identified the corresponding simulated equivalents with the same replication number in the set of no CRCCP intervention replications (Step 6).

3.7 Outcomes Simulated

For both of our CRCCP cohorts, we report the number of cancer cases averted both overall and by stage compared to no CRC testing across the individuals’ lifetimes. We also report the number of CRC deaths averted, and the number of life-years gained, of the CRCCP intervention compared to no intervention.

4 RESULTS

4.1 Screening Colonoscopy Cohort

Using the simulated equivalent method, we simulated different possible CRC related pathways for the screening colonoscopy cohort while being true to their current diagnosis and assessed the potential impact of the screening colonoscopy intervention compared to doing nothing over their lifetimes. Table 2 summarizes the number of CRC cases and deaths expected over these individuals’ lifetimes without intervention, and the number of cases and deaths averted as a result of the CRCCP screening colonoscopy intervention. All reported incremental changes in outcomes are statistically significant and the 95% confidence intervals are shown for each outcome.

Table 2: CRC cases and deaths over the simulated individuals’ lifetimes without intervention, and the expected change associated with the CRCCP screening colonoscopy.

	No intervention-- status quo (Mean)	No intervention-- status quo (95% CIs)	Incremental change compared to status quo (Mean)	Incremental change compared to status quo (95% CIs)
Total CRC cases	1,494.18	(1490.78, 1497.59)	-791.71	(-794.23, -789.19)
CRC cases by stage at diagnosis				
Stage 1	160.83	(159.69, 161.97)	-40.95	(-42.57, -39.33)
Stage 2	217.49	(216.08, 218.89)	-90.44	(-92.17, -88.71)
Stage 3	603.02	(600.85, 605.18)	-342.34	(-345.08, -339.60)
Stage 4	512.85	(510.81, 514.90)	-317.98	(-320.51, -315.45)
CRC deaths	698.16	(695.67, 700.65)	-407.87	(-409.75, -405.99)

In the absence of the CRCCP screening colonoscopy, and assuming no future CRC screening or surveillance other than diagnostic testing in the case of CRC symptoms, we estimated a total of 1,494 cancers over the lifetimes of the 22,605 individuals in this cohort. Of these CRC cases, 74.7 percent would be diagnosed at advanced stages (i.e., stage 3 or 4), which are associated with higher mortality. In this cohort, we projected a total of 698 CRC-specific deaths, which means that nearly half of the diagnosed cancers would result in a CRC death. The cohort was projected to have a combined 8,533 life years lost due to cancer without intervention, with an average of 12.2 years lost per individual who died due to CRC.

Compared to no intervention, the one-time CRCCP screening colonoscopy led to substantially improved health outcomes. With the screening colonoscopy, there would be an estimated 792 CRC cases averted; of these averted cancer cases, more than 300 would be advanced-stage cancers. The number of cancer-related deaths consequently averted was 409, which was associated with 5,132 (+/- 27.56) life years lost averted. Therefore, receipt of the CRCCP intervention is associated with reduced CRC diagnoses, the

shifting of remaining cancer cases from more advanced to earlier stage cancers, lower CRC mortality, and longer length of life, compared to no intervention.

In addition to capturing the overall and incremental change in the numbers of CRC cases and life years, we assessed the distribution of CRC cases averted each year from the time of receipt of the colonoscopy. Figure 4 shows the cumulative number of cancers averted by the number of years after receiving the colonoscopy. The negative numbers in early years reflect cancers detected due to screening that would have gone undetected until later years. Investment in providing this CRCCP screening colonoscopy quickly pays off after approximately 3 years, the point at which the removal of polyps through colonoscopy begins to prevent the development of cancers. Additional cancer cases are averted each year until approximately 40 years post-intervention when the trend starts stabilizing with no additional cancers being averted.

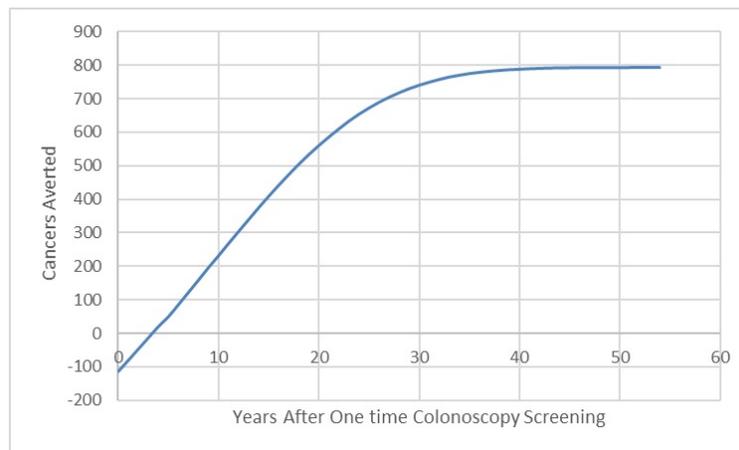


Figure 4: Cumulative CRC cases averted by years after receipt of the one-time CRCCP screening colonoscopy (N=22,605 patients).

4.2 Diagnostic Colonoscopy after Positive Stool Test Cohort

We replicated the simulated equivalent method for this cohort and outputted similar outcome measures as the screening colonoscopy cohort to identify the impact of the diagnostic colonoscopy after a positive FIT/FOBT. Table 3 summarizes the average number of CRC cases and deaths without the stool test plus diagnostic follow-up, assuming no future screening tests, and the expected change with the CRCCP intervention. All presented values are statistically significant at the 5% significance level with 95% confidence intervals shown, except for stage 2 averted cancers where the interval contains zero.

In the absence of the FIT/FOBT and follow-up diagnostic colonoscopy, an estimated 255 CRC cases would be found over the lifetime of this cohort. The majority (78.1%) of these CRC cases would be diagnosed at stage 3 or stage 4, similar to the findings from the screening colonoscopy cohort. We projected that the cancers detected in this cohort without intervention would result in 121 deaths. This would lead to a combined 1,639 life years lost with an average of 13.5 life years lost per individual who died of cancer.

With the diagnostic colonoscopy following the abnormal FIT/FOBT test, 115 (+/- 1.2) CRC cancers are expected to be averted; of these averted cases, 61 would be stage 3 cancers and 70 would be stage 4 cancers. It is important to note that the incremental change in stage 1 cancers is a positive value, indicating that more cancers are detected early before progressing to advanced stage cancers. The number of stage 2 cancers, in contrast, is the same before and after the intervention. Approximately 63 CRC deaths would be averted as a result of the FIT/FOBT plus diagnostic colonoscopy, with an associated number of life years gained of 712. Therefore, there is also a large benefit of investing in the CRCCP intervention for this cohort compared to the status quo, with meaningful differences in the ability to detect polyps and cancers in the earliest possible stage.

Table 3: CRC cases and deaths over the simulated individuals’ lifetimes without intervention, and the expected change associated with the CRCCP diagnostic colonoscopy after positive FIT/FOBT.

	No intervention-- status quo (Mean)	No intervention-- status quo (95% CI’s)	Incremental change compared to status quo (Mean)	Incremental change compared to status quo (95% CI’s)
Total CRC cases	255.24	(253.56, 256.92)	-115.08	(-116.24, -113.92)
CRC cases by stage at diagnosis				
Stage 1	22.51	(22.03, 23.00)	16.34	(15.53, 17.15)
Stage 2	33.25	(32.63, 33.87)	0.037	(-0.83, 0.900)
Stage 3	103.39	(102.27,104.52)	-61.13	(-62.44, -59.83)
Stage 4	96.09	(95.07, 97.11)	-70.32	(-71.46, -69.18)
CRC deaths	120.95	(119.80, 122.10)	-63.11	(-63.94, -62.28)

In Figure 5, we show that it takes, on average, 6 years for the CRCCP FIT/FOBT plus diagnostic colonoscopy to begin averting CRC cases, which is approximately a 3-year longer timeframe than for the screening colonoscopy cohort. This could be due to a higher number of cancers detected in this group per capita (0.0411) as compared to the screening colonoscopy group (0.0350). The stool test group was slightly older, and as mentioned earlier diagnostic colonoscopies after positive FIT/FOBT may result in increased likelihood that polyps are detected (Ebner and Kisiel 2020; Kligman et al. 2018). As seen with the screening colonoscopy cohort, cancers continue to be averted for approximately 40 years, demonstrating the long-term impact of this one-time CRCCP intervention.

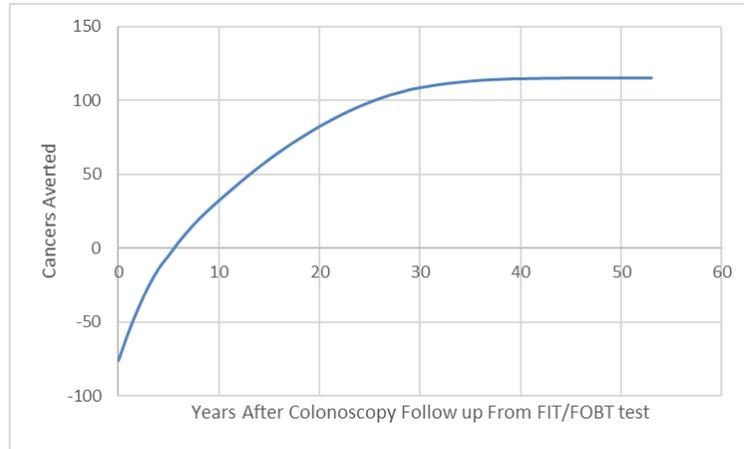


Figure 5: Cumulative CRC cases averted by years after receipt of CRCCP diagnostic colonoscopy after a positive FIT/FOBT (N=2,802 patients).

5 CONCLUDING REMARKS

By assigning simulated equivalents to members of both of our CRCCP modality-based cohorts, we were able to replicate the CRC-related health status of each individual. We were also able to assess the impact of the screening colonoscopy intervention and the FIT/FOBT testing followed by a diagnostic colonoscopy compared to no intervention for each respective cohort. Both intervention types proved to be effective in averting cancers and reducing both the number of deaths and life years lost by more than half over the

individuals' lifetimes. For this application, one aspect to keep in mind is that both cohorts were assumed to be screening naive and so the impact observed would be lessened for a cohort with prior CRC screenings.

Regarding our simulation model, we calibrated three natural history parameters based on the real clinical results of the screening colonoscopy cohort. This was especially important given that the CRCCP specifically aims to provide CRC screening to patients who are low-income, underinsured or uninsured, and thus experience higher than average barriers to seeking preventive care. If this model is used to project the long-term health outcomes of another cohort with different screening behaviors, access to care, or known cancer/polyp rates, we would need to revisit these parameters and similarly re-calibrate our model to match the new cohort's specific demographic characteristics and clinical results.

In general, the simulated equivalent method proved to be effective and can be extended to include past screening history and/or other aspects relevant to simulating a cohort. Planned future work includes estimating the quality-adjusted life years (QALYs) gained and cost-effectiveness of the CRCCP intervention for both cohorts compared to no intervention. We also plan to estimate these same outcomes for the full CRCCP population, which includes patients who also received FIT/FOBT or colonoscopy but did not follow-up on these tests and/or do not have a confirmed diagnosis. Informed assumptions will be made to handle these cases to estimate the full impact of CRC testing provided through the CRCCP.

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