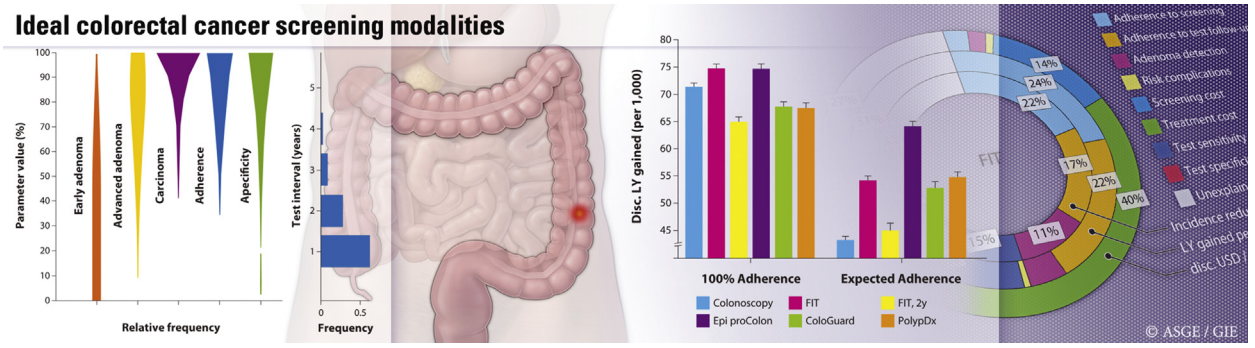
Evaluating key characteristics of ideal colorectal cancer screening modalities: the microsimulation approach

Ansgar Deibel, MD,[1] Lu Deng, PhD,[2] Chih-Yuan Cheng, MD, MSc,[3,4] Michael Schlander, MD, MBA,[3,4] Tao Ran, PhD,[3] Brian Lang, MSc,[5,6] Niklas Krupka, MD,[7] Niko Beerenwinkel, PhD,[5,6] Gerhard Rogler, MD,[1] Reiner Wiest, MD,[7] Amnon Sonnenberg, MD, MSc,[8] Jan Poleszczuk, PhD,[9,10,*] Benjamin Misselwitz, MD[7,*]

Zurich, Basel, Bern, Switzerland; Heidelberg, Mannheim, Germany; Portland, Oregon, USA; Warsaw, Poland

GRAPHICAL ABSTRACT



Background and Aims: Screening for colorectal cancer (CRC) can effectively reduce CRC incidence and mortality. Besides colonoscopy, tests for the detection of biomarkers in stool, blood, or serum, including the fecal immunochemical test (FIT), ColoGuard, Epi proColon, and PolypDx, have recently been advanced. We aimed to identify the characteristics of theoretic, highly efficient screening tests and calculated the effectiveness and cost effectiveness of available screening tests.

Methods: Using the microsimulation-based colon modeling open-source tool (CMOST), we simulated 142,501 theoretic screening tests with variable assumptions for adenoma and carcinoma sensitivity, specificity, test frequency, and adherence, and we identified highly efficient tests outperforming colonoscopy. For available screening tests, we simulated 10 replicates of a virtual population of 2 million individuals, using epidemiologic characteristics and costs assumptions of the United States.

Results: Highly efficient theoretic screening tests were characterized by high sensitivity for advanced adenoma and carcinoma and high patient adherence. All simulated available screening tests were effective at 100% adherence to screening and at expected real-world adherence rates. All tests were cost effective below the threshold of 100,000 U.S. dollars per life year gained. With perfect adherence, FIT was the most effective and cost-efficient intervention, whereas Epi proColon was the most effective at expected real-world adherence rates. In our sensitivity analysis, assumptions for patient adherence had the strongest impact on effectiveness of screening.

Conclusions: Our microsimulation study identified characteristics of highly efficient theoretic screening tests and confirmed the effectiveness and cost-effectiveness of colonoscopy and available urine-, blood-, and stool-based tests. Better patient adherence results in superior effectiveness for CRC prevention in the whole population. (Gastrointest Endosc 2021;94:379-90.)

(footnotes appear on last page of article)

Colorectal cancer (CRC) is the third most common cancer in the world[1] and causes the fourth highest number of cancer-related deaths, resulting in high economic impact.[2] However, CRC offers optimal opportunities for preventive efforts because malignant transformation occurs slowly via adenomatous precursors, and early CRC has much lower mortality compared with advanced disease.[3-6] Therefore, CRC screening is recommended by current gastroenterologic guidelines,[7,8] although CRC screening is limited by low patient adherence.[9-13] Increasing patient participation in CRC screening remains a central task in current gastroenterology practice.

The effectiveness of 2 screening principles has been established: (1) detection of biomarkers (eg, occult blood by the guaiac fecal occult blood test) in stool and (2) visual detection of (pre-)cancerous lesions by endoscopy. The guaiac fecal occult blood test and rectosigmoidoscopy can reduce the relative risk for CRC-related mortality by 16% and 31%, respectively.[4,5] The effect of colonoscopy has not been tested in randomized controlled trials, but many observational studies suggest a risk reduction of more than 60%.[6] Recently, tests detecting DNA with CRC-associated mutations in stool or blood have been advanced. Epi proColon (Epigenomics Inc, Berlin, Germany) is based on the detection of DNA in the blood with methylated cytosine in the v2 region of the SEPT9 gene, as found predominantly in colon cancer tissue.[14] ColoGuard (Exact Sciences, Madison, Wisc, USA) is a stool-based multitarget DNA test that includes quantitative molecular assays for K-*ras* mutations, aberrant NDRG4 and BMP3 methylation, and β-actin, plus a hemoglobin immunoassay.[15] For both, high sensitivity for CRC has been shown, whereas for adenoma it was lower.[14,15] Another similarly effective approach is the urine metabolomic test called PolypDx (PolypDx, Metabolomic Technologies Inc, Edmonton, AB, Canada), in which key metabolites are quantified and analyzed by a multivariate algorithm.[16-19] However, for none of these newer tests, effectiveness regarding reduction of CRC incidence and mortality has been shown in clinical trials.

In the search for a highly efficient screening test, sensitivity and specificity are just one part of the equation. Clinical experience shows that adherence of patients to diagnostic tests may differ substantially and could depend on different aspects, such as invasiveness, required preparation, or associated feeling of shame. The test modality seems to play an important role. In the case of colon cancer screening, no comparative study regarding patient preferences of testing modality has been undertaken. In the literature, uptake of colonoscopy screening is reported to be ~56% over a 10-year period.[11,12] Clinical trials involving screening of the general public for various diseases show moderate willingness to undertake stool- and urine-based tests (~49.3% and 51.4%)[10,20-26] and higher willingness for blood tests (~68%).[27,28] In addition, the interval timing of a screening test can have a significant impact on its effectiveness, especially in regard to the previously mentioned parameters. Hypothetically, repetitive use of a screening test with a lower sensitivity or adherence but short test interval can outperform another test with better test characteristics but longer test intervals (ie, colonoscopy). Last, a screening test has to be (the most) cost effective to justify its application. For many questions regarding CRC screening and prevention, randomized controlled trials are impracticable because of the large parameter space and the ethical and logistical challenges. Therefore, computational approaches have been developed, which simulate the natural history of CRC and screening interventions in a large patient population.[29,30] Colon modeling open source tool (CMOST) is an open-source computational microsimulation tool, with similar predictions compared with randomized CRC prevention trials and other well-established microsimulation tools.[30,31]

In this study, we first simulated theoretic CRC screening with a broad variation of key test characteristics in comparison with colonoscopy screening, to identify the characteristics of highly efficient screening tests. Then we used CMOST to calculate the incidence reduction, mortality reduction, life-years gained (LYGs), and cost effectiveness of screening with the available screening modalities: colonoscopy, fecal immunochemical test (FIT, Eiken Chemical Co, Ltd, Tokyo, Japan), ColoGuard, Epi proColon, and PolypDx, including various assumptions regarding screening adherence.

METHODS

We simulated the use of several theoretic screening tests and varied 5 parameters independently: (1) sensitivity for early adenoma detection, (2) sensitivity for advanced adenoma detection, (3) sensitivity for carcinoma detection, (4) test specificity, and (5) adherence to testing. The first and second tests were varied in a range from 0% to 100% in 10% steps, and the third, fourth, and fifth tests were varied from 10% to 100% in 10% increments. Furthermore, for plausibility, sensitivity for cancer detection needed to be at least as good as the sensitivity for advanced adenoma detection, and the sensitivity for advanced adenoma detection needed to be at least as good as the sensitivity for early adenoma detection ($Sens_{Cancer} \geq Sens_{AdvAd} \geq Sens_{EarlAd}$), resulting in the exclusion of several potential tests. Each test was applied either yearly or every 2, 3, 4, or 5 years, resulting in 142,501 theoretic tests. Adherence to follow-up colonoscopy after a positive test result was assumed to be 82%.[32,33] The results of theoretic tests were compared with the results of CRC screening with colonoscopy at 100% adherence at ages 50, 60, and 70 years. Predictive models for discounted life-years gained (dLYG) and discounted U.S. dollars (dUSD) saved were calculated by a stepwise regression method that automatically adds or removes predictors (test characteristics in our case) starting from a constant model. More precisely, at each step of the method we added

or removed a predictor term to the model if the *P*-value for an F-test of the change in the resulting sum of squared error was smaller than <.05 and and larger than >.1, respectively. We constrained the model to linear terms only (no interactions were considered), and the method stopped when no term was selected for removal or addition.

The model structure and basic assumptions of CMOST have been described previously.[31] CMOST observes a given population from birth until death (maximum age, 100 years). The age distribution corresponds to a stable population without migration, with declining population size with increasing age. The ethnicity would correspond to the average distribution in the United States in the years 2005 to 2009 (66% white, 15% Latino-American, 12% African-American, 4% Asian-American) but has not been explicitly modeled. The sex distribution is 1:1 for male:female. For the natural history, the model was calibrated to reproduce the age- and sex-specific adenoma prevalence rates as well as carcinoma incidence and mortality from the Surveillance Epidemiology and End Results (SEER) Program database for 2005 to 2009. CRC develops through adenomatous precursors or spontaneous. CMOST considers 6 distinct adenoma stages, depending on size, and 4 cancer stages. Adenoma initiation and progression as well as cancer progression, screening, and surveillance are all modeled in time increments of 3 months. Adenomas can be detected during diagnostic examinations such as endoscopy. Cancer can be diagnosed by screening at an early stage or by symptoms. After detection, treatment can cure cancer with a stage-dependent probability.

Compared with the original code,[31] the program code has been optimized for faster computational speed and now enables calculations with larger patient populations of ≤2 million individuals in each run. In contrast to the original model, CMOST now uses SEER CRC incidence and mortality data from the years 1988 to 2002,[34] before the onset of widespread CRC screening. The new code is available at https://github.com/poljan/CMOSTv2.

For the current study, the following screening strategies were applied: colonoscopy screening according to practice guidelines,[7,8] from age 50 to 75. As recommended by practice guidelines and/ or the individual manufacturers, screening with FIT was conducted yearly or biennially and Epi proColon yearly, whereas ColoGuard and PolypDx were performed every 3 years. Sensitivity and specificity for adenoma and carcinoma detection for ColoGuard,[35] Epi proColon,[36,37] FIT,[10,20-24] and PolypDx[17,19] were taken from the literature (Table 1). A positive result led to colonoscopy with a given adherence. Detection probabilities for adenomas of various sizes were provided (Table 1); detection probabilities for adenomas would translate nonlinearity to adenoma detection rates (ADRs) (Supplementary Fig. 1, available online at www.giejournal.org). ADR is defined as the percentage of screening colonoscopies with ≥1 adenoma and is widely used in clinical practice. For a single screening colonoscopy at age 60 years, our baseline adenoma detection probabilities would translate to an ADR of ∼15% in women and ∼27% in men. The detection and removal of adenoma and/or cancer led to endoscopic surveillance, with intervals as recommended by practice guidelines (5 years after nonadvanced adenoma detection, 3 years after advanced adenoma detection with lifelong 5-year intervals).[38] Noninvasive screening was resumed at the earliest 10 years after inconspicuous colonoscopy. Finally, for the purpose of comparison, a no-screening strategy was also run.

Regarding adherence to screening, 2 scenarios were of interest: full (100%) and real-world adherence. The purpose of the prior scenario was to capture the full potential of each screening modality and thereby provide a contrast point to better understand the influence of adherence on the simulation outcome. Here, adherence to screening was 100% for all available screening tests, as well as diagnostic and surveillance colonoscopy after a positive result. For the real-world scenario, adherence was derived from the literature. Here, colonoscopy screening was assumed to have an annual adherence of 0.0822, resulting in a 10-year adherence of 0.56.[11,12] Several large studies have shown the adherence to FIT to average ∼0.493.[10,20-24] The adherence to ColoGuard (stool) was assumed to be the same. Uptake of PolypDx (urine) and Epi proColon (blood), was assumed to be similar to the willingness of the general public to undergo microalbuminuria or prostate specific antigen (PSA) and dyslipidemia screening, respectively (0.514, 0.68).[25-28] Adherence to diagnostic and surveillance colonoscopy after positive screening was 0.82 in the real-world scenario.[32,33]

The cost assumptions for the United States were taken from a recent study[39] and transformed to 2018 U.S. dollars (Supplementary Table 1, available online at www.giejournal.org).[40] In CMOST, costs are computed at 3-month intervals. Three time periods are distinguished: the first 12 months after diagnosis, the last 12 months before CRC-related death, and the follow-up period in between, with a maximum total of 5 years after cancer diagnosis. Overlap of periods is not possible. In a case of short survival after diagnosis, the last period took precedence. CRC-related costs differ according to CRC stage (Supplementary Table 1). In a case of death unrelated to CRC, additional costs apply as described.[39] When indicated, costs and life-years gained were discounted by 3% per year after the start of screening at age 50. Costs for colonoscopy, FIT, Epi pro Colon, ColoGuard, and PolypDx screening were derived from the Centers for Medicare and Medicaid Services, 2018 Clinical Laboratory Fee Schedule Public Use File.[41] Here, the costs for colonoscopy include only moderate sedation by the gastroenterologist, not full anesthesia care. The costs calculated in the nonendoscopic screening scenarios include those for colonoscopy resulted by a positive screening test result. The model does not distinguish

TABLE 1. Characteristics and assumptions regarding colorectal cancer (CRC) screening tests

Variable	Colonoscopy	FIT	ColoGuard	Epi proColon	PolypDx	PolypDx low specificity
Screening interval, y	10	1	3	1	3	3
Specificity	1	0.95	0.87	0.96	0.913	0.800
Sensitivity						
Adenoma 2-5 mm	0.65-0.75	0.05	0.17	0.20	0.43	0.53
Adenoma 6-9 mm	0.81-0.87	0.101	0.17	0.20	0.43	0.53
Adenoma ≥10 mm	0.95	0.22	0.42	0.22	0.43	0.53
CRC	0.95-1	0.7	0.92	0.69	0.75	0.80
Scenario with full adherence						
Yearly adherence	1	1	1	1	1	1
Cumulative lifetime adherence	1	1	1	1	1	1
Adherence to diagnostic colonoscopy	-	1	1	1	1	1
Scenario with real-world adherence						
Yearly adherence	0.0822	0.493	0.493	0.68	0.5135	0.5135
Cumulative lifetime adherence	0.883	0.581	0.785	0.744	0.931	0.931
Adherence to diagnostic colonoscopy	-	0.82	0.82	0.82	0.82	0.82

For PolypDx, in addition to the regular tests, characteristics for a variant with lower specificity are provided.
FIT, Fecal immunochemical test.

between true- and false-positive tests. Cost effectiveness was calculated on a comparison with no screening, with a cutoff of 100,000 dUSD per dLYGs considered cost effective and values below zero considered cost saving.

For all analyses, CMOST was used, and calculations were performed on a high-performance Linux cluster. A population of 2 million individuals was simulated in each individual run. The results are the average of 10 replicate analyses. For all outcomes, normal distribution of the replicates was confirmed through the Anderson-Darling test and are shown as means with the respective standard deviations. Postprocessing analyses were performed with customized scripts in Matlab, version R2018b. Data were further processed with Excel (version 16, Microsoft, Redmond, Wash, USA) and Graphpad Prism (version 8, Graphpad, San Diego, Calif, USA).

For the sensitivity analysis we focused on 3 model output variables: (1) incidence reduction, (2) life-years gained, and (3) dUSD per dLYG. We assessed the uncertainty (perturbations) of 8 model parameters: (1) adherence to screening, (2) adherence to test follow-up, (3) probability of adenoma detection during colonoscopy (eg, due to suboptimal bowel preparation[42]), (4) risk for colonoscopy adverse events, (5) screening cost, (6) treatment cost, (7) test sensitivity, and (8) test specificity. Each set of variables was perturbed within a specified range (Supplementary Table 1) by use of a uniform random variable. All variables and sensitivity indices—defined as fraction of total output variance generated by the uncertainty in the respective parameter value—were perturbed simultaneously by the Fourier Amplitude Sensitivity Test (FAST) sampling method.[43] The higher the value of the sensitivity index, the more influential is the uncertainty (variation) in the parameter compared with the others. Correlation coefficients between analyzed model output variables and sampled model parameters were calculated by the Pearson method.

RESULTS

Key characteristics of highly efficient screening tests

Colonoscopy screening is assumed to be highly efficient for prevention of life-years lost to CRC. We were looking for highly efficient screening tests that would be able to match or outperform the efficiency of colonoscopy screening. We systematically varied the sensitivity for early and advanced adenoma, carcinoma, test specificity, adherence, and the frequency with which this hypothetical test was applied. All theoretic tests were compared with colonoscopy screening regarding dLYG and costs (see Methods).

Out of 142,501 theoretic tests, 6299 tests saved more life-years than standard colonoscopy screening (Fig. 1A). When characteristics of efficient screening tests were looked at, all of them were associated with moderate adherence (at least ~50%). Further, efficient tests had a sensitivity threshold for advanced adenomas of at least ~40% and carcinomas of at least ~70%, with a specificity of at least ~40% (Fig. 1B). Most theoretic efficient tests were applied yearly or biyearly, and almost no efficient tests were used less frequently than every 4 years (Fig. 1B). Life-years gained and costs saved associated with the use of these tests followed closely simple linear equations (Fig. 1C).

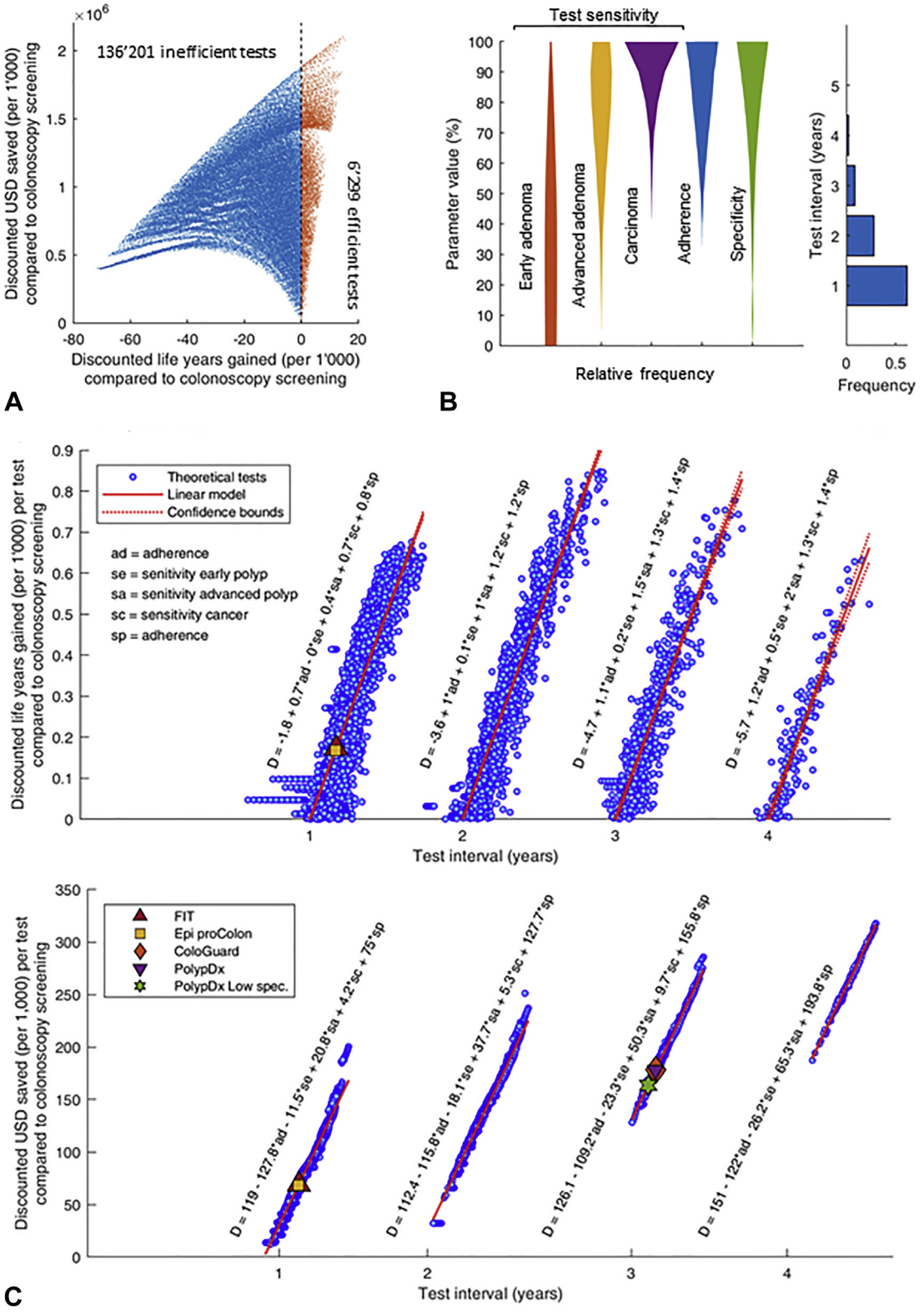


Figure 1. Characteristics of highly efficient colorectal cancer (CRC) screening tests. A, Simulation of 142,501 theoretical CRC screening tests with varying sensitivities for early and advanced adenoma as well as CRC, varying specificity, adherence to testing, and test intervals. Displayed are discounted life-years gained as well as discounted costs compared with colonoscopy screening with 100% adherence. *Blue dots,* inefficient tests compared with colonoscopy. *Red dots,* tests that save a higher number of discounted life-years compared with colonoscopy. B, Key characteristics of highly efficient theoretic tests, surpassing effectiveness of colonoscopy. Highly efficient tests tended to have higher sensitivity for advanced adenoma and CRC, as well as high specificity and adherence to testing and a test interval of 1 or 2 years. C, Effectiveness (discounted life-years gained, *upper panel*) and costs (discounted U.S. dollars, *lower panel*) of highly efficient tests are plotted according to the test interval. We performed stepwise linear regression to predict effectiveness and costs of highly efficient tests from the indicated screening parameters (*red line*).

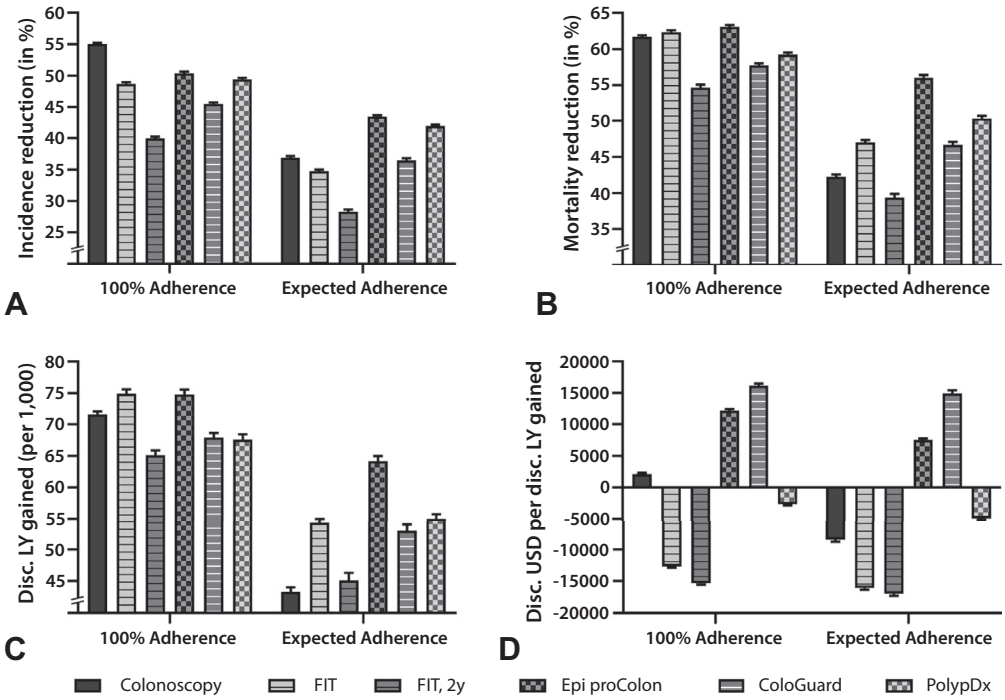


Figure 2. Colorectal cancer (CRC) screening with full and real-world adherence. A, CRC incidence reduction. B, CRC mortality reduction. C, Life-years gained because of CRC screening. D, Cost effectiveness for each screening interventions.

Simulation of CRC screening strategies with hypothetical 100% adherence to screening

In the hypothetical scenario with 100% patient adherence, colonoscopy screening reduced CRC incidence by 55% and mortality by 62% compared with no screening (Fig. 2A and B). Colonoscopy screening resulted in the gain of 71.6 discounted life-years per 1000 individuals (Fig. 2C). Colonoscopy-based CRC screening was cost effective compared with no screening, with 2101 dUSD for each dLYG (Fig. 2D, Table 2).

All nonendoscopic screening tests reduced CRC incidence and mortality and resulted in a gain in life-years (Fig. 1). Here, the yearly FIT and Epi proColon tests were the most effective, surpassing even colonoscopy screening (Fig. 2C). Performing FIT biennially led to a significant reduction of this effectiveness. Compared with no screening, all tests were cost effective with <50,000 dUSD per dLYG; only the FIT and PolypDx were cost saving (Fig. 2D, Table 2) (Supplementary Fig. 2, available online at www.giejournal.org).

Simulation of CRC screening with expected, test-specific adherence rates

Compared with the hypothetical 100% adherence, the incidence and mortality reduction of all screening tests were reduced, as were the life-years gained (Fig. 2). Owing to higher adherence to blood-based tests, Epi proColon now achieved a discrepantly higher gain of discounted life-years. However, compared with the prior scenario, the cost effectiveness of all screening tests increased and now, next to FIT and PolypDx, colonoscopy was also cost saving (Fig. 2D, Table 2, Supplementary Fig. 2) when compared with no screening.

Incremental cost-effectiveness ratio

To compare the cost-effectiveness of all screening methods, incremental cost-effectiveness ratios (ICERs) were calculated. For hypothetical 100% adherence, yearly FIT was the dominating strategy, yielding the highest number of dLYG (74.9 discounted life-years per 1000 individuals compared with no screening) at the second lowest discounted costs (Table 3). Only biennial FIT was slightly more cost effective, however, yielding in the lowest number of discounted life-years. For real-life adherence rates, yearly FIT was surpassed by PolypDx and Epi proColon in efficacy (55 and 64.2 vs 54.3 dLYG) but was still the most cost-efficient screening strategy. PolypDx and Epi proColon came with an incremental cost of 860,378 and 137,060 dUSD per dLYG, respectively (Table 3).

Systematic variation of adherence rates

To demonstrate the impact of screening adherence on screening effectiveness, we calculated dose-response curves for each screening strategy (Fig. 3) (Supplementary Fig. 3, available online at www.giejournal.org). Higher adherence rates yielded superior effectiveness of all measures of screening effectiveness. As expected, higher adherence resulted in higher ICERs compared with no screening for all screening tests (Fig. 3D). In other words, the lowest number of dUSD per dLYG was found at very low

TABLE 2. CRC screening with a theoretic 100% and real-world adherence to the screening intervention

Variable	No screening	Colonoscopy	FIT	FIT, 2 y	ColoGuard	Epi proColon	PolypDx
CRC cases (per 1000)	67.4 (0.2)	30.3 (0.1) *42.5 (0.1)*	34.6 (0.1) *44.0 (0.2)*	40.4 (0.1) *48.3 (0.2)*	36.7 (0.1) *42.8 (0.2)*	33.4 (0.1) *38.1 (0.2)*	34.1 (0.1) *39.1 (0.1)*
Screening tests (per 1000)		0 (0) *0 (0)*	14,248 (4.9) *8559 (4.1)*	8831 (2.3) *6203 (1.3)*	5482 (1.7) *4445 (2.1)*	13,587 (3.7) *10,673 (3.8)*	5420 (1.3) *4444 (1.4)*
Colonoscopies (per 1000)	242 (0.8)	3145 (1.6) *1632 (1.0)*	1464 (2.0) *934 (1.2)*	1084 (1.5) *768 (1.6)*	1438 (0.8) *1087 (1.5)*	1627 (1.6) *1281 (1.2)*	1545 (1.8) *1227 (1.3)*
Incidence reduction (%)		55.0 (0.16) *36.9 (0.25)*	48.7 (0.24) *34.7 (0.27)*	40.0 (0.3) *28.3 (0.4)*	45.5 (0.3) *36.5 (0.3)*	50.4 (0.3) *43.5 (0.2)*	49.4 (0.2) *41.9 (0.2)*
CRC stage distribution (%)							
Stage I	23.4 (0.1)	31.2 (0.2) *27.6 (0.1)*	40.5 (0.2) *33.8 (0.2)*	36.8 (0.2) *31.5 (0.2)*	35.1 (0.2) *31.6 (0.1)*	39.6 (0.2) *35.9 (0.1)*	33.4 (0.2) *30.7 (0.2)*
Stage II	32.6 (0.1)	33.4 (0.2) *32.6 (0.2)*	31.1 (0.2) *32.9 (0.2)*	33.3 (0.2) *33.3 (0.1)*	33.8 (0.2) *33.4 (0.2)*	31.3 (0.2) *32.5 (0.2)*	33.4 (0.2) *33.1 (0.2)*
Stage III	25.2 (0.1)	21.1 (0.2) *23.2 (0.2)*	17.2 (0.2) *20.0 (0.1)*	18.3 (0.1) *21.1 (0.1)*	19.2 (0.2) *21.0 (0.2)*	17.5 (0.2) *19.2 (0.1)*	20.1 (0.1) *21.6 (0.1)*
Stage IV	18.9 (0.1)	14.3 (0.1) *16.6 (0.1)*	11.3 (0.2) *13.3 (0.1)*	11.6 (0.1) *14.2 (0.1)*	12.0 (0.2) *14.0 (0.1)*	11.5 (0.2) *12.4 (0.1)*	13.1 (0.1) *14.6 (0.1)*
CRC deaths (per 1000)	25.6 (0.1)	9.8 (0.04) *14.8 (0.1)*	9.6 (0.04) *13.6 (0.1)*	11.6 (0.1) *15.5 (0.1)*	10.8 (0.1) *13.7 (0.1)*	9.4 (0.1) *11.3 (0.1)*	10.4 (0.1) *12.7 (0.1)*
Mortality reduction (%)		61.7 (0.2) *42.3 (0.3)*	62.4 (0.2) *47.0 (0.3)*	54.7 (0.4) *39.4 (0.5)*	57.8 (0.3) *46.7 (0.4)*	63.1 (0.2) *56.0 (0.4)*	59.2 (0.3) *50.4 (0.4)*
Total costs (per capita, in USD)	7858 (21.0)	6473 (10.7) *6296 (13.7)*	5181 (11.1) *5613 (18.0)*	5290 (13.2) *5926 (20.0)*	7963 (16.4) *7821 (21.3)*	7627 (13.0) *7220 (10.8)*	6206 (12.2) *6280 (17.4)*
Screening costs	0	2481 (0.9) *1120 (0.5)*	1171 (0.6) *642 (0.4)*	759 (0.8) *476 (0.4)*	3672 (0.8) *2871 (1.2)*	3575 (0.8) *2738 (0.7)*	1976 (0.7) *1535 (0.7)*
Treatment costs	7660 (20.2)	3063 (10.5) *4525 (13.7)*	3274 (9.3) *4414 (17.8)*	3911 (13.0) *4965 (19.8)*	3580 (15.7) *4359 (19.8)*	3187 (12.4) *3727 (11.0)*	3382 (11.9) *4013 (17.4)*
Follow-up costs	199 (0.9)	928 (2.2) *650 (1.3)*	735 (2.1) *557 (1.6)*	620 (1.4) *485 (1.8)*	710 (1.0) *591 (1.5)*	865 (1.4) *756 (1.1)*	847 (1.7) *732 (1.5)*
LYG (per 1000)		177.4 (1.3) *112.2 (1.8)*	184.7 (1.8) *135.7 (1.7)*	160.9 (1.9) *113.1 (2.5)*	168.1 (1.7) *132.3 (1.7)*	184.6 (1.8) *160.3 (2.0)*	168.7 (1.9) *139.4 (1.8)*
dLYG (per 1000)		71.6 (0.5) *43.3 (0.7)*	74.9 (0.7) *54.3 (0.7)*	65.1 (0.8) *45.1 (1.1)*	67.9 (0.7) *53.0 (1.0)*	74.8 (0.8) *64.2 (0.8)*	67.6 (0.8) *55.0 (0.7)*
dUSD per dLYG		2101 (201) *-8419 (332)*	-12,643 (190) *-16,086 (272)*	-15,352 (213) *-16,992 (334)*	16,169 (338) *14,965 (486)*	12,209 (267) *7530 (230)*	-2696 (156) *-4931 (229)*

For each screening modality, a population of 2 million individuals was simulated 10 times. The numbers shown are the means of these 10 simulations. The values of incidence and mortality reduction as well as LYG, dLYG, and dUSD per dLYG are compared with no screening. Italic numbers represent the real-world scenario; standard deviation is provided in parenthesis.

CRC, Colorectal carcinoma; *FIT*, fecal immunochemical test; *LYG*, life-years gained; *dLYG*, discounted life-years gained; *USD*, U.S. dollars, *dUSD*, discounted U.S. dollars.

adherence rates, and a rise in adherence increased the number of dUSD for each dLYG.

Sensitivity analysis

To determine the sensitivity of various performance parameters including ADR, incidence reduction, life-years gained, and cost effectiveness to our choice of parameters, we performed a sensitivity analysis (Fig. 4) (Supplementary Fig. 4, Supplementary Table 2, available online at www.giejournal.org). A considerable variation in incidence reduction and life-years gained was observed (Fig. 4A, Supplementary Fig. 3). Cost effectiveness also varied; however, results were almost consistently below a threshold of 100,000 dUSD per dLYG (Fig. 4A, Supplementary Fig. 4). Incidence reduction and life-years gained were most sensitive to variations in screening adherence and follow-up colonoscopies (Fig. 4B and C, Supplementary Fig. 4). Both outcomes were also sensitive to adenoma detection, but to a lower degree. Cost effectiveness was mainly sensitive to variations in screening and treatment costs (Fig. 4B and C) (Supplementary Fig. 4).

DISCUSSION

In this study, we used the open-source microsimulation tool CMOST to model effectiveness and cost effectiveness of various screening strategies for CRC. Simulating a large

TABLE 3. Incremental cost effectiveness ratio (ICER) table

100% Adherence							
	No screening	**FIT, 2 y**	**PolypDx**	**ColoGuard**	**Colonoscopy**	**Epi proColon**	**FIT**
No screening		Dominated	Dominated	$16,169	$2101	$12,209	Dominated
FIT, 2 y			$326,866	$749,032	$176,900	$197,180	$5353
PolpypDx				$4,267,082	$83,170	$152,150	Dominated
ColoGuard					Dominated	Dominated	Dominated
Colonoscopy						$238,376	Dominated
Epi proColon							Dominated
FIT							

Real-world adherence							
	No screening	**Colonoscopy**	**FIT, 2 y**	**ColoGuard**	**FIT**	**PolypDx**	**Epi proColon**
No screening		Dominated	Dominated	$14,965	Dominated	Dominated	$7530
Colonoscopy			Dominated	$119,349	Dominated	$7978	$40573
FIT, 2 y				$19,7403	Dominated	$50,014	$65433
ColoGuard					Dominated	Dominated	Dominated
FIT						$860,378	$137,060
PolypDx							$82,025
Epi proColon							

Read left to right. The tables shows the relationship of index screening method (*left*) compared with another screening method shown above. The numbers illustrate the costs per life-year gained. If a screening method is surpassed at life-years gained at lower costs, it is considered to be dominated by the other. All calculations were done with discounted life-years and costs. Upper part of table: 100% adherence. Lower part of table: real-word adherence rates.
FIT, Fecal immunochemical test.

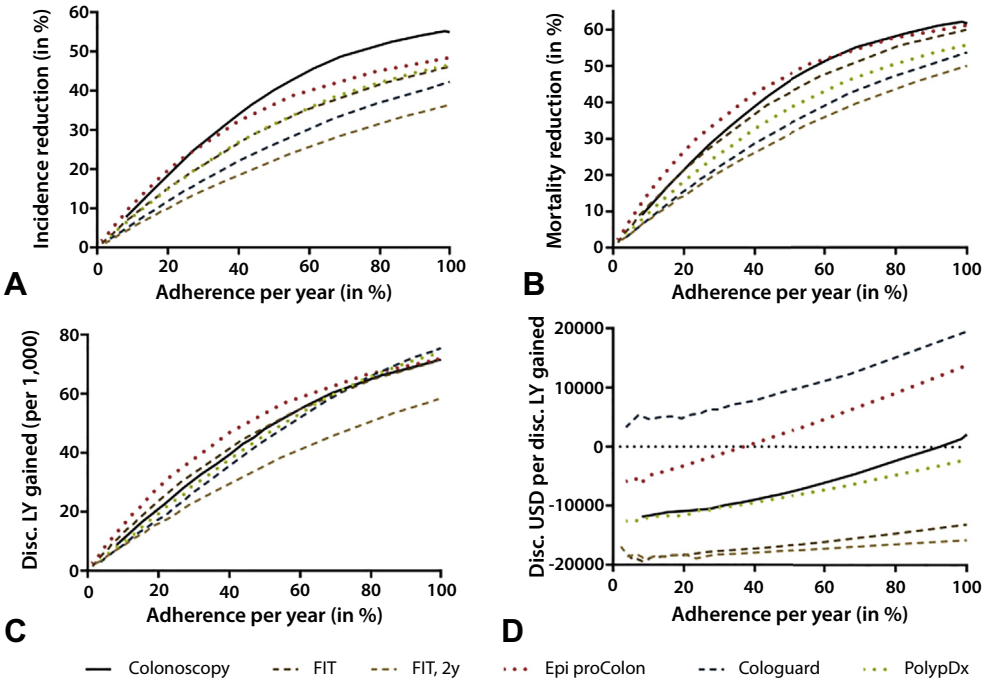


Figure 3. Systematic variation of screening adherence. A, Colorectal cancer (CRC) incidence reduction. B, CRC mortality reduction. C, Life-years gained because of CRC screening. D, Cost effectiveness for each screening intervention. Cost effectiveness at low adherence showed pronounced stochastic variations for some tests even with large study populations; therefore, the range from 0% to 5% is not shown. *FIT*, Fecal immunochemical test.

range of theoretic screening tests, we identified tests characterized by good advanced adenoma and carcinoma sensitivity and test adherence that could outperform even colonoscopy screening with perfect adherence. When simulated available screening tests, yearly FIT, and yearly Epi proColon saved the highest number of life-years

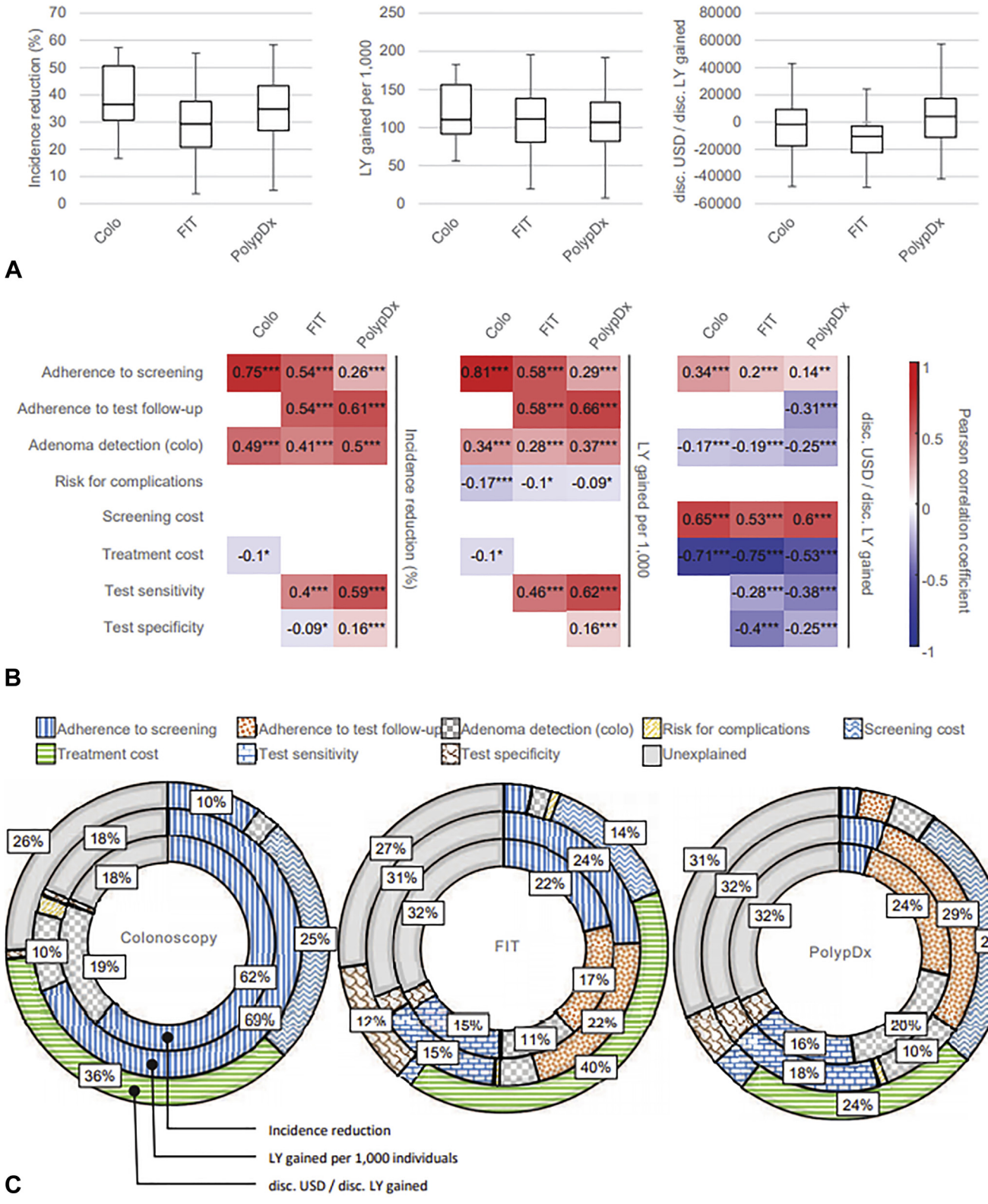


Figure 4. Sensitivity analysis results for colonoscopy (colo), FIT, and PolypDx. Selected model parameters were varied simultaneously. A, Boxplots of analyzed output variables. Shown are medians (*horizontal lines*), 25th and 75th percentiles (*bottom* and *top* of boxes, respectively). Whiskers show minimal and maximal values after removal of outliers (values outside of 1.5 × interquartile range). B, Pearson correlation coefficients between each perturbed parameter and analyzed output variables. *, **, and *** denote *P* values < .05, < .01, and < .001, respectively. C, First-order sensitivity indices, defined as the fraction of the total variance in the output variable explained by the variation in each parameter value, calculated by the Fourier amplitude sensitivity test. Unexplained part refers to the part of variance that cannot be attributed to any single parameter and is related to higher-order interactions between parameters. LY, Life-years; USD, U.S. dollars; disc., discounted. *FIT*, fecal immunochemical test.

when 100% adherence to screening was assumed. The efficiency of all available screening modalities did not differ greatly, but their cost effectiveness did. Here, the cheap FIT performed best and was even cost saving.

As demonstrated by our adherence titration, incidence reduction and the number of life-years gained by each screening modality critically depends on adherence to screening protocol. When real-world adherence rates were applied, our simulation thus shows a superior effectiveness of some noninvasive screening methods compared with colonoscopy. Our sensitivity analysis also demonstrates that the effectiveness of screening strategies was strongly dependent on adherence to the screening test and follow-up colonoscopies, more so than on the individual test's sensitivity for detecting CRC. Therefore, a noninvasive test with high acceptance could outperform even colonoscopy regarding CRC and adenoma detection. Given that patient preferences naturally differ between individuals, an ability to offer a variety of tests and patient-centered counseling might be optimal for improving adherence.

We identified several theoretic tests that could outperform colonoscopy screening. This seems counterintuitive because all adenomas and carcinomas were only detected and/or removed by colonoscopy. However, the higher testing frequency of noninvasive screening tests allowed in our simulations for an efficient early detection of advanced lesions. The effects of an increased testing frequency would be similar to those of improved testing adherence.

In our calculations, all screening strategies were effective and cost effective (<100,000 dUSD/dLYG) at preventing CRC. Cost effectiveness was primarily dependent on screening and treatment costs. Having the lowest price by far allows FIT to remain highly cost effective despite yearly application. The high test specificity for FIT compared favorably with those of most other noninvasive screening tests except Epi proColon and likely also contributed to its cost effectiveness. At real-world adherence rates, the effectiveness of FIT was only slightly surpassed by Epi proColon and PolypDx at additional costs (ICER) of 137,060 and 860,378 dUSD/dLYG, respectively. In the same scenario, 3 screening tests (colonoscopy, FIT, and PolypDx) were cost saving. However, with an increasing number of expensive drug therapies for advanced CRC, the cost effectiveness of all screening tests can be expected to rise.

Our study has several strengths and limitations. (1) We use a novel, versatile, and open-source microsimulation tool, validated against existing tools and literature data, and freely available to reproduce all simulation results.[31] In contrast to proprietary microsimulation tools, our calculations can be independently validated and advanced. (2) Improved CMOST implementation combined with substantial computational power allowed us to simulate very large populations and enabled us (3) to explore >140,000 theoretic tests to identify characteristics of highly efficient tests and (4) to simulate a high number of scenarios in our extensive sensitivity analysis, thus increasing confidence in our results. Limitations include (1) the in silico nature of our study, necessarily relying on assumptions from the literature for all variables. Therefore, recent increases in the incidence of colorectal cancer are not taken into account, and serrated polyps are not included. (2) The natural history of CRC is partially unknown, and the adenoma dwell time—the average time an adenoma would reside in the colon until transformation to CRC—has not been empirically determined.[29,30] CMOST assumes an average dwell time of 13 years, but shorter assumptions of the dwell time might result in a lower efficiency of strategies partially relying on early adenoma detection, such as colonoscopy. (3) Calibration of CMOST and cost assumptions were specific to the CRC epidemiology and health economy of the United States, and our calibrations might not be applicable to other geographic regions. For instance, a lower CRC incidence and/or lower CRC treatment costs in developing countries would fundamentally change the results of our calculations. (4) For the United States, the costs for colonoscopy provided by the Medicare and Medicaid 2018 Clinical Laboratory Fee Schedule Public Use File include only moderate sedation but not anesthesia care. Performing colonoscopy under full anesthesia would result in a less favorable cost effectiveness. (5) A scenario with patient-specific screening preferences and application of CRC screening according to patient choices has not been modeled because of the complexity of that scenario.

In summary, we report the efficacy and cost effectiveness of a variety of CRC screening approaches. Our results point to the crucial importance of adherence to screening. Thereby, incidence and mortality reduction by a test with a lower efficacy but better adherence and/or testing frequency can surpass the effectiveness of colonoscopy in a population-based screening program.

ACKNOWLEDGMENTS

This project was supported by a grant from the Swiss Cancer League (grant No. KFS-2977-08-2012) and the Horten Foundation to Benjamin Misselwitz.

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Abbreviations: ADR, adenoma detection rate; CMOST, colon modeling open-source tool; CRC, colorectal cancer; dLYG, discounted life-year gained; dUSD, discounted U.S. dollars; FAST, Fourier amplitude sensitivity test; FIT, fecal immunochemical test; ICER, incremental cost-effectiveness ratio; LYGs, life-years gained.

DISCLOSURE: *The following author disclosed financial relationships: B. Misselwitz: recipient of grants from the Swiss Cancer League and the Helmut Horton Foundation. All other authors disclosed no financial relationships.*

*J. Poleszczuk and B. Misselwitz contributed equally to this work and share last authorship.

0016-5107
https://doi.org/10.1016/j.gie.2021.02.013

Received November 2, 2020. Accepted February 9, 2021.

Current affiliations: Department of Gastroenterology and Hepatology, University Hospital Zurich, Zurich University, Zurich, Switzerland (1); Metabolomic Technologies, Inc. (2); Division of Health Economics, German Cancer Research Center, Heidelberg, Germany (3); Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany (4); Department of Biosystems Science and Engineering, ETH Zurich, Basel, Switzerland (5); SIB Swiss Institute of Bioinformatics, Basel, Switzerland (6); Department of Visceral Surgery and Medicine, Inselspital Bern and Bern University, Bern, Switzerland (7); Oregon Health and Science University, Portland, Oregon, USA (8); Department of Computational Oncology, Maria Skłodowska-Curie Institute-Oncology Center, Warsaw, Poland (9); and Nalecz Institute of Biocybernetics and Biomedical Engineering, Polish Academy of Sciences, Warsaw, Poland (10).

Reprint requests: Ansgar Deibel, Department of Gastroenterology and Hepatology, University Hospital Zurich, Raemistrasse 100, 8091 Zürich, Switzerland.

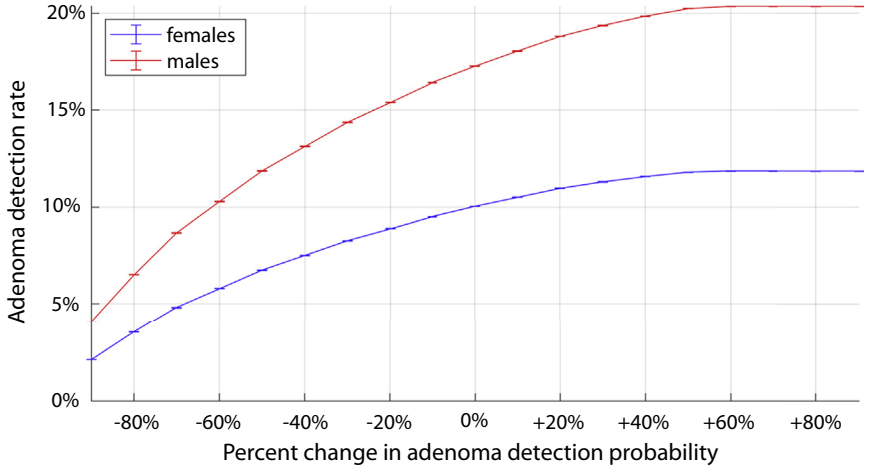
APPENDIX 1. METHODS

Two thresholds for PolypDx were analyzed in this study: (1) Specificity of 91% and sensitivity 43% for adenomas[1] and 74% for colorectal cancer (CRC).[2] (2) Specificity of 80% and sensitivity of 53% for adenomas[1] and 80% for CRC.[2]

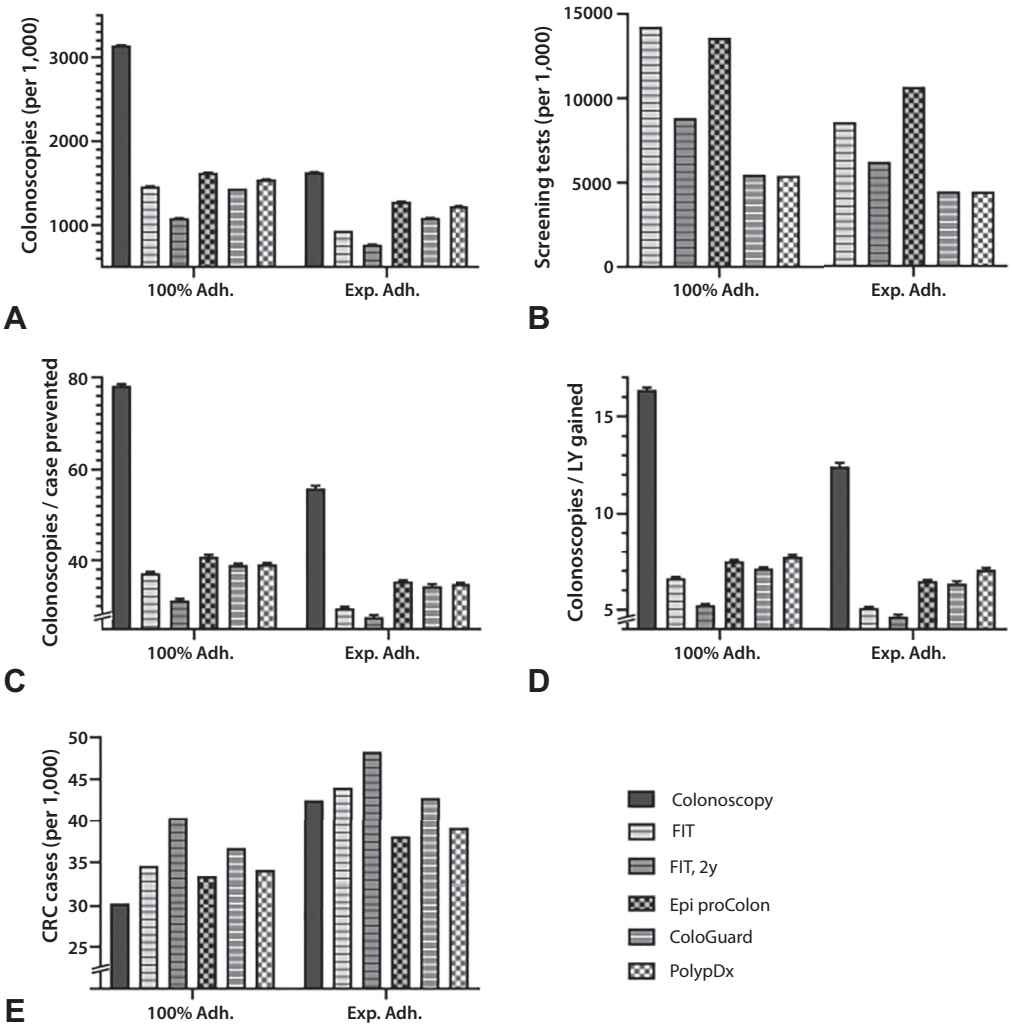
RESULTS

Variation in PolypDx Specificity

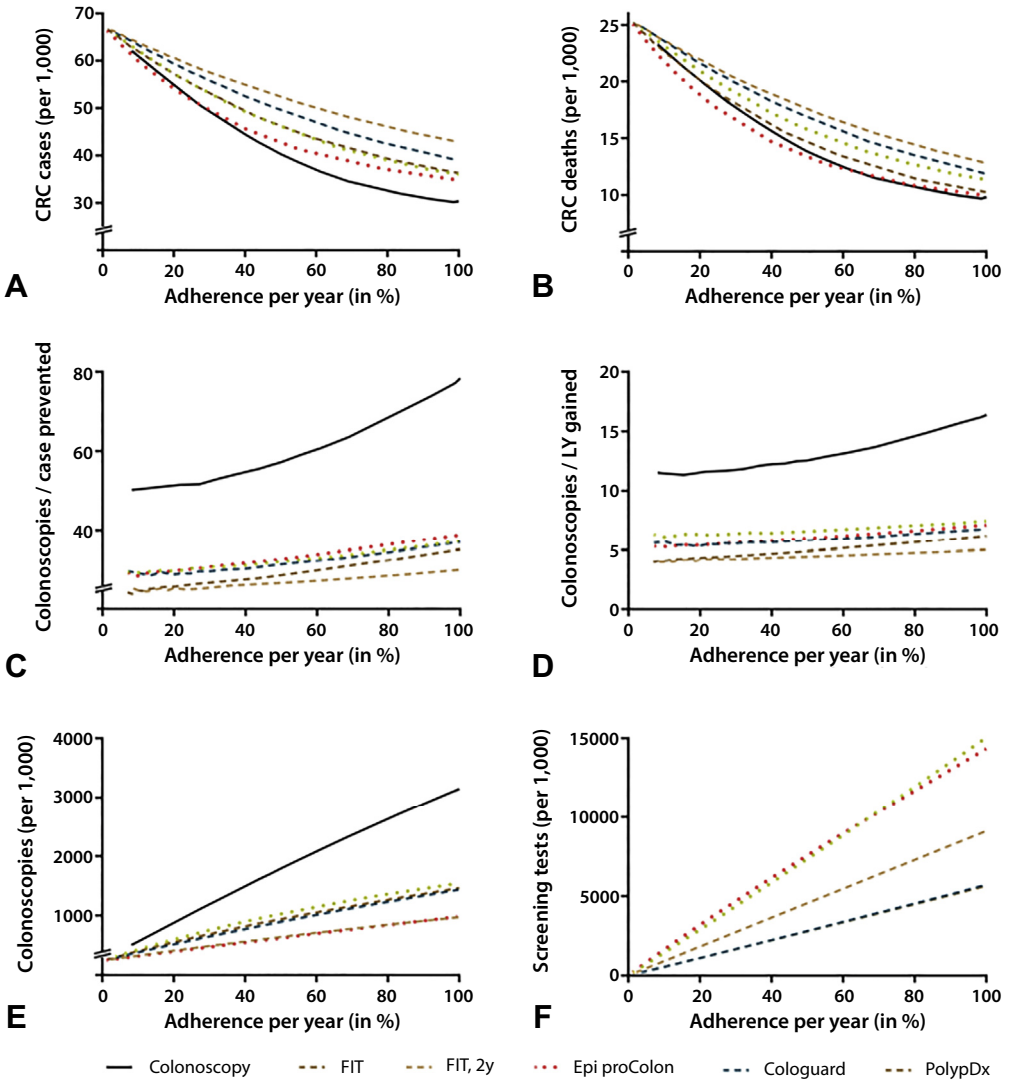
Specificity for colorectal cancer was similar between the current version of PolypDx and FIT (0.913 for PolypDx vs 0.95 for FIT). We simulated another version of PolypDx with reduced specificity (0.80 instead of 0.91) but higher sensitivity for adenomas (0.53 instead of 0.43) and CRC (0.8 instead of 0.74). With 100% adherence, incidence and mortality reduction slightly increased (incidence reduction 51.5% compared with 49.4%; mortality reduction 60.3% compared with 59.2% along with a decrease in cost effectiveness (−586 discounted U.S. dollars [dUSD] per discounted life-year gained [dLYG] compared with −2969 dUSD per dLYG). This was due to a high rise in colonoscopy numbers after PolypDx with reduced specificity (Supplementary Table 3).



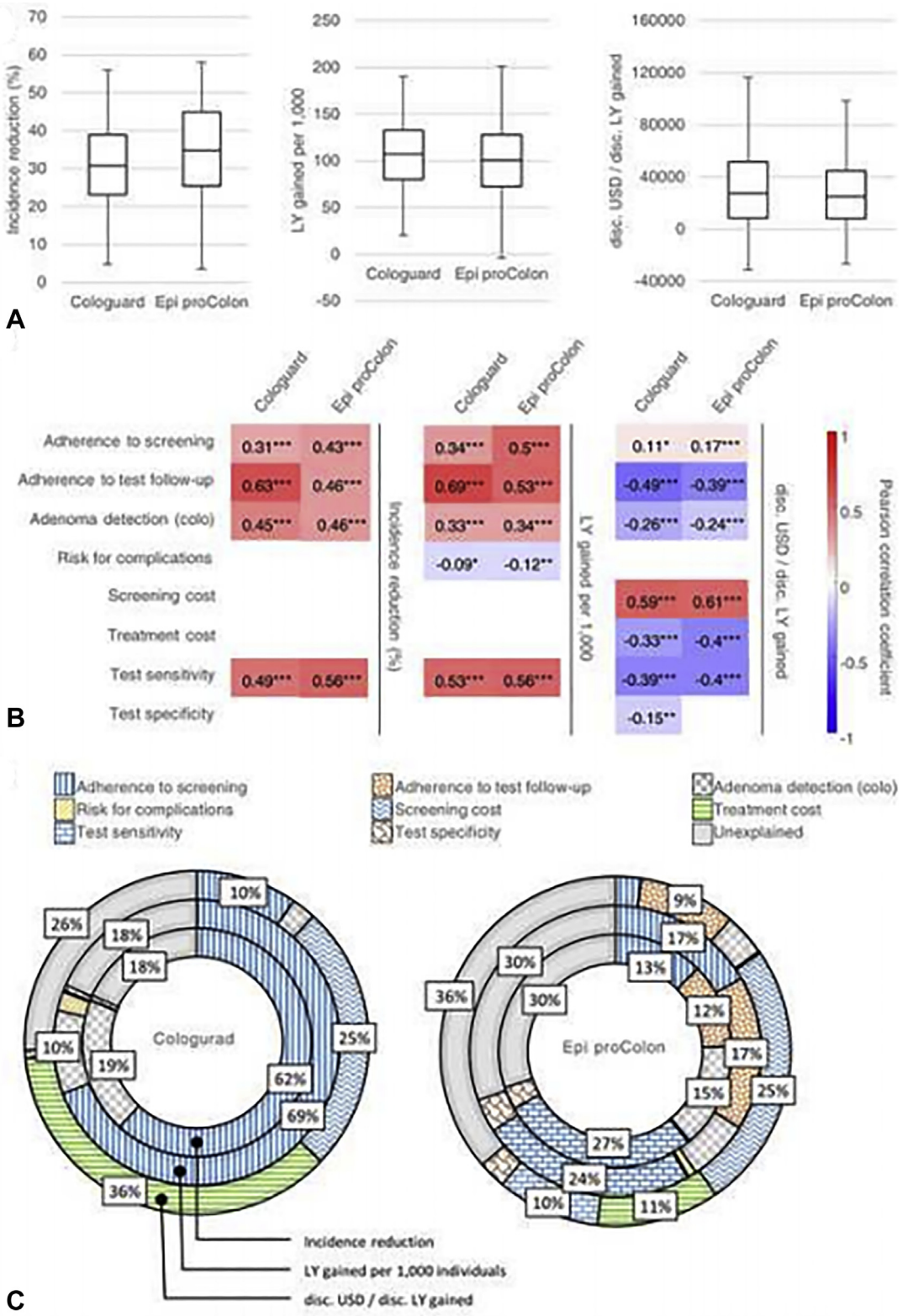
Supplementary Figure 1. Relationship between detection probabilities of adenomas and adenoma detection rates (ADR). We simulated a single screening colonoscopy at age 60 years with detection of adenomas according to the probabilities provided in Table 1. The ADR was defined as the percentage of colonoscopies with at least 1 early or advanced adenoma detected and is provided separately for women and men. Baseline detection parameters were decreased and increased as indicated (censored at 100%). Error bars indicate mean and standard deviation of 10 repeated calculations with 20 million individuals.



Supplementary Figure 2. Effects of colorectal cancer (CRC) screening with full and real-world adherence (Adh.). As in Figure 1, but A, Total number of colonoscopies. B, Total number of screening tests. C, Number of colonoscopies per CRC case prevented. D, Number of colonoscopies per life-year gained. E, Total number of CRC cases. *FIT*, Fecal immunochemical test; *exp.*, expected.



Supplementary Figure 3. Systematic variation of screening adherence. As in Figure 2, but A, Number of CRC cases. B, Colorectal cancer (CRC) mortality cases. C, Colonoscopies per CRC case prevented. D, Colonoscopies per life-year gained. E, Total number of colonoscopies. F, Total number of screening tests. *FIT*, Fecal immunochemical test.



Supplementary Figure 4. Sensitivity analysis results for Epi proColon and ColoGuard. As in Figure 3; selected model parameters were varied simultaneously. A, Boxplots of analyzed output variables. Shown are medians (*horizontal lines*), 25th and 75th percentiles (*bottom* and *top* of boxes, respectively). Whiskers show minimal and maximal values after removal of outliers (values outside of 1.5 × interquartile range). B, Pearson correlation coefficients between each perturbed parameter and analyzed output variables. indicated; *, **, and *** denote P values < .05, < .01, and < .001, respectively. C, First-order sensitivity indices, defined as the fraction of the total variance in the output variable explained by the variation in each parameter value, calculated by the Fourier amplitude sensitivity test. Unexplained part refers to the part of variance that cannot be attributed to any single parameter and is related to higher order interactions between parameters. *disc.*, discounted; *LY*, life-years.

SUPPLEMENTARY TABLE 1. Costs of screening interventions, colonoscopy adverse events, and CRC treatment

CRC screening				
Costs screening tests			**Costs colonoscopy complications**	
FIT	$19.64		Bleeding	$1333
Epi proColon	$192		Severe bleeding	$7723
PolypDx	$200		Serosa burn	$9269
ColoGuard	$508.87		Perforation	$14,349
Colonoscopy	$1020			
Colonoscopy with polypectomy	$1260			
CRC treatment	**Stage I**	**Stage II**	**Stage III**	**Stage IV**
Year of diagnosis	$42,187	$56,621	$68,725	$89,462
Follow-up year	$3508	$3301	$4625	$14,005
Year of death	$73,383	$73,091	$77,100	$101,627
Year of death, other causes	$22,053	$24,676	$19,872	$57,348

Costs were used as described[3,4] and adjusted for inflation to 2018 USD.[5]
CRC, Colorectal cancer; *FIT*, fecal immunochemical test.

SUPPLEMENTARY TABLE 2. Strategy for sensitivity analysis

Category	Starting value	Minimum	Maximum
Adherence to screening			
Urine-based test	0.836	0.2	0.95
Stool-based test	0.493	0.2	0.95
Blood-based test	0.7	0.2	0.95
Colonoscopy	0.0822	0.05	0.95
Adherence to follow-up			
	0.75	0.20	1.00
Adenoma detection by colonoscopy			
3-mm adenoma		0.30	0.85
5-mm adenoma	0.75	0.35	0.90
7-mm adenoma	0.81	0.40	0.90
9-mm adenoma	0.87	0.40	0.92
Advanced adenoma ≥10 mm	0.95	0.50	0.99
Sensitivity of screening tests for adenoma and carcinoma detection			
FIT: 3-5 mm adenoma	0.05	0.02	0.125
FIT: 6-9 mm adenoma	0.101	0.04	0.25
FIT: advanced adenoma ≥10 mm	0.22	0.08	0.40
FIT: CRC	0.7	0.30	0.90
PolypDx: 3-9 mm adenoma	0.43	0.172	0.80
PolypDx: advanced adenoma ≥10 mm	0.43	0.172	0.80
PolypDx: CRC	0.75	0.30	0.90
Epi pro Colon: 3-9 mm adenoma	0	0	0.25
Epi pro Colon: advanced adenoma ≥10 mm	0	0	0.25
Epi pro Colon: CRC	0.806	0.345	0.92
ColoGuard: 3-9 mm adenoma	0.17	0.0729	0.4
ColoGuard: advanced adenoma ≥10 mm	0.42	0.18	0.8
ColoGuard: CRC	0.92	0.394	0.95
Specificity of screening tests for adenoma and carcinoma detection			
FIT	0.95	0.70	0.98
PolypDx	0.913	0.68	0.96
Epi proColon	0.969	0.72	0.99
ColoGuard	0.87	0.64	0.94
Colonoscopy risk (25%–300%)			
Perforation	0.0007	0.000175	0.0021
Death after perforation	0.052	0.013	0.156
Bleeding	0.0011	0.000275	0.0033
Severe bleeding	0.0004	0.0001	0.0012
Death after bleeding	0.0052	0.0013	0.0156
Serosa burn	0.0003	0.000075	0.0009
Screening costs (50%–180%)			
Colonoscopy	$1020.00	$510.00	$1836.00
Colonoscopy with polypectomy	$1260.00	$630.00	$2268.00
FIT	$25.00	$12.50	$45.00
PolypDx	$475.00	$237.50	$855.00
ColoGuard	$508.87	$254.44	$915.97

(*continued on the next page*)

SUPPLEMENTARY TABLE 2. Continued

Category	Starting value	Minimum	Maximum
Epi proColon	$192.00	$96.00	$345.60
Costs perforation	$14,349.00	$7174.50	$25,828.20
Costs bleeding	$1333.00	$666.50	$2399.40
Costs severe bleeding	$7723.00	$3861.50	$13,901.40
Costs serosa burn	$9269.00	$4634.50	$16,684.20
Treatment costs (50%–180%)			
First year, stage I	$42187.00	$21,093.50	$75,936.60
First year, stage II	$56,621.00	$28,310.50	$101,917.80
First year, stage III	$68,725.00	$34,362.50	$123,705.00
First year, stage IV	$89,462.00	$44,731.00	$161,031.60
Follow-up stage I	$3508.00	$1754.00	$6314.40
Follow-up stage II	$3301.00	$650.50	$5941.80
Follow-up stage III	$4624.00	$2312.00	$8323.20
Follow-up stage IV	$14,005.00	$7,002.50	$25,209.00
Final year, stage I	$73,383.00	$36,691.50	$132,089.40
Final year, stage II	$73,091.00	$36,545.50	$131,563.80
Final year, stage III	$77,100.00	$38,550.00	$13,8780.00
Final year, stage IV	$101,627.00	$50,813.50	$182,928.50
Death other causes, stage I	$22,053.00	$11,026.50	$39,695.40
Death other causes, stage II	$19,872.00	$9,936.00	$35,769.60
Death other causes, stage III	$24,676.00	$12,338.00	$44,416.80
Death other causes, stage IV	$57,348.00	$28,674.00	$103,226.40

For each parameter group, all indicated parameters were varied in the same direction to the same relative extent, assuming a flat distribution. For the combined variation, all parameters groups were varied in different directions to different extends. The starting value and the minimum and maximum of variations are indicated.
CRC, Colorectal cancer.

SUPPLEMENTARY TABLE 3. PolypDx versus low-specificity PolypDx

	PolypDx		PolypDx (low spec.)	
Scenario	**100% adherence**	**Real-world adherence**	**100% adherence**	**Real-world adherence**
CRC cases (per 1000)	34.1	39.1	32.7	36.8
Screening tests (per 1000)	5420	4444	4592	3995
Colonoscopies (per 1000)	1545	1227	1945	1560
Incidence reduction (%)	49.4	41.9	51.5	45.5
CRC deaths (per 1000)	10.4	12.7	10.2	11.9
Mortality reduction (%)	59.2	50.4	60.3	53.5
Total costs (per capita, USD)	6206	6280	6336	6531
LYG (per 1000)	168.7	139.4	172.4	149.0
dLYG (per 1000)	67.6	55.0	69.3	59.0
dUSD (per dLYG)	−2696	−4931	−586	−3408

We provide outcome parameters of 2 versions of PolypDx, with a high or lower specificity (0.91 vs 0.80 for CRC (for complete test characteristics see Table 1), for 100% adherence and real-world adherence, as indicated. The values of incidence and mortality reduction as well as LYG, dLYG, and dUSD per dLYG are compared with no screening.
CRC, Colorectal cancer; *dLYG*, discounted life-year gained; *dUSD*, discounted U.S. dollars; *LYG*, life-years gained; *USD*, U.S. dollars.