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ORIGINAL PAPER

Personalized medicine for prevention: can risk stratified screening decrease colorectal cancer mortality at an acceptable cost?

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Abstract
Purpose Tailored health care interventions are expected to transform clinical practice. The objective of this study was to develop an innovative model to assess the effectiveness, cost, and harms of risk stratified colorectal cancer screening.
Methods We updated a previously validated microsimulation model consisting of three interlinked components: risk assessment, natural history, and screening/treatment modules. We used data from representative national surveys and the literature to create a synthetic population that mimics the family history and genetic profile of the US population. We applied risk stratification based on published risk assessment tools to triage individuals into five risk categories: high, increased, medium, decreased, and low.
Results On average, the incremental cost of risk stratified screening for colorectal cancer compared to the current approach at 60% and 80% compliance rates is $18,342 and $23,961 per life year gained. The harms in terms of false positives and perforations are consistently lower for personalized scenarios across all compliance rates. False positives are reduced by more than 47.0% and perforations by at least 9.9%. There is considerable uncertainty in the life years gained, but the reduction in harms remains stable under all scenarios.
Conclusion A key finding is that risk stratified screening can reduce harms at all levels of compliance. Therefore, selection of screening scenarios should include comprehensive comparisons of mortality, harms from screening, and cost. This study provides guidance for evaluating risk stratified cancer screening and further research is required to identify optimal implementation approaches in the real-world setting.

Keywords Precision medicine · Risk stratification · Cost-effectiveness · Colorectal cancer · Prevention

Introduction

Colorectal cancer is the third most common cancer in the United States and is the second leading cause of cancer-related death [1]. Only about 58.2% of individuals aged 50–74 years underwent recommended colorectal cancer screening in 2013, much lower than the Health People 2020 target of 70.5% and the National Colorectal Cancer Roundtable goal of an 80.0% compliance rate by 2018 [2]. Several types of tests are available for colorectal cancer screening and each has advantages and limitations, but as stated by the US Preventive Services Task Force, screening for colorectal cancer remains an underused preventive health intervention [3–5].

Implementing strategies to increase use and overall effectiveness of colorectal screening is essential to reduce the burden from this highly preventable cancer. Colorectal cancer screening in the United States is predominantly provided through primary screening colonoscopies [6]. The proportion of colonoscopies has increased steadily over the past decade; currently, about 85% of all colorectal cancer screening involve a colonoscopy, and fecal-based tests

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comprise the majority of the remainder. Modeling studies suggest that colonoscopy and fecal-based screening are both effective approaches, but under circumstances of finite budgets, fecal-based tests are likely to provide better population-level outcomes [7, 8]. In addition, capacity-related constraints may make colonoscopy-based screening unsustainable across many regions. Even when adequate national capacity exists for optimal screening, the geographic distribution of endoscopic services may still lead to sub-optimal screening rates [9].

Personalized screening can stratify individuals by predicted risk and improve the efficiency of the screening process by optimizing both the type of screening test and frequency of testing to match an individual's risk of developing colorectal cancer. Genetic predisposition to colorectal cancer—such as that affiliated with Familial Adenomatous Polyposis (FAP) or Lynch syndrome—affects a small proportion of the population, but these individuals have an extremely high incidence rate [10]. In addition, 8–9% of the population has increased risk due to family history of colorectal cancer [11]. Almost 90% of the population would be considered average risk, and these individuals account for 75% of all colorectal cancers diagnosed. Several risk models have been published and numerous online tools are available to predict colorectal cancer risk, both for average and higher risk individuals. For increased and high-risk individuals, family history and, when available, genetic testing serve as key predictors of colorectal cancer risk [12]. For average risk individuals, several risk models are available, but their discriminatory power as measured by the C statistic has generally been only fair. The range has been in the 0.60 to 0.74 threshold with predominantly white populations [13–15], while studies using more representative populations have reported values in the 0.60 to 0.68 threshold [16, 17].

Numerous studies have established the cost-effectiveness of colorectal cancer screening [18–20], and other modeling studies have evaluated variation in screening schedule based on race or gender [21, 22], but none, to date, has assessed the benefits of risk stratified colorectal cancer screening. Risk stratified screening may have substantial clinical and economic benefits, because targeted screening schedules can ensure that testing frequency and intensity are tailored to individual risk. The ability of current risk prediction tools to adequately stratify patients to yield positive impacts in terms of adequate mortality reduction needs to be tested. Better risk prediction tools will likely be available in the near future as genomics and other high-throughput technologies, such as proteomics, and advances in informatics fuel the growth in personalized medicine [23].

The objective of this study is to systematically evaluate and compare current screening practice with that of a risk stratified approach. We assess the harms and benefits of risk stratification using accuracy levels of current risk prediction tools and also those of a future 'best-case' scenario of a very high level of prediction accuracy. The findings from this study will add to the growing debate on personalized medicine and offer guidance on the potential ability of risk stratified screening approaches, based on present and potential future scenarios, to reduce colorectal cancer mortality. This modeling study will also inform the direction of future research by identifying key gaps that need to be addressed to systematically assess application of risk stratified screening in the real-world setting.

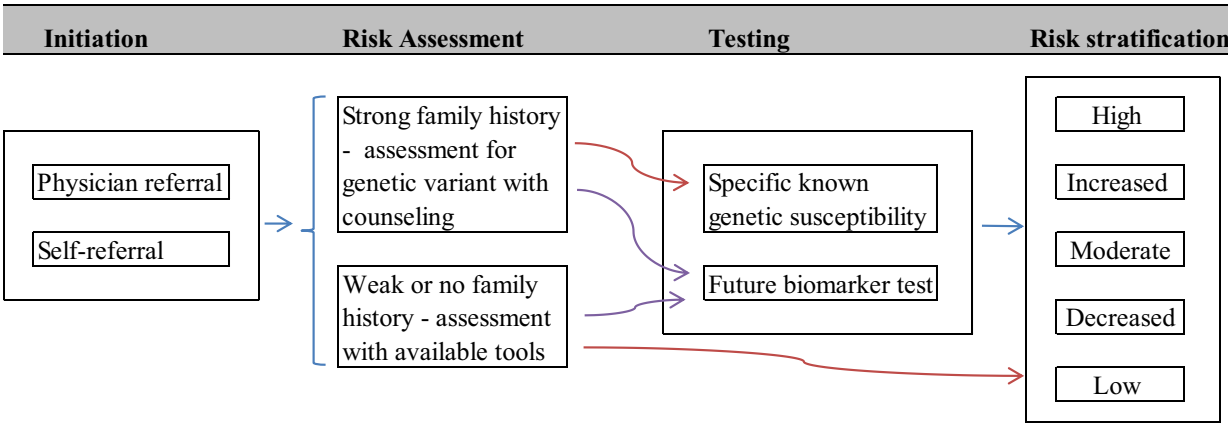
Materials and methods

We adapted and updated a previously validated microsimulation model to assess the impact of personalized screening on colorectal cancer mortality and healthcare costs [8, 20]. The personalized risk-based screening model consists of three interconnected components: (1) risk assessment, (2) natural history, and (3) screening/treatment.

As shown in Table 1, risk assessment was performed in multiple stages: the first step was initiation of risk assessment which was followed by risk evaluation using risk tools that are currently available for use in clinical practice [13–16]. Risk assessment was incorporated in the model in a manner that reflects clinical practice; individuals or physicians use risk tools that are readily available to determine individual scores to assess probability of developing colorectal cancer. These tools use information on individual demographics, smoking status, family history, dietary preferences, and other factors to assign risk scores. The modeling approach also mimics procedures that are utilized in the real-world setting to stratify based on family history. In our model, individuals with strong family history (two or more relatives with colorectal cancer, or one relative diagnosed before the age of 50) were offered counseling and genetic testing, while individuals with none or weak family history only received risk assessment using the risk tools. Finally, to project availability of improved molecular testing in the future, we offered a low-cost biomarker test and included it as an additional step in the risk stratification process.

The risk assessment module determined the predicted risk for each individual, and the true risk was incorporated in the natural history component to determine the likelihood and age at which polyps that subsequently result in colorectal cancer develop. We created a synthetic cohort that reflects the population of the United States and the distribution of true risk as described in Table 1. The levels of true risk for each risk category were based on the risk factors available in the 2010 National Health Interview Survey

Table 1 Framework for risk stratification, screening schedules, and scenarios



Risk Category	% Pop	Screening Schedule
High*	<0.01%	Colonoscopy every 2 years starting at age 20
Increased	~10%	Colonoscopy every 5 years starting at age 40
Medium	~30%	Colonoscopy every 10 years or fecal test annually starting at age 50**
Decreased	~30%	Colonoscopy at age 50 only, or fecal test every 2 years starting at age 50**
Low	~30%	Colonoscopy at age 50 only
Scenarios	Description	
Present	Majority of individuals are considered average risk and begin screening at age 50 using either colonoscopy or fecal tests. Individuals only undergo risk assessment when family history is present; they are then assigned to high or increased risk and begin screening colonoscopies at an earlier age	
Personalized	Individuals undergo risk assessment when family history is known and at ages 40 and 50. Individuals are assigned to the five risk categories described above and screening schedule is based on assigned risk category	
Future	Individuals undergo risk assessment and biomarker testing when family history is known and at ages 40 and 50. Individuals are assigned to the five risk categories described above and screening schedule is based on assigned risk category	

* Distribution based on published prevalence of Lynch and FAP

** 85% select colonoscopy based on current test preference from the 2013 National Health Interview Survey

(NHIS) and adjusted to ensure that the overall incidence of colorectal cancer was similar to those obtained from the Surveillance, Epidemiology, and End Results data. Based on the proportions reported in the 2010 National Health Interview Survey, we assigned to individuals a strong or weak family history, and an age at which family history was known. Additional details on the risk module and other model components, including the screening test characteristics and cost, are provided in the Supporting Information.

As described in Table 1, we analyzed three scenarios with varying risk assessments and screening schedules: present, personalized, and future scenarios. In the "present" scenario, individuals were screened based on current guideline recommendations which include endoscopy or fecal testing starting at age 50 for those at average risk.

To reflect the limited assessment of cancer risk currently in clinical practice, we assumed that individuals underwent risk assessment at the time family history was known and categorized as high or other risk groups as appropriate. This approach reflects the current practice where high-risk individuals with conditions, such as Lynch syndrome, are identified and offered more aggressive screening schedules. In the "personalized" scenario, risk assessment was performed when family history was known and also at ages 40 and 50 to stratify individuals into the five perceived risk categories. We elected to perform the first assessment at age 40 to identify higher risk individuals who should begin screening prior to the age of 50. Individuals were assigned to five risk categories under the personalized scenario and underwent screening based on predefined schedules: the high, increased, and medium groups followed screening schedules based on current American Cancer Society guidelines for higher risk and average risk individuals, while the decreased and low groups followed less intensive schedules determined through literature review of prior studies and recommendation of our clinical expert (Table 1). To keep the complexity manageable for the modeling process, we did not vary risk scores between the ages of 40 and 50 except for situations when new family history information became known. The same pattern was followed for the "future" scenario, though individuals also underwent biomarker testing at each risk assessment.

Table 2 provides the key input parameters for the risk assessment component (additional parameter values related to the screening test features and cost are provided in the Supporting Information). We have used a conservative discriminatory power of 0.60 for the personalized scenario to reflect the level that is likely to be achieved in real-world clinical practice, given issues related to availability and accuracy of family history and other information for risk stratification [14, 16]. This level of accuracy has also been reported in validation of colorectal cancer risk tools [16]. The accuracy of assignment in the model is included as a matrix comparing the true risk versus the predicted risk. We also evaluated the worst- and best-case distribution of accuracy across the risk categories; a better discrimination could be achieved if cases were assigned to risk categories just below or above their true risk category (narrow distribution and closer to their true risk category, e.g., an individual with true increased risk assigned to medium risk) rather than much higher or lower risk categories (wider distribution and very different assignment than their true risk category, e.g., an individual with true increased risk assigned to low-risk). The future scenario reflects the optimal case of a very high level of accuracy, with discriminatory power of 0.90; higher than this level will likely not be possible in clinical practice. Costs were approached from the payer perspective and reflect rates likely to be reimbursed and only include direct medical costs. Risk assessment was assumed to occur in most cases during annual visits and assigned a base cost of $40 based on a prior study [24]. Risk tools are available online and individuals could also calculate and print out their scores prior to a routine physician visit and an average or lower scores may require no action and no additional discussion. In other cases, potentially a physician visit may be scheduled specifically for evaluation of cancer risk. Therefore, there could be a range of scenarios and we assumed an average cost of $40 and tested a range of cost from $20 to $80 (this was selected to reflect Medicare reimbursement for low to moderately intensive physician office visit for new or established patient). Biomarker testing can be very expensive, and for the purposes of this modeling study, we wanted to understand whether a low or modestly priced test would be a viable option. We, therefore, assumed that the biomarker test would cost $200 in the base case and we varied the cost from $100 to $400.

For each scenario, we report the discounted (at 3%) life years gained and the cost for 60%, 80%, and 100% compliance. The current compliance rate is approximately 60%, and the target rate is 80%; as in prior studies, 100% compliance was included to compare the model scenarios under the theoretical framework of perfect compliance. We also present the total number of colonoscopy and fecal-based tests. We calculate potential harms due to colorectal cancer screening based on the volume of screens performed. The number of false positives is based on the likelihood reported by Hubbard et al. [25] for repeated rounds of screening: 4.6%, 4.0%, 3.4%, 3.1%, and 2.7% for first, second, third, fourth, and subsequent rounds of fecal-based screening. Perforations due to colonoscopies are estimated based on the 0.001% rate reported in the literature [26, 27].

We compared both the personalized and future scenarios with the present scenario, as our goal was to assess the cost-effectiveness of these approaches in comparison to current clinical practice. To assess sensitivity of the incremental cost-effectiveness of each scenario, we vary both the accuracy of the risk assignment algorithm and the cost of the risk assessment, as shown in Table 2. The threshold for cost-effectiveness is based on WHO criteria: highly cost-effective is less than the Gross Domestic Product (GDP) per capita of $53,000, and cost-effective is between one and three times the GDP per capita.

Results

Table 3 presents the results for each scenario at 60%, 80%, and 100% compliance rates. For both 60% and 80% compliance, the personalized and future scenarios produce higher life years gained than the present scenario

Table 2 Key parameters for the risk model component

Risk model parameters	Base case						Sensitivity Analysis	Source
Accuracy								
Personalized risk assessment & assignment	Predicted risk						Varied—better and worse distribution	Discriminatory power of 0.6 is a conservative estimate based on numerous studies [13–15]. We choose the low value as we did not have guidance on the distribution across the risk groups. We therefore estimate the impact of changing from a tight distribution around the correct assignment (best-case) and wide distribution to other categories (worse case)
Base case	True risk	L	D	M	I			
L = low; D = decreased; M = medium; I = increased; H = high. H (high-risk) is only assigned when strong family history is present and verified by genetic testing	L	0.6	0.2	0.2	0			
	D	0.2	0.6	0.2	0			
	M	0	0.2	0.6	0.2			
	I	0	0.2	0.2	0.6			
Worst case	True risk	Predicted risk						
	L	0.6	0.1	0.1	0.1			
	D	0.1	0.6	0.1	0.2			
	M	0.2	0.1	0.6	0.1			
	I	0.2	0.1	0.1	0.6			
Best-case	True risk	Predicted risk						
	L	0.6	0.4	0	0			
	D	0.2	0.6	0.2	0			
	M	0	0.2	0.6	0.2			
	I	0	0	0.4	0.6			
Future biomarker Test Assessment & Assignment		L	D	M	I	H	Not varied	Assumption
	L	0.9	0.1	0	0	0		
	D	0	0.9	0.1	0	0		
	M	0	0.1	0.9	0	0		
	I	0	0	0.1	0.9	0		
	H	0	0	0	0.1	0.9		
Sensitivity—Lynch Syndrome	1							33
Specificity—Lynch Syndrome	0.93							33
Sensitivity—Familial Adenomatous Polyposis (FAP)	0.9							34
Specificity—FAP	0.99							34
Cost								
Risk Stratification (using paper/online risk tools)*	$40						20,60,80	24
Genetic counseling and testing								
Lynch Syndrome—unknown germline**	$4,535						Not varied	35
FAP test	$1,500						Not varied	34
Biomarker test (future)	$200						100, 300, 400	Assumption

* We have assumed that the risk stratification discussion with the physician will occur during annual visits or other appropriate visits

** We have assumed that for 10%, the germline will be known and the cost will be $350 for these individuals (fightlynch.org 2013). In addition, 75% with strong family history will receive Lynch syndrome testing, while 25% will receive FAP testing

on average, and have incremental cost per life years gained which would be considered cost-effective. At 60% compliance, the incremental cost per life year gained is $18,342 for the personalized scenario and $47,108 for the future scenario. When compliance is increased to 80%, the values are $23,961 and $91,379, respectively. A more complex picture arises at 100% compliance, with the personalized scenario resulting in lower life years gained. The future scenario results in higher life years gained than the present scenario, but the cost per life years gained is very high ($199,366). The harms in terms of false positives and perforations are consistently lower for personalized and future scenarios compared with the present scenario across all compliance rates. False positives are reduced by more than 48.6%, and perforations are reduced by at least 9.9%. The harms decrease as

Table 3 Incremental cost per life years gained and harms by scenario and compliance

	Life years gained* (per 100,000) (years)	Cost (per 100,000) (millions)	Incremental cost per life years gained**	Number of tests		Harms (number)		Harms (%reduction)	
				Fecal-based tests	Colonoscopy	False positives	Perforation	False positives	Perforation
60% compliance									
Present	5,423 [420]***	$173.04 [1.41]	–	108,799 [1,239]	132,956 [567]	3,294	133	–	–
Personalized	5,717 [422]	$178.43 [1.43]	$18,342	57,442 [822]	119,761 [513]	1,691	120	48.6%	9.9%
Future	5,750 [381]	$188.47 [1.38]	$47,108	58,791 [931]	112,098 [526]	1,728	112	47.5%	15.7%
80% compliance									
Present	7,270 [356]	$188.24 [1.17]	-	144,707 [1357]	175,698 [606]	5,529	176	–	–
Personalized	7,481 [417]	$193.30 [1.35]	$23,961	61,570 [797]	152,415 [543]	1,972	152	64.3%	13.3%
Future	7,512 [331]	$210.33 [1.19]	$91,379	66,806 [937]	136,926 [593]	2,113	137	61.8%	22.1%
100% compliance									
Present	9,142 [415]	$203.77 [1.15]	–	180,514 [1805]	218,692 [559]	6,901	219	–	–
Personalized	9,074 [390]	$207.79 [1.18]	*D*	63,249 [849]	183,624 [594]	2,095	184	69.6%	16.0%
Future	9,296 [364]	$234.38 [1.13]	$199,366	79,206 [1,002]	161,280 [429]	2,526	161	63.4%	26.3%

* Compared to no screening

** Compared to present scenario

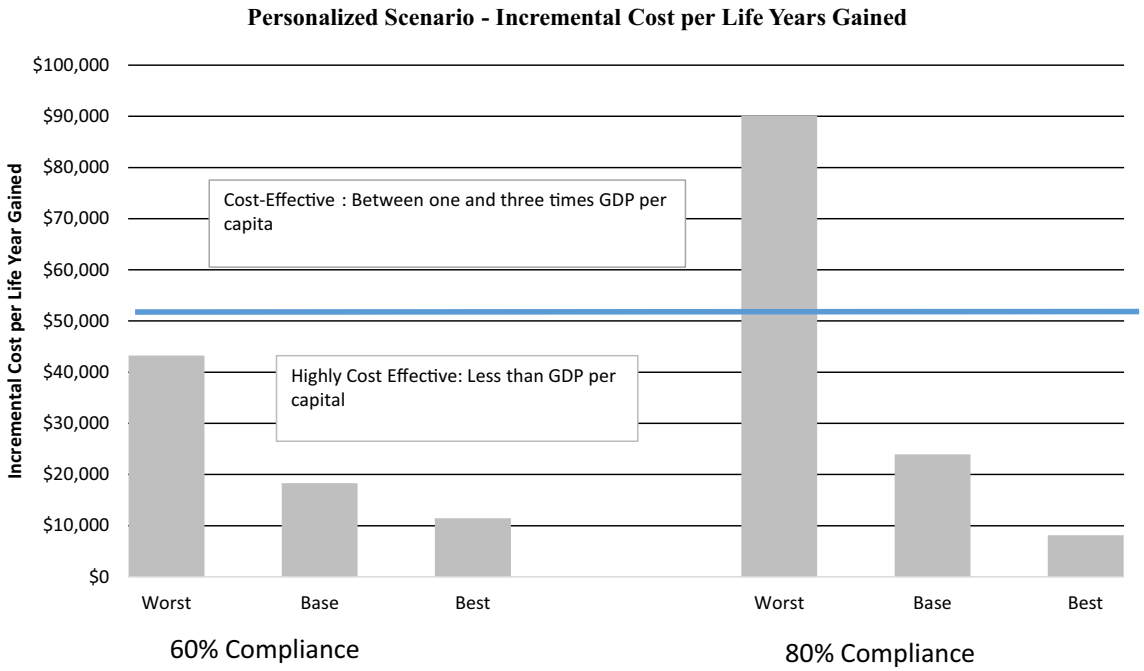
*** Standard deviations based on the model runs are presented in brackets

the compliance rate increases for both the personalized and future scenarios when compared with the present scenario.

As seen by the standard deviations shown in Table 3, the values for the life years gained are quite large relative to the difference between the present and personalized or future scenarios. Therefore, although on average, in most instances, the personalized and future scenarios result in an increase in life years saved, there are large variations and, therefore, the increase in life years gained is not a robust finding. The future scenario, especially at the 80% level of compliance, is the most likely scenario to consistently provide an increase in life years gained. The cost-effectiveness plans showing the uncertainty in the cost-effectiveness estimates (see Supporting Information Fig. 1A though 1D) provide a graphically representation of this variability in the life years saved. In contrast, the variability in the cost and that in the number of tests performed remain quite stable with relatively small standard deviations compared to the differences between the scenarios. The reduction in harms related to the personalized and future scenarios remains consistent across all modeling runs performed.

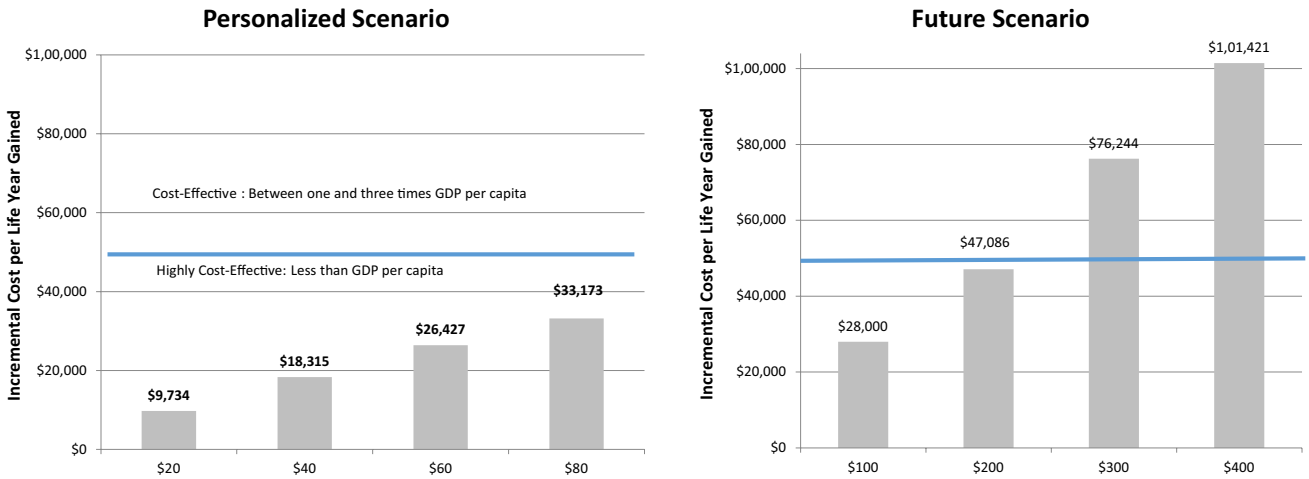
We further tested the worst- and best-case distribution of the risk assessment matrix (as specified in Table 1) to assess impact on the findings. Figure 1 illustrates that varying the accuracy of the risk assessment to reflect worst- and best-case situations has a substantial impact on the incremental cost per life years gained; much of this difference though is due to difference in cost rather than life years saved which continues to exhibit large variability. In most instances, the estimates based on the average values are still highly cost-effective. The worst case has the largest variation between 60% and 80% compliance, with a difference of almost $50,000 per life year gained. This clearly indicates that inaccurate distribution across the risk groups has a large impact as compliance increases. It is important to also note that harms from screening (data not shown) are higher with more inaccurate distributions; the best-case has the lowest harms, while worst case has the highest harms regardless of compliance, but these rates are all lower than the present scenario.

Figure 2 shows the changes in incremental cost per life year gained when the cost of risk assessment is varied. Risk stratification using paper and online tools remains cost-effective for a wide range of cost, from $20 to $80



Note: The 100% compliance is not presented, as all cases are dominated by present scenario.

Fig. 1 Shows the incremental cost per life years saved when accuracy of the risk prediction test is varied. We show the results at 60% and 80% levels of compliance for risk stratification and screening recommendations. The *blue line* represents the Gross Domestic Product (GDP) per capital for the United States. Incremental cost per life years saved below this threshold is considered highly cost-effective



Note: All values are shown at 60% level of compliance.

Fig. 2 Presents the incremental cost per life years saved for the personalized and future scenarios when cost of risk stratification is varied. All values are shown at the 60% level of compliance. The personalized scenario remains highly cost-effective across the range from $20 to $80 for risk assessment. In the future scenario, cost of approximately less than $200 is highly cost-effective

per session. Individuals in the model underwent at least two sessions (one at age 40 and one at 50), and some may have had an additional session at the age when family history was known; therefore, the cost per person is at least $40 to $160. In the case of the future biomarker test, cost of $200 or under per test or $400 per person remains highly cost-effective (in the model, individuals had two tests). At a cost of $300 and $400 per test, the incremental cost per life year gained is quite large, at $76,244 and $101,421, respectively.

Discussion

The personalized screening scenarios under 60% or 80% compliance are on average cost-effective, but there is large variability in the life years saved. Therefore, risk stratified screening, with the discriminatory power of 0.60, will likely not consistently result in improvements in mortality but will always result in lower harms than the present screening scenario. This finding, therefore, will hold true even when based on the currently available risk stratification tools. The future scenario, with discriminatory power of 0.90, is more likely to result in an increase in life years saved at the 60% and 80% levels of compliance. At very high levels of compliance (90% or 100%), more accurate approaches to stratify risk will be required to reduce colorectal cancer mortality. A key finding is that risk stratified screening reduces harms at all levels of compliance, and therefore, a comprehensive comparison that includes colorectal cancer mortality, harms from screening, and total cost should be performed to guide optimal scenario selection.

High-cost risk stratification tools or biomarkers may not be cost-effective. Risk stratification approaches that cost more than $500 per person are not likely to be cost-effective even when very high levels of accuracy of 90% can be achieved. If risk stratification increases compliance—especially among those at medium, increased, or high-risk—then a high-cost test can be highly cost-effective. Currently, available tools have discrimination rates of less than 0.70 [16, 17]; if these tools can be improved further and provided at a reasonable cost, then personalized screening can be highly cost-effective. There may not be large improvements in life years gained, but there will be substantial reduction in harms from screening.

In this study, we only considered five different risk categories and screening schedules, thus it is possible that a different set of highly tailored and individualized screening schedules could lead to additional improvements. Several types of tests are recommended for colorectal cancer screening and therefore additional combinations of tests are possible [3]. Known genetic syndromes account for about 5% of colorectal cancers, and family history accounts for another 20%, but the majority are diagnosed among those with sporadic disease [10]. To substantially reduce colorectal cancer mortality, it is important to stratify the higher risk individuals from among the large pool of those currently classified as average risk.

One key consideration is stakeholder acceptance of risk stratified screening. Individuals, providers, and health insurers will all need to accept screening based on projected risk. Low-risk individuals, who could still develop colorectal cancer, will need to be comfortable with undergoing fewer screenings to reduce unnecessary harms from frequent screening. One-time colonoscopy, as modeled in this study, may be a reasonably effective approach to reduce mortality from colorectal cancer for the low-risk population [28]. Patient and provider education and guidance tools are needed to support personalized decision-making, weighing all the benefits and drawbacks of the recommended screening approaches. Further research is needed to identify patient preferences and the decision-making process when details on both the benefits and harms of the screening intervention are provided.

Implementation can also be hampered by difficulties gathering and reporting accurate data on family history. Historically, individuals have reported incomplete or inaccurate information about the cancer history in their family, and recall bias has complicated the risk assessment process [29, 30]. However, a recent literature review [31] indicates that patients are generally able to provide accurate reports of cancer diagnosis in first- and second-degree relatives. This improvement may be because people are increasingly aware that it is important to document and maintain detailed health histories of extended family members. However, clinicians may still lack the expertise to collect, assess, and interpret the information, and therefore, standardized tools are needed to guide family history discussions [29].

This modeling study has several potential limitations. First, though our model is highly innovative, we needed to create a synthetic cohort and true risk distributions to project cumulative colorectal cancer risk for each risk group. For the high-risk group, we drew upon published studies about Lynch syndrome; for the other groups, we had to base population distribution and lifetime risk on "best estimates" and assumptions drawn from available cancer surveillance data. Nevertheless, a key strength is that the distribution selected in the model is an accurate overall reflection of the US population, because the distribution and rates match the incidence and mortality rates from the Surveillance, Epidemiology, and End Results database. Furthermore, the distributions used remain consistent across the three scenarios compared in this study; we varied some parameter assignments (such as family history) and found no material change in the results. Second, we have presented life years gained and not quality adjusted life years (QALYs), which also consider a person's quality of life. We decided to follow the precedent set by the majority of past colorectal cancer modeling assessments that have reported effectiveness in terms of life years gained, so as not to subject our findings to potential conflicts surrounding the measurement of QALYs [32]. Third, we attempted to include costs that provide a reasonable estimate of the risk stratification testing process. Real-world implementation may be far more costly than projected, and this could impact the cost-effectiveness of the personalized and future scenarios. To accurately

gauge the resources required, additional assessment in the real-world clinical setting is needed. Fourth, improvements in the sensitivity and specificity of screening and other tests and procedures can impact the cost-effectiveness of risk stratified screening. Therefore, changes along the continuum of care—which includes screening, diagnosis, and treatment—should be monitored, and the cost-effectiveness of personalized screening should be reassessed as required.

This study shows that using even modestly accurate risk stratification can improve the efficiency of colorectal cancer screening, especially by reducing the harms related to screening. Additional research is required to improve the accuracy of the risk stratification process and to assess optimal approaches to implement personalized screening in clinical practice. Precision medicine can increase the benefits gained from screening, but to realize these gains, adequate investment in developing optimal implementation processes is required [33–35].

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interest or financial disclosures to report.

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