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DECISION TREE FRAMEWORK FOR SELECTING EVIDENCE-BASED COLORECTAL CANCER SCREENING INTERVENTIONS USING METAMODELS

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ABSTRACT

Colorectal cancer (CRC) is the third leading cause of cancer-related death in the U.S., despite being largely preventable through screening. Interventions such as mailing fecal immunochemical tests (FIT) or sending patient reminders have shown varying success in increasing screening rates. Simulation modeling has played a key role in estimating the impact of these interventions on long-term health outcomes by representing the natural history of CRC. Using a simulation model of CRC, in this work, we developed a metamodeling-based decision tree to help clinics and health systems select CRC screening interventions that best match their population. Our approach uses estimates of intervention effectiveness based on pre-intervention screening levels, eliminating the need for users to assume how an intervention will impact outcomes. By tailoring recommendations to population characteristics and baseline screening rates, the decision tree supports data-driven decisions to improve CRC screening and, ultimately, population health.

1 INTRODUCTION AND MOTIVATION

1.1 Colorectal Cancer

Colorectal cancer (CRC) is the third most common cause of death by cancer for men and the fourth most common cause of death by cancer for women in the United States (Siegel et al. 2024). Numerous studies have shown that increasing CRC screening can significantly improve health outcomes, by preventing death and detecting precancerous polyps before they become cancerous (Mandel et al. 1993; Shaukat et al. 2013; Cheng et al. 2021). Average-risk individuals ages 45-75 are recommended to be screened for CRC using modalities including routine colonoscopy or a fecal immunochemical test (FIT). If someone screens with FIT and the result is negative, no further action is needed until the next annual screening. However, if the FIT result is positive, a diagnostic colonoscopy is recommended to locate and remove any polyps. Alternatively, individuals may undergo a routine screening colonoscopy, which allows for both detection and removal of polyps in a single procedure. Once screened, individuals are considered to be up-to-date with CRC screening: 10 years for colonoscopy and 1 year for FIT. (U.S. Preventive Services Task Force 2021). As of 2021, only 72.2 percent of age-eligible individuals were up-to-date with CRC screening nationally (Cox et al. 2021).

1.2 Screening Interventions

Interventions are strategies implemented to improve health outcomes within a target population. There is a substantial evidence base demonstrating the effectiveness of many different types of interventions in increasing CRC screening uptake in age-eligible populations (Dougherty et al. 2018; Young et al. 2019; Davis et al. 2018). Each intervention typically involves a cost and yields a certain level of effectiveness, usually compared to usual care (no intervention). Ideally, the most desirable interventions are those that

are highly effective while remaining low in cost.

Dougherty (2018) compares 73 different clinical trials to assess the effectiveness of various interventions on specific populations. They evaluated six individual interventions as well as combined approaches. Risk ratios were computed by comparing the number of individuals that screened before the intervention (under usual care) to those who screened during the intervention, relative to the total population. These risk ratios varied across trials due to differences in population demographics, sizes, and levels of acceptance to screening recommendations. This study demonstrates that selecting an appropriate intervention is not a straightforward process. Another study applied the Exploration, Preparation, Implementation and Sustainment (EPIS) framework to describe how interventions are selected, prepared and implemented in clinical settings. This process underscores the complexity of selecting an intervention tailored to a population's current screening levels and barriers (Ferrari et al. 2023). More recent work has focused on creating causal-loop diagrams to illustrate the complexity of factors influencing the selection and implementation of interventions within populations. These causal-loop diagrams highlight how variables such as cost dynamics, sustainability challenges, and the complexities of screening contribute to the decision-making process, as well as the overall costs and long-term sustainability of an intervention (Cancer Control Pop Sim 2025). Overall, these findings emphasize the need for more sophisticated decision-making tools, as results for the same intervention varied considerably.

1.3 Evolution of Simulation Modeling to Inform Intervention Selection

Our goal with this work is to build on previous simulation work done to estimate population-level health outcomes and help stakeholders make data-driven decisions related to interventions. In this section, we will briefly discuss the evolution of this work over time. The previous work done to model CRC health outcomes is a necessary precursor to this work, and the results motivate the current approach. The NC-CRC (North Carolina Colorectal Cancer) Simulation model is a validated tool designed to estimate long-term health outcomes for a given population under different screening scenarios (e.g., usual care, mailed FIT outreach, policy change, etc.) (Koutouan et al. 2021). The NC-CRC model uses a discrete-time microsimulation approach to represent colorectal cancer development and screening behaviors at the individual level, enabling detailed tracking of disease progression and the effects of different interventions over time. Using data on cancer incidence and natural history progression timelines, and age and stage specific survival probabilities, the model simulates the development and growth of polyps and CRC over time at the individual level. The model simulates the potential for individuals to develop one or more adenomas, incorporating growth patterns and transition probabilities based on lesion size and cancer stage, which in turn shape the likelihood of CRC detection and probability of survival dependent on age, race and sex under varying screening strategies. These individual level outcomes can then be used to generate population level outcomes. The model relies on multiple input sources, with two key inputs being: (1) a population of individuals who are age-eligible for CRC screening, and (2) baseline CRC screening rates within that population. It produces a range of health outcomes, including the number of CRC cases and deaths, as well as the estimated life years lost - defined as the difference between an individual's actual lifespan and their expected lifespan had they not died from CRC. While the natural history of CRC remains unchanged in the model, health outcomes can be improved through intervention implementation of an intervention. By running the model under baseline screening levels and then re-running it with increased screening rates associated with a specific intervention, we can evaluate the potential improvements in outcomes that would result if the higher screening level were achieved (Koutouan et al. 2021).

The NC-CRC simulation model has been used to answer a range of research questions related to CRC screening, including: the impact of screening interventions and insurance expansion on health outcomes and costs (Lich et al. 2017; Davis et al. 2019; Lich et al. 2019), the level of intervention and associated costs needed to reach national screening targets (Hicklin et al. 2022), and the impact of interventions on addressing screening gaps in prioritized populations (Powell et al. 2020). Additionally, the NC-CRC model results were used to create a decision-making tool that walked users through exploring the expected

health and financial impact of different interventions for a population of Oregon Medicaid enrollees or a population of North Carolina residents (O'Leary et al. 2023). While this decision tool helped users understand the impact of intervention choice on health outcomes and associated costs across subgroups (e.g., by age or race), some users noted limitations due to the tool's inclusion of only a few interventions, focus on two US states, and inability to adjust the baseline characteristics to reflect their local population. This feedback highlighted the need for a more adaptable decision support tool capable of adjusting to any population and intervention type, motivating our development of a metamodeling approach.

In order to address stakeholder concerns over limited use of the decision-making tool, we chose to create a unique metamodeling approach which allows us to generate health outcomes for any population and any intervention screening level scenario. Our team recently demonstrated how linear regression, polynomial regression, and random forest metamodels can be used to predict cancer cases and life years lost instantaneously without requiring additional simulation runs (Stanfield et al. 2024). Instead of simulating entire populations, this approach ran 5,000 replications of each individual to create individual-level metamodels for each person type. A total of 180 person types were considered, based on age (45-74), race (Black, White, Other), and sex (Male, Female). The experimental design involved changing six input screening levels based on screening modality (FIT and colonoscopy) and by period (before, during or after the intervention). The intervention period lasted five years, with before and after periods representing the number of years an individual remained age-eligible. A decision tool was created to allow users to input their population's demographic information and current screening (i.e., pre-intervention) levels, target screening levels to achieve during the intervention, and the expected post-intervention screening levels. This tool may be most useful for stakeholders who have a strong understanding of their population's screening levels and the expected impact of an intervention. However, for many stakeholders, this level of certainty is not available, highlighting the need for a more flexible tool to guide intervention selection.

Thus, in this work, we prioritized the design of a metamodel tool that requires minimal user inputs to project intervention effectiveness and downstream health outcomes. Rather than requiring users to estimate the effectiveness of an intervention themselves, our approach only requires knowledge of the population's current screening rate and basic demographic information. Using these inputs, based on our simulations, we generate individualized metamodels and build a decision support tool in the form of a decision tree. This tool recommends the most suitable intervention based on the user's context and can be tailored to minimize cancer cases, life years lost, or overall costs. Here, we describe the development of the tool and apply it specifically to interventions to support uptake of CRC screening by stool testing. We assume that FIT screening during an intervention depends on baseline screening behavior. Our goal was to develop the framework for this type of metamodel decision tree-based decision support tool, with future work intended to build the tool to incorporate other screening modalities and intervention scenarios.

1.4 Decision Trees for Colorectal Cancer

Decision trees have been used in the context of colorectal cancer with a variety of objectives. Some examples of decision tree applications for CRC-related objectives are: prediction of CRC risk factors (Vanezis et al. 2014), early diagnosis and screening (Khalil et al. 2020), survival prediction (Kwon et al. 2016), treatment response (Hossain et al. 2018), and identification of biomarkers (Wang et al. 2017). While they have been applied to diagnosing and estimating outcomes such as survival prediction and treatment response for the individual, there is much less work in the area of selecting CRC screening interventions using decision trees. Some papers use decision trees to evaluate the cost effectiveness of a given intervention (Rice et al. 2018), and others have compared screening modalities using decision trees (Nur et al. 2025). We add to this work by developing a population-level decision tree to aid users across health settings in identifying the most effective CRC screening intervention based on their population's unique demographics and current screening level. This tool can be used across any population or scenario, making it a powerful resource for guiding evidence-based, context-specific intervention selection in diverse healthcare settings.

2 METHODOLOGY

To create our population-level decision tree, we followed a structured approach. First, we sampled screening level scenarios to input into the simulation model. Screening levels are defined as the proportion of people who are not up to date with screening with a given modality (FIT or colonoscopy). A screening level scenario is a combination of these different screening levels. These scenarios were then run through the model for each intervention, generating metamodels for our outcome of interest, dollars per cancer case averted. After training the individual-level metamodels, we simulated various weights for different person types to reflect diverse population demographics and derive a population-based weighted average of cancer cases averted per unit cost. Finally, using the screening levels, demographic information, and intervention effectiveness estimates in terms of dollars per cancer case averted, we constructed the decision tree.

2.1 Intervention Scenarios Simulated

In this work, we consider a decision between two intervention approaches: mailed FIT and reminders. In a mailed FIT intervention, patients recieve a notification that they are due for screening and will receive a FIT test in the mail to be completed and returned for testing. In a reminders intervention, patients receive an automated call informing them that they are overdue for screening and briefly informs them why screening is important and of their options.

2.2 Sampling for Screening Level Scenarios

We considered nine different screening parameters for each scenario. Each screening parameter had a range of screening levels that could be achieved. For example, FIT_{before} was one of our screening parameters and it could take on screening levels between 0% and 40%, as demonstrated in the literature and shown in Figure 3. The screening parameters considered are listed in Table 1 below.

Table 1: Screening Parameters for Colorectal Cancer.

Screening Parameter	Description
$FIT_{before}, FIT_{during}, FIT_{after}$	The proportion of people who screened with FIT each year before, during or after the 5-year intervention period.
$COLON_{before}, COLON_{during}, COLON_{after}$	The proportion of people not up-to-date with screening that screened with routine colonoscopy, during or after the 5-year intervention period.Note, colonoscopies are offered every five years if an individual is not up-do-date. Once received, and individual is up-to-date for 10 years.
$DIAG_{before}, DIAG_{during}, DIAG_{after}$	The proportion of people who received a diagnostic colonoscopy after a positive FIT test before, during or after the 5-year intervention period.

We focus on CRC screening interventions that aim to increase FIT screening during the intervention period. The extent of this increase depends on the FIT screening level before the intervention. To simplify the model, we made several assumptions regarding routine and diagnostic colonoscopy screening levels. We assume that $COLON_{before} = COLON_{during} = COLON_{after}$ and $DIAG_{before} = DIAG_{during} = DIAG_{after}$. We also assume that $FIT_{before} = FIT_{after}$. In other words, the intervention is assumed to only increase FIT screening during the years of intervention. Note that these assumptions suggest that our estimates for long-term health outcomes are conservative, as we anticipate that in a real world implementation, the intervention would likely have a positive impact on the number of individuals who consistently screen over time (after the intervention) and that increased focus on FIT screening would likely have spill over effects on other screening modalities. However, these secondary effects have not been well documented in the literature. We assume that FIT screening levels range from 0%-40%, routine colonoscopy screening levels range from 0%-80% and diagnostic colonoscopy screening levels range from 0% to 90%. In the model, we assume that once individuals recieve a diagnostic colonscopy, their future screening modality switches to colonoscopy. Routine colonoscopy parameters are incorporated to reflect this change in screening behavior.

Since we made assumptions about screening levels during and after the intervention, we only sample screening parameters before the intervention, (FIT_{before},$COLON_{before}$,$DIAG_{before}$), as follows:

1. Generate N=10,000, 3-dimensional, (FIT_{before},$COLON_{before}$,$DIAG_{before}$), screening vectors.
2. Use k-means clustering to test different number of clusters (n), where $N >> n$.
3. Measure the normalized euclidean distances between each pair of centroids.
4. Select the smallest n such that the normalized euclidean distance is less than .025, which represents sampling values for screening levels that are less than 1% apart.
5. Generate n centroids and use those as our scenarios to be run through the model for metamodel training set.

We tried values of n=500, 1,000, 1,500 and 2,000. The relationship between number of centroids and minimum normalized euclidean distance and the scatterplots of centroids are shown for all n in Figure 1 and for $n = 500$ and 2000 in Figure 2, respectively. Our goal, as outlined in Step 4 of our approach, was to generate a sufficient number of centroids to ensure that the minimum normalized Euclidean distance was less than or equal to 0.025. To achieve this, we selected the 2,000 centroids generated, as this number successfully met the required distance threshold.

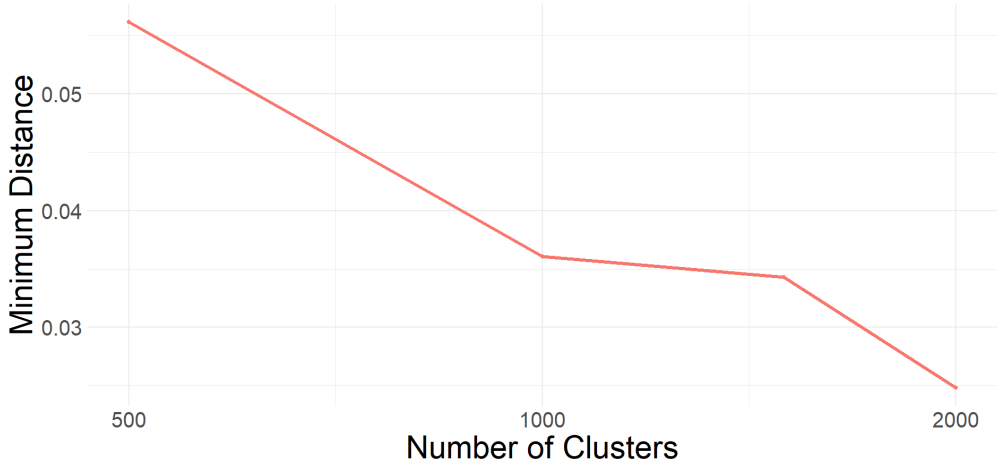

Figure 1: Minimum Distance between two centroids vs number of clusters.

2.3 Assumed Impact on Screening of Different Interventions

After generating 2,000 screening levels (see section 2.2), we determined the values for 8 out of the 9 screening level parameters (FIT_{before},FIT_{after},$COLON_{before}$,$COLON_{during}$,$COLON_{after}$,$DIAG_{before}$,$DIAG_{during}$,$DIAG_{after}$). The next step was to develop a function to estimate the FIT_{during} parameter for each intervention approach. To do this, we incorporated estimates from the literature on intervention effectiveness with respect to screening uptake, which allowed us to directly calculate the FIT_{during} levels within the simulation model.

In Dougherty (2018), risk ratios were calculated based on the proportion of individuals who screened under the usual care (or no intervention) scenario compared to those who received a mailed FIT or reminder intervention. We used these risk ratios to generate curves that illustrate the relationship between usual care and each intervention. Since the highest no-intervention FIT screening was 39.4%, we assumed FIT_{before} screening must be between 0% and 40%. For the mailed FIT intervention, we found that a cubic equation worked best with the data provided. For the reminder intervention, due to a lack of data for screening increases when no intervention screening levels exceed 30%, we applied a linear equation for the FIT_{before} values between 0%-30%. For FIT_{before} values greater than 30% and less than or equal to 40%, we assumed

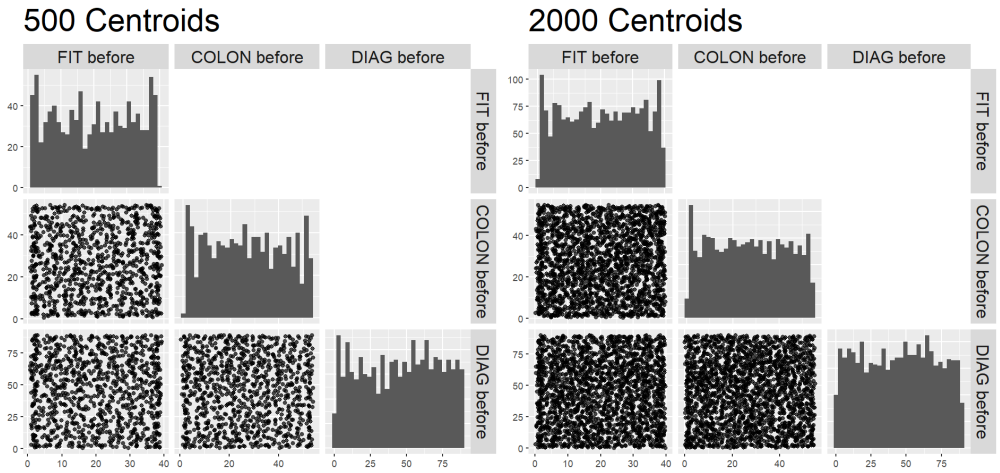

Figure 2: Scatterplots of centroids for $n = 500$ and $n = 2000$.

they had the same level of effectiveness as interventions at 30%.The effectiveness of each intervention was calculated using Equation (1), which quantifies the change in screening levels based on pre-intervention screening data.

$$\text{Risk Ratio} = 1 + \frac{(FIT_{during} - FIT_{before})}{FIT_{before}}, \text{ where} \tag{1}$$

FIT_{before} =no intervention screening levels and FIT_{during} = intervention screening levels

The equations to calculate the intervention level screening for both mailed FIT (2) and reminders (3) are shown below. The corresponding curves are shown in Figures 3 and 4 for the mailed FIT and reminder interventions, respectively. In each figure, the blue dots represent the risk ratios reported in Dougherty (2018), while the orange curves depict the fitted effectiveness functions as shown in equations (2) and (3).

$$FIT_{during} = 9.4103FIT_{before}^3 - 7.6205FIT_{before}^2 + 2.5342FIT_{before} + 0.1506, \ 0 \leq FIT_{before} \leq 40. \tag{2}$$

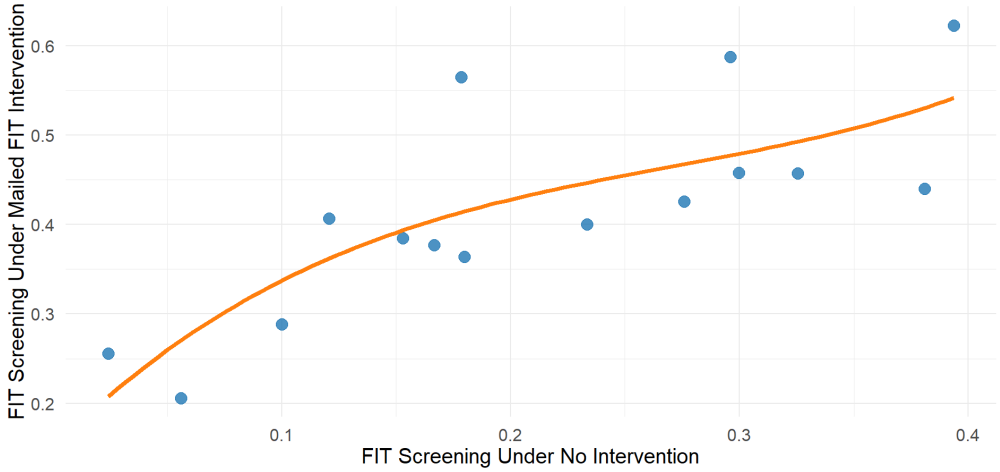

Figure 3: Mailed FIT Intervention Curve

$$FIT_{during} = f(FIT_{before}) = \begin{cases} 0.8212 FIT_{before} + 0.0592 & \text{if } FIT_{before} \leq 30 \\ 1.006 FIT_{before} & \text{if } FIT_{before} > 30 \end{cases} \tag{3}$$

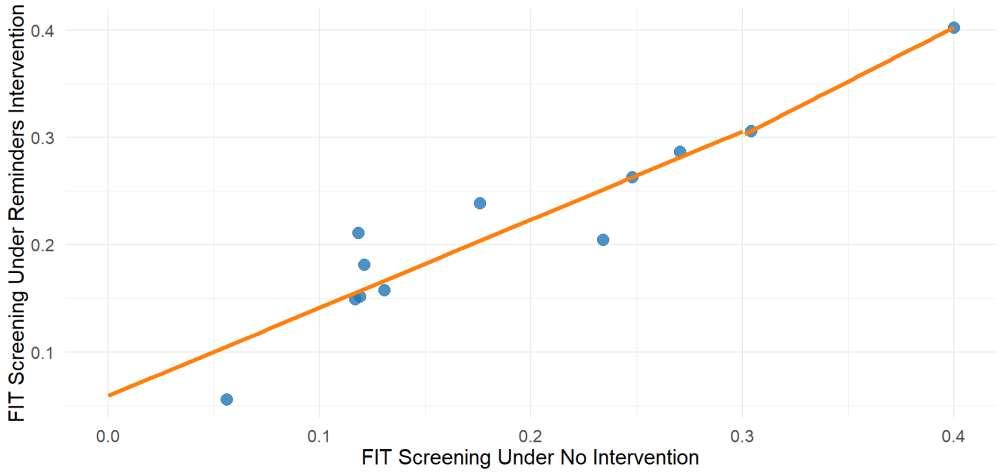

Figure 4: Reminders Intervention Curve

Once we selected n=2,000, we multiplied that by 3 to determine the total number of runs per person type, as each of the 2,000 scenarios needed to be simulated under three scenarios: usual care (no intervention), mailed FIT, and reminders.

2.4 Metamodeling Approach

We used a metamodeling approach to guide our metamodel generation (Stanfield, Mayorga, O'Leary, and Lich 2024). The outcome of interest for developing the decision tree to choose between interventions was the cost of the intervention divided by the number of cancer cases averted (CCA) (dollars per CCA). Cancer cases averted refers to the difference between the number of people who developed cancer with an intervention compared to usual care. We also needed to know the number of FIT tests (Num_{FITS}) and number of diagnostic colonoscopies (Num_{COLON}) to derive costs. We assumed a routine FIT test costs \$15.92 and a colonoscopy costs \$813.49, based on 2024 Medicare reimbusement data, literature on the likelihood of events during colonoscopy (e.g., polyp removal, complications), and clinician input. The cost per cancer case averted was then estimated using equation 4:

$$\frac{Cost}{CCA} = \frac{\$15.92 * Num_{FITS} + \$813.49 * Num_{COLON} + c_i}{CCA} \tag{4}$$

Here, c_i represents the fixed intervention cost per person for intervention i. We estimate $c_{MF} = \$20.84$ for mailed FIT and $c_R = \$1.43$ for reminders. These intervention costs were derived from the literature (Davis et al. 2019). We assumed this cost would be applied to every individual in the target population for screening.

The simulation model was developed using AnyLogic version 8.5.2, a widely used multi-method simulation software. We conducted 6,000 simulation runs, covering all combinations of 2,000 screening level scenarios and 3 intervention strategies (usual care, mailed FIT, and reminders). Following a previously cited metamodeling approach (Stanfield et al. 2024), we simulated 180 person types—defined by age, race, and gender—with 5,000 replications each. For each screening scenario, a simulation run (5000 replications by 180 person types) required approximately 1 to 2 minutes to complete. From our simulation runs, we estimated the number of cancer cases following an intervention, along with the number of

FITs and colonoscopies used during an intervention. We generated cubic regression metamodels for the cost-effectiveness ratios based on these three health outcomes.

2.5 Simulating Demographic Mixes

To generate population-level health outcomes, we considered a weighted average of the individual-level estimates of health outcomes generated by the individual-level metamodels. Since we had 180 person types, we considered 180 weights. The decision tree we trained used screening levels and population level estimates to choose between the mailed FIT and reminders interventions based on the minimum dollars per cancer cases averted. The splits in the decision tree were based on screening levels before the intervention as well as demographic characteristics in the population. Therefore, we could have generated 180 demographic-based weights directly and had the decision tree split based on the proportion of one person type there was in the population. However, we know that clinics or health systems do not always know what proportion of their populations are in each of the 180 person type categories. On the other hand, they typically are required to report demographic characteristics of their population and, thus, are likely to have estimates of the proportion of patients by sex (male, female), race (black, white, other) and age. For age we use the following brackets which align with US Census data: 45-49, 50-54, 55-59, 60-64, 65-69 and 70-74. Therefore, we generated decision trees using the following approach, where the users know their clinic pre-intervention screening levels and their populations sex, race, and age distributions:

1. Randomly generate $M = 1000$ combinations of the following 14 variables shown in Table 2, making sure all of same category sum to 1.

Table 2: Values for Clinic to Select

Variable	Value
FIT_{before}	0–40
$COLON_{\text{before}}$	0–80
$DIAG_{\text{before}}$	0–90
Sex Weights (Male, Female)	Values between 0–1, sum to 1
Race Weights (Black, White, Other)	Values between 0–1, sum to 1
Age Weights (45–49, 50–54, ..., 70–74)	Values between 0–1, sum to 1

2. Assume relationships between sex, race and age are similar to US Census (U.S. Census Bureau 2020), and assume proportion of people in each age within an age bracket are uniformly distributed.
3. Use US Census assumptions to filter the M combinations of 14 weights into the 180 person types.
4. Use before intervention screening levels to estimate 3 health outcomes for each of the 180 person types.
5. Find the weighted average of the 180 person types using 180 generated weights.
6. Train the decision tree using before screening levels and independent demographic characteristics instead of 180 person types.

3 RESULTS

Once we generated the population level estimates, we were able to generate a decision tree as shown in Figure 5 below.

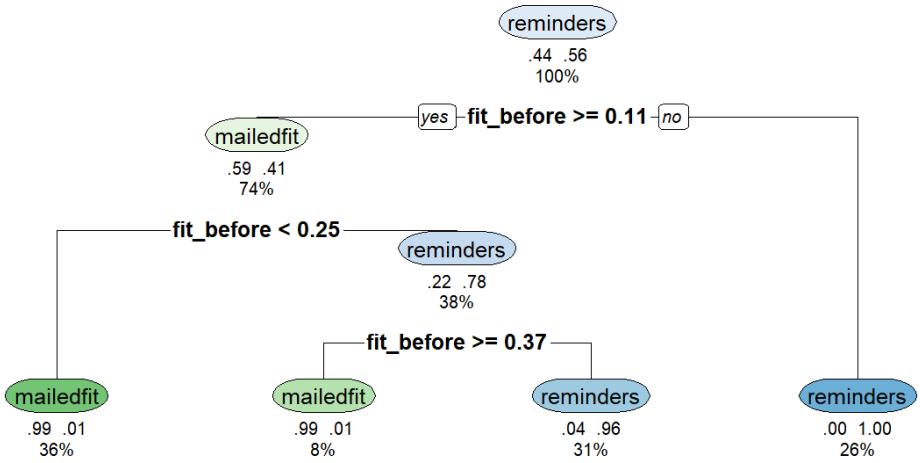

Figure 5: Decision Tree for Selecting Best CRC Intervention for a Given Population

The decision tree illustrates the optimal intervention strategy at each split based on population-level predictors (as shown by the bold inequality) and shows how well the model performed in identifying the intervention that maximized cancer cases averted per dollar. For instance, if a population has a pre-intervention FIT screening rate below 11%, the model recommends reminders as the preferred strategy. Within each terminal node, the value displayed beneath the intervention label indicates the proportion of simulated scenarios (out of $M = 1000$) classified into each intervention group. The number on the left reflects the proportion of scenarios assigned to mailed FIT, and the number on the right reflects those assigned to reminders. For example, in the 1000 scenarios with different screening levels and demographic weights, out of all of the scenarios where FIT_{before} screening was greater than or equal to 11% but less than 25%, the decision tree correctly classified mailed fit as the best intervention in 99% of those scenarios, while 1% were classified as reminders. The percentages below represent the proportion of populations simulated which ended up in each terminal node. Based on this figure, the main driver for intervention selection is FIT screening before the intervention is applied. The other two screening predictors and our demographic predictors did not ultimately determine which intervention was the most cost effective. We could expect that FIT_{before} is the most important of the screening levels, since we assume that the other screening levels remain the same before, during and after the intervention. If we were to remove this assumption about diagnostic colonoscopy and routine colonoscopy screening, these screening levels may influence the decision. Additionally, in this work, our demographic weights represent the proportion of people who are that person type in the population. Therefore, our cancer cases averted per unit cost used to derive the decision tree is a weighted average, instead of a total number based on the number of people of each person type in the population. Calculating cost at the population level instead of the individual level and then averaging with population weights could result in the inclusion of demographic predictors in the decision tree. Finally, our costs were limited to the cost per FIT, the cost per colonoscopy, and the cost of an intervention for one person. If we were to consider the costs associated with cancer care, this may influence our final decision since cancer care costs are age dependent.

4 CONCLUSION AND FUTURE WORK

In this work, based on our validated CRC model, we have trained cubic regression metamodels to estimate the cost-effectiveness of interventions, created synthetic populations to generate population-level estimates, and trained a decision tree to help users make an informed decision on which intervention to choose based on their population such cost per cancer cases averted is minimized. We have used a validated simulation

model to generate metamodels which feed into a decision tree, making the estimates from the simulation interpretable and likely easy to apply for end-users. We learned that with FIT-based interventions, the most important factor to consider when choosing an intervention is the current FIT screening level of the population.

Looking ahead, important areas for future development include integrating additional intervention strategies under consideration (e.g., patient navigation), as well as incorporating other colorectal cancer screening modalities. Another area of future work is to develop more complex metamodels with higher performance to estimate outcomes and train the decision tree while still maintaining some level of interpretability. In this work, we considered 1,000 combinations of inputs to generate the decision trees (see section 2.5) .In future work, we could also consider sensitivity analysis on the number of weights and see how that impacts decision making. To create 180 different weights from assumptions about demographic characteristics (e.g., combinations of age, sex, and race), we assumed that the populations resembled the US Census population. This way, decision makers only needed to know proportions of each sex, race and age bracket independently, and not how they relate to one another (i.e. what proportion of females are black, etc). In the future, we could generate different versions of this based on what the decision makers may know, whether it is assuming these three variables are independent, assuming that they know how two out of the three are related, or assuming they know the proportion of people in each of the 180 person type categories. Lastly, we could expand our model by incorporating additional data from the literature on intervention effectiveness and use it to develop new effectiveness functions. This work establishes a framework for generating decision trees that inform population-level intervention decisions. By translating complex simulation outputs into interpretable, actionable guidance, this approach represents a meaningful advancement in supporting evidence-based public health strategy. While future enhancements can further improve precision and generalizability, the methods developed here already offer a powerful tool for making informed, data-driven decisions at the population level.

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