Risk Prediction and Value of Polygenic Risk Scores in Colorectal Cancer Screening

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Abstract

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Risk prediction models that are based on common genetic variants, known as Polygenic risk Score (PRS), have shown promises to guide personalized screening for colorectal cancer (CRC). Continuous efforts to improve PRS risk prediction are needed for clinical use, and understanding its added value of guiding CRC screening is needed to inform screening guidelines, clinical adoption, and reimbursement decisions.

In Chapter 1, we assessed whether the clinical validity of PRS risk prediction models could be improved by a new approach, called Multiple Polygenic Score (MPS) approach. This approach leverages PRSs developed for other diseases to enrich the risk prediction model. We first used machine learning models and large datasets to develop the MPS risk prediction models. We then used an independent dataset to validate the clinical validity of these models, measured by Area under the Receiver Operating Curve (AUC). Our results showed that MPS was a statistically

significant predictor of CRC risk. Additionally, the increment in AUC associated with the MPS approach was small but was statistically significant. Our findings suggested that the MPS approach is able to improve PRS risk prediction models for CRC, and yet more efficient approaches to improve the AUC in a more noticeable way should be explored in the future.

In Chapter 2, we developed a decision analytic model to simulate the long-term clinical and economic value of a population-level genomic screening to inform CRC screening. The genomic screening interventions included (1) population-level screening for PRS, (2) population-level screening for Lynch Syndrome, a rare but very high penetrance genetic syndrome associated with high risk of CRC (lifetime risk up to 70%), (3) population-level screening for both PRS and Lynch Syndrome. We compared these interventions with standard of care. We found that genomic screening for both Lynch Syndrome and PRS was marginally cost-effective and yet genomic screening for PRS only or Lynch Syndrome only was unlikely to be cost-effective. Our study also found that potential harms associated with false reassurance, i.e., reduced screening due to negative genomic results, could nullify the clinical benefits of genomic screening. The findings suggested that both Lynch Syndrome and PRS are important components of the value of population-level genomic screening. Additionally, our study emphasizes that proper risk communication with patients is critical to reduce the harm of false reassurance. Lastly, we found that the age of genomic screening generated the largest clinical benefits when it was offered at age of 0 years, and delayed genomic screening had a greater negative impact on individuals with LS than individuals with a high PRS.

Our studies first help inform methodological development of PRS risk prediction in CRC. Future studies should continue to develop and examine new methods to improve the clinical validity of PRS efficiently. Our findings also help understand the economic value of population-level

genomic screening for CRC. Future studies should continue to assess the value of genomic screening for other diseases to facilitate the understanding of the value of genomics in disease screening and prevention.

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Chapter 1. Introduction

Colorectal cancer (CRC) is the third leading cause of cancer-related death in the United States and associated with sizable healthcare resource and economic burden to patients and healthcare systems.[1,2] However, CRC is among the most preventable cancers via screening.[3] Screening for CRC helps detect and/or remove precancerous lesions and diagnose CRC patients in earlier stages, leading to better health outcomes.[4] However, screening has been underutilized and overutilized.[5-8] One potential way to improve appropriate utilization of CRC screening is to use individualized risk prediction.[9,10] The current CRC screening guideline is based on age family history (FH) of CRC.[11] However, age and FH do not inform risk for CRC with great precision because FH may not be universally defined and shared between individuals, or collected and reported.[12] Thus, an individualized risk prediction model for CRC to guide personalized screening is needed.

There have been a few CRC risk prediction models developed based on demographic and clinical data.[9,13,14] The most common predictors include age, sex, physical activities, body mass index (BMI), lifestyle factors, and drug use etc.[9,13,14] However, although the Area under the Receiver Operating Curve (AUROC, also called AUC) of these models was promising (ranging from 0.65 to 0.75), external validation of these models was few, resulting in unclear predictive performance in broader population.[9,13,14] In addition, none of these models has been widely adopted and implemented in clinical practice in the United States, which potentially results from the difficulty of routinely collecting demographic and clinical information.[9,13,14]

Recently, genome-wide information studies (GWAS) have revealed the polygenic architecture of CRC and identified loci associated with CRC risk.[15] Based on these discoveries, there have been a few PRSs developed for predicting CRC risk using these loci.[16-20] Unlike mendelian genes

which are rare and with high penetrance such as MLH1 for Lynch Syndrome, these loci are common and have low penetrance for CRC risk.[16,21,22] However, collectively, they can inform risk of CRC with promising predictive power.[16,21,22]

Among all PRS risk prediction models, the one with the highest predictive power, measured by AUC, was developed, validated and tested on large-scale data from European individuals using multiple methods: GWAS known loci, clumping and thresholding, and LDpred, a Bayesian risk prediction method based on genome-wide information.[16,23] Ultimately, its highest AUC was 0.654 (95%CI: 0.639 to 0.669).[16] Patients in the top 5% PRS were predicted to have a lifetime CRC risk of 7.5% (95%CI: 5.6% to 8.3%).[16] In addition, this PRS helped capture additional 30% individuals who had a 2.2-fold risk of CRC but would have been missed using FH assessment.[16] These suggest that PRS for CRC may have the potential to predict CRC risk with precision compared to risk informed by age and FH, and potentially be used to guide personalized screening.[24]

Because of the promising potential for PRS in guiding CRC screening, efforts to improve its risk prediction are sought. Recently, a new risk prediction model approach has been proposed, called Multiple PRS (MPS).[25] In this MPS, the risk prediction model is not only based on the PRS for the outcome of interest, but also the PRSs for traits that are associated with the outcomes of interest.[25] The rationale is that PRSs of traits associated with the outcome of interest may help capture missed genetic information in the PRS of the outcome of interest.[25] An advantage of the MPS approach is its minimal requirement of demographic and clinical data collection.[26] Because all traits are incorporated into the risk prediction model by their corresponding PRSs, once patients' genotyped data are obtained, PRSs for various traits can be readily incorporated into the MPS model.[26]

Previous studies have developed MPS risk prediction models and shown that MPS improved the predictive performance compared to a model where there was only a PRS of the disease of interest.[25,27-29] However, few studies performed validation on external data, or included a comprehensive list of PRSs of traits associated with the outcome of interest.[25,27-29] In CRC, because there are many known risk factors,[30] in order to improve risk prediction, it is critical to incorporate as many PRSs of the risk factors for CRC as possible. In this case, machine learning (ML) methods may help prioritize PRSs of risk factors with the most predictive performance for CRC, reduce the dimension of the model, and prevent overfitting via external validation.[31]

Although an individualized risk prediction model based on PRS is promising to guide CRC screening, a formal value assessment is needed.[32] In the US and even across the world, there has been growing evidence around the cost-effectiveness of genomic screening in various disease areas.[33] In the context of CRC, in order inform the policy maker whether risk prediction using a genomic screening test should be used to guide personalized CRC screening, the value assessment is critical because it informs long-term costs and benefits, enabling explicit comparison between possible interventions and demonstrating tradeoffs.[34] In particular, a few important issues around population screening using PRS should be paid attention to in the value assessment.

First, individualized CRC risk prediction using genomic screening for the population should incorporate Lynch Syndrome (LS) and PRS altogether. In particular, though 0.3% people in the population are LS carriers, they are at 15-20 folded risk for CRC.[1,35,36] In addition, a study found population screening for LS provides marginally good value.[37] Thus, in order to understand the value of a genomic screening for CRC in guiding downstream CRC screening, a value assessment should incorporate both PRS and LS.

Second, before genomic screening for CRC is implemented in clinical practice, the optimal age at which individuals should undergo the screening need to be identified, and the clinical action rule of PRS needs to be understood.[38] Particularly, the latter entails understanding of potential risk stratification methods of PRS, clinical accuracy associated with each stratification method, and long-term outcomes for each stratification.

Third, a potential risk of genomic screening is the false reassurance, meaning that individuals who receive a "negative" genomic result may adopt risky behaviors such as non-adherence to screening.[39] Previous cost-effectiveness analysis studies have not yet assessed the impact of false reassurance on the value of PRS screening.

The overall goal of this dissertation was to assess whether an MPS approach could improve CRC-PRS risk prediction and examine the value of a population-level genomic screening program for CRC that returned information for both LS and PRS. The results of this dissertation could guide the methods for future CRC risk prediction models based on PRS and inform future guidelines for personalized CRC screening and reimbursement of genomic screening test in CRC.

Chapter 2. Multiple Polygenic Risk Score Approach in Colorectal Cancer (CRC) Risk Prediction

Abstract

Background: Recent literature demonstrated that for various diseases, incorporating polygenic risk scores (PRSs) for other traits and diseases into the PRS-based risk prediction model may improve predictive performance (i.e., Multiple Polygenic Score (MPS) approach). We aimed to examine whether the MPS approach improved risk prediction for colorectal cancer (CRC).

Methods: We included 2187 non-CRC PRSs available from PGS Catalog and used machine learning (ML) models to select non-CRC PRSs that were most predictive, based on the Genetic and Epidemiology of CRC Consortium (GECCO) database (31,257 cases and 33,408 controls). An independent dataset, the Genetic Epidemiology Research in Adult Health and Aging (GERA) cohort (4852 cases and 67,939 controls) was split into training and validation subsets. We developed models that combined the MPS with two existing CRC-PRSs and validated the Area under the Receiver Operating Curve (AUC). We bootstrapped the validation dataset 1000 times and compared whether AUCs significantly changed after incorporating MPS into the model.

Results: The ML model selected 337 non-CRC PRSs. Adding the MPS to the CRC-PRSs models statistically significantly improved the AUC with the improvement of 0.17 (95% confidence interval (CI): 0.011, 0.022, $p<0.0001$) when combined with the known loci CRC-PRS, 0.005 (95%CI: 0.002, 0.007, $p=0.0005$) when combined with a genome-wide CRC-PRS, and 0.004 (95%CI: 0.002, 0.006, $p=0.0005$) when combined with both the known loci and genome-wide CRC-PRSs.

Conclusions: MPS helped improve the AUC of CRC-PRS models, but the increase was small. MPS may not be an efficient approach to considerably boost predictive performance for CRC.

Introduction

Colorectal cancer (CRC) is one of the most common causes of cancer death.[40] It is projected that more than 150,000 individuals would be diagnosed in 2024 and more than 50,000 individuals would die from CRC.[41] However, screening CRC is effectively reducing the incidence of CRC, diagnosing patients at an earlier stage and ultimately improving health outcomes.[40] One approach to guide personalized CRC screening is to use risk prediction models for CRC.[9]

There have been a few risk prediction models for CRC, and these models are largely based on environmental and lifestyle risk factors, such as smoking, alcohol, diet, obesity and diabetes.[9,14,42] In recent years, prediction algorithms based on common variants across the human genome have shown promise in identifying individuals with a higher risk of CRC.[16,24] Those predictors are known as Polygenic Risk Score (PRS). PRSs leverage information that is based on either known loci from the genome-wide association study (GWAS) or genome-wide common variants.[21] Literature has shown that incorporating the PRS developed for CRC was able to predict individuals at a higher risk for CRC, and adding PRS into existing clinical-based risk prediction algorithms improved the risk prediction.[16,24,43]

There have been many advances in the development of PRSs. With more data available in GWAS, more known loci have been identified and their associations with CRC have been better understood.[20,24] In addition, machine learning (ML) models that can use genome-wide information and shrink information from less predictive common variants have demonstrated further improvements in PRS development.[44,45] In independent validations, these CRC-PRSs developed from genome-wide information and based on ML models had a high Area Under the Receiver Operating Curve (AUROC, AUC), a measure for predictive performance, which ranged from 0.63 to 0.65, showing the promise to predict the risk of CRC.[16,24]

In recent years, another approach has been able to further improve the PRS risk prediction. This approach is known as Multiple PRS (MPS) approach, where PRSs for other traits are incorporated into the risk prediction model.[25] The motivation of our study is two-fold. First, there are many risk factors of CRC, and genetics contributes to the risk of many of those factors.[30] For example, type 2 diabetes is a risk factor for CRC, and there are PRSs developed for diabetes that have a promising AUC to predict diabetes.[30,46,47] Other examples are smoking, obesity or chronic inflammation.[48] Thus, the inclusion of PRSs for risk factors of CRC may supplement the risk information in addition to CRC-PRSs. Second, when developing the PRS for a given trait, models with penalization are often used and may result in loss of information. This information could potentially be captured by PRSs for other traits.[21] Previous literature has shown that the inclusion of PRSs from other traits could improve risk prediction in mental health outcomes and diabetes among others.[25,26,29] However, this approach has not been tested for CRC. In addition, most studies did not comprehensively include PRSs for other traits.[25,26,29] Because the goal is to improve risk prediction, a more comprehensive approach with an unselected list of PRSs for other traits is needed in order to understand whether this MPS approach works for CRC. [25,29,49]

To address this knowledge gap, we aimed to assess whether a comprehensive MPS approach could improve risk prediction in comparison to a PRS risk prediction model that is developed for CRC only (i.e., CRC-PRS model).

Methods

The overall approach of developing and validating the MPS risk prediction model for CRC is illustrated in Figure 1.

Briefly, our approach has three steps. The first step was to incorporate all PRSs for other traits (i.e., non-CRC PRSs) that are available on the PGS catalog into our large GWAS dataset for

CRC from the Genetic and Epidemiology of CRC Consortium (GECCO).[48] Then, we used ML models to select the ones that were most relevant and predictive of CRC. We used penalized ML models including Lasso, Ridge and Elastic Net. We then selected the best performing model across all models. This model returned the list of selected non-CRC PRSs and their estimated coefficients. The second step was to construct different risk prediction models using logistic regression based on an independent training dataset, which was the first subset from the Genetic Epidemiology Research in Adult Health and Aging (GERA) dataset (i.e., training). After this step, we validated the risk predictive performance in an independent validation dataset, which was the second subset of GERA (i.e., validation), and compared the predictive performance of the MPS models with that of the CRC-PRS models. Details of each step are illustrated in the following sections.

PRS calculation

We used the individual-level imputed GWAS data to calculate all PRSs for each individual. Details on the imputation, GWAS, and sub-studies are provided in our previous publications.[16,20] For a given PRS, we calculated the weighted sum across all common variants required for this PRS for each individual. For each PRS, we obtained the scoring file from PGS Catalog where the information of the SNP, the effect allele, the reference allele, and the weight that corresponds to the effect allele, is available.[48] All PRS were standardized with mean of zero and standard deviation (SD) of one.

Sex-specific PRSs

Some PRSs were sex-specific and only interpretable for one sex, such as PRSs for prostate cancer and breast cancer. Thus, we assigned zero values to PRSs to individuals with the sex where the PRSs were not meaningful or interpretable. For example, we manually assigned the

PRS of prostate cancer for females to zero. This approach ensured that the PRSs with zero-value would not contribute to risk prediction for a given sex.

PRS selection

We used two CRC-PRSs, both of which were published previously.[16,24] Briefly, the first CRC-PRS was based on GWAS known loci (CRC-KL200); and the second one was based on genome-wide information constructed using LDpred2 approach (CRC-LDpred).[16,24] For more details of these 2 CRC-PRSs, please refer to previous publications.[16,24]

Because the goal of our study was to examine whether adding non-CRC PRSs to CRC-PRS models can increase predictive performance, we decided to comprehensively incorporate non-CRC PRSs available without prior selection. We downloaded all 2,724 PRSs' scoring files from PGS Catalog available as of November 8, 2022.[48] There were some SNPs required in several PRSs that were not available in our individual-level GWAS data, and losing a large proportion of SNPs might harm the predictive performance of a PRS, and thus we excluded PRSs with more than 20% SNPs unavailable in our GWAS data. Then, we excluded PRSs that were predicting CRC, colon cancer, and rectal cancer because we only focused on non-CRC PRSs. Additionally, we further excluded PRSs that predicted a trait that might include many CRC cases, including three PRSs for two traits - gastrointestinal cancer, and rectal and anal cancer. Ultimately, we included 2187 non-CRC PRSs in the ML model (Figure 2).

Among the 2187 non-CRC PRSs, there were several PRSs that predicted precursor lesions of CRC, including rectal polyps, benign neoplasm of colon, and benign neoplasm of digestive systems. We decided to include these PRSs because these traits were not CRC and their PRSs might provide valuable information to predict CRC.

Step 1. Selection of non-CRC PRSs

The first step was to select non-CRC PRSs that were most predictive for CRC. We used penalized ML models, including Ridge, Lasso, and Elastic Net models. We conducted 10-fold cross-validation (CV) to select the optimal penalization parameter value to maximize the confounder-adjusted AUC. This metric standardizes the distribution of confounders in the case group to the control group and thus helps understand the predictive performance attributable to main predictors of interest only.[50]

We used in total 64,665 individuals who are European ancestral adults in the GECCO database. Briefly, there are 26,884 individuals diagnosed with CRC, 4,373 individuals diagnosed with advanced adenomas (AA). There were 33,408 individuals without CRC (i.e., controls). The mean age was 64.8 years (SD=11.4) and 50.2% were females (Table 1).

We adjusted for age, sex and the platform for GWAS in each ML model. Only PRSs were eligible for penalization, and other variables (age, sex, and platform of GWAS) were not penalized. After the 10-fold CV, we obtained the mean confounder-adjusted AUC and selected the model that returned the highest confounder-adjusted AUC. This model also returned the optimal values of tuning parameters. We then used these values to re-fit the model on the full GECCO data to obtain the estimated coefficients for non-CRC PRSs.

At the end of this step, we generated a composite MPS score, which is a linear combination of selected non-CRC PRSs weighted by the estimated coefficients.

Step 2. Developing risk prediction models

The second step was to construct risk prediction models including both CRC-PRS and MPS. In total, there were 6 models, including 3 CRC-PRS models (CRC-KL200 only, CRC-LDpred only,

and CRC-KL200 and CRC-LDpred combined), and 3 MPS+CRC-PRS models where MPS was added to each of the 3 CRC-PRSs models. As we were able to significantly reduce the number of predictors in the risk prediction models by ML models and had a sufficient sample size for development of risk prediction models, we used the logistic regression method for this step. CRC-PRSs and MPS were normalized with a mean of zero and a SD of one, and we controlled for age and sex in all models.

We used the GERA dataset for this step, where 72,791 adults who were defined as European ancestry based on genetic data were included. These individuals are within the Kaiser Permanente Northern California integrated healthcare delivery system.[51] Descriptions of this dataset has been published previously.[24]

We randomly split this dataset into two subsets - training and validation. The training was used for this step and the validation was used for the next step.

We defined cases as individuals with advanced neoplasia, including CRC or advanced adenomas, and controls as all other individuals, in the main analysis. If an individual had multiple outcomes, we used the worst outcome to determine the case/control status of this individual. In total, among 72,791 individuals, there were 4852 cases and 67,939 controls (Table 1).

We developed risk prediction models for both sexes combined, and sex-stratified risk prediction models (i.e., for males only and for females only). Additionally, we conducted a subgroup analysis comparing individuals with CRC to the controls.

Step 3. Validation and Comparison

We evaluated the performance of the 6 risk prediction models using the GERA validation dataset. We estimated the confounder-adjusted AUC for each model and obtained the standard errors (SE) and the 95% confidence intervals (CI) based on 1000 bootstrap samples.

There were three pairs of comparisons: (1) comparing CRC-KL200 combined with MPS to CRC-KL200 only, (2) comparing CRC-LDpred combined with MPS to CRC-LDpred only, and (3) comparing CRC-KL200 + CRC-LDpred combined with MPS to CRC-KL200 + CRC-LDpred.

In order to compare the difference of AUC between MPS+CRC-PRS models and CRC-PRS models, we first calculated the difference in confounder-adjusted AUC by subtracting the AUC of a CRC-PRS model from the AUC of an MPS+CRC-PRS model in the GERA validation dataset. Then, we calculated the difference in AUC in the 1000 bootstrapped samples. We calculated the SE of the difference of AUC and derived the 95% CI.

To test whether the difference in AUC significantly differed from zero, we calculated the z-score and obtained the two-sided p-values. A p-value smaller than 0.05 is considered statistically significant.

Results

Step 1. Selection of non-CRC-PRSs

The best performing ML model was an Elastic Net model. In 10-fold CV, models converged when the alpha value reached around 0.75 and the lambda value reached around 0.003. This model generated a mean confounder-adjusted AUC across 10-fold CV in GECCO data of 0.607 (Figure S1) and had a total of 337 non-CRC PRSs with non-zero coefficient estimates. The list of

selected 337 non-CRC PRSs along with their coefficient estimates can be found in Table S1. Non-CRC PRSs with the highest absolute values of coefficients were PRSs for benign neoplasm of colon, any cancer, college education, hemorrhoids, and body mass index (BMI) (Table S1).

Step 2. Developing risk prediction models

Main analysis

Across all six models, CRC-PRS and MPS+CRC-PRS were significant predictors (Table 2). For example, the odds ratios (ORs) for MPS, CRC-KL200, and CRC-LDpred were 1.11 (95%CI: 0.05, 1.16, $p<0.0001$), 1.12 (95%CI: 1.06, 1.18, $p=0.0001$), and 1.45 (95%CI: 1.36, 1.53, $p<0.0001$), respectively (Table 2).

Sex-stratified analysis

Similarly, in the risk prediction models for females, most predictors had a statistically significant coefficient (Table S2). However, CRC-KL200 became non-significant when CRC-LDpred was also included in the model as a predictor (Table S2). All CRC-PRS and MPS+CRC-PRS remained significant in all models for males (Table S3). MPS continued to be statistically significant even when both CRC-KL200 and CRC-LDpred were included with an estimated OR of 1.21 (95%CI: 1.05, 1.20, $p=0.001$) (Table S3).

Subgroup analysis

MPS was a non-significant predictor when the model included CRC-LDpred, with an estimated OR of 1.09 (95%CI: 1.00, 1.20, $p=0.059$) (Table S4).

Step 3. Validation and Comparison

Main analysis

When comparing individuals with advanced neoplasia to all others in both females and males, the AUC was 0.600 (95%CI: 0.589, 0.612), 0.631 (95%CI: 0.620, 0.643), and 0.632 (95%CI: 0.621, 0.644) for CRC-KL200, CRC-LDpred, and CRC-KL200+CRC-LDpred, respectively (Table 3). The AUCs of 3 MPS+CRC-PRS models are 0.617 (95%CI: 0.606, 0.629), 0.636 (95%CI: 0.625, 0.648), and 0.636 (95%CI: 0.625, 0.648), respectively (Table 3).

After incorporating MPS, the CRC-KL200 model had an increase in AUC of 0.017 (95% CI: 0.011, 0.022; p<0.0001); the CRC-LDpred model had an increase in AUC of 0.005 (95%CI: 0.002, 0.007; p=0.0005); and the CRC-KL200 combined with CRC-LDpred model had an increase in AUC of 0.0004 (95%CI: 0.002, 0.006; p=0.0005) (Table 4, Figure S2-S4).

Sex-stratified analysis

The addition of MPS did not improve the AUC significantly when both CRC-KL200 and CRC-LDpred were included in the model for females (Comparison 3: AUC difference=0.003, 95%CI: 0.000, 0.007; p=0.067) (Table S5). MPS continued to improve risk prediction consistently for 3 CRC-PRS models for males (Comparison 1: AUC difference=0.016; 95%CI: 0.009, 0.023; p<0.001; Comparison 2: AUC difference=0.005; 95%CI: 0.001, 0.010; p=0.015; Comparison 3: AUC difference=0.004, 95%CI: 0.001, 0.008; p=0.019) (Table S6).

Subgroup analysis

The addition of MPS improved the risk prediction performance of the CRC-KL200 model (AUC difference=0.015; 95%CI: 0.007, 0.023; p=0.0002), but did not improve the performance significantly when CRC-LDpred was the main predictor (Comparison 2: AUC difference=0.002;

95%CI: 0.000, 0.015; p=0.13) or when CRC-LDpred and CRC-KL200 were both included (Comparison 3: AUC difference=0.002; 95%CI: 0.000, 0.004; p=0.098) (Table S7).

Discussion

Study findings

We found that MPS was a statistically significant predictor in addition to CRC-PRSs in the main analysis and sex-stratified analysis in logistic regression models. This suggests that the information contained in non-CRC PRSs helped predict CRC. However, the estimated coefficient of MPS in logistic models became small once CRC-LDpred was included in the model, indicating that the magnitude of the association between MPS and CRC was small. This explained why MPS did not improve the AUC in a noticeable way, especially when CRC-LDpred was included in the model, and that demonstrated that CRC-LDpred was a strong predictor of CRC.

Among 337 non-CRC PRSs selected by the Elastic Net model, PRSs with the largest coefficient estimates were the ones developed to predict benign neoplasm, which is a type of precursor lesions of CRC.[52] Thus, in the subgroup analysis where we removed individuals with advanced adenomas from the case group, MPS's contribution in risk prediction was somewhat weakened. This was reflected by a less significant or even non-significant p-value in the logistic models, especially when CRC-LDpred was included in the model, which explained MPS did not improve AUC significantly.

Although MPS might improve the AUC significantly, the increment in AUC was small. Truong et al. found that incorporating more than 2000 PRSs to predict coronary artery disease, the increase in AUC ranged from 0.003 to 0.023 compared to a model without MPS, and the p-value

for the increase in AUC were all highly significant ($p<2e-16$).[26] Additionally, Krapohl et al. found that the MPS approach improved the variance explained of educational achievement, general cognitive ability, and BMI by 0.011 to 0.016 and this increase was statistically significant ($p<0.004$).[25] The magnitude of the effect size of MPS in these findings is in line with ours.[25,26]

Implications

There are two factors that may influence whether an MPS approach can contribute to risk prediction. The first one is the genetic architecture of a given trait and the second factor is how much of heritability has already been captured by the trait/disease-specific PRS (i.e., CRC-PRSs in our study).[26] CRC is a complex trait, and both genetic variants and environmental risk factors contribute to its risk deposition.[15] CRC is highly polygenic and impacted by both common genetic risk factors as well as rare variants in high-penetrance genes, such as mismatch repair genes.[15] Rare variants in high-penetrance genes can increase the risk of CRC to up to 70%,[15] and account for 3-5% of CRC cases.[53,54] To date, more than 200 common variants have been discovered in GWAS of CRC, which explain close to 20% of the familiar risk; however, it is estimated that all common variants (including undiscovered) explain over 70% of the familiar risk.[24,55] This suggests that in addition to the known GWAS loci, other common variants can contribute to the risk prediction. This is supported by our finding that the AUC was improved from 0.012 to 0.017 after we added MPS to CRC-KL200.

However, because CRC-LDpred was developed using genome-wide data from a large sample of individuals with European ancestry and Asian ancestry, and constructed by LDpred2, one of the state-of-the-art methods for developing PRS,[45,56] it is possible that CRC-LDpred has captured the majority of the genome-wide information of CRC, especially undiscovered common variants, leaving minimal space for MPS to play a role in improving the AUC. This suggests that in order

to further boost risk predictive performance beyond this CRC-LDpred, incorporating PRSs for other traits might not be an efficient approach. There exist many non-genetic risk factors of CRC such as lifestyle factors and comorbidities and previous literature have shown that combining these risk factors with CRC-PRS can further improve the risk prediction for CRC.[43,56,57] Additionally, new methods for PRS development, such as incorporating functional information, may also help improve risk predictive performance.[58-60] Future studies should focus on developing more effective approaches to improve PRS risk prediction.

There are two potential mechanisms of why the MPS approach might improve risk prediction. The first one is pleiotropy, i.e., the genetic correlations among complex traits.[61] Recent pleiotropic analyses have found novel genetic risk factors associated with CRC.[62-64] These novel genetic risk factors might not have been included in the CRC-PRSs but may be captured by PRS for other traits. Secondly, methods of PRS development may over-shrink the effect sizes of common variants, which then leads to loss of information of PRSs.[65-67] In this case, these common variants can be supplemented by PRSs of other traits in the MPS approach.

The improvement in AUC attributable to MPS, although small, is an important and necessary step in the risk prediction model development. However, how much the improvement in AUC translates into clinical utility requires further investigation. In general, the increase in AUC suggests higher sensitivity and specificity at a certain threshold, and yet in clinical practice, given that CRC is not a common disease, the PRS-based predicted risk (i.e., positive predicted risk) may be small and still carry large uncertainty.[68] In our study, the improvement in AUC, although statistically significant, is small and therefore may not result in a clinical impact. It is true that a risk prediction model with a higher AUC should have a smaller uncertainty and better

precision, and yet understanding how much improvement in AUC can make a clinically and economic meaningful impact is important and needed before implementation.[38,69]

Strengths

First, we designed the MPS approach in a comprehensive way. We did not pre-select any traits based on current understanding of risk factors of CRC.[30] Instead, we adopted an approach where we included all available non-CRC PRSs from PGS Catalog.[48] Then, we used ML models to select PRSs that predicted CRC well. This approach ensured that we had a large number of non-CRC PRSs to choose from and developed an unbiased MPS model. Second, after we developed the risk prediction models, we validated all models in an independent dataset and obtained the validated AUC. This helped us avoid overfitting. We also bootstrapped the validation dataset 1000 times and compared AUC across models. Third, the AUC that we used in this study was confounder-adjusted AUC.[50] This metric only reflected the predictive performance of CRC-PRSs and MPS, excluding prediction attributable to potential confounders that are also predictors, such as age and sex.[50] Using this metric, we were able to make fair comparison between CRC-PRS models and MPS models.

Limitations

First, our study only focused on MPS approach in European ancestral individuals. When we developed this study and constructed the model, PRSs for different traits were mostly available for European individuals.[48] Future studies should examine the performance of the MPS approach in CRC for individuals with other ancestries. Second, we examined the linear relationship between CRC and PRSs of other traits. Some previous literature has also used deep neural networks, a ML method that might capture non-linearity, and found that it performed equally well or outperformed the ridge regression.[70] However, a recent article found that XGBoost,

another ML method that captures non-linearity, improved the predictive performance of MPS models compared to lasso, but the improvement was only via covariates rather than PRSs.[71] Future studies should examine how and why different ML models perform in the context of MPS in CRC and other disease areas.

Conclusion

Inclusion of MPS, which was developed from PRS for non-CRC traits, helped improve CRC-PRS risk prediction models, although the magnitude of the improvement was small.

Tables and figures

Table 1. Sample descriptives of GECCO and GERA

GECCO					
	Cases (N=31,257)			Controls (N=33,408)	Overall (N=64,665)
	CRC (N=26,884)	Advanced adenoma (N=4,373)	Total (N=31,257)	Total	Total
Age, mean (SD)	65.7 (11.4)	64.3 (8.0)	65.5 (11.0)	64.2 (11.6)	64.8 (11.4)
Female, n (%)	12,811 (47.7%)	1,858 (42.5%)	14,669 (46.9%)	17,780 (53.2%)	32,449 (50.2%)
GERA					
	Cases (N=4,852)			Controls (N= 67,939)	Overall (N= 72,791)
	CRC (N=1,311)	Advanced adenoma (N=3,541)	Total (N=4,852)	Total	Total
Age, mean (SD)	70.9 (11.7)	68.5 (9.1)	69.2 (9.9)	71.3 (13.3)	71.1 (13.1)
Female, n (%)	674 (51.4%)	1,643 (46.4%)	2,317 (47.8%)	40,203 (59.2%)	42,520 (58.4%)

Abbreviations. CRC: colorectal cancer. GECCO: Genetic and Epidemiology of CRC Consortium. GERA: Genetic Epidemiology Research in Adult Health and Aging (GERA) cohort. SD: standard deviation.

Table 2. Main analysis: Odds ratios (ORs) in logistic regression, both sexes

Model No.	Predictors	OR	95% CI: Lower limit	95% CI: Upper limit	P-value
1	CRC-KL200	1.49	1.43	1.56	<0.0001
2	CRC-LDpred	1.64	1.57	1.71	<0.0001
3	CRC-KL200	1.15	1.08	1.21	<0.0001
	CRC-LDpred	1.50	1.42	1.59	<0.0001
4	Composite MPS	1.22	1.16	1.28	<0.0001
	CRC-KL200	1.36	1.29	1.42	<0.0001
5	Composite MPS	1.13	1.08	1.19	<0.0001
	CRC-LDpred	1.54	1.47	1.62	<0.0001
6	Composite MPS	1.11	1.05	1.16	<0.0001
	CRC-KL200	1.12	1.06	1.18	0.0001
	CRC-LDpred	1.45	1.36	1.53	<0.0001

Abbreviations. CRC: colorectal cancer. CI: confidence interval. MPS: multiple PRS.

Table 3. Main analyses: AUC of risk prediction models, both sexes

Main analysis			
Model No.	Main predictors	Point estimate of confounder-adjusted AUC	95% CI of confounder-adjusted AUC
1	CRC-KL200	0.600	0.589, 0.612
2	CRC-LDpred	0.631	0.620, 0.643
3	CRC-KL200, CRC-LDpred	0.632	0.621, 0.644
4	CRC-KL200, MPS	0.617	0.606, 0.629
5	CRC-LDpred, MPS	0.636	0.625, 0.648
6	CRC-KL200, CRC-LDpred, MPS	0.636	0.625, 0.648

Abbreviations. AUC: area under the Receiver Operating Curve. CRC: colorectal cancer. CI: confidence interval. MPS: multiple PRS.

Table 4. Main analysis: Comparison of AUCs, both sexes

Comparison pair No.	Model A	Model B	Point estimate of difference in AUC	95% CI of the difference in AUC	P-value
1	CRC-KL200 + MPS	CRC-KL200	0.017	0.011, 0.022	<0.0001
2	CRC-LDpred + MPS	CRC-LDpred	0.005	0.002, 0.007	0.0005
3	CRC-KL200 + CRC-LDpred + MPS	CRC-KL200 + CRC-LDpred	0.004	0.002, 0.006	0.0005

Abbreviations. AUC: area under the Receiver Operating Curve. CRC: colorectal cancer. CI: confidence interval. MPS: multiple PRS.

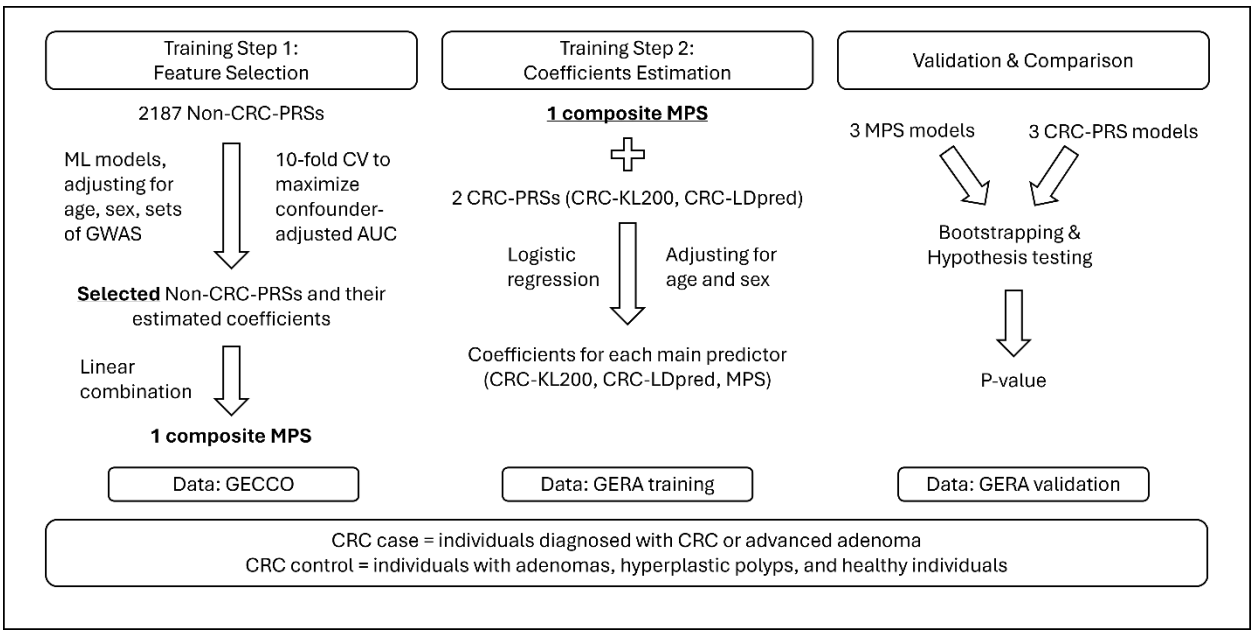


Figure 1. Overall approach

The first step was to select the most predictive non-CRC PRSs among 2187 non-CRC PRSs by ML models (Lasso, Ridge and Elastic Net) with 10-fold CV. This step was done in GECCO data. We adjusted age, sex and platforms of GWAS. We selected the best performing model with the highest confounder-adjusted AUC. Afterwards, we constructed a composite MPS by taking the linear combination of selected non-CRC PRSs, weighing by their coefficient estimates. The second step was to construct risk prediction models by adding MPS to CRC-PRSs only models. We adjusted age and sex for this step. The data was the training subset of GERA cohort. The last step was to validate the confounder-adjusted AUC on the validation dataset. We used bootstrapping to compare confounder-adjusted AUC in CRC-PRS only models and MPS models and calculated the two-sided p-values.

Abbreviations. AUC: area under the Receiver Operating Curve. CRC: colorectal cancer. CV: cross-validation. GECCO: Genetic and Epidemiology of CRC Consortium. GERA: Genetic

Epidemiology Research in Adult Health and Aging (GERA) cohort. GWAS: genome-wide association study. ML: machine learning. MPS: multiple PRS. PRS: polygenic risk score.

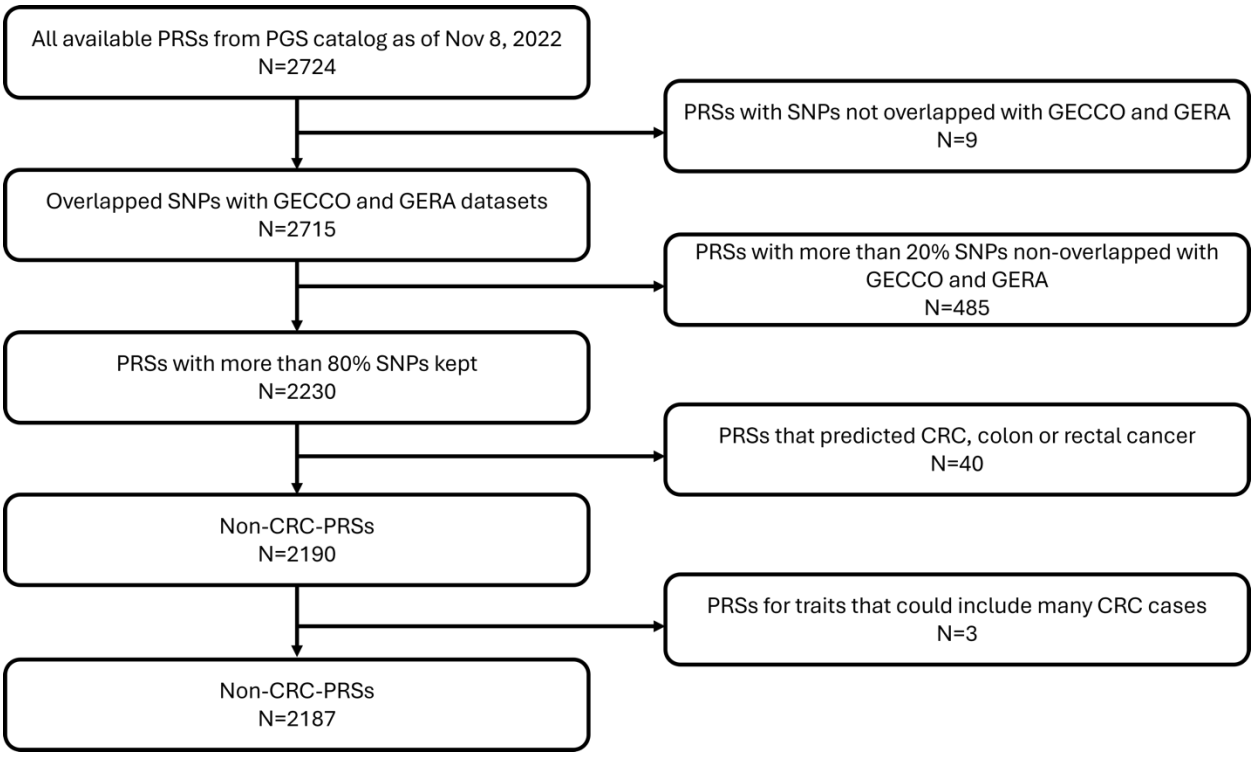


Figure 2. Selection of non-CRC-PRSs

We downloaded all PRSs available as of Nov 8, 2022, from PGS Catalog. We first excluded 9 PRSs without overlapping SNPs with GECCO and GERA datasets.[48] Then, we further exclude 485 PRSs with at least 20% SNPs unavailable in GECCO and GERA datasets. Because our focus was non-CRC PRSs, we excluded 40 PRSs that predicted CRC, colon cancer, and rectal cancer. Additionally, three PRSs were excluded because they predicted the trait where many CRC cases were included. Eventually, we had 2187 non-CRC PRSs.

Abbreviations. CRC: colorectal cancer. GECCO: Genetic and Epidemiology of CRC Consortium. GERA: Genetic Epidemiology Research in Adult Health and Aging (GERA) cohort.

MPS: multiple PRS. PGS: Polygenic Score. PRS: polygenic risk score. SNP: single nucleotide polymorphisms.

Supplementary materials

Table S1. Selected 337 non-CRC PRSs by Elastic Net model

Polygenic Score ID & Name	Reported Trait	Estimated Coefficient
PGS002019(portability-ldpred2_208)	Benign neoplasm of colon	0.061474
PGS001811(portability-PLR_208)	Benign neoplasm of colon	0.013656
PGS000354 (PRSWEB_PHECODE10001_UKBB-SAIGE-HRC-X10001_PRS-CS_MGI_20200608)	Any Cancer	0.011092
PGS002319(cov_EDU_COLLEGE.BOLT-LMM)	College education	-0.009830
PGS002058(portability-ldpred2_455)	Hemorrhoids	-0.006804
PGS000910(PRS_BMI)	Body mass index	0.006350
PGS001057(GBE_INI1458)	Cereal consumption	-0.005968

PGS001158(GBE_INI23118)	Left leg mass (predicted)	0.005534
PGS002070(portability-ldpred2_565.1)s	Anal and rectal polyp	0.005507
PGS000938(GBE_HC990)	Varicose veins of lower extremities (time-to-event)	0.005372
PGS000877(uwGRS53_IR)	Insulin resistance	0.004865
PGS002148(portability-ldpred2_income)	Average total household income before tax	-0.004645
PGS002096(portability-ldpred2_785)	Abdominal pain	-0.004146
PGS001284(GBE_BIN_FC10006152)	Allergic disease (hay fever, allergic rhinitis, or eczema)	-0.004138
PGS002025(portability-ldpred2_250.1)	Type 1 diabetes	0.004060
PGS000982(GBE_BIN_FC10002267)	Use of sun / ultraviolet protection (never / rarely)	0.004047

PGS001763(GBE_INI25562)	WA MO in tract posterior thalamic radiation (R)	-0.004043
PGS000253(IL-6RA)	Interleukin-6 receptor subunit alpha (IL-6RA) serum levels	-0.003942
PGS002356(body_WHRadjBMIz.BOLT-LMM)	Waist-Hip Ratio	0.003908
PGS001641(GBE_INI25007)	Volume of white matter (normalised for head size)	0.003882
PGS000356(PRSWEB_PHECODE10001_UKBB-SAIGE-HRC-X10001_LASSOSUM_MGI_20200608)	Any Cancer	0.003748
PGS000725(PRS_Pancreas)	Pancreatic cancer	0.003682
PGS001322(GBE_HC276)	Glaucoma	-0.003596
PGS001831(portability-PLR_335)	Multiple sclerosis	0.003525
PGS000491(PRSWEB_PHECODE174.1_Onco-iCOGS-ER-negative-BRCA_PRS-CS_MGI_20200608)	Breast cancer (female)	0.003487
PGS000701(snpnet.Urea)	Urea [mmol/L]	-0.003475
PGS002296(PRS2166_HT)	Hypertension	-0.003472

PGS000855(T2D_Lipodystrophy)	Type 2 diabetes (based on SNPs associated with lipodystrophy)	0.003460
PGS000155(cGRS_Glioma)	Glioma	-0.003455
PGS000265(MMP-10)	Matrix metalloproteinase-10 (MMP-10) serum levels	0.003430
PGS000803(wGRS41_SLE)	Systemic lupus erythematosus	-0.003384
PGS000798(157SNP_GRS)	Coronary heart disease	-0.003327
PGS000359(PRSWEB_PHECODE145.2_C3-TONGUENAS_PRS-CS_MGI_20200608)	Cancer of tongue	0.003250
PGS000325(GRS-JIA-Oli-20)	Oligoarthritis Juvenile Idiophatic Arthritis	-0.003249
PGS001088(GBE_INI1588)	Average weekly alcohol	0.003237

	consumption (beer and cider)	
PGS002240(prscs_prostatecancer)	Prostate cancer	0.003132
PGS001859(portability-PLR_565.1)	Anal and rectal polyp	0.003114
PGS000760(VIT)	Vitiligo	-0.003107
PGS001018(GBE_BIN_FC10006160)	Attending social / leisure activities (attend any of the followings in once a week or more often: sports club, gym, pub, social club, religious group, adult edication class, or other group activity)	-0.003034
PGS001470(GBE_INI25352)	Mean ICVF in medial lemniscus on FA skeleton (R)	-0.003023

PGS001574(GBE_INI25827)	Volume of grey matter in Lateral Occipital Cortex, inferior division (R)	-0.002999
PGS001970(portability-PLR_log_platelet_crit)	Platelet crit	-0.002997
PGS002092(portability-ldpred2_728.71)	Contracture of palmar fascia [Dupuytren's disease]	0.002993
PGS002034(portability-ldpred2_286.12)	Congenital deficiency of other clotting factors (including factor VII)	-0.002991
PGS000320(PRS_BMI)	Body mass index	0.002900
PGS002804(GIANT_HEIGHT_YENGO_2022_PGS_WEIGHTS_EUR)	Height	0.002869
PGS002068(portability-ldpred2_562.1)	Diverticulosis	-0.002858
PGS002095(portability-ldpred2_743.1)	Osteoporosis	0.002818
PGS001386(GBE_INI21049)	Degree bothered by pain in	-0.002808

	arms/legs/joints in the past 3 months	
PGS001985(portability-PLR_logMAR)	logMAR in round (left/right)	0.002739
PGS002153(portability-ldpred2_less_happy_with_health)	General happiness with own health	-0.002635
PGS000851(T2D_Insulin_Action_Secretion)	Type 2 diabetes (based on SNPs associated with insulin action/secretion)	0.002584
PGS002358(disease_ASTHMA_DIAGNOSED.BOLT-LMM-BBJ)	Asthma	0.002581
PGS001373(GBE_INI2217)	Age started wearing glasses or contact lenses	0.002530
PGS001319(GBE_HC708)	Other metabolic disorders (time-to-event)	-0.002507
PGS001281(GBE_HC86)	Migraine	-0.002458
PGS002159(portability-ldpred2_log_AST)	Aspartate aminotransferase	-0.002442

PGS001548(GBE_INI25864)	Volume of grey matter in Central Opercular Cortex (L)	0.002428
PGS002365(biochemistry_Glucose.BOLT-LMM-BBJ)	Glucose	0.002416
PGS002290(GRS10_PUA)	Uric acid level	0.002398
PGS000221(CCL3)	C-C motif chemokine 3 (CCL3) serum levels	0.002390
PGS001394(GBE_INI20414)	Freq. of drinking alcohol	0.002387
PGS001698(GBE_INI25725)	WA ISOVF in tract superior longitudinal fasciculus (L)	0.002381
PGS002201(portability-ldpred2_log_waist_circ)	Waist circumference	0.002362
PGS001853(portability-PLR_540)	Appendiceal conditions	-0.002341
PGS000991(GBE_BIN_FC4006144)	Never eat sugar	-0.002320

PGS000620(PRSWEB_PHECODE191.11_C71_LASSOSUM_MGI_20200608)	Cancer of brain	-0.002289
PGS000017(GPS_IBD)	Inflammatory bowel disease	-0.002289
PGS002055(portability-ldpred2_443.9)	Peripheral vascular disease, unspecified	0.002256
PGS002259(metaPRS_Stroke)	Stroke	-0.002251
PGS001783(1kgeur_gbmi_COPD_pst_eff_a1_b0.5_phiauto)	Chronic obstructive pulmonary disease	-0.002223
PGS001082(GBE_INI23028)	MC VP1 antigen for Merkel Cell Polyomavirus	0.002207
PGS002226(portability-ldpred2_sodium_urine)	Sodium in urine	0.002204
PGS002223(portability-ldpred2_sensitive_stomach)	Sensitive stomach	-0.002187
PGS001430(GBE_INI25075)	Mean FA in posterior limb of internal capsule on FA skeleton (L)	0.002171
PGS000210(LF279)	Lung function (FEV1/FVC)	-0.002137

PGS000011(GRS50)	Coronary artery disease	-0.002091
PGS001893(portability-PLR_calcium)	Calcium	0.002066
PGS000386(PRSWEB_PHECODE157_GWAS-Catalog-r2019-05-03-X157_PT_UKB_20200608)	Pancreatic cancer	0.002054
PGS000909(PRS_Headaches)	Headache	-0.002035
PGS002255(PRS_measured)	Physical activity (measured)	-0.002023
PGS000963(GBE_HC1184)	Follicular cysts of skin and subcutaneous tissue (time-to-event)	0.002017
PGS000332(PRS_BC)	Breast cancer	0.002005
PGS002012(portability-PLR_years_of_edu)	Qualifications (years of education)	-0.001996
PGS000691(snpnet.Non_albumin_protein)	Non-albumin protein [g/L]	-0.001994
PGS002152(portability-ldpred2_less_alcohol)	Alcohol intake frequency	0.001986

PGS000853(T2D_Insulin_Secretion_2)	Type 2 diabetes (based on SNPs associated with insulin secretion)	-0.001981
PGS000766(PRS56_CM)	Cutaneous melanoma	0.001974
PGS002126(portability-ldpred2_ever_smoked)	Ever smoked	-0.001872
PGS001975(portability-PLR_log_pulse_rate)	Pulse rate, automated reading	0.001844
PGS000206(RISK_PC_FT12)	Risk-taking tendency (4-domain principal component model)	-0.001839
PGS002036(portability-ldpred2_296.2)	Depression	-0.001821
PGS001119(GBE_INI46)	Left hand grip strength	-0.001796
PGS002304(PRS6_FL)	Follicular lymphoma	0.001795
PGS001689(GBE_INI25705)	WA ISOVF in tract acoustic radiation (R)	0.001789

PGS000727(AF_PGS)	Atrial fibrillation	0.001781
PGS002062(portability-ldpred2_496)	Chronic airway obstruction	-0.001780
PGS002166(portability-ldpred2_log_ECG_QRS_duration)	QRS duration	0.001760
PGS001306(GBE_HC201)	Ulcerative colitis	-0.001692
PGS002085(portability-ldpred2_702.2)	Seborrheic keratosis	0.001679
PGS000276(PlGF)	Placenta growth factor (PlGF) serum levels	0.001675
PGS001658(GBE_INI25509)	WA FA in tract superior longitudinal fasciculus (L)	-0.001672
PGS001172(GBE_INI30150)	Eosinophill count	-0.001655
PGS001592(GBE_INI25842)	Volume of grey matter in Precuneous Cortex (L)	-0.001649
PGS000640(PRSWEB_PHECODE201_UKBB-SAIGE-HRC-X201_LASSOSUM_MGI_20200608)	Hodgkin's disease	0.001644

PGS000924(GBE_HC702)	Disorders of porphyrin and bilirubin metabolism (time-to-event)	0.001642
PGS000687(snpnet.IGF_1)	IGF-1 [nmol/L]	0.001625
PGS000479(PRSWEB_PHECODE174.1_C3-BREAST-3_LASSOSUM_MGI_20200608)	Breast cancer (female)	-0.001594
PGS001008(GBE_QT_FC1002178)	Overall health rating	-0.001582
PGS002689(disease_ALLERGY_ECZEMA_DIAGNOSED.SBayesR)	Eczema	-0.001572
PGS000728(CKD_PGS)	Chronic kidney disease	-0.001568
PGS000781(GRS7_Glio)	Glioma	-0.001557
PGS000284(ST2)	ST2 protein (ST2) serum levels	-0.001530
PGS001391(GBE_INI20453)	Ever taken cannabis	0.001525
PGS002161(portability-ldpred2_log_BMI)	Body mass index (BMI)	0.001503

PGS000301(GRS970_SBP)	Systolic blood pressure	-0.001500
PGS001580(GBE_INI25860)	Volume of grey matter in Occipital Fusiform Gyrus (L)	-0.001489
PGS001129(GBE_BIN_FC30022506)	Smoking status (ever vs never smokers)	0.001483
PGS000311(GRS234_TC)	Total cholesterol	0.001475
PGS002231(portability-ldpred2_years_of_edu)	Qualifications (years of education)	-0.001475
PGS001367(GBE_INI5097)	6mm weak meridian (L)	0.001469
PGS002114(portability-ldpred2_diastolic_BP)	Diastolic blood pressure, automated reading	0.001459
PGS000608(PRSWEB_PHECODE189.2_C3-BLADDER_PRS-CS_MGI_20200608)	Cancer of bladder	-0.001433
PGS000799(GRSw_TAGC)	Asthma	0.001430
PGS002368(body_HEIGHTz.BOLT-LMM-BBJ)	Height	0.001430

PGS000299(GRS462_WHRadjBMI)	Waist-to-hip ratio (body mass index adjusted)	0.001421
PGS002257(GRS901_SBP)	Systolic blood pressure	-0.001420
PGS002292(PRS36_KC)	Keratoconus	-0.001418
PGS002222(portability-ldpred2_self_harm_thoughts)	Ever contemplated self-harm / Recent thoughts of suicide or self-harm	-0.001397
PGS002323(disease_ALLERGY_ECZEMA_DIAGNOSED.BOLT-LMM)	Eczema	-0.001387
PGS002104(portability-ldpred2_bad_hearing)	Hearing difficulty/problems	-0.001370
PGS001903(portability-PLR_ECG_PP_interval)	PP interval	-0.001367
PGS001003(GBE_INI137)	Number of medications taken	-0.001345
PGS000961(GBE_HC987)	Phlebitis and thrombophlebitis (time-to-event)	0.001318

PGS001140(GBE_HC1190)	Seborrheic keratosis (time-to-event)	0.001313
PGS000222(CCL4)	C-C motif chemokine 4 (CCL4) serum levels	-0.001308
PGS001995(portability-PLR_narcolepsy)	Daytime dozing / sleeping (narcolepsy)	-0.001301
PGS001588(GBE_INI25869)	Volume of grey matter in Planum Polare (R)	0.001294
PGS001563(GBE_INI25886)	Volume of grey matter in Hippocampus (L)	-0.001289
PGS000242(Gal-3)	Galectin-3 (Gal-3) serum levels	-0.001278
PGS001526(GBE_INI22331)	QT interval	0.001275
PGS002105(portability-ldpred2_birth_weight)	Birth weight	0.001271
PGS002197(portability-ldpred2_log_triglycerides)	Triglycerides	0.001260

PGS002178(portability-ldpred2_log_IGF1)	IGF-1	0.001252
PGS001049(GBE_BIN2040)	Risk taking behaviour	-0.001248
PGS002691(blood_EOSINOPHIL_COUNT.SBayesR)	Eosinophil count	-0.001237
PGS001864(portability-PLR_594)	Urinary calculus	0.001234
PGS002293(PRS62_psoriasis)	Psoriasis	-0.001224
PGS001557(GBE_INI25862)	Volume of grey matter in Frontal Operculum Cortex (L)	-0.001200
PGS001581(GBE_INI25877)	Volume of grey matter in Occipital Pole (R)	0.001174
PGS002031(portability-ldpred2_275.1)	Disorders of iron metabolism	0.001170
PGS001935(portability-PLR_less_happy_with_health)	General happiness with own health	-0.001161
PGS002745 (metaPGS_RA)	Rheumatoid arthritis	-0.001159
PGS000842(WHR)	Waist-hip ratio	0.001150

PGS001473(GBE_INI25370)	Mean ICVF in posterior corona radiata on FA skeleton (R)	-0.001136
PGS001728(GBE_INI25622)	WA L2 in tract uncinate fasciculus (R)	0.001134
PGS000054(ALZ21_EFIGA)	Alzheimer's disease (late onset)	0.001111
PGS001273(GBE_HC22)	Osteoporosis	0.001106
PGS001099(GBE_INI5085)	Spherical power (left eye)	0.001104
PGS002281(PRS23_MM)	Multiple myeloma	-0.001101
PGS000604(PRSWEB_PHECODE187.2_GWAS-Catalog-r2019-05-03-X187.2_PT_UKB_20200608)	Malignant neoplasm of testis	0.001094
PGS001779(BRSprs)	Brugada syndrome	0.001093
PGS000821(PRS_hypomed)	Thyroid medication use	-0.001090
PGS002359(disease_AID_ALL.BOLT-LMM-BBJ)	Autoimmune disease	0.001085

PGS000685(snpnet.Glycated_haemoglobin_HbA1c)	HbA1c [mmol/mol]	0.001067
PGS001996(portability-PLR_neuroticism)	Neuroticism score	0.001050
PGS002767 (Knee_osteoarthritis_prscs)	Knee osteoarthritis	-0.001032
PGS001128(GBE_BIN_FC20020116)	Previous Smoker	-0.001032
PGS002314(body_BALDING1.BOLT-LMM)	Balding Type 1	0.001032
PGS001047(GBE_BIN_FC20001249)	Past tobacco smoking (Smoked occasionally)	-0.001026
PGS000817(GRS200_GGT)	Gamma-glutamyl transferase	-0.001021
PGS001621(GBE_INI25897)	Volume of grey matter in VI Cerebellum (L)	-0.001020
PGS001951(portability-PLR_log_fat_mass)	Whole body fat mass	0.001008
PGS001854(portability-PLR_550.1)	Inguinal hernia	-0.001006
PGS001495(GBE_INI25443)	Mean ISOVF in body of corpus callosum on FA skeleton	0.000996

PGS001623(GBE_INI25906)	Volume of grey matter in VIIb Cerebellum (L)	0.000975
PGS001830(portability-PLR_318)	Tobacco use disorder	-0.000973
PGS001842(portability-PLR_428)	Congestive heart failure; nonhypertensive	0.000963
PGS001717(GBE_INI25600)	WA L2 in tract cingulate gyrus part of cingulum (L)	0.000943
PGS001953(portability-PLR_log_HbA1c)	Glycated haemoglobin (HbA1c)	0.000926
PGS001593(GBE_INI25882)	Volume of grey matter in Putamen (L)	-0.000926
PGS000140(GPpsy)	Broad Depression (seen a General Practitioner for nerves, anxiety,	-0.000908

	tension or depression)	
PGS001490(GBE_INI25391)	Mean ICVF in tapetum on FA skeleton (L)	-0.000895
PGS001716(GBE_INI25599)	WA L2 in tract anterior thalamic radiation (R)	-0.000892
PGS002342(mental_NEUROTICISM.BOLT-LMM)	Neuroticism	0.000892
PGS001607(GBE_INI25797)	Volume of grey matter in Temporal Pole (R)	-0.000888
PGS000722(PRS_Kidney)	Kidney cancer	0.000887
PGS002318(other_MORNINGPERSON.BOLT-LMM)	Chronotype (morning person)	-0.000886
PGS000010(GRS27)	Coronary heart disease	-0.000885
PGS001834(portability-PLR_362.29)	Macular degeneration (senile) of retina NOS	-0.000876

PGS001694(GBE_INI25717)	WA ISOVF in tract inferior fronto-occipital fasciculus (R)	-0.000876
PGS000776(GRS9_Cirr)	Cirrhosis	0.000866
PGS000772(GRS95_SLEgen)	Systemic lupus erythematosus	-0.000864
PGS001583(GBE_INI25848)	Volume of grey matter in Parahippocampal Gyrus, anterior division (L)	-0.000861
PGS001288(GBE_HC95)	Inflammatory bowel disease	-0.000843
PGS002065(portability-ldpred2_550.1)	Inguinal hernia	-0.000840
PGS002145(portability-ldpred2_headaches_for_3m)	Headaches for 3+ months	-0.000831
PGS001061(GBE_INI1289)	Cooked vegetable consumption	-0.000831

PGS001713(GBE_INI25594)	WA L1 in tract uncinate fasciculus (L)	0.000831
PGS001687(GBE_INI25676)	WA ICVF in tract uncinate fasciculus (R)	-0.000827
PGS000237(FABP4)	Fatty acid-binding protein, adipocyte (FABP4) serum levels	0.000827
PGS000993(GBE_QT_FC1001329)	Oily fish consumption	-0.000817
PGS001795(1kgeur_gbmi_leaveUKBBout_UtC_pst_eff_a1_b0.5_phiauto)	Uterine cancer	-0.000817
PGS002295(GRS413_IGF-1)	Insulin growth-like factor-1 level	0.000794
PGS000281(RETN)	Resistin (RETN) serum levels	0.000789
PGS000856(T2D_LiverLipids)	Type 2 diabetes (based on SNPs associated with liver lipids)	0.000786

PGS000651(PRSWEB_PHECODE204.12_UKBB-SAIGE-HRC-X204.12_LASSOSUM_MGI_20200608)	Lymphoid leukemia, chronic	-0.000783
PGS000329(PRS_CHD)	Coronary heart disease	-0.000761
PGS001910(portability-PLR_ever_cannabis)	Ever taken cannabis	-0.000748
PGS001337(GBE_FH1002)	Family history of breast cancer	-0.000747
PGS001046(GBE_BIN_FC40001249)	Past tobacco smoking (Smoked at least once)	-0.000746
PGS001810(portability-PLR_200.1)	Polycythemia vera	0.000744
PGS002288(PRS_POP)	Pelvic organ prolapse	0.000743
PGS000891(GLGC_2021_EAS_LDL_PRS_weights_PT)	Low density lipoprotein (LDL) cholesterol	0.000740
PGS001610(GBE_INI25895)	Volume of grey matter in V Cerebellum (L)	-0.000713
PGS001068(GBE_INI1548)	Variation in diet	-0.000709

PGS001544(GBE_INI25006)	Volume of grey matter	-0.000697
PGS000871(IS_14)	Insulin secretion	-0.000696
PGS002174(portability-ldpred2_log_heel_BUA)	Heel Broadband ultrasound attenuation, direct entry	-0.000694
PGS001400(GBE_INI30020)	Haemoglobin concentration	-0.000689
PGS000857(T2D_Obesity)	Type 2 diabetes (based on SNPs associated with obesity)	0.000672
PGS002311(disease_ASTHMA_DIAGNOSED.BOLT-LMM)	Asthma	-0.000670
PGS002787(BD1_SDPR)	Type 1 bipolar disorder	-0.000662
PGS000326(GRS-JIA-RFN-20)	Rheumatoid-factor-negative Polyarthritis (Juvenile Idiophatic Arthritis)	-0.000661

PGS002352(biochemistry_Cholesterol.BOLT-LMM)	Total cholesterol	0.000660
PGS000230(CXCL1)	C-X-C motif chemokine 1 (CXCL1) serum levels	-0.000648
PGS001484(GBE_INI25369)	Mean ICVF in superior corona radiata on FA skeleton (L)	-0.000636
PGS001476(GBE_INI25373)	Mean ICVF in posterior thalamic radiation on FA skeleton (L)	-0.000630
PGS002588(disease_DERMATOLOGY.P+T.5e-08)	Dermatologic diseases	-0.000623
PGS001645(GBE_INI25490)	WA FA in tract anterior thalamic radiation (L)	0.000604
PGS000365(PRSWEB_PHECODE150_C3-OESOPHAGUS_PRS-CS_MGI_20200608)	Cancer of esophagus	-0.000601

PGS001770(GBE_INI25699)	WA OD in tract superior longitudinal fasciculus (R)	0.000598
PGS001586(GBE_INI25851)	Volume of grey matter in Parahippocampal Gyrus, posterior division (R)	-0.000595
PGS001078(GBE_INI30190)	Monocyte %	-0.000593
PGS001916(portability-PLR_fall_1y)	Falls in the last year	0.000590
PGS000908(PRS_Insomnia)	Insomnia	-0.000590
PGS001616(GBE_INI25898)	Volume of grey matter in Vermis VI Cerebellum	0.000585
PGS001005(GBE_INI134)	Number of self reported cancers	0.000583
PGS001514(GBE_INI87)	Non-cancer illness year/age first occurred	0.000563

PGS002283(GRS15_NAFLD)	Nonalcoholic fatty liver disease	-0.000545
PGS000718(PRPBB_44)	Beta-blocker survival benefit	0.000538
PGS000780(PRS135_allergy)	Allergic diseases	-0.000535
PGS002017(portability-ldpred2_189.2)	Cancer of bladder	-0.000530
PGS002125(portability-ldpred2_ever_cannabis)	Ever taken cannabis	-0.000526
PGS000139(MDDRecur)	Lifetime Major Depressive Disorder (with recurrence)	-0.000519
PGS000249(IL-18)	Interleukin-18 (IL-18) serum levels	-0.000513
PGS001756(GBE_INI25539)	WA MD in tract superior thalamic radiation (R)	0.000508
PGS000858(T2D_Proinsulin)	Type 2 diabetes (based on SNPs associated with proinsulin levels)	0.000506

PGS002020(portability-ldpred2_211)	Benign neoplasm of other parts of digestive system	0.000501
PGS001513(GBE_INI25027)	Median T2star in thalamus (R)	-0.000497
PGS000292(TRANCE)	TNF-related activation-induced cytokine (TRANCE) serum levels	0.000493
PGS002678(disease_AID_ALL.SBayesR)	Autoimmune disease	-0.000488
PGS000628(PRSWEB_PHECODE193_C3-THYROID-GLAND_LASSOSUM_MGI_20200608)	Thyroid cancer	-0.000488
PGS000217(ADM)	Adrenomedullin (ADM) serum levels	0.000488
PGS000324(GRS-JIA-ERA-20)	Enthesitis-related Juvenile Idiophatic Arthritis	-0.000481

PGS001114(GBE_BIN_FC8006154)	Ibuprofen use self-reported	-0.000474
PGS000303(GRS253_eGFR)	Estimated glomerular filtration rate	-0.000466
PGS002218(portability-ldpred2_poorer_health)	Overall health rating	0.000465
PGS001292(GBE_FH1044)	Family history of prostate cancer	0.000462
PGS002316(disease_CARDIOVASCULAR.BOLT-LMM)	Cardiovascular disease	0.000457
PGS001603(GBE_INI25854)	Volume of grey matter in Temporal Fusiform Cortex, anterior division (L)	-0.000451
PGS000634(PRSWEB_PHECODE193_UKBB-SAIGE-HRC-X193_PRS-CS_MGI_20200608)	Thyroid cancer	-0.000440
PGS001814(portability-PLR_241.2)	Nontoxic multinodular goiter	0.000440

PGS000258(KLK6)	Kallikrein-6 (KLK6) serum levels	-0.000437
PGS000080(CC_NHL)	Non-Hodgkin's lymphoma	0.000437
PGS002074(portability-ldpred2_593)	Hematuria	0.000423
PGS000387(PRSWEB_PHECODE165_UKBB-SAIGE-HRC-X165_LASSOSUM_MGI_20200608)	Cancer within the respiratory system	-0.000420
PGS000234(ECP)	Eosinophil cationic protein (ECP) serum levels	0.000406
PGS001550(GBE_INI25838)	Volume of grey matter in Cingulate Gyrus, anterior division (L)	0.000391
PGS001611(GBE_INI25896)	Volume of grey matter in V Cerebellum (R)	0.000389
PGS001351(MAGICTA_EUR_PGS_FI)	Fasting insulin	0.000382
PGS001375(GBE_INI22426)	Average heart rate	-0.000374
PGS002785(SCZ_SDPR)	Schizophrenia	0.000372

PGS002677(disease_ASTHMA_DIAGNOSED.SBayesR)	Asthma	-0.000364
PGS000232(CXCL6)	C-X-C motif chemokine 6 (CXCL6) serum levels	-0.000361
PGS001735(GBE_INI25635)	WA L3 in tract inferior fronto-occipital fasciculus (L)	0.000360
PGS000087(CC_Thyroid)	Thyroid cancer	0.000351
PGS000654(PRSWEB_PHECODE204.4_GWAS-Catalog-r2019-05-03-X204.4_PT_UKB_20200608)	Multiple myeloma	-0.000346
PGS001494(GBE_INI25462)	Mean ISOVF in anterior corona radiata on FA skeleton (R)	-0.000343
PGS001829(portability-PLR_296.2)	Depression	0.000342
PGS000077(CC_LL)	Lymphocytic leukemia	-0.000337
PGS000944(GBE_HC261)	Eczema, dermatitis	-0.000303

PGS001251(GBE_HC1052)	Other interstitial pulmonary diseases (time-to-event)	0.000299
PGS002738(PRS_AUD)	Alcohol use disorder	0.000295
PGS001333(GBE_HC1582)	Chronic obstructive pulmonary disease (algorithmically-defined)	0.000284
PGS002198(portability-ldpred2_log_urea)	Urea	-0.000283
PGS000730(PRS_BCC)	Basal cell carcinoma	0.000282
PGS001069(GBE_INI1528)	Water intake	-0.000278
PGS001817(portability-PLR_250.1)	Type 1 diabetes	0.000270
PGS002043(portability-ldpred2_365)	Glaucoma	-0.000270
PGS000126(Urate_GRS)	Serum urate	-0.000265
PGS001767(GBE_INI25692)	WA OD in tract inferior longitudinal fasciculus (R)	0.000260
PGS001126(GBE_INI1498)	Coffee intake	0.000256

PGS001062(GBE_INI1309)	Fresh fruit intake	-0.000256
PGS001882(portability-PLR_740)	Osteoarthrosis	-0.000244
PGS002156(portability-ldpred2_log_age_first_sex)	Age first had sexual intercourse	-0.000243
PGS000747(PRS_EB)	Coronary artery disease	0.000232
PGS002680(body_BALDING1.SBayesR)	Balding Type 1	0.000231
PGS001983(portability-PLR_log_waist_circ)	Waist circumference	0.000219
PGS001791(1kgeur_gbmi_leaveUKBBout_IPF_pst_eff_a1_b0.5_phiauto)	Idiopathic pulmonary fibrosis	0.000217
PGS001868(portability-PLR_654.2)	Rhesus isoimmunization in pregnancy	0.000213
PGS001419(GBE_INI25091)	Mean FA in cingulum cingulate gyrus on FA skeleton (L)	-0.000209
PGS002284(GRS_286_HDL)	High density lipoprotein cholesterol	0.000177

PGS000625(PRSWEB_PHECODE191.11_UKBB-SAIGE-HRC-X191.11_PT_MGI_20200608)	Cancer of brain	0.000170
PGS002370(blood_LYMPHOCYTE_COUNT.BOLT-LMM-BBJ)	Lymphocyte Count	0.000168
PGS001502(GBE_INI25471)	Mean ISOVF in sagittal stratum on FA skeleton (L)	0.000161
PGS001252(GBE_BIN_FC3002247)	Hearing difficulty and deafness	-0.000160
PGS000305(GRS31_FG)	Fasting glucose	-0.000155
PGS002122(portability-ldpred2_erythrocyte_width)	Red blood cell (erythrocyte) distribution width	-0.000135
PGS002362(bp_DIASTOLICadjMEDz.BOLT-LMM-BBJ)	Diastolic blood pressure	-0.000121
PGS002763 (Hip_osteoarthritis_prscs)	Hip osteoarthritis	-0.000120
PGS001656(GBE_INI25507)	WA FA in tract posterior thalamic radiation (L)	0.000114
PGS001331(GBE_HC322)	Crohns disease	0.000114

PGS002346(blood_RBC_DISTRIB_WIDTH.BOLT-LMM)	Red Blood Cell Distribution Width	-0.000110
PGS000255(IL16)	Pro-interleukin-16 (IL16) serum levels	-0.000109
PGS000338(GRS97_AF)	Atrial fibrillation	0.000104
PGS002298(PRS14_esophageal)	Esophageal cancer	0.000104
PGS001759(GBE_INI25553)	WA MO in tract forceps minor	-0.000103
PGS000096(irf)	Immature fraction of reticulocytes	0.000094
PGS001055(GBE_QT_FC1001180)	Chronotype (morning/evening person)	0.000078
PGS002121(portability-ldpred2_ECG_RR_interval)	RR interval	-0.000074
PGS002728(PRS_hip)	Hip osteoarthritis	0.000067
PGS001418(GBE_INI25071)	Mean FA in cerebral peduncle on FA skeleton (L)	-0.000062
PGS001226(GBE_INI20022)	Birth weight	0.000058

PGS001538(GBE_INI25024)	Volume of accumbens (R)	0.000054
PGS001264(GBE_HC166)	Deep vein thrombosis	0.000050
PGS001579(GBE_INI25805)	Volume of grey matter in Middle Temporal Gyrus, posterior division (R)	-0.000042
PGS000357(PRSWEB_PHECODE145_C3-LIP-ORAL-PHARYNX_PT_MGI_20200608)	Cancer of mouth	0.000032
PGS000446(PRSWEB_PHECODE172.21_20001-1061_PRS-CS_MGI_20200608)	Basal cell carcinoma	0.000032
PGS001771(GBE_INI25701)	WA OD in tract superior thalamic radiation (R)	0.000024
PGS002217(portability-ldpred2_play_computer)	Plays computer games	-0.000024
PGS002140(portability-ldpred2_glasses)	Wears glasses or contact lenses	-0.000021

PGS002193(portability-ldpred2_log_pulse_rate)	Pulse rate, automated reading	0.000017
PGS001629(GBE_INI25920)	Volume of grey matter in X Cerebellum (R)	0.000016
PGS001259(GBE_HC49)	Hayfever/allergic rhinitis	-0.000007
PGS000937(GBE_HC401)	Varicose veins	0.000003
PGS001917(portability-PLR_fat_perc)	Body fat percentage	0.000003

Table S2. Stratified analysis: Odds ratios (ORs) in logistic regression, female only

Model No.	Predictors	OR	95% CI: Lower limit	95% CI: Upper limit	P-value
1	CRC-KL200	1.42	1.34	1.50	<0.0001
2	CRC-LDpred	1.60	1.51	1.70	<0.0001
3	CRC-KL200	1.08	1.00	1.17	0.057
	CRC-LDpred	1.52	1.40	1.64	<0.0001
4	Composite MPS	1.25	1.17	1.34	<0.0001
	CRC-KL200	1.27	1.19	1.36	<0.0001
5	Composite MPS	1.14	1.07	1.22	0.00013
	CRC-LDpred	1.49	1.39	1.59	<0.0001
6	Composite MPS	1.13	1.06	1.21	0.0005
	CRC-KL200	1.05	0.97	1.13	0.26
	CRC-LDpred	1.45	1.33	1.58	<0.0001

Abbreviations. CRC: colorectal cancer. CI: confidence interval. MPS: multiple PRS.

Table S3. Stratified analysis: Odds ratios (ORs) in logistic regression, male only

Model No.	Predictors	OR	95% CI: Lower limit	95% CI: Upper limit	P-value
1	CRC-KL200	1.53	1.44	1.62	<0.0001
2	CRC-LDpred	1.65	1.55	1.75	<0.0001
3	CRC-KL200	1.19	1.10	1.28	<0.0001
	CRC-LDpred	1.47	1.36	1.59	<0.0001
4	Composite MPS	1.23	1.15	1.31	<0.0001
	CRC-KL200	1.39	1.30	1.48	<0.0001
5	Composite MPS	1.15	1.08	1.23	<0.0001
	CRC-LDpred	1.53	1.43	1.64	<0.0001
6	Composite MPS	1.12	1.05	1.20	0.0011
	CRC-KL200	1.16	1.07	1.25	0.0003
	CRC-LDpred	1.41	1.30	1.53	<0.0001

Abbreviations. CRC: colorectal cancer. CI: confidence interval. MPS: multiple PRS.

Table S4. Subgroup analysis: Odds ratios (ORs) in logistic regression

Model No.	Predictors	OR	95% CI: Lower limit	95% CI: Upper limit	P-value
1	CRC-KL200	1.57	1.45	1.70	<0.0001
2	CRC-LDpred	1.79	1.65	1.94	<0.0001
3	CRC-KL200	1.13	1.02	1.26	0.021
	CRC-LDpred	1.65	1.49	1.84	<0.0001
4	Composite MPS	1.22	1.11	1.33	<0.0001
	CRC-KL200	1.43	1.30	1.56	<0.0001
5	Composite MPS	1.09	1.00	1.20	0.059
	CRC-LDpred	1.71	1.56	1.88	<0.0001
6	Composite MPS	1.07	0.97	1.18	0.15
	CRC-KL200	1.11	1.00	1.24	0.051
	CRC-LDpred	1.61	1.44	1.80	<0.0001

Abbreviations. CRC: colorectal cancer. CI: confidence interval. MPS: multiple PRS.

Table S5. Stratified analysis: Comparison of AUCs, females

Comparison pair No.	Model A	Model B	Point estimate of difference in AUC	95% CI of the difference in AUC	P-value
1	CRC-KL200 + MPS	CRC-KL200	0.012	0.003, 0.021	0.008
2	CRC-LDpred + MPS	CRC-LDpred	0.004	0.001, 0.009	0.031
3	CRC-KL200 + CRC-LDpred + MPS	CRC-KL200 + CRC-LDpred	0.003	0.000, 0.007	0.067

Abbreviations. AUC: area under the Receiver Operating Curve. CRC: colorectal cancer. CI: confidence interval. MPS: multiple PRS.

Table S6. Stratified analysis: Comparison of AUCs, males

Comparison pair No.	Model A	Model B	Point estimate of difference in AUC	95% CI of the difference in AUC	P-value
1	CRC-KL200 + MPS	CRC-KL200	0.016	0.009, 0.023	<0.0001
2	CRC-LDpred + MPS	CRC-LDpred	0.005	0.001, 0.010	0.015
3	CRC-KL200 + CRC-LDpred + MPS	CRC-KL200 + CRC-LDpred	0.004	0.001, 0.008	0.019

Abbreviations. AUC: area under the Receiver Operating Curve. CRC: colorectal cancer. CI: confidence interval. MPS: multiple PRS.

Table S7. Subgroup analysis: Comparison of AUCs

Comparison pair No.	Model A	Model B	Point estimate of difference in AUC	95% CI of the difference in AUC	P-value
1	CRC-KL200 + MPS	CRC-KL200	0.015	0.007, 0.023	0.0002
2	CRC-LDpred + MPS	CRC-LDpred	0.002	0.000, 0.015	0.13
3	CRC-KL200 + CRC-LDpred + MPS	CRC-KL200 + CRC-LDpred	0.002	0.000, 0.004	0.098

Abbreviations. AUC: area under the Receiver Operating Curve. CRC: colorectal cancer. CI: confidence interval. MPS: multiple PRS.

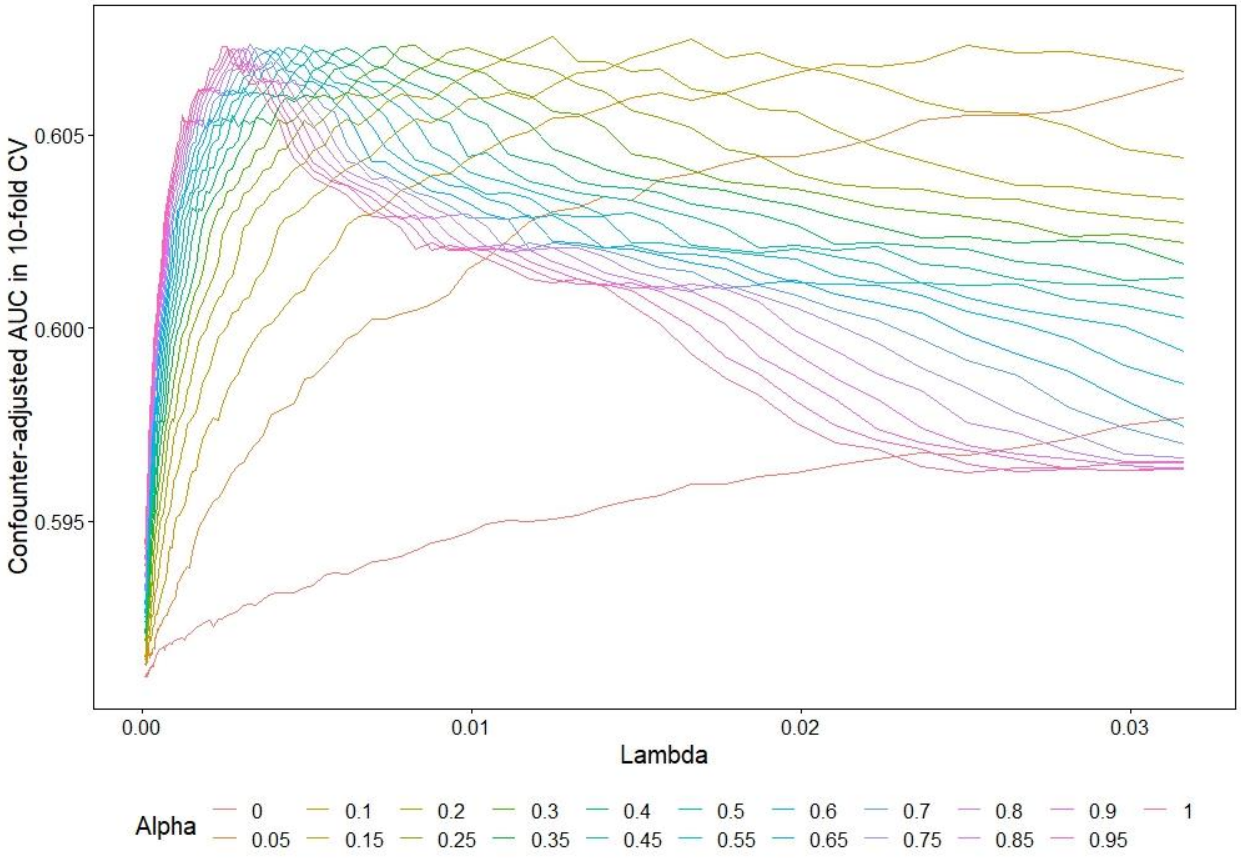


Figure S1. Confounder-adjusted AUC in 10-fold CV

The mean value of the confounder-adjusted AUC in 10-fold CV by different combinations of alpha and lambda values in penalized regression ML models.

Abbreviations. AUC: area under the Receiver Operating Curve. CV: cross-validation. ML: machine learning.

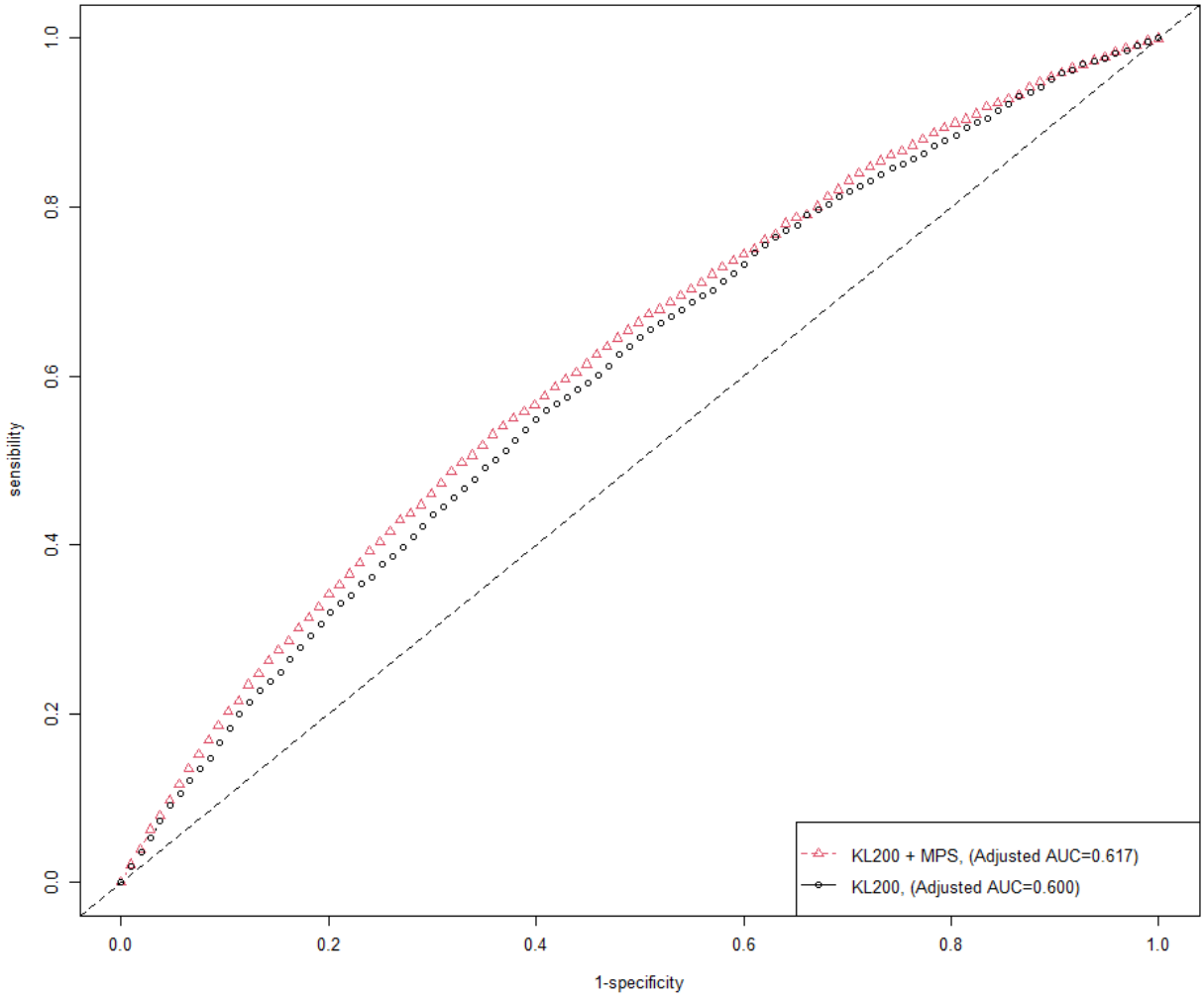


Figure S2. Main analysis: Confounder-adjusted AUC comparing MPS+CRC-KL200 to CRC-KL200 only

The red line is the confounder-adjusted ROC curve of a risk prediction model with CRC-KL200 and MPS, and the AUC was 0.617 in the validation dataset; the black line is the confounder-adjusted ROC curve of a risk prediction model with CRC-KL200 only, and the AUC was 0.600 in the validation dataset.

Abbreviations. AUC: area under the Receiver Operating Curve. CRC: colorectal cancer. CI: confidence interval. MPS: multiple PRS. ROC: Receiver Operating Curve.

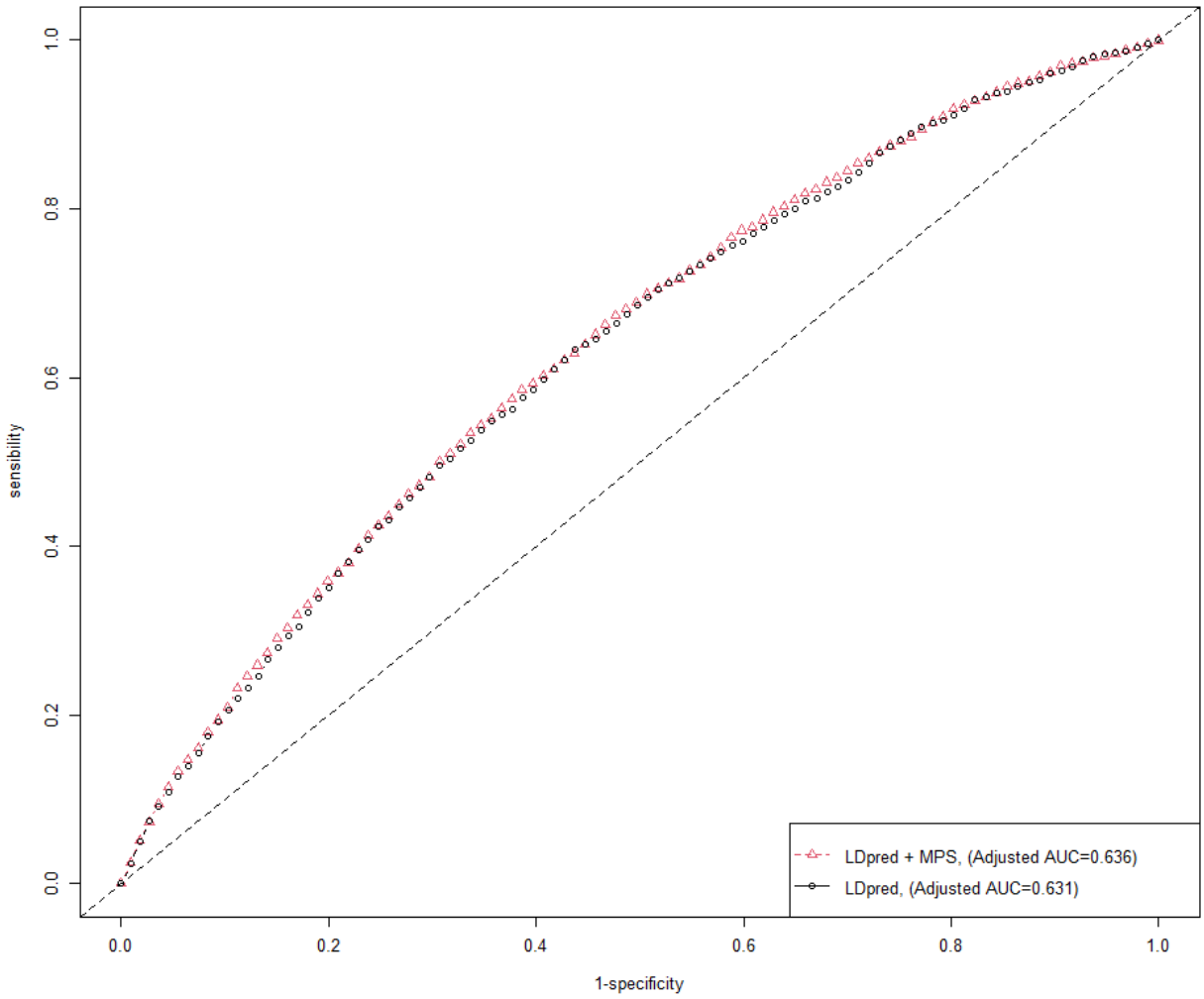


Figure S3. Main analysis: Confounder-adjusted AUC comparing MPS+CRC-LDpred to CRC-LDpred only

The red line is the confounder-adjusted ROC curve of a risk prediction model with CRC-LDpred and MPS, and the AUC was 0.636 in the validation dataset; the black line is the confounder-

adjusted ROC curve of a risk prediction model with CRC-LDpred only, and the AUC was 0.631 in the validation dataset.

Abbreviations. AUC: area under the Receiver Operating Curve. CRC: colorectal cancer. CI: confidence interval. MPS: multiple PRS. ROC: Receiver Operating Curve.

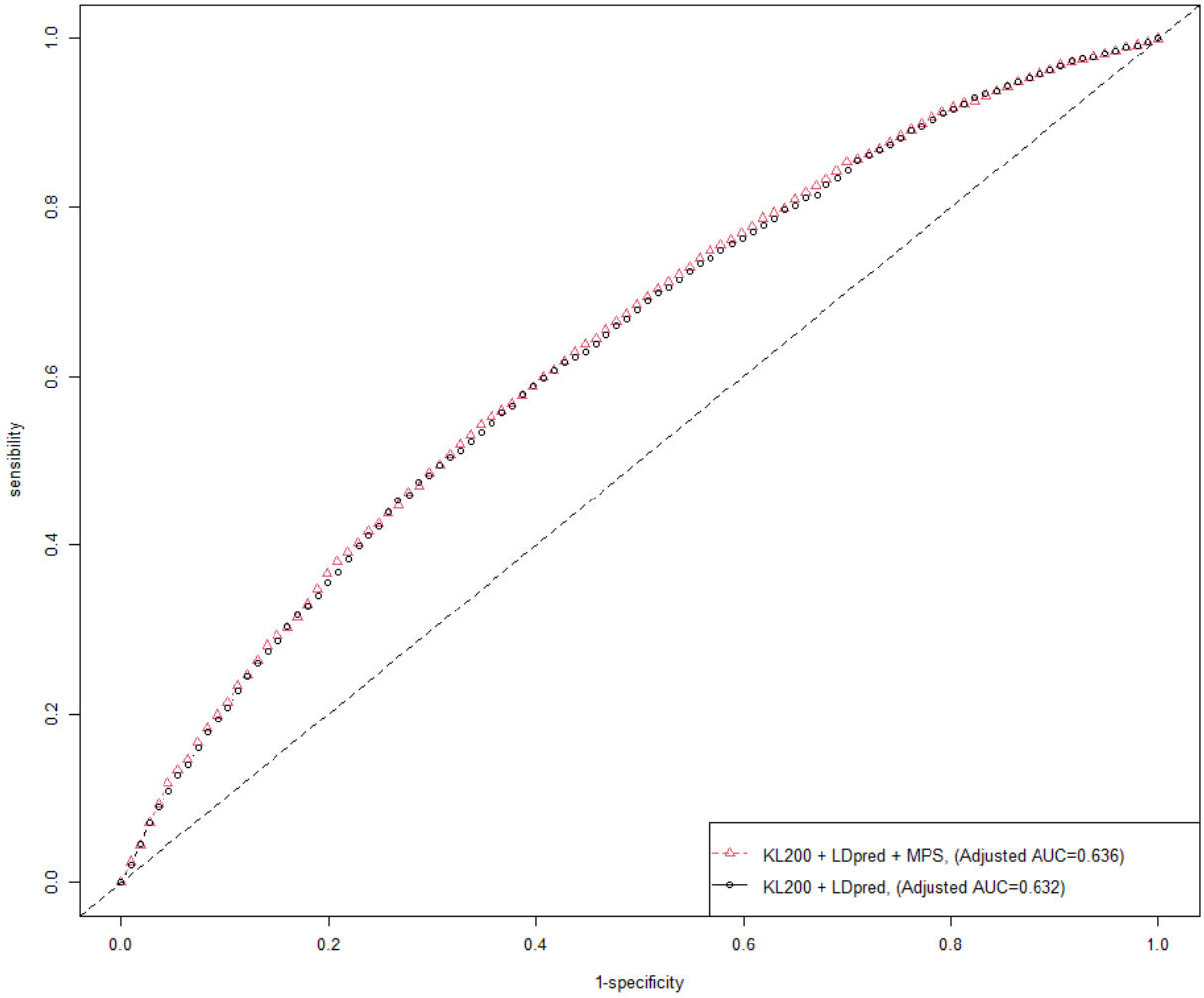


Figure S4. Main analysis: Confounder-adjusted AUC comparing MPS+CRC-KL200+CRC-LDpred to CRC-KL200+CRC-LDpred

The red line is the confounder-adjusted ROC curve of a risk prediction model with CRC-KL200, CRC-LDpred, and MPS, and the AUC was 0.636 in the validation dataset; the black line is the confounder-adjusted ROC curve of a risk prediction model with CRC-KL200 combined with CRC-LDpred, and the AUC was 0.632 in the validation dataset.

Abbreviations. AUC: area under the Receiver Operating Curve. CRC: colorectal cancer. CI: confidence interval. MPS: multiple PRS. ROC: Receiver Operating Curve.

Chapter 3. Cost-effectiveness of population-wide genomic screening for Lynch Syndrome and Polygenic Risk Scores to inform Colorectal Cancer screening

Abstract

Introduction

Genomic screening to identify individuals with Lynch Syndrome (LS) and those with a high polygenic risk score (PRS) promises to personalize Colorectal Cancer (CRC) screening. Understanding its clinical and economic impact is needed to inform screening guidelines and reimbursement policies.

Methods

We developed a Markov model to simulate individuals over a lifetime. We compared LS+PRS genomic screening to standard of care (SOC) for a cohort of US adults at age 30. The Markov model included health states of "no CRC", CRC stages (A-D) and death. We estimated incidence, mortality, and discounted economic outcomes of the population under different interventions.

Results

Screening 1000 individuals for LS+PRS resulted in 1.36 fewer CRC cases and 0.65 fewer deaths compared to SOC. The incremental cost-effectiveness ratio (ICER) was $124,415 per quality-adjusted life-year (QALY); screening had a 69% probability of being cost-effective using a willingness to pay threshold of $150,000/QALY. Setting the PRS threshold at the 90th percentile

of the LS+PRS screening program to define individuals at high risk was most likely to be cost-effective compared to 95th, 85th, and 80th percentiles. Genomic screening at age of 0 years yielded the largest incremental QALYs per person of 0.0007 and 0.0006, attributable to individuals with LS and individuals with a high PRS, respectively.

Conclusion

Population-level LS+PRS screening is marginally cost-effective and a threshold of 90th percentile is more likely to be cost-effective than other thresholds.

Introduction

Colorectal cancer (CRC) is a leading cause of cancer death in the US and globally.[41] It is estimated that more than 150,000 people will be diagnosed with CRC and more than 50,000 people will die from CRC in 2024 in the US.[41] However, CRC is one of the most preventable cancers by screening.[40] Screening strategies, such as colonoscopy, reduce the incidence of CRC by removing polyps and improves morbidity and mortality by diagnosing patients at an earlier stage.[40] Many studies have shown that CRC screening improves health outcomes and is cost-effective.[72]

Current CRC screening guidelines are primarily based on age and family history (FH).[11,73] However, FH is assessed inconsistently across practices and requires detailed information about relatives affected by CRC and the age at diagnosis, which results in the under-utilization and over-utilization of CRC screening.[12]

CRC screening based on genetic risk shows promises to advance risk stratification and personalized screening. Monogenic rare variants that results in genetic syndrome, such as Lynch Syndrome (LS), are associated with an absolute lifetime risk of CRC of up to 70%.[74] These individuals should undergo annual or biennial screening starting early in adulthood.[75] Recently, polygenic risk scores (PRSs) for CRC have been developed to measure risks associated with common, low-penetrance variants across the genome.[24] Individuals with a PRS higher than the 95th percentile of the population are at twice the risk for CRC (6-8%), which is similar in magnitude as having a first-degree relative with CRC, compared to the average-risk individuals.[24] These increased-risk individuals may receive early and more frequent screening.[73]

Although both LS and PRS screening promise to risk stratify individuals,[16,24,37] their clinical and economic impact on the population is unknown. In particular, understanding the costs and

clinical benefits of implementing population-level genomic screening for CRC will guide policymakers to determine access and reimbursement.

Our previous publication examined the cost-effectiveness of population-level LS screening and found that it was marginally cost-effective.[37] Several publications found that risk stratification based on CRC-PRS was not cost-effective compared to uniform screening.[76,77] However, our study sought to inform a few key remaining issues. First, a genomic screening program that informs both LS and PRS status should be examined. A single screening assay could modify screening strategies based on both monogenic and polygenic risk. Second, the optimal age at which the genomic screening is implemented should be understood. Third, PRS is a continuous metric, and individuals will be identified at a higher risk based on a given threshold of PRS. Yet the optimal threshold is unclear. Lastly, the impact of false reassurance after receiving a "negative genomic result" on the value of genomic screening is unclear.

Methods

General approach

We conducted a cost-effectiveness analysis. We modeled a cohort of US adults aged 30 years and simulated their lifetime trajectories until death under different interventions. These interventions were (1) population-level LS+PRS screening, (2) population-level LS screening only, (3) population-level PRS screening only, and (4) standard of care (SOC) where CRC screening strategies were determined by age and FH.

For each intervention, we modeled the following outcomes: (1) CRC incidence, (2) CRC mortality, (3) life-years (LYs), (4) quality-adjusted life-years (QALYs), and (5) costs. We calculated incremental outcomes by comparing across interventions and the incremental cost to

effectiveness ratio (ICER). The ICER was then compared to a willingness-to-pay (WTP) threshold of $100,000 and $150,000 per QALY gained.[78] If an ICER between an intervention of interest and a comparator intervention was below a given WTP threshold, then the intervention of interest was considered cost-effective.

Population screening model

Our model had two components. The first component was a decision tree, in which all individuals were categorized into different groups based on (1) CRC risk, (2) uptake of genomic screening, (3) recommended colonoscopy screening based on the perceived risk, and (4) adherence to the recommended colonoscopy screening. (Figure 1) After the decision tree, all individuals entered the Markov model, which was used to track the trajectories over a lifetime time horizon (Figure S1). All individuals were free of CRC at the entry, and some might be diagnosed with CRC at different stages (A-D), and some might die from CRC or other causes (Figure S1). The model cycle was 1-year.

The model was developed in Microsoft Excel. We used a US healthcare sector perspective. LYs, QALYs, and costs were discounted at 3% annually.

CRC risk and screening

Three types of risk factors impacted the CRC risk level of the modeled population. The first factor was LS status. The prevalence of LS in the population was based on Geisinger MyCode Community Health Initiative.[79] LS patients followed LS surveillance guidelines, where individuals underwent intensive colonoscopy annually until the age of 75 years.[75]

The second factor was PRS status. In the base-case, the threshold was set at 95th percentile, meaning that 5% of the individuals were designated as "high risk". In scenario analyses, we explored different thresholds of PRS.

The third factor is FH status. We defined positive FH as having at least 1 first-degree relative with CRC. FH assessment in clinical practice is complex and the implementation of FH assessment is heterogenous in practice.[12] Because the focus of this analysis was the value of genomic screening, we chose to primarily focus on the first-degree relatives' CRC status. To account for inconsistent evaluation of FH in practice, we assumed only 50% of individuals with positive FH knew about their FH status.[12]

Based on PRS status and FH status, the non-LS population was categorized into 4 risk groups: (1) average-risk individuals who underwent 10-yearly colonoscopy screening starting from age 45 years, based on United States Preventive Service Task Force (USPSTF) guidelines,[11] (2) increased-risk individuals due to a high PRS only, (3) increased-risk individuals due to positive FH only, and (4) increased-risk individuals due to both a high PRS and positive FH. The last three groups underwent 5-yearly colonoscopy starting from age 40 years.[80]

Clinical Parameters

All parameters can be found in Table S1 and are summarized below. More details can be found in Appendix B.

LS patients

The CRC risk of LS patients was modeled based on a logistic model from Snowsill et al.[81] The hazard ratio (HR) associated with colonoscopy screening was obtained from Jarvinen et al., who analyzed the incidence among LS patients from families with hereditary nonpolyposis CRC.[82]

Additionally, the stage distribution at diagnosis among LS patients was obtained from Stupart et al., who analyzed data from 200 LS patients with a mean follow-up of four years and found that intensive colonoscopy significantly reduced the proportion of late-stage CRC at diagnosis.[83]

Non-LS individuals

CRC risk and stage distribution without colonoscopy screening

We used the CRC risk and the stage distribution from the Surveillance, Epidemiology, and End Results (SEER) Program to represent the risk and stage distribution for the general population in the natural history in 1990s, when CRC screening was not yet widely adopted.[84] We then obtained the annualized incidence rate for modeling.

Prevalence and relative risk (RR) of high PRS without colonoscopy screening

We selected a PRS for CRC that Thomas et al. developed and reported RRs of individuals with a high PRS by different PRS thresholds.[24] We chose this article to inform our model because this PRS was developed based on genome-wide information using large and diverse samples, and was validated in an independent sample.[24] We then re-weighted the CRC risk of individuals with a non-high PRS such that the CRC risk for the general population remained the same across different thresholds. We varied the RRs in sensitivity analyses to account for uncertainty in PRS-predicted risk.

Incidence reduction associated with colonoscopy screening

We utilize studies by Nishihara et al., Doubeni et al., and Heisser et al. to inform the CRC incidence reduction associated with colonoscopy screening.[85-87] In these articles, the HR of colonoscopy vs no screening ranged from 0.3 to 0.6.[85-87] Nishihara et al. also reported the HR by

FH status, which was used in our model to inform the incidence reduction for individuals with positive FH.[85]

Stage shift associated with colonoscopy screening

Stage shift was obtained from a publication that examined the stage distribution before and after screening in multiple countries in Europe.[88] Roughly, 20% more individuals were identified at stage A, the percentage of individuals diagnosed at stage B remained largely unchanged, 3-5% fewer individuals were identified at stage C, and 15-20% fewer individuals were identified at stage D.[88] We used these estimates to inform the stage shift in our model.

Survival after CRC diagnosis

We obtained the 10-year survival from SEER 2000-2019 and obtained annualized transition probabilities.[89] Survival by FH and PRS can be found in Appendix B.

Cost parameters

We included (1) cost of genetic screening for LS+PRS, LS only and PRS only, (2) cost of colonoscopy screening, and (3) medical costs associated with CRC treatment. Previous cost-effectiveness studies assumed $200 per test for LS or PRS.[37,76] Based on feedback from a subject matter expert, a single genetic test might be able to return information on both LS and PRS where the information of LS is based on the sequencing data whereas the information of PRS is based on the genotyping data.[90,91] To account for efforts for data reporting on both LS and PRS, we assumed $250 per LS+PRS genomic screening. Additionally, we assumed a confirmatory genetic testing cost of $200, which was applied to those who tested positive for LS and/or PRS. The cost of colonoscopy was obtained from our previous work.[37] The medical costs associated

with CRC by the first year, continuing treatment and terminal year were obtained from Zauber et al.[92] All costs were inflated to 2023 US dollars.

Health-related Quality of Life (HRQOL) parameters

HRQOL for individuals in the "no CRC" state was assumed to be 1.0. Disutility for individuals with CRC was obtained from Djalalov et al, who systematically reviewed 26 publications, modeled the association between the disutility and a variety factor of CRC, and reported HRQOL by CRC stages.[93] Based on these estimates, we applied 0.05 disutility for individuals diagnosed at stage A, B and C in the first year, and 0.20 disutility for the following year (i.e., year 2), 0.24 disutility for individuals diagnosed at stage D in the first year and 0.20 disutility for following years.

We incorporated a disutility of 0.04 in year 1 for 4 months associated with confirmed LS status, similar to previous CEA studies on LS genomic screening.[37,81] Because "PRS high" elevated the CRC risk much less than LS, we assumed no disutility year 1 associated with knowing a high PRS status in the base-case. We varied this parameter value from 0 to 0.02 applicable for 4 months in sensitivity analysis.

Behavioral parameters

In the base-case, we assumed 100% uptake of LS and PRS genomic screening.

Based on the literature, we assumed LS patients who were identified via SOC had a 70% likelihood being adherent to intensive colonoscopy screening, and those who were identified through genomic screening had an increased adherence of 80%.[37]

Based on several studies, we assumed 50% of the general population was adherent to CRC screening and having positive FH boosted adherence by 10%.[94,95] For individuals with positive

FH and/or a high PRS who were not adherent to the 5-yearly colonoscopy screening starting from age 40 years, we assumed 50% of them still received average screening (10-yearly colonoscopy screening starting from age 45 years).

Additionally, a recent meta-analysis suggested that receiving a positive PRS result might promote health-related behaviors, and yet the heterogeneity in these studies were high and the long-term impact was unknown.[96] Thus, we assumed that having a high PRS boosted adherence by 3% in the base-case but varied this parameter value in sensitivity analysis.

Butterfield et al. surveyed more than 300 patients who received a negative genomic result on 17 genes related to 11 medically actionable conditions and found that participants did not intend to change health-related behaviors.[39] In the base-case, we assumed no impact of knowing a negative genomic result on screening adherence. We conducted a threshold analysis to examine this assumption.

External Validation

We first simulated the CRC natural history and effectiveness of colonoscopy screening. We compared our results to previously observational and cost-effectiveness studies.[85,92,97-100] Second, we compared the QALYs and LYs of LS genomic screening in our model with a published study on the population-level LS genomic screening in the US.[37] Finally, we compared our results of PRS genomic screening with previously published studies on PRS screening in CRC screening.[76,77,101]

Analysis

We calculated the lifetime CRC incidence, CRC mortality, LYs, QALYs, and total costs for each intervention arm. We ranked the interventions by the increasing order of clinical outcomes, and

then we calculated the incremental outcomes comparing an intervention to its next best intervention and the ICER.

We performed one-way and probabilistic sensitivity analyses. In one-way sensitivity analysis, each parameter was varied at a time to the low value or to the high value. In probabilistic sensitivity analysis, all parameters' values were varied simultaneously by randomly drawing from their distributions. In total, we simulated the population in 3000 runs and obtained the 95% credible range (CR) of each outcome.

Additional analyses

We first explored the value of LS+PRS genomic screening implemented at different ages. All individuals entered the model at age 0 years and were followed up for life. LS+PRS screening could be implemented from 0 to 70 years of age. Across all ages at screening, we calculated model outcomes comparing the LS+PRS screening to SOC. We calculated the number of CRC cases and deaths prevented per 1000 individuals in the model, and incremental LYs and QALYs per person in the model. Additionally, we changed the baseline age of model entry to the age of 20 years and 40 years. In this case, genomic screening was offered upon model entry, and we calculated the ICER per person accordingly.

Second, we examined the impact of the PRS threshold on clinical and economic outcomes, including 90^{th}, 85^{th}, and 80^{th} percentiles. Third, we adopted a limited societal perspective by incorporating costs associated with productivity loss due to CRC.[102] Lastly, we performed a threshold analysis to examine the impact of harms associated with knowing a result of "PRS non-high" on the value of LS+PRS genomic screening – at what proportion of the individuals without LS and FH who were "PRS non-high" became less adherent the QALYs of LS+PRS genomic screening could be nullified.

Results

Base-case

In the base-case, screening 1000 US adults aged at 30 years for LS only resulted in 0.40 fewer CRC cases compared to SOC, screening for PRS further resulted in 0.57 fewer CRC cases compared to LS screening, and screening for both LS and PRS resulted in 0.40 fewer cases compared to PRS screening (Table S2).

Across all interventions, PRS screening was dominated by LS screening by having fewer QALYs (25.1321 vs 25.1322) but more costs ($3,101 vs $3,092) (Table 1, Table S3). When compared to SOC, LS screening had an 0.0016 incremental QALYs at an incremental cost of $258, resulting in an ICER of $165,896. LS+PRS screening then extendedly dominated LS screening by having an ICER of $80,091 compared to LS screening. Ultimately, LS+PRS screening had an incremental QALYs of 0.0030 at an incremental cost of $374, leading to an ICER of $124,415/QALY (Table 1, Table S3).

Sensitivity analysis

In one-way sensitivity analysis, the ICER of LS+PRS screening compared to SOC was most sensitive to RR of CRC for individuals with a high PRS, the proportion of CRC Stage D at diagnosis for LS patients, cost of genetic screening, and risk of CRC among LS patients by age 70 (Figure S1).

LS+PRS screening had a probability of 14% and 69% of being the most cost-effective intervention among all interventions, using a WTP threshold of $100,000/QALY and $150,000/QALY, respectively. LS only screening had a probability 0.4% and 5% of being the most cost-effective among all interventions under WTP thresholds of $100,000/QALY and

$150,000/QALY, respectively; and PRS screening had a probability of 1% and 0.7% of being the most cost-effective under WTP thresholds of $100,000/QALY and $150,000/QALY, respectively (Figure S2).

External validation

Among 1000 average-risk individuals aged 40 years, previous cost-effectiveness studies estimated that 30-72 individuals would be diagnosed with CRC without screening, and the estimate from our model was 63-64 individuals.[92,98,99] Additionally, with 10-yearly colonoscopy starting from age 45 years and assuming perfect adherence, our model estimated an incidence reduction of 57-59%, which was also in line with previous literature.[92,97-99] Furthermore, in our model, population-level LS screening resulted in 0.0018 QALYs, 0.0017 LYs and 0.0005 fewer CRC cases, which was very close to the published results of LS genomic screening.[37] More details can be found in Appendix C.

Age at LS+PRS testing

For a cohort of 1000 unselected US adults at age 0, screening for LS+PRS resulted in 1.36 fewer CRC cases, including 0.95 fewer CRC cases attributable to PRS and 0.41 fewer CRC cases attributable to LS. This means that, in order to prevent 1 CRC case, genomic screening needed to be offered to 735 individuals. If delaying the LS+PRS testing to age 30, only 0.39 CRC cases would be prevented by LS testing (Figure 2 Panel A). Furthermore, screening at age 0 yielded an incremental discounted LYs of 0.007 and 0.006 per person from LS and PRS, respectively; if the screening was delayed to the age of 30 years, the incremental LYs saved from LS decreased to 0.005 (Figure 2 Panel B). Results for mortality and QALYs can be found in Figure S3-S4.

Additionally, if LS+PRS genomic screening was offered to a cohort of individuals at the age of 20 years, the incremental cost per person was $376 and the incremental QALY per person was 0.0024, resulting in an ICER of $156,250 per QALY gained. If genomic screening was offered to individuals at the age of 40 years, the incremental cost was $378 per person and the incremental QALY was 0.0035 per person, resulting in an ICER of $109,359 per QALY gained.

PRS thresholds

Screening for LS and PRS with a PRS threshold of 80th percentile resulted in the largest clinical benefits if screening for LS and PRS at age 30 years: 2.3 fewer CRC cases and 1.2 fewer CRC deaths, compared to SOC per 1000 people in the model (Table S4).

However, under WTP thresholds of $100,000 and $150,000/QALY, LS+PRS screening with 90th percentile as the threshold had a probability of being the most cost-effective intervention of 23% and 28%, respectively, among all PRS thresholds (Figure 3).

Societal perspective

The incorporation of productivity loss associated with CRC for patients diagnosed with CRC resulted in an incremental cost of $353, an incremental QALY of 0.003, and an incremental LYs of 0.003 per person, between LS+PRS screening and SOC. The ICER decreased to $117,396 per QALY.

Harms associated with a negative genomic result

Among all individuals who did not have LS or positive FH and received a “negative result” from LS+PRS screening, if 15% of these individuals completely avoided screening for the rest of their lives because of the false reassurance, the harms could nullify the incremental QALYs of LS+PRS screening.

Discussion

Key findings

We conducted a cost-effectiveness analysis of a population-level genomic screening program for an unselected cohort of 30-year-olds within the US. We found that a LS+PRS genomic screening program had a 69% probability of being cost-effective under a WTP threshold of $150,000/QALY, whereas other genomic screening strategies had a much lower probability of being the most cost-effective intervention (Figure S2).

We also found that PRS-only screening was dominated by LS-only screening (Table S3). There are two mechanisms. First, the risk of CRC for LS patients is higher than for high-PRS patients, and CRC occurs earlier in life for LS patients compared to individuals with a high PRS (Figure 2).[103] Second, LS patients have a greater stage shift benefit from screening than high-PRS patients.[83]

We also found that offering genomic screening to individuals at age of 20 years resulted in a higher ICER, but offering genomic screening to individuals at age of 40 years resulted in a lower ICER. There are two mechanisms: the risk of CRC was relatively low prior to age of 40 years for the majority of the population,[84] and thus clinical benefits would occur later in the lifetime; and yet the cost of genomic screening occurred in the first year.

However, we found that delayed genomic screening led to fewer clinical benefits because individuals might have developed CRC or even died from CRC before the genomic screening. Additionally, we found that delaying genetic screening had a larger clinical impact for LS patients than high-PRS patients and the effect of PRS screening remained largely unchanged before age 40 years (Figure 2, Figure S3-S4). There are two mechanisms. First, the risk of CRC

for LS patients is higher in earlier life compared to individuals with a high PRS,[103] and thus LS patients were more likely to be already diagnosed with CRC or die from CRC than individuals with a high PRS. Second, colonoscopy screening intervention began from the age of 20 years for LS patients but the age of 40 years for individuals with a high PRS.[75,80]

Additionally, we found that a 90th percentile threshold to define a high PRS was more likely to be cost-effective than 95th, 85th and 80th percentiles, even though the 80th percentile had the highest clinical benefits (Figure 3, Table S4). This is because the increased screening cost was 1.4 times higher for the 80th vs. 90th percentile, whereas the clinical benefit was only 1.2 times greater.

Comparison to previous PRS screening literature

Naber et al. reported that PRS testing resulted in <1 fewer CRC case, <1 fewer CRC death, and minimal LYs saved.[77] In our model, PRS screening for 1000 adults aged 40 years resulted in 0.7 fewer CRC cases, 0.2 fewer CRC deaths, and 0.9 LYs saved compared to uniform screening with full adherence. The differences in modeled results might be due to different PRS risk stratification. In our model, the population was dichotomized based on PRS whereas in Naber et al., the population was stratified into 60 groups.[77]

Cenin et al. reported that the most cost-effective PRS-guided screening strategy among 1000 adults aged 40 years resulted in 12 more CRC cases, 3 more CRC deaths, 8 fewer QALYs and 7 fewer LYs, compared to uniform screening.[76] Whereas in our model, PRS screening resulted in 2 fewer CRC cases, 0.6 fewer CRC deaths, 2 QALYs gained, and 2 LYs saved compared to uniform screening.[76] Interventions examined in Cenin et al. reduced the utilization of colonoscopy,[76] and frontier strategies were not aligned with our screening strategy or the screening strategies in the US.[11]

Lastly, van den Puttelaar et al. examined the cost-effectiveness of a risk prediction model that incorporated both PRS and environmental risk score in guiding CRC screening.[101] This intervention led to 23 LYs saved and 2 QALYs gained compared to a uniform screening with full adherence per 1000 individuals aged 40 years;[101] yet it was unclear why the QALYs gained was less than one tenth of the LYs saved. In our model, PRS-guided screening resulted in 0.7 fewer CRC cases, 0.2 fewer CRC death, 0.9 LYs saved and 1 QALYs gained, compared to uniform screening with full adherence for the same population in van den Puttelaar et al.[101] Additionally, authors stratified individuals into 800 risk groups,[101] which might be challenging to be implemented in clinical practice.

We noted that Cenin et al., Naber et al, and van den Puttelaar et al. did not perform probabilistic sensitivity analyses to examine the uncertainty of the cost-effectiveness of personalized CRC screening.[76,77,101] Examining uncertainty via probabilistic sensitivity analysis is good practice in economic modeling, particularly for models that use calibration to derive parameter values.[104] Additionally, different PRS algorithms might result in different risk stratification for the same individual.[68,105] However, it is unknown whether and how likely the PRS-guided CRC screening was cost-effective in probabilistic sensitivity analysis in these studies.[76,77,101]

More details of comparisons can be found in Appendix C.

Implications

Our study has a few important implications. First, genomic screening for LS is a significant and clinically meaningful component of population-level screening for CRC risk. Although previous studies have primarily focused on population-level PRS screening among individuals with an average risk or individuals with FH,[76,77] in clinical practice, genetic screening might be offered to the general population, including those with LS or positive FH.

Second, our study demonstrated the importance of carefully selecting PRS thresholds to stratify the population. With more individuals categorized into a "high risk" group, the predicted risk for that group decreased, and therefore it might not result in impactful clinical and economic outcomes. Previous literature on clinical utility and economic analyses has not yet paid attention to exploring the impact of different PRS thresholds.[76,77] Future studies should continue to understand the impact of threshold of PRS risk stratification in CRC and other disease areas.

Third, our study demonstrated the importance of communication regarding negative genomic results. Previous economic analyses have not incorporated the possibility that patients with a non-high PRS could become less adherent.[76,77] Our study showed that if 15% of patients with a negative genomic result chose not to adhere to recommended screening, the harms associated with this risk-taking behavior could cancel out the clinical value of LS+PRS genomic screening accrued by high-risk individuals.

Fourth, in our study, individuals with a high PRS began colonoscopy screening from age of 40 years. This was based on the current screening guidelines for individuals with positive FH.[73] However, it is possible that the value of genomic screening changes if these individuals begin colonoscopy screening before the age of 40 years. This is especially relevant if genomic screening is provided to individuals whose predicted risk is high but are much younger than 40 years. Future studies can examine the value of different screening strategies based on PRS levels to inform potential updates of screening guidelines.

Fifth, genomic screening has economy of scale because once the genetic information is obtained, generating PRS results for additional diseases may not entail substantial additional efforts. Additionally, genetic information may be obtained via existing CRC screening and early detection tools such as liquid biopsy via cell-free DNA,[106] which may enable the generation of

PRSs CRC as well as other diseases and the detection of rare mutations. Thus, it is anticipated that the obtainment of genomic information may become easier, and the cost may become more acceptable.

Lastly, our study emphasized a careful selection of age at LS+PRS genomic screening. Offering genomic screening to individuals with an age of 20 years may lead to a higher ICER compared to that of individuals with an age of 40 years. However, individuals who have developed CRC or died from any cause prior to age of 40 years would not be eligible to receive the benefits of genomic screening, especially individuals with LS. A previous study found that the population-level LS genomic screening should be offered no later than the age of 40 years.[37] These individuals represented the "missed opportunity" and were not reflected by the ICER. Policy makers should explicitly consider not only the ICER of genomic screening offered at different ages of individuals but also the clinical benefits that are missed prior to the genomic screening.

Strengths

Our study has a few strengths. First, we performed extensive external validation by comparing our results with previous literature in colonoscopy screening, LS screening, and PRS screening.[37,77,92,97-99] This supported the validity of our model and the results. Second, we conducted probabilistic sensitivity analyses to examine the impact of uncertainty on the outcomes. Particularly, we incorporated a wide range of RR of CRC risk of individuals with a high PRS and examined its impact on the outcomes. The one-way sensitivity analysis showed that the RR for those with a high PRS was one of the most influential parameters on the cost-effectiveness of genomic screening. Third, our analysis focused on the general population, where individuals with LS, positive FH and a high PRS were all included. This allowed us to simulate

the trajectories for different risk groups and assess the benefits of LS+PRS, LS-only, and PRS-only genomic screening programs.

Limitations

Our study has several limitations. First, direct evidence for long-term CRC screening effectiveness and adherence is scarce. We addressed this limitation by assessing uncertainty through sensitivity analyses. Second, our model does not yet incorporate the differential predictive performance of PRS for underserved and understudied populations.[24] Understanding the relationship between genomic screening and health disparities is planned for future analyses. Similarly, PRS for CRC might be more predictive for early-onset patients than late-onset patients.[107] Future studies can assess the cost-effectiveness of PRS in this younger-age group. Third, a single genetic assay that returns information of both LS and PRS is not currently available. However, with rapid advances in genomic sequencing and genotyping technology, it is foreseeable that this assay may become available. Fourth, we only examined one PRS algorithm.[24] Future studies may evaluate the cost-effectiveness of different PRS algorithms. Lastly, our study focused on CRC and did not examine the value of genomic screening that may guide screening for other diseases. Future studies can fill these knowledge gaps.

Conclusion

Population-level genomic screening for LS and PRS to guide personalized CRC screening may be cost-effective assuming a single genetic test is available at a cost of $250. Additionally, setting a high-risk threshold for PRS at 90% will provide the optimal value for a screening policy.

Tables and figures

Table 1. Base-case results per individual in the model, ranked by increasing LYs

	LYs	QALYs	Costs
SOC	25.1335 (25.1268, 25.1398)	25.1306 (25.1235, 25.1373)	$2,835 ($2,464, $3,278)
PRS screening	25.1348 (25.1283, 25.1409)	25.1321 (25.1251, 25.1385)	$3,101 ($2,713, $3,558)
LS screening	25.1350 (25.1284, 25.1412)	25.1322 (25.1251, 25.1387)	$3,092 ($2,703, $3,539)
LS+PRS screening	25.1363 (25.1299, 25.1423)	25.1336 (25.1267, 25.1400)	$3,209 ($2,810, $3,685)

Abbreviations. LS: Lynch Syndrome. PRS: polygenic risk score. SOC: standard of care. ICER: incremental cost-effectiveness ratio. QALY: quality-adjusted life years. LY: life-year.

Table 2. PRS threshold results: LS+PRS screening and SOC per individual in the model, ranked by increasing LYs

	Results by percentile strategy (95% CR)		
	LYs	QALYs	Costs
SOC	25.1335 (25.1268, 25.1398)	25.1306 (25.1235, 25.1373)	$2,835 ($2,464, $3,278)
LS+PRS screening with a PRS threshold of 95th percentile	25.1363 (25.1299, 25.1423)	25.1336 (25.1267, 25.1400)	$3,209 ($2,810, $3,685)
LS+PRS screening with a PRS threshold of 90th percentile	25.1371 (25.1311, 25.1429)	25.1345 (25.1280, 25.1405)	$3,297 ($2,902, $3,781)
LS+PRS screening with a PRS threshold of 85th percentile	25.1377 (25.1318, 25.1433)	25.1351 (25.1287, 25.1411)	$3,390 ($2,982, $3,886)
LS+PRS screening with a PRS threshold of 80th percentile	25.1380 (25.1324, 25.1436)	25.1355 (25.1294, 25.1414)	$3,490 ($3,076, $3,259)

Abbreviations. LS: Lynch Syndrome. PRS: polygenic risk score. SOC: standard of care. ICER: incremental cost-effectiveness ratio. QALY: quality-adjusted life years. LY: life-year.

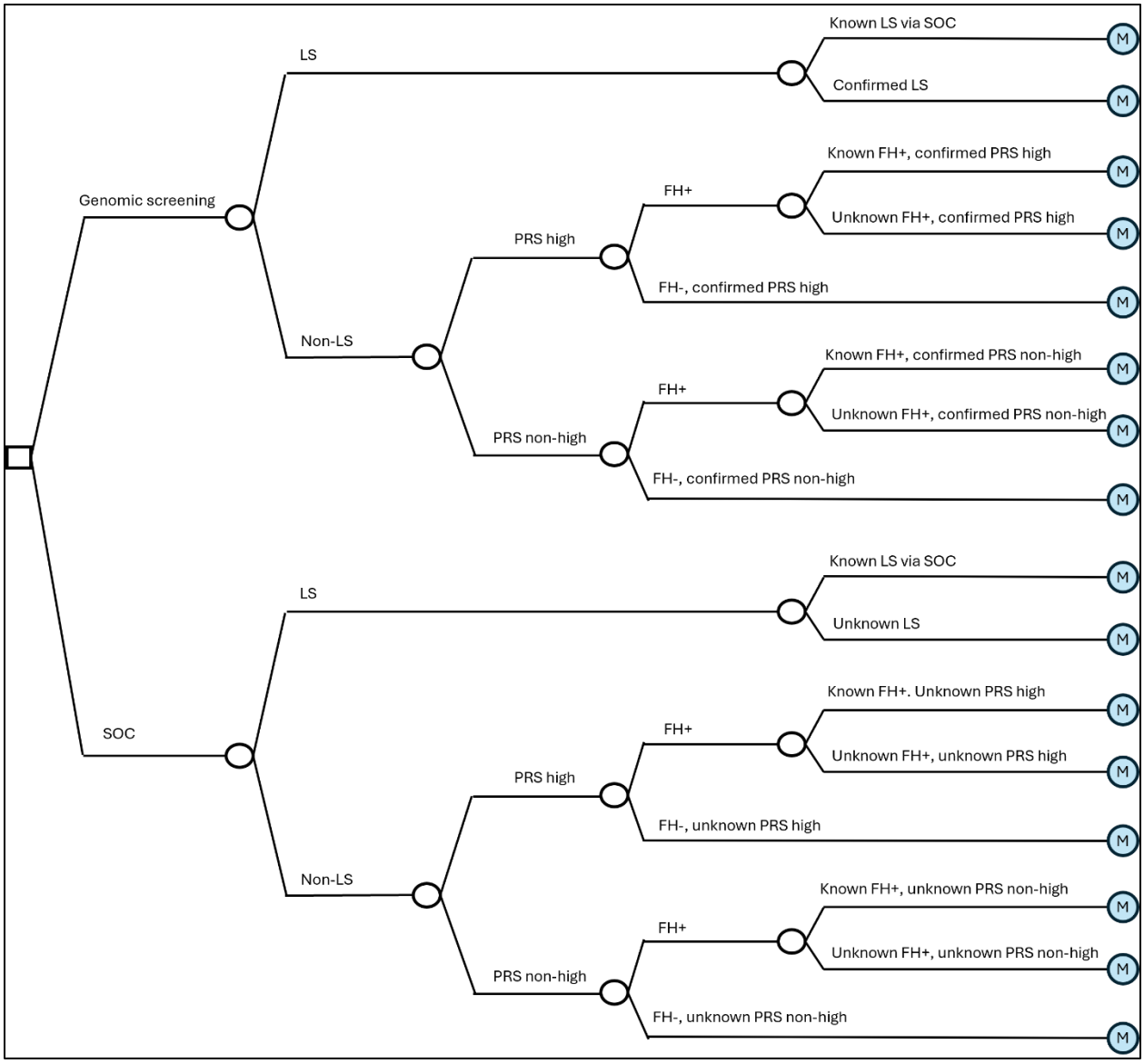


Figure 1. Decision tree

Individuals were stratified in the decision tree based on (1) risk status, (2) uptake of genomic screening, (3) recommended colonoscopy screening based on perceived risk, and (4) adherence to recommended colonoscopy screening. After the decision tree, individuals entered the Markov model (circle M) and were followed lifetime. The Markov model was shown in Figure S2.

Abbreviations. FH: family history. LS: Lynch Syndrome. PRS: polygenic risk score. SOC: standard of care.

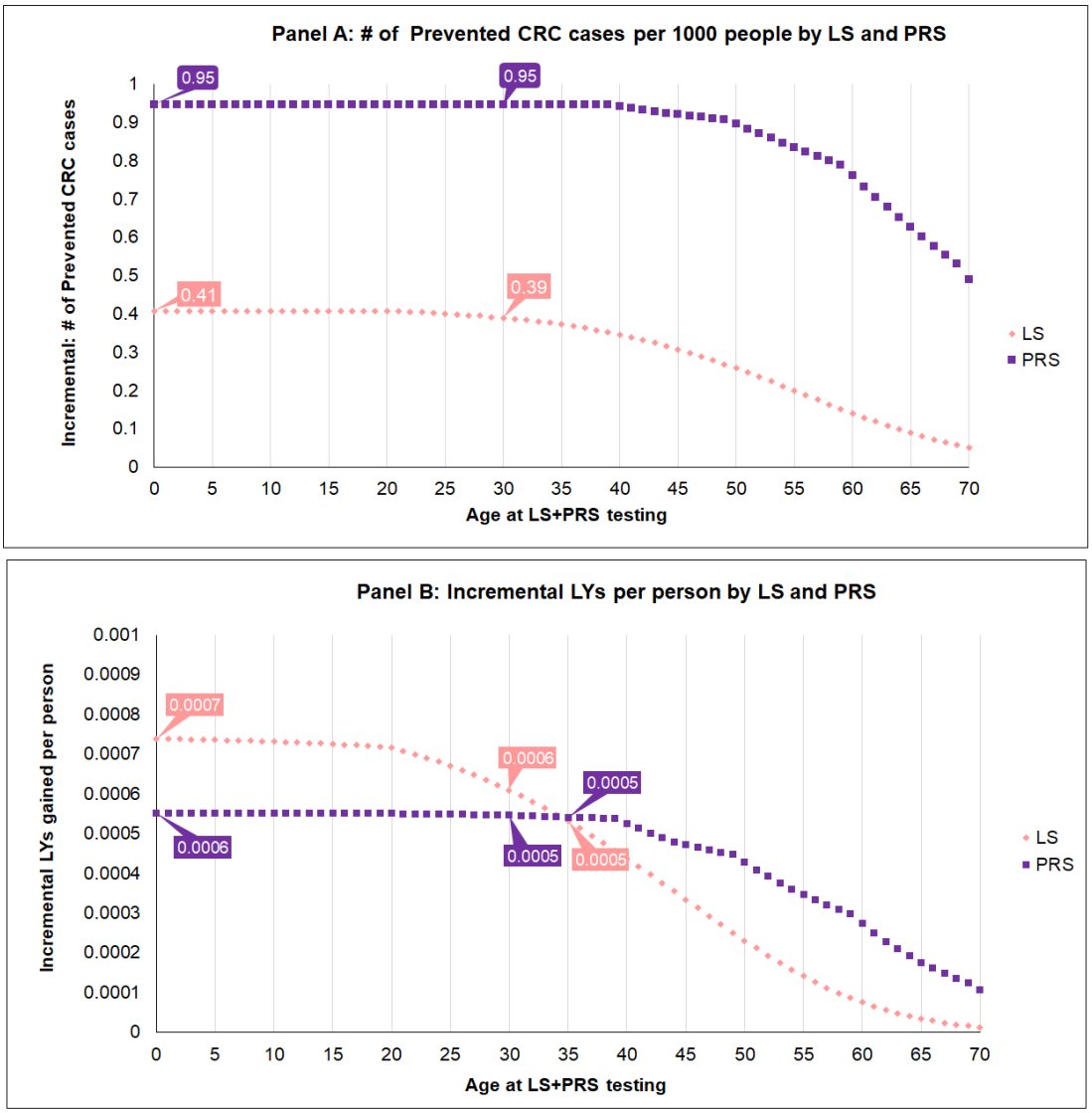


Figure 2. Prevented CRC cases per 1000 people and LYs saved per person of LS+PRS screening compared to SOC.

(A) Lifetime number of CRC cases prevented for a cohort of 1000 individuals by different age of LS+PRS screening, attributable to LS (pink) and PRS (purple) separately. (B) Lifetime number

of LYs saved per person by different age of LS+PRS screening, attributable to LS (pink) and PRS (purple) separately.

Abbreviations. CRC: colorectal cancer. LY: life-year. LS: Lynch Syndrome. PRS: polygenic risk score. SOC: standard of care.

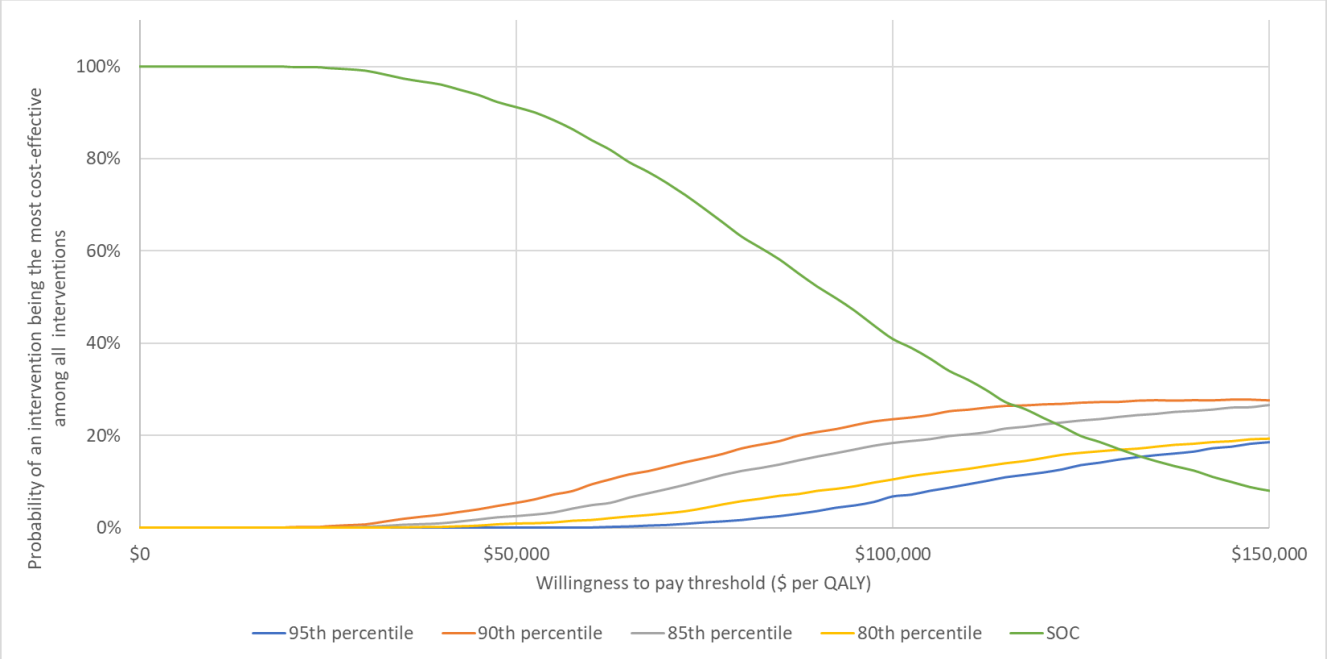


Figure 3. Probability of LS+PRS screening with different PRS thresholds being the most cost-effective at different WTP thresholds, including SOC.

The probability of each strategy is the most cost-effective at different WTP thresholds are presented. The green line represents the probability of SOC being the most cost-effective; the blue line represents the probability of LS+PRS genomic screening with a PRS threshold of 95th percentile being the most cost-effective; the orange line represents the probability of LS+PRS genomic screening with a PRS threshold of 90th percentile only being the most cost-effective; the grey line represents the probability of LS+PRS genomic screening with a PRS threshold of 85th

percentile being the most cost-effective; and the yellow line represents the probability of LS+PRS genomic screening with a PRS threshold of 80th percentile being the most cost-effective.

Abbreviations. Lynch Syndrome. PRS: polygenic risk score. QALY: quality-adjusted life years. SOC: standard of care. WTP: willingness to pay.

Supplementary materials

Appendix A. Model approaches and simulation methods

Modeling approaches in CRC screening

There are 2 general modeling approaches in CRC screening. Below we describe these approaches and our rationale for selecting our approach.

The first approach consists of a natural history module and a screening module and relies on calibration (i.e., calibration-based approach). The natural history module simulates the adenoma-carcinoma sequence, such as Microsimulation Screening Analysis (MISCAN), Simulation Model of CRC (SimCRC), and CRC Simulated Population model for Incidence and Natural History (CRC-SPIN).[108-110] Each individual will have an assigned risk of adenoma, informed by autopsy studies in early 60s to 90s.[111-119]. Each adenoma may progress to preclinical CRC and later preclinical CRC will becomes clinical CRC.[120] Available clinical evidence only exists for CRC incidence and stage distribution at diagnosis without screening from SEER data in early 70s.[84] Information of how fast the adenoma progresses to preclinical CRC and then to clinical CRC is unknown and thus, parameter values are calibrated.[120] Once patients are diagnosed with CRC, survival will be applied using SEER survival information.[121]

Sensitivity, specificity, and reach of a screening modality are incorporated in the screening module.[122] Screening can remove adenomas and therefore adenoma progression is terminated; screening can also detect preclinical cancer, delaying CRC death.[108] However, incidence reduction and stage shift due to screening is not directly informed by clinical evidence; rather, it is a function of how many adenomas are removed and the subsequent risk of CRC.[120] These are affected by multiple parameters simultaneously, including those determining dwelling and sojourn time.[120] Thus, parameters are calibrated so the model can fit observed data in clinical studies.[123-133]

The second model structure is to directly incorporate screening effectiveness to people who receive screening, and thus, no calibration is needed. An example is Barzi et al.[97] Screened individuals will receive benefits and risks of screening, informed by trials and/or observational studies of fecal occult blood test,[123,124,126-129,133] flexible sigmoidoscopy,[130-133] and colonoscopy (COL).[85,134] Screening reduces CRC incidence and changes stage distribution at diagnosis. In the no screening arm, people follow the incidence of CRC and stage distribution at diagnosis using SEER data in early 70-80s.[84] After diagnosis, survival by stage at diagnosis is applied.[121]

Simulation methods in CRC screening

Two simulation methods are used in modeling studies of CRC screening – patient-level simulation (PLS) and cohort-level Markov model (Markov).[135-138] PLS models individuals and tracks everyone's trajectory over time, and it allows for patients' history to update the future transition probabilities and thereby overcome the Markovian assumption.[139] PLS can display clinical pathways of each individual and generate the distribution of outcomes; and expected outcomes can be calculated using the mean.[139] However, in Markov model, a proportion of the

cohort may enter a state in a time cycle, and thus, Markov generates the population-average outcomes directly.[139]

In the calibration approach, PLS is extensively used, such as MISCAN-Colon, CRC-SPIN, and SimCRC.[108,140,141] Markov is also used in this approach.[98] PLS is relatively easy to be adapted in this approach because of the need of a large number of calibrated parameters.[139] In the no-calibration approach, Markov has been used.[97]

Modeling approach in this study

In our study, we chose a non-calibration approach. This is because the calibration approach relies heavily on the model assumption and calibrated parameters, which makes a probabilistic sensitivity analysis (PSA) computationally challenging.[139] In CRC, PSA is particularly important because limited data exists in the natural history of CRC by PRS. However, few modeling studies that used the calibration approach performed PSA, including those that assessed the value of PRS in CRC screening.[76,77,101] Furthermore, because the calibration approach is complex and parameters correlated, outcomes are affected by multiple parameters simultaneously, dampening the audience's ability to assess key parameters driving the model outcomes.[110,120,142] This feature also limits the transparency of the model and the ability to communicate with the audience.

Thus, we used a Markov model to simulate the CRC natural history, effectiveness of CRC screening, and assess the value of LS+PRS testing in CRC screening.

Decision tree

In the decision tree, there are four intervention arms – (1) LS+PRS genomic screening, (2) LS genomic screening, (3) PRS genomic screening, and (3) SOC. Under each intervention, individuals were first categorized by their true risk status, based on LS, PRS, and FH. Then, the

model accounted for a proportion of individuals who might have known FH+ status via SOC, noted as “Known FH+ via SOC”, and individuals who might have known LS+ status via SOC, noted as “Known LS via SOC”. (Figure 1 in the main text).

Markov Model

Everyone in the decision tree would then enter a Markov model in which their lifetime trajectories were simulated. Each individual entered the model from the health state of “No CRC”. Over time, each individual might develop CRC, and the model accounted for stages at diagnosis. We modeled the year 1 and year 2+ separately for those with CRC. This means that the health states of “CRC Year 1” were tunnel states. Individuals might die from CRC or other cause (i.e., background mortality), and then enter “Death”, which was an absorbing health state (Figure S1).

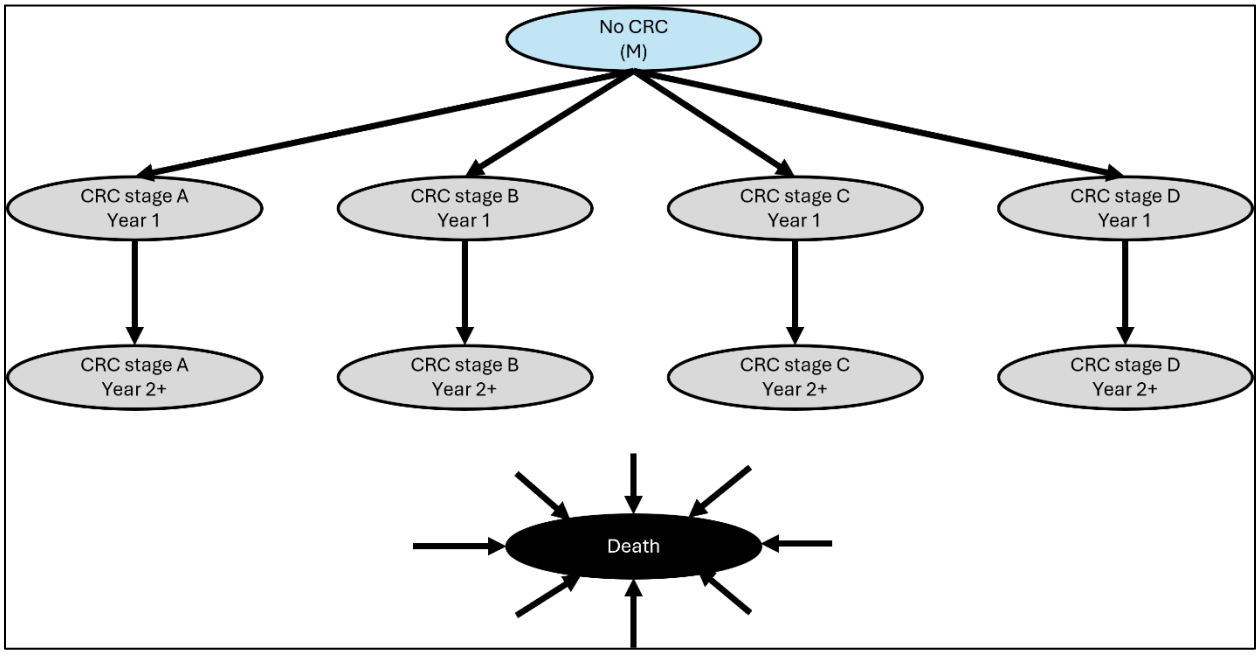


Figure S1. Markov model

Once individuals were stratified by the decision tree (Figure 1 in the main text), they entered the Markov model from the “No CRC” health state. Individuals might develop CRC at different stages over time and die from CRC or other causes of death.

Abbreviations. CRC: colorectal cancer.

Appendix B. Additional model parameters

Screening modality

There exists a variety of CRC screening modalities recommended in the guidelines, such as stool-based tests, colonoscopy, and sigmoidoscopy.[11,73,80,143,144] Because colonoscopy is used for CRC diagnosis,[145] and the goal of this analysis was to examine the value of LS and PRS testing rather than identifying the best screening modality, in our analysis, we only focused on colonoscopy screening.

Background mortality

We used the US lifetable 2020 to inform the background mortality for all individuals.[146] We also adjusted the background mortality by subtracting the CRC mortality rate from it to avoid double-counting of CRC death in the general population. The CRC mortality rate was based on SEER mortality data from 2018 to 2022.[147]

LS patients – the use of PRS results

Although LS carriers might receive information of their PRS status, this result was unlikely to provide actionable information. First, Jenkins et al. reported that PRS for CRC was not able to predict CRC among LS carriers by analyzing 826 individuals with confirmed LS mutation genes.[148] The similar finding was observed in Duenas et al and Hassanin et al.[149,150] Second, even if individuals with LS were informed as PRS high, they still needed to undergo colonoscopy screening annually per LS screening guidelines.[103] Under the "PRS screening" arm, unknown LS patients with a high PRS result might adhere to 5-yearly colonoscopy starting from age 40 years. However, the mean age of onset of CRC for patients with LS is 40 years and thus LS patients would not be able to benefit from a screening starting from age 40 years.[151].

Non-LS individuals

Prevalence and relative risk (RR) of positive FH

Henrikson et al. systematically reviewed 8 studies, including 6 from the US.[152] These articles reported a prevalence of having a first-degree relative of CRC ranging from 3% to 10%.[152] In the base-case, we assumed 6.5% of individuals had positive FH. Lowery et al. conducted a systematic review on 12 articles that reported risk of CRC associated with FH.[95] The pooled analysis found the RR associated with positive FH ranged from 1.5 to 2.5.[95] In the base-case, the RR was set at 2.0.

PRS threshold

Among the non-LS population, a proportion of individuals at a higher risk of CRC would be identified by a high PRS (i.e., PRS high group). Previous literature adopted an approach where the population of interest was categorized into a large number of groups, such as 20; and individuals with a low PRS would undergo CRC screening less frequently.[76,77] However, based on clinical inputs, we believe that it was not realistic to decrease the frequency of CRC screening in the US for lower-risk individuals, and that individuals with a higher risk should receive more frequent CRC screening. Thus, we only dichotomized the non-LS adults into two groups: “PRS high” and “PRS non-high”, based on a given threshold of PRS.

Interaction between PRS and FH in CRC risk

Mars et al. systematically compared the relationship between PRS and FH across 24 common diseases, including CRC.[153] In this study, the odds ratio (OR) of CRC risk of PRS per standard deviation (SD) changed minimally before and after controlling for FH.[153] Hassanin et al. analyzed data from UK Biobank and found that the interaction between FH and PRS on CRC

incidence was not significant.[150] Thus, in our model, FH and PRS were independent risk factors of CRC.

Interaction between PRS status and colonoscopy screening effectiveness

Choi et al. reported that there existed an interaction between PRS and incidence reduction when PRS was categorized by tertiles.[154] Yet, the incidence reduction reported in this article was inconsistent with prior literature and the categorization of PRS was not aligned with ours.[154] Because individuals with a high PRS had a similar risk as individuals with positive FH, we used the RR of CRC associated with screening for individuals with positive FH as a proxy for individuals with a high PRS.

Survival by FH

Li et al. systematically reviewed the impact of FH on the prognosis of CRC patients and found that FH might be associated with a better survival of CRC, but heterogeneity in the evidence was high.[155] Thus, we assumed that FH did not impact the stage-specific survival.

Survival by PRS

He et al. reported that PRS did not predict CRC survival once controlling for stage at diagnosis, and PRS was not associated with overall survival.[156] Thus, in our model, CRC survival was not associated with PRS.

Appendix C. External validation

We first validated our model by comparing the outcomes of CRC natural history and CRC outcomes associated with colonoscopy screening with estimates in observational studies and previous cost-effectiveness analysis (CEA) literature.[85,86,92,97-99,157] For 1000 individuals with an average risk aged at 40-50 years, our model estimated that around 63-64 individuals would be diagnosed with CRC, in the absence of CRC screening. Previous CEA literature reported an estimate ranging from 30-72.[92,98,99] With 10-yearly colonoscopy screening, our model estimated an incidence reduction ranging from 57% to 59%. Sharaf et al. reported an incidence reduction of 73%, and Knudsen et al. reported an incidence reduction ranging from 66% to 92%.[98,99] Estimates from observational studies were 40-70%.[85,86]

Furthermore, our model showed that with 10-yearly colonoscopy screening, the CRC mortality was reduced by 67-70%. Previous CEA studies and observational studies reported a mortality reduction from 46% to 93% and from 30-70%, respectively.[92,97,99]

Projecting to lifetime, our model yielded an undiscounted life-years (LYs) saved of 194-198 attributable to CRC screening. Barzi et al. reported a smaller estimate of 137, and other CEA studies reported a higher estimate ranging from 230 to 369.[92,97,99,157] The majority of studies reported an estimate of LYs saved per CRC case prevented by colonoscopy screening ranging from 4.4 to 6.6, except that one model in Zauber et al. reported 15 LYs saved per CRC case prevented.[92,99,157] Our study estimated that 5.2-5.5 LYs saved per CRC case was attributable to colonoscopy screening. Taken altogether, our model was able to generate estimates that were aligned with previous literature.

Then, we compared our results with a previously published population-level LS testing in the US.[37] In our model, population-level LS testing resulted in 0.0018 quality-adjusted life-years

(QALYs) gained, 0.0017 LYs saved, and 0.0005 fewer CRC cases per person in the population aged at 30 years. Guzauskas et al. reported 0.0019 QALYs gained, 0.0018 LYs saved, and 0.0005 fewer CRC cases per person tested at the same age.[37] Our model results were very close to the published estimates.

Lastly, we compared our results with estimates in previous CEA studies that examined the value of PRS testing in CRC screening.[76,77,101] Cenin et al. reported that the optimal screening strategy based on PRS and FH risk stratification was to screen with stool-based tests every 2 years starting from age 54 for individuals with a very low risk, stool-based tests every year starting from age 54 for individuals with a low risk, stool-based tests every year starting from age 50 for individuals with an average risk or a high risk, and colonoscopy every 5 years starting from age 50 for individuals with a very high risk.[76] Compared to uniform screening where all individuals were screened by colonoscopy every 5 years starting from age 46 years, this PRS strategy resulted in 12 more CRC cases, 3 more CRC deaths, 8 fewer QALYs gained and 7 fewer LYs saved per 1000 people tested.[76] However, in our study, PRS testing resulted in 2 fewer CRC cases, 0.6 fewer deaths, 2 QALYs gained, and 2 LYs saved per 1000 people tested. There are many differences between our study and Cenin et al such as risk stratification based on PRS.[76] Cenin et al. categorized individuals into 5 groups whereas we only dichotomized the population based on PRS.[76] We also believe that reducing screening even for individuals with a lower risk is not relevant for clinical practice and policy making.[76] In addition, Cenin et al. evaluated 39 strategies based on PRS testing results, and none was similar to our screening strategy.[76]

Naber et al. reported that PRS-guided CRC screening resulted in 1 fewer CRC case, 1 fewer CRC death, less than 1 LYs saved and less than 1 QALYs gained, compared to uniform screening.[77] In our model, PRS testing resulted in 0.7 fewer CRC case, 0.2 fewer CRC death, 0.9

LYs saved and 1 QALYs gained compared to uniform screening. Our results were close to Naber et al.'s estimates.[77]

Van den Puttelaar et al. examined the value of a risk prediction model to guide CRC screening that incorporated both environmental risk score and a PRS and found that PRS resulted in 1 CRC case prevented (35 vs 34), 0 CRC death averted (9 vs 9), 2 QALYs gained (118 vs 120) and 23 LYs saved (23,391 vs 23,414), compared to uniform screening, i.e., 10-yearly colonoscopy from age 45 to 75 years, with full adherence, for 1000 individuals at age 40 years.[101] In our model, compared to uniform screening with full adherence, PRS-guided CRC screening resulted in 0.7 CRC case prevented, 0.2 CRC death averted, 0.9 LYs saved and 1 QALYs gained, per 1000 individuals at age 40 years. It was unclear to us why the QALYs gained was less than one tenth of the LYs saved in van den Puttelaar's et al.[101] It is possible that the LYs saved in van den Puttelaar et al. was undiscounted whereas the QALYs were discounted; however, as the average life expectancy for US adults at age 40 years is estimated to be 37 years,[158] and the reported LYs were around only 23 years per person, it was likely that both LYs and QALYs were discounted.[101] Additionally, the intervention examined in this article was to stratify individuals into 800 risk groups based on PRS and an environmental risk score,[101] which may be challenging to be implemented in clinical practice.

We noted that Cenin et al., Naber et al, and van den Puttelaar et al. did not perform probabilistic sensitivity analyses to examine the uncertainty of the cost-effectiveness of personalized CRC screening.[76,77,101] Examining uncertainty via probabilistic sensitivity analysis is good practice in health economic modeling, particularly for decision models that use calibration to derive parameter values.[104] Additionally, previous literature has found that different PRS algorithms might result in different risk stratification for the same individual,[68,105] and thus the uncertainty

of the PRS-predicted risk should be accounted for in economic modeling. However, it is unclear to us whether PRS-guided CRC screening might have been cost-effective in probabilistic sensitivity analysis in previous studies.[76,77,101]

Table S1. Model Parameters

Clinical parameters – LS					
Parameter name	Base-case value	Low-value for OWSA	High-value for OWSA	Distribution for PSA	Source
Prevalence of LS	0.341%	0.305%	0.377%	Beta	Geisinger [79]
Proportion of known LS via SOC	10%	10.80%	16.10%	Beta	Assumption
CRC risk by age 70, no screening, female	0.464	0.303	0.715	Beta	Snowsill et al.[81] / Bonadona et al.[159]
CRC risk by age 70, no screening, male	0.435	0.265	0.697	Beta	Snowsill et al.[81] / Bonadona et al.[159]
HR of CRC risk reduction due to LS screening	0.387	0.310	0.464	Log normal	Snowsill et al.[81] / Bonadona et al.[159]
Stage distribution, no screening					
Proportion of Stage A	13.5%	2.5%	24.5%	Beta/Dirichlet	Stupart et al.[83]
Proportion of Stage B	35.1%	19.8%	50.5%	Beta/Dirichlet	Stupart et al.[83]

Proportion of Stage C	32.4%	17.3%	47.5%	Beta/Dirichlet	Stupart et al.[83]
Proportion of Stage D	18.9%	6.3%	31.5%	Beta/Dirichlet	Stupart et al.[83]
Stage distribution, LS screening					
Proportion of Stage A	50.0%	23.8%	76.2%	Beta/Dirichlet	Stupart et al.[83]
Proportion of Stage B	7.1%	0.0%	20.6%	Beta/Dirichlet	Stupart et al.[83]
Proportion of Stage C	42.9%	16.9%	68.8%	Beta/Dirichlet	Stupart et al.[83]
Proportion of Stage D	0.0%	0%	0%	Beta/Dirichlet	Stupart et al.[83]
Clinical parameters – non-LS					
Parameter name	Base-case value	Low-value for OWSA	High-value for OWSA	Distribution for PSA	Source
Prevalence of positive FH	6.5%	3.0%	10.0%	Beta	Henrikson et al.[152]
Proportion of known positive FH via SOC, among individuals with FH+	50%	40%	60%	Beta	Assumption
Prevalence of PRS high	5%	NA	NA	NA	Assumption
RR of CRC risk due to positive FH, no screening	2.0	1.6	2.4	LogNormal	Talylor et al.[160], Henriskon et al.[152]

RR of CRC risk due to PRS high, threshold of 95th percentile, no screening	2.0	1.6	2.4	LogNormal	Thomas et al.[24]
RR of CRC risk due to PRS high, threshold of 90th percentile, no screening	1.7	1.36	2.04	LogNormal	Thomas et al.[24]
RR of CRC risk due to PRS high, threshold of 85th percentile, no screening	1.5	1.2	1.8	LogNormal	Thomas et al.[24]
RR of CRC risk due to PRS high, threshold of 80th percentile, no screening	1.3	1.04	1.56	LogNormal	Thomas et al.[24]
HR of CRC risk reduction due to increased screening, for increased risk group, compared to no screening	0.44	0.30	0.50	LogNormal	Nishihara et al.[85]
HR of CRC risk reduction due to average screening, for increased risk group, compared to no screening	0.55	0.50	0.60	LogNormal	Nishihara et al.[85]

HR of CRC risk reduction due to average screening, for average risk group, compared to no screening	0.40	0.30	0.51	LogNormal	Nishihara et al.[85], Bretthauer et al.[161], Heisser et al.[87], Doubeni et al.[86]
Stage distribution, no screening					
Proportion of Stage A	19.3%	15.4%	23.2%	Beta/Dirichlet	SEER 1990-1995[84]
Proportion of Stage B	19.3%	15.4%	23.2%	Beta/Dirichlet	SEER 1990-1995[84]
Proportion of Stage C	39.6%	31.7%	47.5%	Beta/Dirichlet	SEER 1990-1995[84]
Proportion of Stage D	21.8%	17.4%	26.2%	Beta/Dirichlet	SEER 1990-1995[84]
Stage distribution, increased or average screening					
Proportion of Stage A	39.3%	31.4%	47.2%	Beta/Dirichlet	Cardoso et al.[88]
Proportion of Stage B	19.3%	15.4%	23.2%	Beta/Dirichlet	Cardoso et al.[88]
Proportion of Stage C	36.6%	29.3%	43.9%	Beta/Dirichlet	Cardoso et al.[88]

Proportion of Stage D	4.8%	3.8%	5.8%	Beta/Dirichlet	Cardoso et al.[88]
Survival after CRC diagnosis for both LS and non-LS individuals					
Parameter name	Base-case value	Low-value for OWSA	High-value for OWSA	Distribution for PSA	Source
CRC mortality, year 1					
Stage A at diagnosis	4.25%	3.40%	5.10%	Beta	SEER 2000-2019[89]
Stage B at diagnosis	4.25%	3.40%	5.10%	Beta	SEER 2000-2019[89]
Stage C at diagnosis	9.04%	7.23%	10.85%	Beta	SEER 2000-2019[89]
Stage D at diagnosis	44.54%	35.63%	53.45%	Beta	SEER 2000-2019[89]
CRC mortality, year 2+					
Stage A at diagnosis	1.33%	1.33%	1.34%	Beta	SEER 2000-2019[89]
Stage B at diagnosis	1.33%	1.33%	1.34%	Beta	SEER 2000-2019[89]
Stage C at diagnosis	3.70%	3.68%	3.72%	Beta	SEER 2000-2019[89]

Stage D at diagnosis	6.66%	6.51%	6.80%	Beta	SEER 2000-2019[89]
Genetic testing uptake parameters					
Parameter name	Base-case value	Low-value for OWSA	High-value for OWSA	Distribution for PSA	Source
LS testing uptake					
For unknown LS individuals	100%	80%	100%	Beta	Assumption
For known LS via SOC individuals	10%	0%	20%	Beta	Assumption
PRS testing uptake					
For unknown risk individuals	100%	80%	100%	Beta	Assumption
For known positive FH via SOC individuals	100%	80%	100%	Beta	Assumption
Colonoscopy screening adherence parameters					
Parameter name	Base-case value	Low-value for OWSA	High-value for OWSA	Distribution for PSA	Source
LS surveillance for confirmed LS via LS testing	80%	70%	90%	Beta	Palomaki et al.[162]

Average screening for average risk individuals	50%	40%	60%	Beta	Fiala,[94] Lowery et al.[95], Tsai et al.[163]
Boosted adherence to increased screening for increased risk individuals due to positive FH	10%	8%	12%	Beta	Fiala,[94] Lowery et al.[95], Tsai et al.[163]
Boosted adherence to increased screening for increased risk individuals due to PRS high	3%	2.4%	3.6%	Beta	Assumption
Average screening for increased risk individuals, among individuals who are not adherent to increased screening	50%	40%	60%	Beta	Assumption
% of individuals with LS negative and PRS non-high became less adherent to screening	0%	NA	NA	NA	Assumption, examined in the threshold analysis
Cost parameters					

Parameter name	Base-case value	Low-value for OWSA	High-value for OWSA	Distribution for PSA	Source
LS+PRS testing	$250	$200	$300	Normal	Assumption
PRS testing	$200	$160	$240	Normal	Assumption
LS testing	$200	$160	$240	Normal	Assumption
Screening colonoscopy	$1,628	$1,303	$1,954	Normal	Dinh et al.[164]
CRC treatment cost					
Initial year					
Stage A	$39,401	$31,521	$47,281	Normal	Zauber et al.[92]
Stage B	$49,737	$39,790	$59,685	Normal	Zauber et al.[92]
Stage C	$66,297	$53,038	$79,556	Normal	Zauber et al.[92]
Stage D	$86,572	$69,258	$103,886	Normal	Zauber et al.[92]
Continuing year (every year)					
Stage A	$3,135	$2,508	$3,762	Normal	Zauber et al.[92]
Stage B	$2,922	$2,337	$3,506	Normal	Zauber et al.[92]
Stage C	$4,177	$3,342	$5,013	Normal	Zauber et al.[92]
Stage D	$12,947	$10,358	$15,537	Normal	Zauber et al.[92]
Terminal year					

Stage A	$70,632	$56,505	$84,758	Normal	Zauber et al.[92]
Stage B	$70,432	$56,346	$84,519	Normal	Zauber et al.[92]
Stage C	$74,214	$59,371	$89,057	Normal	Zauber et al.[92]
Stage D	$99,601	$79,681	$119,521	Normal	Zauber et al.[92]
Other death, terminal year					
Stage A	$17,403	$13,922	$20,883	Normal	Zauber et al.[92]
Stage B	$15,221	$12,177	$18,265	Normal	Zauber et al.[92]
Stage C	$20,137	$16,110	$24,165	Normal	Zauber et al.[92]
Stage D	$54,069	$43,255	$64,883	Normal	Zauber et al.[92]
HRQOL parameters					
Parameter name	Base-case value	Low-value for OWSA	High-value for OWSA	Distribution for PSA	Source
Disutility of knowing LS+ (1 year)	0.04	0.03	0.05	Beta	Snowsill et al.[81]
# of month of disutility of knowing LS	4 months	NA	NA	NA	Snowsill et al.[81]
Disutility of knowing PRS high (1 year)	0.00	0.00	0.01	NA	Assumption

# of month of disutility of knowing PRS high	4 months	NA	NA	NA	Assumption
Disutility by CRC stages					
Stage A	0.05	0.01	0.09	Beta	Djalalov et al.[93]
Stage B	0.05	0.01	0.09	Beta	Djalalov et al.[93]
Stage C	0.05	0.01	0.09	Beta	Djalalov et al.[93]
Stage D, year 1	0.19	0.14	0.25	Beta	Djalalov et al.[93]
Stage D, year 2+	0.20	0.16	0.24	Beta	Djalalov et al.[93]

CRC: colorectal cancer. FH: family history. HR: hazard ratio. HRQOL: health related quality of life. LS: Lynch Syndrome. OWSA: one-way sensitivity analysis. PRS: polygenic risk score. RR: relative risk. SEER: the Surveillance, Epidemiology, and End Results. SOC: standard of care.

Table S2. Base-case results: CRC incidence and mortality per 1000 individuals in the model, ranked by decreasing incidence.

	Results by arm		Comparing to the next best strategy	
	CRC incidence (95%CR)	CRC mortality (95%CR)	Incremental incidence (95%CR)	Incremental mortality (95%CR)
SOC	45.43 (40.54, 50.29)	16.19 (14.21, 18.27)	Reference	Reference
LS screening	45.03 (40.14, 49.91)	15.97 (13.99, 18.04)	-0.40 (-0.53, -0.27)	-0.22 (-0.31 -0.14)
PRS screening	44.47 (39.65, 49.37)	15.76 (13.82, 17.82)	-0.57 (-1.28, -0.04)	-0.20 (-0.51, -0.02)
LS+PRS screening	44.07 (39.32, 48.97)	15.54 (13.60, 17.58)	-0.40 (-0.53, -0.27)	-0.22 (-0.31, -0.14)

Abbreviations. CR: credible range. LS: Lynch Syndrome. PRS: polygenic risk score. SOC: standard of care. ICER: incremental cost-effectiveness ratio. QALY: quality-adjusted life years. LY: life-year.

Table S3. Base-case results per individual in the model, ranked by increasing LYs

	Results by arms (95% CR)			Comparison with the next best strategy (95% CR)			
	LYs	QALYs	Costs	Incremental LYs	Incremental QALYs	Incremental Costs	ICER ($ per QALY)
SOC	25.1335 (25.1268, 25.1398)	25.1306 (25.1235, 25.1373)	$2,835 ($2,464, $3,278)	Reference	Reference	Reference	Reference
PRS screening	25.1348 (25.1283, 25.1409)	25.1321 (25.1251, 25.1385)	$3,101 ($2,713, $3,558)	Dominated by LS screening			
LS screening	25.1350 (25.1284, 25.1412)	25.1322 (25.1251, 25.1387)	$3,092 ($2,703, $3,539)	Extendedly dominated by LS+PRS screening			
LS+PRS screening	25.1363 (25.1299, 25.1423)	25.1336 (25.1267, 25.1400)	$3,209 ($2,810, $3,685)	0.0029 (0.0019, 0.0040)	0.0030 (0.0020, 0.0042)	$374 ($299, $467)	$124,415 ($79,364, $208,636)

Abbreviations. CR: credible range. LS: Lynch Syndrome. LY: life-year. PRS: polygenic risk score. QALY: quality-adjusted life years. SOC: standard of care. ICER: incremental cost-effectiveness ratio.

Table S4. PRS thresholds results: CRC incidence and mortality per 1000 individuals in the model by different PRS thresholds, ranked by decreasing incidence

	Results by arm		Comparing to the next best strategy	
	CRC incidence (95%CR)	CRC mortality (95%CR)	Incremental incidence (95%CR)	Incremental mortality (95%CR)
SOC	45.43 (40.54, 50.29)	16.19 (14.21, 18.27)	Reference	Reference
LS+PRS screening, 95th percentile	44.07 (39.32, 48.97)	15.54 (13.60, 17.58)	-1.36 (-2.05, -0.82)	-0.65 (-0.94, -0.42)
LS+PRS screening, 90th percentile	43.64 (39.01, 48.33)	15.31 (13.45, 17.27)	-0.43 (-4.05, 2.91)	-0.23 (-1.55, 0.97)
LS+PRS screening, 85th percentile	43.31 (38.72, 47.73)	15.13 (13.32, 17.02)	-0.33 (-3.75, 2.90)	-0.18 (-1.43, 0.92)
LS+PRS screening, 80th percentile	43.10 (38.71, 47.43)	15.02 (13.21, 16.89)	-0.20 (-3.31, 2.86)	-0.11 (-1.17, 0.93)

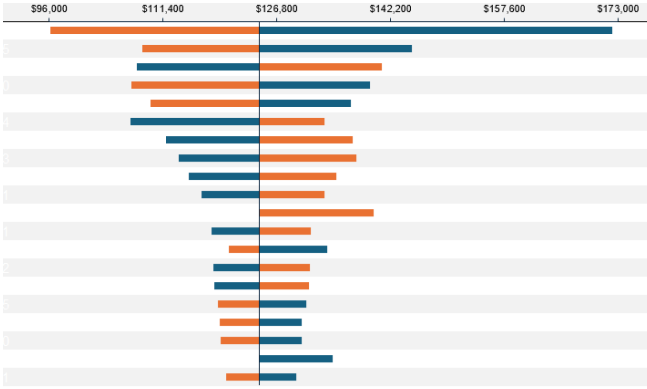
Abbreviations. CR: credible range. LS: Lynch Syndrome. PRS: polygenic risk score. SOC: standard of care. ICER: incremental cost-effectiveness ratio. QALY: quality-adjusted life years. LY: life-year.

Table S5. PRS thresholds results: LS+PRS screening and SOC per individual in the model, ranked by increasing LYs

	Results by arms (95% CR)			Comparison with the next best strategy (95% CR)			
	LYs	QALYs	Costs	Incremental LYs	Incremental QALYs	Incremental Costs	ICER ($ per QALY)
SOC	25.1335 (25.1268, 25.1398)	25.1306 (25.1235, 25.1373)	$2,835 ($2,464, $3,278)	Reference	Reference	Reference	Reference
LS+PRS screening, 95th percentile	25.1363 (25.1299, 25.1423)	25.1336 (25.1267, 25.1400)	$3,209 ($2,810, $3,685)	Extendedly dominated by 90th percentile			
LS+PRS screening, 90th percentile	25.1371 (25.1311, 25.1429)	25.1345 (25.1280, 25.1405)	$3,297 ($2,902, $3,781)	0.0036 (-0.0016, 0.0058)	0.0038 (-0.0001, 0.0078)	$462 ($299, $648)	$120,783 (dominated, $887,025)
LS+PRS screening, 85th percentile	25.1377 (25.1318, 25.1433)	25.1351 (25.1287, 25.1411)	$3,390 ($2,982, $3,886)	0.0006 (-0.0029, 0.0043)	0.0006 (-0.0031, 0.0046)	$93 (-$38, $230)	$145,545 (dominated, $1,105,580)

LS+PRS screening, 80th percentile	25.1380 (25.1324, 25.1436)	25.1355 (25.1294, 25.1414)	$3,490 ($3,076, $3,259)	0.0004 (-0.0029, 0.0034)	0.0004 (-0.0031, 0.0078)	$100 (-$6, $230)	$247,453 (dominated, $948,026)

Abbreviations. CR: credible range. ICER: incremental cost-effectiveness ratio. LS: Lynch Syndrome. LY: life-year. PRS: polygenic risk score. QALY: quality-adjusted life years. SOC: standard of care.



Parameter	Low input	High input	Low result	High result	Spread
RR of CRC for high PRS (95th percentile)	1.6	2.4	$172,151	$96,178	$75,973
Stage D, stage distribution, no screening, for LS	6%	32%	$145,010	$108,613	$36,398
Genetic screening cost	$200	$300	$107,789	$141,041	$33,251
CRC risk for LS, by age 70, no screening. Males	0.303	0.715	$139,418	$107,125	$32,293
CRC risk for LS, by age 70, no screening. Females	0.265	0.697	$136,824	$109,671	$27,154
CRC HR: Increased screening vs No screening, increased risk individuals	0.30	0.66	$106,928	$133,177	$26,250
COL surveillance cost per year	$1,303	$1,954	$111,790	$137,041	$25,251
Stage B, stage distribution, no screening, for LS	20%	51%	$113,459	$137,502	$24,043
Screening compliance, average screening for general population	0.40	0.60	$114,889	$134,825	$19,936
Screening compliance, no screening for increased risk people	0.40	0.60	$116,621	$133,262	$16,641
Disutility (1y): knowledge of PRS high	0.00	0.02	$124,415	$139,871	$15,456
CRC HR screening vs no screening, for LS	0.31	0.46	$117,993	$131,339	$13,345
Age start screening, increased screening	35	45	$133,569	$120,243	$13,327
Stage A, stage distribution, no screening, for LS	2%	25%	$118,208	$131,243	$13,035
Stage C, stage distribution, screening, for LS	27%	59%	$118,302	$131,134	$12,831
LS screening compliance for confirmed LS	0.70	0.90	$130,766	$118,861	$11,905
Stage A, stage distribution, screening, for LS	34%	66%	$130,217	$119,069	$11,148
Stage D, stage distribution, no screening, non-LS	17%	26%	$130,105	$119,149	$10,956
Genetic screening uptake: LS screening	80%	100%	$134,402	$124,415	$9,987
LS prevalence	0.31%	0.38%	$129,436	$119,912	$9,524

Figure S1. Results of one-way sensitivity analysis

In one-way sensitivity analysis, each parameter was varied at a time to its high value or low value, and the corresponding ICER was generated. Across all parameters, we ranked the 20 most influential parameters and generated the tornado diagram. The "high input" represents the maximal value of a given parameter, which results in the "high result" as the ICER under this highest parameter value; the "low input" represents the minimal value of a given parameter, which results in the "low result" as the ICER under this lowest parameter value. The range

between “high result” and “low result” is represented by “spread”. Parameters are ranked by a decreasing order of “spread”.

Abbreviations. FH: family history. HR: hazard ratio. ICER: incremental cost effectiveness ratio. LS: Lynch Syndrome. PRS: polygenic risk score.

Figure S2. Probability of LS+PRS screening, LS screening only, PRS screening only, and SOC being the most cost-effective by different WTP thresholds

The probability of each strategy is the most cost-effective at different WTP thresholds are presented. The yellow line represents the probability of SOC being the most cost-effective; the blue line represents the probability of LS+PRS genomic screening being the most cost-effective; the orange line represents the probability of LS genomic screening only being the most cost-effective; and the grey line represents the probability of PRS genomic screening being the most cost-effective.

Abbreviations. Lynch Syndrome. PRS: polygenic risk score. QALY: quality-adjusted life years. SOC: standard of care. WTP: willingness to pay.

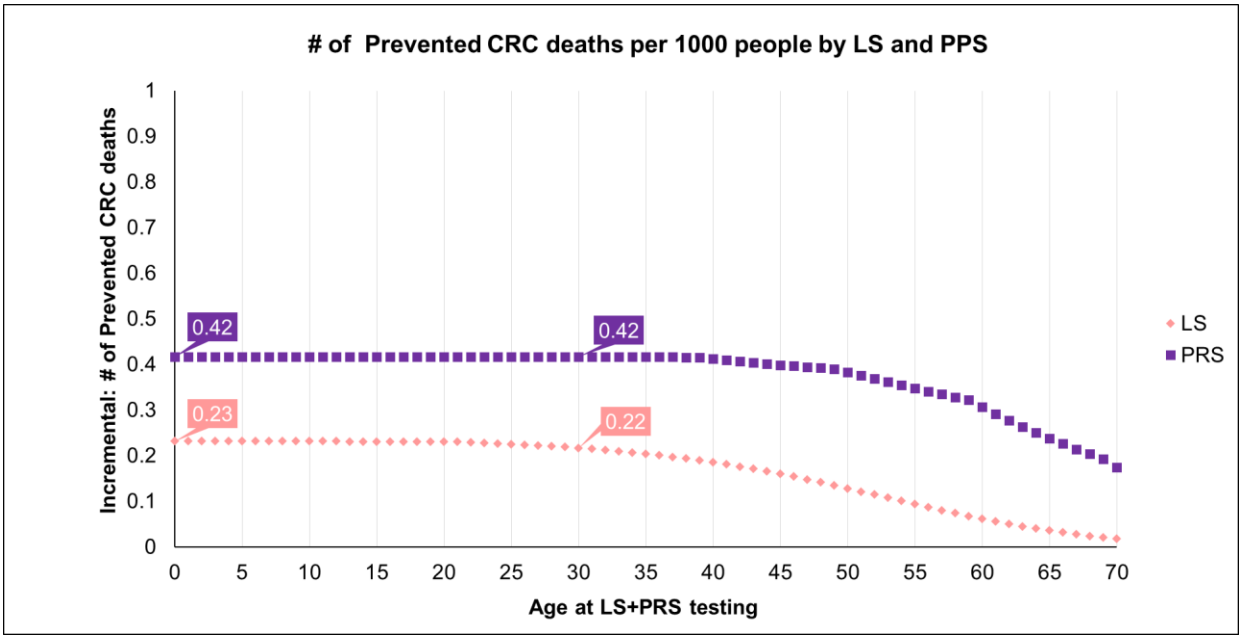


Figure S3. Lifetime number of CRC deaths prevented for a cohort of 1000 individuals by different age of LS+PRS screening

Lifetime number of CRC deaths prevented for a cohort of 1000 individuals by different age of LS+PRS screening, attributable to LS (pink) and PRS (purple) separately.

Abbreviations. CRC: colorectal cancer. LS: Lynch Syndrome. PRS: polygenic risk score. SOC: standard of care.

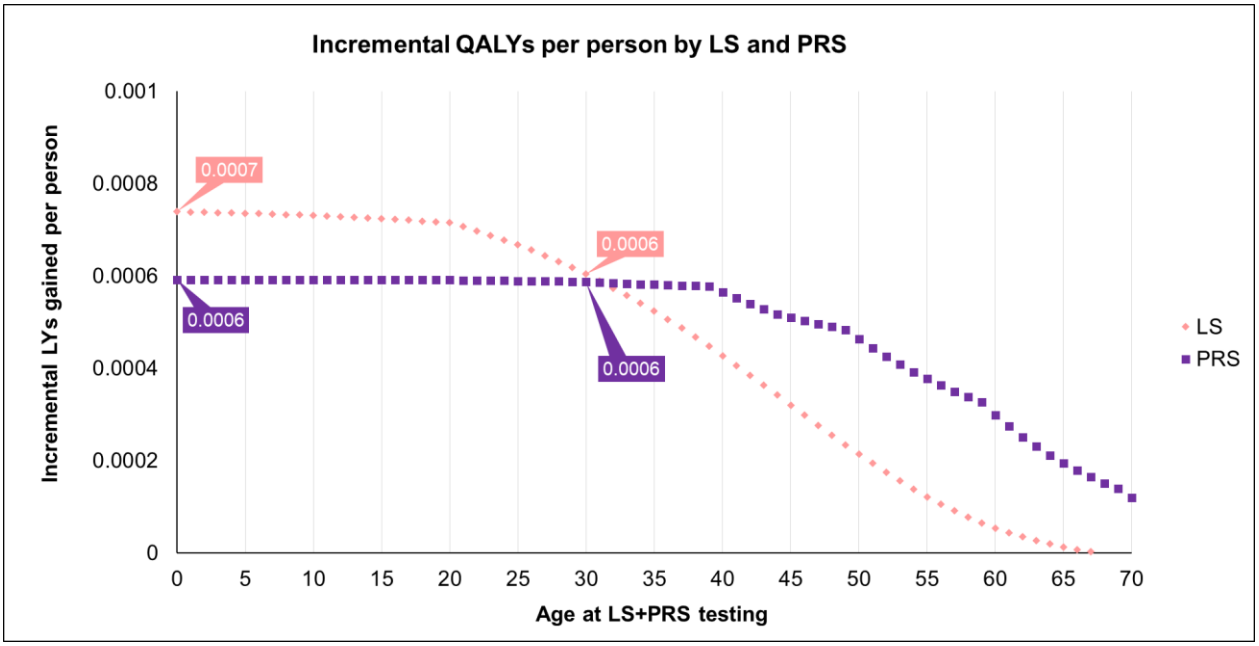


Figure S4. Lifetime QALYs gained for a cohort of 1000 individuals by different age of LS+PRS screening

Lifetime QALYs gained per person by different age of LS+PRS screening, attributable to LS (pink) and PRS (purple) separately.

Abbreviations. CRC: colorectal cancer. LS: Lynch Syndrome. PRS: polygenic risk score. SOC: standard of care. QALY: quality-adjusted life-year.

CHAPTER 4. CONCLUSION

This dissertation aimed to examine risk prediction of PRS in CRC and its value on guiding CRC screening. Particularly, the first objective was to assess whether an MPS approach, where PRSs for traits other than CRC, may improve risk prediction of CRC-PRS-based risk prediction models. The second objective was to assess the cost-effectiveness of a population-level genomic screening of LS+PRS, LS alone, PRS alone, in comparison to SOC.

For the first objective, we constructed risk prediction models where CRC-PRSs alone, or combined with an MPS, which was a linear combination of 337 non-CRC-PRSs, were the main predictors. We found that the inclusion of MPS statistically significantly improved the risk prediction performance, measured by AUC. However, the magnitude of the increment in AUC was small. Our finding was useful for methodological development for PRS-based risk prediction models in CRC. We showed that the MPS approach might not efficiently improve CRC risk prediction models. Additionally, our finding suggested that the existing CRC-PRS might have included the majority of information from common variants in CRC. Future studies should explore other approaches to improve PRS-based risk prediction models of CRC more efficiently, such as incorporating clinical risk factors and information of functional annotations.

In the second aim, we developed a decision analytic Markov model to assess the cost-effectiveness of genomic screening interventions compared to SOC. We found that the genomic screening that returned LS and PRS information was marginally cost-effective in comparison to SOC whereas genomic screening for PRS alone was dominated by genomic screening for LS alone. This suggested that genomic screening that consisted of LS is an important component to guide CRC screening. We also found that categorizing individuals with a PRS ranked above the 90^{th} percentile in the population might provide better value. Our finding filled an important

knowledge gap in risk stratification in PRS. Third, we found that if 15% of individuals who had false reassurance due to a negative genomic screening result, the clinical value of LS+PRS genomic screening result was nullified by the harm. This finding emphasized the importance of clinical communication between clinicians and patients.

PRS for CRC is a fast-evolving space for risk prediction and there is a clear need for better risk prediction algorithms to guide personalized CRC screening.[165] Future studies should assess and develop different methods to improve risk prediction efficiently. Additionally, future studies should also research the clinical and economic value of risk prediction algorithms in guiding population-level CRC screening.

REFERENCES

1. American Cancer Society. Key Statistics for Colorectal Cancer. Accessed May 2, 2022, 2022. https://www.cancer.org/cancer/colon-rectal-cancer/about/key-statistics.html

2. Gellad ZF, Provenzale D. Colorectal cancer: national and international perspective on the burden of disease and public health impact. Gastroenterology. Jun 2010;138(6):2177-90. doi:10.1053/j.gastro.2010.01.056

3. Sharma KP, Grosse SD, Maciosek MV, et al. Preventing Breast, Cervical, and Colorectal Cancer Deaths: Assessing the Impact of Increased Screening. Prev Chronic Dis. Oct 8 2020;17:E123. doi:10.5888/pcd17.200039

4. Lin JS, Perdue LA, Henrikson NB, Bean SI, Blasi PR. Screening for Colorectal Cancer: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. May 18 2021;325(19):1978-1998. doi:10.1001/jama.2021.4417

5. Cooper GS, Doug Kou T. Underuse of colorectal cancer screening in a cohort of Medicare beneficiaries. Cancer. Jan 15 2008;112(2):293-9. doi:10.1002/cncr.23176

6. Cokkinides VE, Chao A, Smith RA, Vernon SW, Thun MJ. Correlates of underutilization of colorectal cancer screening among U.S. adults, age 50 years and older. Prev Med. Jan 2003;36(1):85-91. doi:10.1006/pmed.2002.1127

7. Murphy CC, Sandler RS, Grubber JM, Johnson MR, Fisher DA. Underuse and Overuse of Colonoscopy for Repeat Screening and Surveillance in the Veterans Health Administration. Clin Gastroenterol Hepatol. Mar 2016;14(3):436-444 e1. doi:10.1016/j.cgh.2015.10.008

8. Predmore Z, Pannikottu J, Sharma R, Tung M, Nothelle S, Segal JB. Factors Associated With the Overuse of Colorectal Cancer Screening: A Systematic Review. Am J Med Qual. Sep/Oct 2018;33(5):472-480. doi:10.1177/1062860618764302

9. Usher-Smith JA, Walter FM, Emery JD, Win AK, Griffin SJ. Risk Prediction Models for Colorectal Cancer: A Systematic Review. Cancer Prev Res (Phila). Jan 2016;9(1):13-26. doi:10.1158/1940-6207.CAPR-15-0274

10. Freedman AN, Seminara D, Gail MH, et al. Cancer risk prediction models: a workshop on development, evaluation, and application. J Natl Cancer Inst. May 18 2005;97(10):715-23. doi:10.1093/jnci/dji128

11. U. S. Preventive Services Task Force, Davidson KW, Barry MJ, et al. Screening for Colorectal Cancer: US Preventive Services Task Force Recommendation Statement. JAMA. May 18 2021;325(19):1965-1977. doi:10.1001/jama.2021.6238

12. Burnett-Hartman AN, Newcomb PA, Peters U. Challenges With Colorectal Cancer Family History Assessment-Motivation to Translate Polygenic Risk Scores Into Practice. Gastroenterology. Jan 2020;158(2):433-435. doi:10.1053/j.gastro.2019.10.030

13. Peng L, Weigl K, Boakye D, Brenner H. Risk Scores for Predicting Advanced Colorectal Neoplasia in the Average-risk Population: A Systematic Review and Meta-analysis. Am J Gastroenterol. Dec 2018;113(12):1788-1800. doi:10.1038/s41395-018-0209-2

14. McGeoch L, Saunders CL, Griffin SJ, et al. Risk Prediction Models for Colorectal Cancer Incorporating Common Genetic Variants: A Systematic Review. Cancer Epidemiol Biomarkers Prev. Oct 2019;28(10):1580-1593. doi:10.1158/1055-9965.EPI-19-0059

15. Peters U, Bien S, Zubair N. Genetic architecture of colorectal cancer. Gut. Oct 2015;64(10):1623-36. doi:10.1136/gutjnl-2013-306705

16. Thomas M, Sakoda LC, Hoffmeister M, et al. Genome-wide Modeling of Polygenic Risk Score in Colorectal Cancer Risk. Am J Hum Genet. Sep 3 2020;107(3):432-444. doi:10.1016/j.ajhg.2020.07.006

17. Schmit SL, Edlund CK, Schumacher FR, et al. Novel Common Genetic Susceptibility Loci for Colorectal Cancer. J Natl Cancer Inst. Feb 1 2019;111(2):146-157. doi:10.1093/jnci/djy099

18. Fritsche LG, Patil S, Beesley LJ, et al. Cancer PRSweb: An Online Repository with Polygenic Risk Scores for Major Cancer Traits and Their Evaluation in Two Independent Biobanks. Am J Hum Genet. Nov 5 2020;107(5):815-836. doi:10.1016/j.ajhg.2020.08.025

19. Jia G, Lu Y, Wen W, et al. Evaluating the Utility of Polygenic Risk Scores in Identifying High-Risk Individuals for Eight Common Cancers. JNCI Cancer Spectr. Jun 2020;4(3):pkaa021. doi:10.1093/jncics/pkaa021

20. Huyghe JR, Bien SA, Harrison TA, et al. Discovery of common and rare genetic risk variants for colorectal cancer. Nat Genet. Jan 2019;51(1):76-87. doi:10.1038/s41588-018-0286-6

21. Choi SW, Mak TS, O'Reilly PF. Tutorial: a guide to performing polygenic risk score analyses. Nat Protoc. Sep 2020;15(9):2759-2772. doi:10.1038/s41596-020-0353-1

22. Wray NR, Lin T, Austin J, et al. From Basic Science to Clinical Application of Polygenic Risk Scores: A Primer. JAMA Psychiatry. Jan 1 2021;78(1):101-109. doi:10.1001/jamapsychiatry.2020.3049

23. Vilhjalmsson BJ, Yang J, Finucane HK, et al. Modeling Linkage Disequilibrium Increases Accuracy of Polygenic Risk Scores. Am J Hum Genet. Oct 1 2015;97(4):576-92. doi:10.1016/j.ajhg.2015.09.001

24. Thomas M, Su YR, Rosenthal EA, et al. Combining Asian and European genome-wide association studies of colorectal cancer improves risk prediction across racial and ethnic populations. Nat Commun. Oct 2 2023;14(1):6147. doi:10.1038/s41467-023-41819-0

25. Krapohl E, Patel H, Newhouse S, et al. Multi-polygenic score approach to trait prediction. Mol Psychiatry. May 2018;23(5):1368-1374. doi:10.1038/mp.2017.163

26. Truong B, Hull LE, Ruan Y, et al. Integrative polygenic risk score improves the prediction accuracy of complex traits and diseases. Cell Genom. Mar 12 2024:100523. doi:10.1016/j.xgen.2024.100523

27. Tremblay J, Haloui M, Attaoua R, et al. Polygenic risk scores predict diabetes complications and their response to intensive blood pressure and glucose control. Diabetologia. Sep 2021;64(9):2012-2025. doi:10.1007/s00125-021-05491-7

28. Schoeler T, Choi SW, Dudbridge F, et al. Multi-Polygenic Score Approach to Identifying Individual Vulnerabilities Associated With the Risk of Exposure to Bullying. JAMA Psychiatry. Jul 1 2019;76(7):730-738. doi:10.1001/jamapsychiatry.2019.0310

29. Sinnott-Armstrong N, Tanigawa Y, Amar D, et al. Genetics of 35 blood and urine biomarkers in the UK Biobank. Nat Genet. Feb 2021;53(2):185-194. doi:10.1038/s41588-020-00757-z

30. Sawicki T, Ruszkowska M, Danielewicz A, Niedzwiedzka E, Arlukowicz T, Przybylowicz KE. A Review of Colorectal Cancer in Terms of Epidemiology, Risk Factors,

Development, Symptoms and Diagnosis. Cancers (Basel). Apr 22 2021;13(9)doi:10.3390/cancers13092025

31. Pare G, Mao S, Deng WQ. A machine-learning heuristic to improve gene score prediction of polygenic traits. Sci Rep. Oct 4 2017;7(1):12665. doi:10.1038/s41598-017-13056-1

32. Neumann PJ, Sanders GD, Russell LB, et al. Cost effectiveness in health and medicine. Second edition. ed. Oxford University Press; 2017:xxxiii, 496 pages.

33. Kasztura M, Richard A, Bempong NE, Loncar D, Flahault A. Cost-effectiveness of precision medicine: a scoping review. Int J Public Health. Dec 2019;64(9):1261-1271. doi:10.1007/s00038-019-01298-x

34. Garrison LP, Jr., Neumann PJ, Willke RJ, et al. A Health Economics Approach to US Value Assessment Frameworks-Summary and Recommendations of the ISPOR Special Task Force Report [7]. Value Health. Feb 2018;21(2):161-165. doi:10.1016/j.jval.2017.12.009

35. Stoffel E, Mukherjee B, Raymond VM, et al. Calculation of risk of colorectal and endometrial cancer among patients with Lynch syndrome. Gastroenterology. Nov 2009;137(5):1621-7. doi:10.1053/j.gastro.2009.07.039

36. Jenkins MA, Baglietto L, Dowty JG, et al. Cancer risks for mismatch repair gene mutation carriers: a population-based early onset case-family study. Clin Gastroenterol Hepatol. Apr 2006;4(4):489-98. doi:10.1016/j.cgh.2006.01.002

37. Guzauskas GF, Jiang S, Garbett S, et al. Cost-effectiveness of population-wide genomic screening for Lynch syndrome in the United States. Genet Med. Feb 25 2022;doi:10.1016/j.gim.2022.01.017

38. Lewis ACF, Green RC, Vassy JL. Polygenic risk scores in the clinic: Translating risk into action. HGG Adv. Oct 14 2021;2(4):100047. doi:10.1016/j.xhgg.2021.100047

39. Butterfield RM, Evans JP, Rini C, et al. Returning negative results to individuals in a genomic screening program: lessons learned. Genet Med. Feb 2019;21(2):409-416. doi:10.1038/s41436-018-0061-1

40. Siegel RL, Wagle NS, Cercek A, Smith RA, Jemal A. Colorectal cancer statistics, 2023. CA Cancer J Clin. May-Jun 2023;73(3):233-254. doi:10.3322/caac.21772

41. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin. Jan-Feb 2024;74(1):12-49. doi:10.3322/caac.21820

42. Peng L, Balavarca Y, Weigl K, Hoffmeister M, Brenner H. Head-to-Head Comparison of the Performance of 17 Risk Models for Predicting Presence of Advanced Neoplasms in Colorectal Cancer Screening. Am J Gastroenterol. Sep 2019;114(9):1520-1530. doi:10.14309/ajg.0000000000000370

43. Briggs SEW, Law P, East JE, et al. Integrating genome-wide polygenic risk scores and non-genetic risk to predict colorectal cancer diagnosis using UK Biobank data: population based cohort study. BMJ. Nov 9 2022;379:e071707. doi:10.1136/bmj-2022-071707

44. Elgart M, Lyons G, Romero-Brufau S, et al. Non-linear machine learning models incorporating SNPs and PRS improve polygenic prediction in diverse human populations. Commun Biol. Aug 22 2022;5(1):856. doi:10.1038/s42003-022-03812-z

45. Prive F, Arbel J, Vilhjalmsson BJ. LDpred2: better, faster, stronger. Bioinformatics. Apr 1 2021;36(22-23):5424-5431. doi:10.1093/bioinformatics/btaa1029

46. Hahn SJ, Kim S, Choi YS, Lee J, Kang J. Prediction of type 2 diabetes using genome-wide polygenic risk score and metabolic profiles: A machine learning analysis of population-based 10-year prospective cohort study. EBioMedicine. Dec 2022;86:104383. doi:10.1016/j.ebiom.2022.104383

47. Ge T, Irvin MR, Patki A, et al. Development and validation of a trans-ancestry polygenic risk score for type 2 diabetes in diverse populations. Genome Med. Jun 29 2022;14(1):70. doi:10.1186/s13073-022-01074-2

48. Lambert SA, Gil L, Jupp S, et al. The Polygenic Score Catalog as an open database for reproducibility and systematic evaluation. Nat Genet. Apr 2021;53(4):420-425. doi:10.1038/s41588-021-00783-5

49. Neumann A, Jolicoeur-Martineau A, Szekely E, et al. Combined polygenic risk scores of different psychiatric traits predict general and specific psychopathology in childhood. J Child Psychol Psychiatry. Jun 2022;63(6):636-645. doi:10.1111/jcpp.13501

50. Pepe MS, Cai T. The analysis of placement values for evaluating discriminatory measures. Biometrics. Jun 2004;60(2):528-35. doi:10.1111/j.0006-341X.2004.00200.x

51. About the RPGEH. https://divisionofresearch.kaiserpermanente.org/research/research-program-on-genes-environment-and-health/about-rpgeh/

52. Tannapfel A, Neid M, Aust D, Baretton G. The origins of colorectal carcinoma: specific nomenclature for different pathways and precursor lesions. Dtsch Arztebl Int. Oct 2010;107(43):760-6. doi:10.3238/arztebl.2010.0760

53. Argillander TE, Koornstra JJ, van Kouwen M, et al. Features of incident colorectal cancer in Lynch syndrome. United European Gastroenterol J. Oct 2018;6(8):1215-1222. doi:10.1177/2050640618783554

54. Gordon AS, Rosenthal EA, Carrell DS, et al. Rates of Actionable Genetic Findings in Individuals with Colorectal Cancer or Polyps Ascertained from a Community Medical Setting. Am J Hum Genet. Sep 5 2019;105(3):526-533. doi:10.1016/j.ajhg.2019.07.012

55. Fernandez-Rozadilla C, Timofeeva M, Chen Z, et al. Deciphering colorectal cancer genetics through multi-omic analysis of 100,204 cases and 154,587 controls of European and east Asian ancestries. Nat Genet. Jan 2023;55(1):89-99. doi:10.1038/s41588-022-01222-9

56. Su YR, Sakoda LC, Jeon J, et al. Validation of a Genetic-Enhanced Risk Prediction Model for Colorectal Cancer in a Large Community-Based Cohort. Cancer Epidemiol Biomarkers Prev. Mar 6 2023;32(3):353-362. doi:10.1158/1055-9965.EPI-22-0817

57. Keum N, Giovannucci E. Global burden of colorectal cancer: emerging trends, risk factors and prevention strategies. Nat Rev Gastroenterol Hepatol. Dec 2019;16(12):713-732. doi:10.1038/s41575-019-0189-8

58. Marquez-Luna C, Gazal S, Loh PR, et al. Incorporating functional priors improves polygenic prediction accuracy in UK Biobank and 23andMe data sets. Nat Commun. Oct 18 2021;12(1):6052. doi:10.1038/s41467-021-25171-9

59. Zheng Z, Liu S, Sidorenko J, et al. Leveraging functional genomic annotations and genome coverage to improve polygenic prediction of complex traits within and between ancestries. Nat Genet. Apr 30 2024;doi:10.1038/s41588-024-01704-y

60. Zhuang Y, Kim NY, Fritsche LG, Mukherjee B, Lee S. Incorporating functional annotation with bilevel continuous shrinkage for polygenic risk prediction. BMC Bioinformatics. Feb 9 2024;25(1):65. doi:10.1186/s12859-024-05664-2

61. Bien SA, Peters U. Moving from one to many: insights from the growing list of pleiotropic cancer risk genes. Br J Cancer. Jun 2019;120(12):1087-1089. doi:10.1038/s41416-019-0475-9

62. Sun J, Wang L, Zhou X, et al. Cross-cancer pleiotropic analysis identifies three novel genetic risk loci for colorectal cancer. Hum Mol Genet. Jun 5 2023;32(12):2093-2102. doi:10.1093/hmg/ddad044

63. Cheng I, Kocarnik JM, Dumitrescu L, et al. Pleiotropic effects of genetic risk variants for other cancers on colorectal cancer risk: PAGE, GECCO and CCFR consortia. Gut. May 2014;63(5):800-7. doi:10.1136/gutjnl-2013-305189

64. Pardo-Cea MA, Farre X, Esteve A, et al. Biological basis of extensive pleiotropy between blood traits and cancer risk. Genome Med. Feb 2 2024;16(1):21. doi:10.1186/s13073-024-01294-8

65. Kim H, Grueneberg A, Vazquez AI, Hsu S, de Los Campos G. Will Big Data Close the Missing Heritability Gap? Genetics. Nov 2017;207(3):1135-1145. doi:10.1534/genetics.117.300271

66. Baker E, Escott-Price V. Polygenic Risk Scores in Alzheimer's Disease: Current Applications and Future Directions. Front Digit Health. 2020;2:14. doi:10.3389/fdgth.2020.00014

67. Ge T, Chen CY, Ni Y, Feng YA, Smoller JW. Polygenic prediction via Bayesian regression and continuous shrinkage priors. Nat Commun. Apr 16 2019;10(1):1776. doi:10.1038/s41467-019-09718-5

68. Ding Y, Hou K, Burch KS, et al. Large uncertainty in individual polygenic risk score estimation impacts PRS-based risk stratification. Nat Genet. Jan 2022;54(1):30-39. doi:10.1038/s41588-021-00961-5

69. Lewis CM, Vassos E. Polygenic risk scores: from research tools to clinical instruments. Genome Med. May 18 2020;12(1):44. doi:10.1186/s13073-020-00742-5

70. Klau JH, Maj C, Klinkhammer H, et al. AI-based multi-PRS models outperform classical single-PRS models. Front Genet. 2023;14:1217860. doi:10.3389/fgene.2023.1217860

71. Albinana C, Zhu Z, Schork AJ, et al. Multi-PGS enhances polygenic prediction by combining 937 polygenic scores. Nat Commun. Aug 5 2023;14(1):4702. doi:10.1038/s41467-023-40330-w

72. Gheysariyeha F, Rahimi F, Tabesh E, Hemami MR, Adibi P, Rezayatmand R. Cost-effectiveness of colorectal cancer screening strategies: A systematic review. Eur J Cancer Care (Engl). Nov 2022;31(6):e13673. doi:10.1111/ecc.13673

73. National Comprehensive Cancer Network. Colorectal Cancer Screening. https://www.nccn.org/professionals/physician_gls/pdf/colorectal_screening.pdf

74. Seppala TT, Dominguez-Valentin M, Sampson JR, Moller P. Prospective observational data informs understanding and future management of Lynch syndrome: insights from the Prospective Lynch Syndrome Database (PLSD). Fam Cancer. Jan 2021;20(1):35-39. doi:10.1007/s10689-020-00193-2

75. National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Colorectal. https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf

76. Cenin DR, Naber SK, de Weerdt AC, et al. Cost-Effectiveness of Personalized Screening for Colorectal Cancer Based on Polygenic Risk and Family History. Cancer Epidemiol Biomarkers Prev. Jan 2020;29(1):10-21. doi:10.1158/1055-9965.EPI-18-1123

77. Naber SK, Kundu S, Kuntz KM, et al. Cost-Effectiveness of Risk-Stratified Colorectal Cancer Screening Based on Polygenic Risk: Current Status and Future Potential. JNCI Cancer Spectr. Feb 2020;4(1):pkz086. doi:10.1093/jncics/pkz086

78. Vanness DJ, Lomas J, Ahn H. A Health Opportunity Cost Threshold for Cost-Effectiveness Analysis in the United States. Ann Intern Med. Jan 2021;174(1):25-32. doi:10.7326/M20-1392

79. Buchanan AH, Lester Kirchner H, Schwartz MLB, et al. Clinical outcomes of a genomic screening program for actionable genetic conditions. Genet Med. Nov 2020;22(11):1874-1882. doi:10.1038/s41436-020-0876-4

80. Wilkins T, McMechan D, Talukder A, Herline A. Colorectal Cancer Screening and Surveillance in Individuals at Increased Risk. Am Fam Physician. Jan 15 2018;97(2):111-116.

81. Snowsill T, Coelho H, Huxley N, et al. Molecular testing for Lynch syndrome in people with colorectal cancer: systematic reviews and economic evaluation. Health Technol Assess. Sep 2017;21(51):1-238. doi:10.3310/hta21510

82. Jarvinen HJ, Renkonen-Sinisalo L, Aktan-Collan K, Peltomaki P, Aaltonen LA, Mecklin JP. Ten years after mutation testing for Lynch syndrome: cancer incidence and outcome in

mutation-positive and mutation-negative family members. J Clin Oncol. Oct 1 2009;27(28):4793-7. doi:10.1200/JCO.2009.23.7784

83. Stupart DA, Goldberg PA, Algar U, Ramesar R. Cancer risk in a cohort of subjects carrying a single mismatch repair gene mutation. Fam Cancer. 2009;8(4):519-23. doi:10.1007/s10689-009-9281-5

84. National Cancer Institute. SEER Incidence Data, 1975 - 2019. Accessed May 2, 2022, 22. https://seer.cancer.gov/data/

85. Nishihara R, Wu K, Lochhead P, et al. Long-term colorectal-cancer incidence and mortality after lower endoscopy. N Engl J Med. Sep 19 2013;369(12):1095-105. doi:10.1056/NEJMoa1301969

86. Doubeni CA, Weinmann S, Adams K, et al. Screening colonoscopy and risk for incident late-stage colorectal cancer diagnosis in average-risk adults: a nested case-control study. Ann Intern Med. Mar 5 2013;158(5 Pt 1):312-20. doi:10.7326/0003-4819-158-5-201303050-00003

87. Heisser T, Hoffmeister M, Brenner H. Significant underestimation of preventive effects in colorectal cancer screening trial. Gut. Feb 23 2024;73(3):556-558. doi:10.1136/gutjnl-2022-329165

88. Cardoso R, Guo F, Heisser T, et al. Colorectal cancer incidence, mortality, and stage distribution in European countries in the colorectal cancer screening era: an international population-based study. Lancet Oncol. Jul 2021;22(7):1002-1013. doi:10.1016/S1470-2045(21)00199-6

89. National Cancer Institute Surveillance E, and End Results Program. Cancer Query System: SEER Survival Statistics. https://seer.cancer.gov/canques/survival.html

90. van Dijk EL, Jaszczyszyn Y, Naquin D, Thermes C. The Third Revolution in Sequencing Technology. Trends Genet. Sep 2018;34(9):666-681. doi:10.1016/j.tig.2018.05.008

91. Chen SF, Dias R, Evans D, et al. Genotype imputation and variability in polygenic risk score estimation. Genome Med. Nov 23 2020;12(1):100. doi:10.1186/s13073-020-00801-x

92. Zauber AG, Lansdorp-Vogelaar I, Knudsen AB, Wilschut J, van Ballegooijen M, Kuntz KM. Evaluating test strategies for colorectal cancer screening: a decision analysis for the U.S. Preventive Services Task Force. Ann Intern Med. Nov 4 2008;149(9):659-69. doi:10.7326/0003-4819-149-9-200811040-00244

93. Djalalov S, Rabeneck L, Tomlinson G, Bremner KE, Hilsden R, Hoch JS. A Review and Meta-analysis of Colorectal Cancer Utilities. Med Decis Making. Aug 2014;34(6):809-18. doi:10.1177/0272989X14536779

94. Fiala MA. Screening recommendation adherence among first-degree relatives of individuals with colorectal cancer. Transl Behav Med. Aug 17 2022;12(8):853-859. doi:10.1093/tbm/ibac048

95. Lowery JT, Ahnen DJ, Schroy PC, 3rd, et al. Understanding the contribution of family history to colorectal cancer risk and its clinical implications: A state-of-the-science review. Cancer. Sep 1 2016;122(17):2633-45. doi:10.1002/cncr.30080

96. Wallingford CK, Kovilpillai H, Jacobs C, et al. Models of communication for polygenic scores and associated psychosocial and behavioral effects on recipients: A systematic review. Genet Med. Jan 2023;25(1):1-11. doi:10.1016/j.gim.2022.09.008

97. Barzi A, Lenz HJ, Quinn DI, Sadeghi S. Comparative effectiveness of screening strategies for colorectal cancer. Cancer. May 1 2017;123(9):1516-1527. doi:10.1002/cncr.30518

98. Sharaf RN, Ladabaum U. Comparative effectiveness and cost-effectiveness of screening colonoscopy vs. sigmoidoscopy and alternative strategies. Am J Gastroenterol. Jan 2013;108(1):120-32. doi:10.1038/ajg.2012.380

99. Knudsen AB, Zauber AG, Rutter CM, et al. Estimation of Benefits, Burden, and Harms of Colorectal Cancer Screening Strategies: Modeling Study for the US Preventive Services Task Force. JAMA. Jun 21 2016;315(23):2595-609. doi:10.1001/jama.2016.6828

100. Doubeni CA, Corley DA, Quinn VP, et al. Effectiveness of screening colonoscopy in reducing the risk of death from right and left colon cancer: a large community-based study. Gut. Feb 2018;67(2):291-298. doi:10.1136/gutjnl-2016-312712

101. van den Puttelaar R, Meester RGS, Peterse EFP, et al. Risk-Stratified Screening for Colorectal Cancer Using Genetic and Environmental Risk Factors: A Cost-Effectiveness Analysis Based on Real-World Data. Clin Gastroenterol Hepatol. Dec 2023;21(13):3415-3423 e29. doi:10.1016/j.cgh.2023.03.003

102. Zheng Z, Yabroff KR, Guy GP, Jr., et al. Annual Medical Expenditure and Productivity Loss Among Colorectal, Female Breast, and Prostate Cancer Survivors in the United States. J Natl Cancer Inst. May 2016;108(5)doi:10.1093/jnci/djv382

103. Hall MJ. Lynch syndrome (hereditary nonpolyposis colorectal cancer): Cancer screening and management. In: Lamont JT, Goff B, eds. UpToDate. 2022.

104. Briggs AH, Weinstein MC, Fenwick EA, et al. Model parameter estimation and uncertainty: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--6. Value Health. Sep-Oct 2012;15(6):835-42. doi:10.1016/j.jval.2012.04.014

105. Muslimova D, Dias Pereira R, von Hinke S, van Kippersluis H, Rietveld CA, Meddens SFW. Rank concordance of polygenic indices. Nat Hum Behav. May 2023;7(5):802-811. doi:10.1038/s41562-023-01544-6

106. Veyseh M, Ricker C, Espenschied C, Raymond V, D'Souza A, Barzi A. Secondary Germline Finding in Liquid Biopsy of a Deceased Patient; Case Report and Review of the Literature. Front Oncol. 2018;8:259. doi:10.3389/fonc.2018.00259

107. Archambault AN, Su YR, Jeon J, et al. Cumulative Burden of Colorectal Cancer-Associated Genetic Variants Is More Strongly Associated With Early-Onset vs Late-Onset Cancer. Gastroenterology. Apr 2020;158(5):1274-1286 e12. doi:10.1053/j.gastro.2019.12.012

108. Loeve F, Boer R, van Oortmarssen GJ, van Ballegooijen M, Habbema JD. The MISCAN-COLON simulation model for the evaluation of colorectal cancer screening. Comput Biomed Res. Feb 1999;32(1):13-33. doi:10.1006/cbmr.1998.1498

109. Rutter CM, Miglioretti DL, Savarino JE. Bayesian Calibration of Microsimulation Models. J Am Stat Assoc. Dec 1 2009;104(488):1338-1350. doi:10.1198/jasa.2009.ap07466

110. van Ballegooijen M, Rutter CM, Knudsen AB, et al. Clarifying differences in natural history between models of screening: the case of colorectal cancer. Med Decis Making. Jul-Aug 2011;31(4):540-9. doi:10.1177/0272989X11408915

111. Chapman I. Adenomatous polypi of large intestine: incidence and distribution. Ann Surg. Feb 1963;157:223-6. doi:10.1097/00000658-196302000-00007

112. Bombi JA. Polyps of the colon in Barcelona, Spain. An autopsy study. Cancer. Apr 1 1988;61(7):1472-6. doi:10.1002/1097-0142(19880401)61:7<1472::aid-cncr2820610734>3.0.co;2-e

113. Arminski TC, McLean DW. Incidence and Distribution of Adenomatous Polyps of the Colon and Rectum Based on 1,000 Autopsy Examinations. Dis Colon Rectum. Jul-Aug 1964;7:249-61. doi:10.1007/BF02630528

114. Clark JC, Collan Y, Eide TJ, et al. Prevalence of polyps in an autopsy series from areas with varying incidence of large-bowel cancer. Int J Cancer. Aug 15 1985;36(2):179-86. doi:10.1002/ijc.2910360209

115. Jass JR, Young PJ, Robinson EM. Predictors of presence, multiplicity, size and dysplasia of colorectal adenomas. A necropsy study in New Zealand. Gut. Nov 1992;33(11):1508-14. doi:10.1136/gut.33.11.1508

116. Johannsen LG, Momsen O, Jacobsen NO. Polyps of the large intestine in Aarhus, Denmark. An autopsy study. Scand J Gastroenterol. Sep 1989;24(7):799-806. doi:10.3109/00365528909089217

117. Rickert RR, Auerbach O, Garfinkel L, Hammond EC, Frasca JM. Adenomatous lesions of the large bowel: an autopsy survey. Cancer. May 1979;43(5):1847-57. doi:10.1002/1097-0142(197905)43:5<1847::aid-cncr2820430538>3.0.co;2-l

118. Vatn MH, Stalsberg H. The prevalence of polyps of the large intestine in Oslo: an autopsy study. Cancer. Feb 15 1982;49(4):819-25. doi:10.1002/1097-0142(19820215)49:4<819::aid-cncr2820490435>3.0.co;2-d

119. Williams AR, Balasooriya BA, Day DW. Polyps and cancer of the large bowel: a necropsy study in Liverpool. Gut. Oct 1982;23(10):835-42. doi:10.1136/gut.23.10.835

120. Kuntz KM, Lansdorp-Vogelaar I, Rutter CM, et al. A systematic comparison of microsimulation models of colorectal cancer: the role of assumptions about adenoma progression. Med Decis Making. Jul-Aug 2011;31(4):530-9. doi:10.1177/0272989X11408730

121. National Cancer Institute. Cancer Query System: SEER Survival Statistics. Accessed May 2, 2022, 2022. https://seer.cancer.gov/canques/survival.html

122. Habbema JD, van Oortmarssen GJ, Lubbe JT, van der Maas PJ. The MISCAN simulation program for the evaluation of screening for disease. Comput Methods Programs Biomed. May 1985;20(1):79-93. doi:10.1016/0169-2607(85)90048-3

123. Mandel JS, Church TR, Ederer F, Bond JH. Colorectal cancer mortality: effectiveness of biennial screening for fecal occult blood. J Natl Cancer Inst. Mar 3 1999;91(5):434-7. doi:10.1093/jnci/91.5.434

124. Mandel JS, Church TR, Bond JH, et al. The effect of fecal occult-blood screening on the incidence of colorectal cancer. N Engl J Med. Nov 30 2000;343(22):1603-7. doi:10.1056/NEJM200011303432203

125. Weissfeld JL, Ling BS, Schoen RE, et al. Adherence to repeat screening flexible sigmoidoscopy in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. Cancer. May 15 2002;94(10):2569-76. doi:10.1002/cncr.10538

126. Mandel JS, Bond JH, Church TR, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. N Engl J Med. May 13 1993;328(19):1365-71. doi:10.1056/NEJM199305133281901

127. Kronborg O, Jorgensen OD, Fenger C, Rasmussen M. Randomized study of biennial screening with a faecal occult blood test: results after nine screening rounds. Scand J Gastroenterol. Sep 2004;39(9):846-51. doi:10.1080/00365520410003182

128. Lindholm E, Brevinge H, Haglind E. Survival benefit in a randomized clinical trial of faecal occult blood screening for colorectal cancer. Br J Surg. Aug 2008;95(8):1029-36. doi:10.1002/bjs.6136

129. Pitkaniemi J, Seppa K, Hakama M, et al. Effectiveness of screening for colorectal cancer with a faecal occult-blood test, in Finland. BMJ Open Gastroenterol. 2015;2(1):e000034. doi:10.1136/bmjgast-2015-000034

130. Segnan N, Armaroli P, Bonelli L, et al. Once-only sigmoidoscopy in colorectal cancer screening: follow-up findings of the Italian Randomized Controlled Trial--SCORE. J Natl Cancer Inst. Sep 7 2011;103(17):1310-22. doi:10.1093/jnci/djr284

131. Holme O, Loberg M, Kalager M, et al. Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: a randomized clinical trial. JAMA. Aug 13 2014;312(6):606-15. doi:10.1001/jama.2014.8266

132. Schoen RE, Pinsky PF, Weissfeld JL, et al. Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. N Engl J Med. Jun 21 2012;366(25):2345-57. doi:10.1056/NEJMoa1114635

133. Scholefield JH, Moss SM, Mangham CM, Whynes DK, Hardcastle JD. Nottingham trial of faecal occult blood testing for colorectal cancer: a 20-year follow-up. Gut. Jul 2012;61(7):1036-40. doi:10.1136/gutjnl-2011-300774

134. Garcia-Albeniz X, Hsu J, Bretthauer M, Hernan MA. Effectiveness of Screening Colonoscopy to Prevent Colorectal Cancer Among Medicare Beneficiaries Aged 70 to 79 Years: A Prospective Observational Study. Ann Intern Med. Jan 3 2017;166(1):18-26. doi:10.7326/M16-0758

135. Pignone M, Saha S, Hoerger T, Mandelblatt J. Cost-effectiveness analyses of colorectal cancer screening: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. Jul 16 2002;137(2):96-104. doi:10.7326/0003-4819-137-2-200207160-00007

136. Ran T, Cheng CY, Misselwitz B, Brenner H, Ubels J, Schlander M. Cost-Effectiveness of Colorectal Cancer Screening Strategies-A Systematic Review. Clin Gastroenterol Hepatol. Sep 2019;17(10):1969-1981 e15. doi:10.1016/j.cgh.2019.01.014

137. Smith H, Varshoei P, Boushey R, Kuziemsky C. Simulation modeling validity and utility in colorectal cancer screening delivery: A systematic review. J Am Med Inform Assoc. Jun 1 2020;27(6):908-916. doi:10.1093/jamia/ocaa022

138. van Ballegooijen M, Boer R, Zauber AG. Simulation of colorectal cancer screening: what we do and do not know and does it matter. Best Pract Res Clin Gastroenterol. Aug 2010;24(4):427-37. doi:10.1016/j.bpg.2010.07.001

139. Brennan A, Chick SE, Davies R. A taxonomy of model structures for economic evaluation of health technologies. Health Econ. Dec 2006;15(12):1295-310. doi:10.1002/hec.1148

140. Rutter CM, Savarino JE. An evidence-based microsimulation model for colorectal cancer: validation and application. Cancer Epidemiol Biomarkers Prev. Aug 2010;19(8):1992-2002. doi:10.1158/1055-9965.EPI-09-0954

141. National Cancer Institute. SimCRC (Minnesota/MGH). Accessed May 2, 2022, 2022.

142. Rutter CM, Knudsen AB, Marsh TL, et al. Validation of Models Used to Inform Colorectal Cancer Screening Guidelines: Accuracy and Implications. Med Decis Making. Jul 2016;36(5):604-14. doi:10.1177/0272989X15622642

143. Shaukat A, Kahi CJ, Burke CA, Rabeneck L, Sauer BG, Rex DK. ACG Clinical Guidelines: Colorectal Cancer Screening 2021. Am J Gastroenterol. Mar 1 2021;116(3):458-479. doi:10.14309/ajg.0000000000001122

144. Qaseem A, Harrod CS, Crandall CJ, et al. Screening for Colorectal Cancer in Asymptomatic Average-Risk Adults: A Guidance Statement From the American College of Physicians (Version 2). Ann Intern Med. Aug 2023;176(8):1092-1100. doi:10.7326/M23-0779

145. Triantafillidis JK, Vagianos C, Malgarinos G. Colonoscopy in Colorectal Cancer Screening: Current Aspects. Indian J Surg Oncol. Sep 2015;6(3):237-50. doi:10.1007/s13193-015-0410-3

146. Arias E, Xu J, Tejada-Vera B, Murphy SL, Bastian B. U.S. State Life Tables, 2020. Natl Vital Stat Rep. Aug 2022;71(2):1-18.

147. National Cancer Institute. SEER*Explorer. Colon and Rectum. U.S. Mortality. https://seer.cancer.gov/statistics-network/explorer/application.html?site=20&data_type=2&graph_type=3&compareBy=sex&chk_sex_3=3&chk_sex_2=2&race=1&advopt_precision=1&advopt_show_ci=on&hdn_view=1#resultsRegion1

148. Jenkins MA, Buchanan DD, Lai J, et al. Assessment of a Polygenic Risk Score for Colorectal Cancer to Predict Risk of Lynch Syndrome Colorectal Cancer. JNCI Cancer Spectr. Apr 2021;5(2)doi:10.1093/jncics/pkab022

149. Duenas N, Klinkhammer H, Bonifaci N, et al. Ability of a polygenic risk score to refine colorectal cancer risk in Lynch syndrome. J Med Genet. Nov 2023;60(11):1044-1051. doi:10.1136/jmg-2023-109344

150. Hassanin E, Spier I, Bobbili DR, et al. Clinically relevant combined effect of polygenic background, rare pathogenic germline variants, and family history on colorectal cancer incidence. BMC Med Genomics. Mar 5 2023;16(1):42. doi:10.1186/s12920-023-01469-z

151. Ryan NAJ, Morris J, Green K, et al. Association of Mismatch Repair Mutation With Age at Cancer Onset in Lynch Syndrome: Implications for Stratified Surveillance Strategies. JAMA Oncol. Dec 1 2017;3(12):1702-1706. doi:10.1001/jamaoncol.2017.0619

152. Henrikson NB, Webber EM, Goddard KA, et al. Family history and the natural history of colorectal cancer: systematic review. Genet Med. Sep 2015;17(9):702-12. doi:10.1038/gim.2014.188

153. Mars N, Lindbohm JV, Della Briotta Parolo P, et al. Systematic comparison of family history and polygenic risk across 24 common diseases. Am J Hum Genet. Dec 1 2022;109(12):2152-2162. doi:10.1016/j.ajhg.2022.10.009

154. Choi J, Jia G, Wen W, Long J, Shu XO, Zheng W. Effects of Screenings in Reducing Colorectal Cancer Incidence and Mortality Differ by Polygenic Risk Scores. Clin Transl Gastroenterol. May 6 2021;12(5):e00344. doi:10.14309/ctg.0000000000000344

155. Li P, Li S, Chen J, Shao L, Lu X, Cai J. Association between family history and prognosis of patients with colorectal cancer: a systematic review and meta-analysis. Transl Cancer Res. Jan 2022;11(1):124-133. doi:10.21037/tcr-21-1546

156. He Y, Theodoratou E, Li X, et al. Effects of common genetic variants associated with colorectal cancer risk on survival outcomes after diagnosis: A large population-based cohort study. Int J Cancer. Nov 1 2019;145(9):2427-2432. doi:10.1002/ijc.32550

157. Knudsen AB, Rutter CM, Peterse EFP, et al. Colorectal Cancer Screening: An Updated Modeling Study for the US Preventive Services Task Force. JAMA. May 18 2021;325(19):1998-2011. doi:10.1001/jama.2021.5746

158. Social Security. Actuarial Life Table. https://www.ssa.gov/oact/STATS/table4c6.html

159. Bonadona V, Bonaiti B, Olschwang S, et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. JAMA. Jun 8 2011;305(22):2304-10. doi:10.1001/jama.2011.743

160. Taylor DP, Burt RW, Williams MS, Haug PJ, Cannon-Albright LA. Population-based family history-specific risks for colorectal cancer: a constellation approach. Gastroenterology. Mar 2010;138(3):877-85. doi:10.1053/j.gastro.2009.11.044

161. Bretthauer M, Loberg M, Wieszczy P, et al. Effect of Colonoscopy Screening on Risks of Colorectal Cancer and Related Death. N Engl J Med. Oct 27 2022;387(17):1547-1556. doi:10.1056/NEJMoa2208375

162. Palomaki GE, McClain MR, Melillo S, Hampel HL, Thibodeau SN. EGAPP supplementary evidence review: DNA testing strategies aimed at reducing morbidity and

mortality from Lynch syndrome. Genet Med. Jan 2009;11(1):42-65. doi:10.1097/GIM.0b013e31818fa2db

163. Tsai MH, Xirasagar S, Li YJ, de Groen PC. Colonoscopy screening among US adults aged 40 or older with a family history of colorectal cancer. Prev Chronic Dis. May 21 2015;12:E80. doi:10.5888/pcd12.140533

164. Dinh TA, Rosner BI, Atwood JC, et al. Health benefits and cost-effectiveness of primary genetic screening for Lynch syndrome in the general population. Cancer Prev Res (Phila). Jan 2011;4(1):9-22. doi:10.1158/1940-6207.CAPR-10-0262

165. Lambert SA, Abraham G, Inouye M. Towards clinical utility of polygenic risk scores. Hum Mol Genet. Nov 21 2019;28(R2):R133-R142. doi:10.1093/hmg/ddz187