Gastroenterology 2024;■:1–10

Effectiveness and Cost-Effectiveness of Colorectal Cancer Screening With a Blood Test That Meets the Centers for Medicare & Medicaid Services Coverage Decision

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BACKGROUND & AIMS: A blood-based colorectal cancer (CRC) screening test may increase screening participation. However, blood tests may be less effective than current guideline-endorsed options. The Centers for Medicare & Medicaid Services (CMS) covers blood tests with sensitivity of at least 74% for detection of CRC and specificity of at least 90%. In this study, we investigate whether a blood test that meets these criteria is cost-effective. **METHODS:** Three microsimulation models for CRC (MISCAN-Colon, CRC-SPIN, and SimCRC) were used to estimate the effectiveness and cost-effectiveness of triennial blood-based screening (from ages 45 to 75 years) compared to no screening, annual fecal immunochemical testing (FIT), triennial stool DNA testing combined with an FIT assay, and colonoscopy screening every 10 years. The CMS coverage criteria were used as performance characteristics of the hypothetical blood test. We varied screening ages, test performance characteristics, and screening uptake in a sensitivity analysis. **RESULTS:** Without screening, the models predicted 77–88 CRC cases and 32–36 CRC deaths per 1000 individuals, costing $5.3–$5.8 million. Compared to no screening, blood-based screening was cost-effective, with an additional cost of $25,600–$43,700 per quality-adjusted life-year gained (QALYG). However, compared to FIT, triennial stool DNA testing combined with FIT, and colonoscopy, blood-based screening was not cost-effective, with both a decrease in QALYG and an increase in costs. FIT remained more effective (+5–24 QALYG) and less costly (–$3.2 to –$3.5 million) than blood-based screening even when uptake of blood-based screening was 20 percentage points higher than uptake of FIT. **CONCLUSION:** Even with higher screening uptake, triennial blood-based screening, with the CMS-specified minimum performance sensitivity of 74% and specificity of 90%, was not projected to be cost-effective compared with established strategies for colorectal cancer screening.

Keywords: Biomarkers; Colorectal Cancer; Cost-Effectiveness.

Colorectal cancer (CRC) is the second leading cause of cancer death in the United States.[1] Screening can prevent 10% to 68% of all CRC deaths,[2] depending on screening adherence, modality, and screening frequency. CRC screening is recommended by the US Preventive Services Task Force for individuals aged 45–75 years,[3] with screening performed with annual fecal immunochemical testing (FIT) or colonoscopy every 10 years, among others.[4] Despite the effectiveness and availability of screening, adherence to screening recommendations remains suboptimal at about 60%.[1] There are persistent barriers to screening that include fear of and aversion to the screening test.[5,6] Emerging tests, such as a blood-based CRC screening test, have the potential to circumvent these barriers and increase screening participation.

A blood-based CRC screening test, completed as part of a routine health care visit, may be preferred for some patients over collecting a stool sample or undergoing a screening colonoscopy, potentially leading to increased CRC screening uptake.[7] However, the performance characteristics of blood-based screening tests, especially for the detection of advanced adenomas, may render blood-based tests less effective than current guideline-endorsed modalities. In addition, because they are expensive, the current available blood-based tests may not be cost-effective compared with colonoscopy or FIT.[8]

Despite this, the Centers for Medicare & Medicaid Services (CMS) issued a coverage decision that states that triennial blood-based screening tests for individuals aged 50–85 years will be covered if the blood test meets a minimum performance sensitivity of 74% for detection of CRC

Abbreviations used in this paper: **CRC, colorectal cancer; CMS, Centers for Medicare & Medicaid Services; FIT, fecal immunochemical testing; QALY, quality-adjusted life-years; sDNA-FIT, triennial stool DNA testing combined with fecal immunochemical testing; WTP, willingness to pay.**

0016-5085
https://doi.org/10.1053/j.gastro.2024.02.012

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

There is limited evidence on the (cost-)effectiveness of blood-based screening with a test that meets the minimum Centers for Medicare & Medicaid Services–specified performance sensitivity of 74% and specificity of 90%.

NEW FINDINGS

Even with higher screening uptake, triennial blood-based screening was not projected to be cost-effective compared with established strategies for colorectal cancer.

LIMITATIONS

We assumed either complete screening uptake or no uptake (ie, no screening) at all. Furthermore, we did not consider any substitution effect.

CLINICAL RESEARCH RELEVANCE

Our evaluation of the cost-effectiveness of blood-based screening tests is a critical factor in determining the value of implementing such tests.

BASIC RESEARCH RELEVANCE

Our results contribute to the determination of conditions under which blood test would be cost-effective and could help inform coverage determinations.

and specificity of 90%.[9] In this study, we evaluated the effectiveness and cost-effectiveness of a hypothetical blood-based CRC screening test that meets the CMS coverage criteria as well as the cost-effectiveness of the currently available blood tests (Epi proColon [Epigenomics, Inc] and Shield [Guardant Health, Inc] tests).

Methods

Microsimulation Models

We used 3 independently developed microsimulation models for CRC (MISCAN-Colon, CRC-SPIN, SimCRC) that are part of the US National Cancer Institute's Cancer Intervention and Surveillance Modeling Network and have been used to inform screening recommendations.[10,11] In short, these models generate a cohort, similar to the US in terms of life expectancy and CRC risk, from birth until death. They also simulate the development of CRC and the impact of screening within that cohort. The model structure and underlying assumptions of the models can be found in more detail in other publications.[12,13] We used the same model input parameters and assumptions as used in modeling analyses for the US Preventive Services Task Force in support of its 2021 recommendations for CRC screening, which account for the latest trends in CRC incidence.[10]

Screening Strategies

We simulated screening from ages 45 to 75 years in an average-risk cohort of 10 million individuals, with participation in screening, follow-up, and surveillance consistent with recommendations.[10,14] The screening strategies evaluated were triennial blood-based screening, annual FIT, triennial stool DNA testing combined with an FIT assay (sDNA-FIT), colonoscopy screening every 10 years, and a no-screening scenario. Individuals with a positive result on FIT, sDNA-FIT, or blood test underwent a follow-up colonoscopy. Those with a false-positive screening test result resumed screening 10 years after the negative finding on follow-up colonoscopy with their original modality and schedule. Individuals in whom adenomas were detected and removed were assumed to undergo colonoscopy surveillance based on current US recommendations.[14] For groups for which the recommendations specify a range of intervals, we assumed surveillance was performed according to the shortest interval.

Test Characteristics

Test characteristics of the hypothetical blood test were based on the CMS coverage criteria (Table 1). FIT and sDNA-FIT characteristics were the same as those used in previous analysis from our group.[10] Colonoscopy sensitivities were slightly decreased based on reported adenoma miss rates in a systematic review and meta-analysis.[17]

Costs and Disutilities

Costs of screening, screening-related complications, and cancer care were computed from a health care sector perspective and include reimbursed as well as out-of-pocket payments (Supplementary Table 1). A blood test was assumed to cost $500 per test.[18] For individuals aged 65 years and older, costs were based on CMS reimbursement rates; for individuals younger than 65 years, commercial costs were used.[19] Costs were inflated to 2021 US dollars using the personal health care deflator price index.[20]

We incorporated disutilities for undergoing a CRC screening test, having a colonoscopy complication, and having CRC, in line with previous analyses (Supplementary Table 1).[10,21] Estimates of the test disutility include those associated with the test itself, those related to fear or anxiety while waiting for the test result, and those for waiting for a follow-up colonoscopy after a positive test result. The disutility of a blood test was assumed to be equal to that of an FIT.

Analysis and Outcomes

We used the models to project the lifetime costs and (quality-adjusted) life-years of the different screening strategies, applying a 3% annual discount rate. To compare the blood tests with FIT, colonoscopy, and no screening, incremental cost-effectiveness ratios were calculated with effectiveness expressed in terms of the number of quality-adjusted life-years (QALYs) gained. A strategy was considered cost-effective if the incremental cost-effectiveness ratio was below the willingness-to-pay (WTP) threshold of $100,000 per QALY gained. The main outcomes were computed per 1000 45-year-old individuals.

We also identified the maximum unit cost of a blood test at which blood-based screening would be cost-effective compared to FIT, sDNA-FIT, or colonoscopy screening.

Sensitivity Analysis

We carried out 5 1-way sensitivity analyses. First, we simulated triennial blood-based screening from ages 50 to 85 years, in line with the CMS coverage decision. Second, we

Table 1. Screening Test Characteristics Used in the Analysis

Screening test	1 – specificity	Sensitivity[a] by size of the most advanced lesion				Source
		Adenomas 1 to <6 mm	Adenomas 6 to <10 mm	Adenomas ≥10 mm	CRC	
FIT	0.036		0.076[b]	0.238[c]	0.738	15
sDNA-FIT	0.09		0.15[b]	0.42[c]	0.94	15
Blood test (CMS)	0.1	0.1[d]	0.1[d]	0.1[d]	0.74	9
Colonoscopy	0.1325[e]	0.69	0.81	0.91	0.91	16,17
Sensitivity analysis						
FIT	0.036		0.076[b]	0.238[c]	80%[f]	15,26
Blood test (Epi proColon)	0.196	0.2[d]	0.2[d]	0.204	0.702	22,23
Blood test (Shield)	0.1	0.1[d]	0.1[d]	0.13	0.83	24
Blood test (CMS)	0.1	0.1[d]	0.1[d]	0.1[d]	80%[f]	9,26

[a]Per individual for FIT and blood test, based on most advanced lesion, and per lesion for endoscopy.
[b]Sensitivity for persons with nonadvanced adenomas. For persons with 1- to <6-mm adenomas, MISCAN and SimCRC assumed that the sensitivity of the test is equal to the positivity rate in people without adenomas or cancer (1 – specificity). The sensitivity for persons with adenomas of 6 to <10 mm was chosen such that the weighted average sensitivity is equal to that for nonadvanced adenomas.
[c]Sensitivity for advanced adenomas (ie, adenomas of ≥10 mm and/or adenomas with advanced histology). We assume no advanced histology in adenomas of <10 mm.
[d]Adenomas are only detected by chance, with sensitivity set to the positivity rate in people without adenomas or cancer (1 – specificity).
[e]The lack of specificity with colonoscopy reflects the detection of nonadenomatous lesions that are removed and therefore induce costs due to polypectomy and biopsy.
[f]Relative sensitivity for stage I vs stages II–IV. The absolute sensitivity for stage I and stages II–IV values were calculated such that the weighted overall sensitivity for stages I–IV was equal to the base case sensitivities of 73.8% and 74% for FIT and blood-based screening, respectively.

considered existing blood tests with different sensitivity and specificity. Test characteristics of the Epi proColon test were based on the average values reported in the literature,[22,23] and those of the Shield test (Guardant Health, Inc) were based on reported estimates from one study[24] (see Table 1).

Third, we assumed a more realistic overall screening uptake of 60%.[25] We also increased the uptake of blood-based screening from 60% to 70% and 80% and compared the outcomes to FIT, sDNA-FIT, and colonoscopy screening with 60% uptake. For these differential uptake analyses, we assumed that the adherent part of the population was completely adherent to screening (ie, screened consistent with recommendations/guidelines) and that the remainder was completely nonadherent (ie, never screened).

To highlight the importance of adherence with follow-up after a positive blood test result, we explored a scenario with 100% uptake of screening but imperfect adherence to follow-up testing, with only 60% of individuals with a positive blood test or positive FIT result undergoing follow-up colonoscopy. We assumed that individuals either always or never showed up for follow-up colonoscopy.

Because it has been shown that sensitivity of noninvasive tests for the detection of CRC varies by stage, we finally considered stage-specific sensitivity for CRC (stage I vs stages II–IV) for FIT and blood tests with 100% screening uptake.[26] Our sensitivity estimates were based on reported stage-specific sensitivities for FIT.[26] Due to limited information on the stage-specific sensitivity for CRC of a blood test, we assumed the same sensitivities as for FIT. The relative stage I sensitivity compared to stages II–IV (80%) was used to scale the absolute sensitivities used in the models. The sensitivity for stage I and stages II–IV values were calculated such that the weighted overall sensitivity for stages I–IV was equal to the base case sensitivities of 73.8% and 74% for FIT and blood-based screening, respectively. Stage-specific sensitivities were thus dependent on the stage distribution in the models.

Probabilistic Sensitivity Analysis

In probabilistic sensitivity analysis, we assessed the uncertainty around screening and treatment costs, disutilities, and screening uptake. For every base case strategy, we performed 1000 simulations, each containing a different set of sampled values for costs, disutilities, and screening uptake from distributions that reflect the uncertainty in these model inputs. Costs and disutilities were drawn from gamma probability distributions (Supplementary Tables 2 and 3). For FIT, sDNA-FIT, and colonoscopy, screening uptake was sampled from a uniform distribution between 50% and 70%; uptake of blood-based screening was sampled from a uniform distribution between 70% and 90%. Cost-acceptability curves were constructed for WTP thresholds up to $150,000 per QALY gained.

Results

Without screening, the models predicted that 1000 45-year-old individuals lived, on average, 21,500–21,500 QALYs and spent $5.3–$5.8 million on CRC treatment

Table 2. Lifetime Effects and Costs per 1000 45-Year-Olds for No Screening, FIT, sDNA-FIT, Colonoscopy, and Blood-Based Screening

Screening strategy	Number of tests	Number of colonoscopies	CRC cases, n	CRC deaths, n[a]	Life-years[b]	QALYG[b,c]	Costs[b,d]
No screening	0	77–88[e]	77–88	32–36	21,525–21,544	0	5263–5845
FIT screening	18,483–19,236	1728–1856	18–48	6–12	21,632–21,670	125–163	3814–5376
sDNA-FIT screening	7180–7394	1590–1735	21–53	7–13	21,622–21,665	112–156	6435–8121
Colonoscopy screening	2853–3033	4243–4274	15–38	4–10	21,634–21,678	131–177	5426–7023
Blood-based screening	7439–7653	1335–1408	44–68	14–18	21,603–21,637	83–116	8559–9410
Sensitivity analyses							
Blood-based screening (age 50–85, every 3 y)	7170–7629	1289–1324	48–71	13–17	21,597–21,627	70–104	8052–8699
Blood-based screening (Epi proColon)	5972–7080	1731–2156	28–56	10–15	21,613–21,650	101–137	7663–8867
Blood-based screening (Shield)	7411–7606	1369–1434	41–67	13–17	21,606–21,644	91–125	8376–9361
FIT screening (stage-specific sensitivity)	1713–19,237	1728–1856	18–48	6–12	21,632–21,670	126–163	3816–5059
Blood-based screening (stage-specific sensitivity)	7440–7640	1334–1408	44–67	15–18	21,601–21,636	80–115	8497–9413
FIT screening, 60% uptake	11,090–13,900	1051–1144	42–64	16–21	21,589–21,619	75–98	4394–5586
sDNA-FIT screening, 60% uptake	4308–4437	989–1072	43–67	17–22	21,583–21,615	67–93	5966–7131
Colonoscopy screening, 60% uptake	1712–1851	2580–2641	38–58	15–20	21,590–21,625	79–106	5329–6473
Blood-based screening, 60% uptake	4463–5279	659–880	57–79	22–26	21,564–21,596	38–70	7240–7905
Blood-based screening, 70% uptake	5207–5347	958–1012	54–73	21–23	21,579–21,606	58–81	7570–8281
Blood-based screening, 80% uptake	5951–6111	1083–1144	51–71	19–21	21,587–21,617	66–93	7900–8658
FIT screening, 60% follow-up[f]	18,483–19,236	1072–1144	42–64	16–21	21,589–21,619	75–97	4526–5620
sDNA-FIT screening, 60% follow-up[f]	7180–7394	989–1072	43–67	17–22	21,583–21,615	67–93	5966–7131
Blood-based screening, 60% follow-up[f]	7439–7639	832–880	57–75	22–25	21,571–21,596	49–69	8636–9263

NOTE. Range across models is given.
QALYG, quality-adjusted life-years gained.
[a]Deaths from colonoscopy complications are counted as CRC-related deaths.
[b](Quality-adjusted) life-years (gained) and costs were discounted at an annual rate of 3%.
[c]Quality-adjusted life-years gained compared to no screening.
[d]Costs are in 2021 US dollars and are expressed in thousands (eg, 5263 is 526,300).
[e]Only colonoscopies for CRC diagnosis were considered.
[f]Screening uptake was assumed to be 100%, but only 60% of individuals with a positive test result undergo a follow-up colonoscopy.

(Table 2). A total of 77–88 patients had a CRC diagnosis, of whom 32–36 died of CRC. Compared with no screening, screening reduced the number of CRC cases and CRC deaths (38–60 cases and 24–29 deaths averted per 1000 with FIT, 33–57 cases and 22–28 deaths averted with sDNA-FIT, 48–73 cases and 25–32 deaths averted with colonoscopy, and 19–33 cases and 16–21 deaths averted with blood-based screening) (Figure 1). Lifetime colonoscopies ranged from 1728 to 1856 per 1000 with FIT screening, from 1590 to 1735 with sDNA-FIT screening, from 4243 to 4274 with colonoscopy screening, and from 1335 to 1408 with blood-based screening.

Compared with no screening, blood-based screening increased the number of QALYs by 83–116 per 1000 and costs by $3.0–$3.8 million per 1000 (Figure 2). With an incremental cost of $25,600–$43,700 per QALY gained (Supplementary Table 4), blood-based screening was cost-effective compared to no screening. However, compared to FIT, sDNA-FIT, and colonoscopy screening, blood-based screening was not cost-effective. Compared to FIT screening, blood-based screening resulted in 39–68 fewer QALYs per 1000 while increasing costs by $4.0–$4.8 million. Compared to colonoscopy screening, blood-based screening resulted in 45–84 fewer QALYs while also increasing costs by $2.3–$3.4 million. Compared to sDNA-FIT, blood-based screening resulted in 26–59 fewer QALYs per 1000 and increased costs by $1.3–$2.1 million.

When a blood test would cost $0, blood-based screening was still estimated to be more expensive than FIT screening (Supplementary Figure 1). At zero cost, blood-based screening was estimated to be less expensive than sDNA-FIT and colonoscopy screening; however, at a WTP of $100,000 per QALY gained, blood-based screening was still not cost-effective.

Sensitivity Analysis

Offering blood-based screening from ages 50 to 85 years instead of from ages 45 to 75 years yielded slightly fewer QALYs and slightly lower costs (Table 2), but in terms of cost-effectiveness, results were similar to the base case (Supplementary Table 4). Results were also relatively insensitive to the CRC stage-specific sensitivity assumption. The Epi proColon and Shield tests yielded more QALYs gained at a lower cost than a blood test that meets the CMS performance criteria (+15–34 and +4–9 QALYs gained with a cost decrease of $0.5–$0.9 and $0.05–$0.2 million, respectively). Despite performing best among the blood tests, Epi proColon was still less effective and considerably more costly than FIT screening (Table 2) and therefore not cost-effective.

Lower screening uptake reduced the benefits of screening. However, screening with 60% uptake would still be cost-effective compared to no screening. If uptake of blood-based screening was 20% higher than uptake of FIT or colonoscopy screening (ie, 80% vs 60%), blood-based screening that meets the CMS performance criteria was still estimated to result in lower QALYs and higher costs (5–24 QALYs lost with a cost increase of $3.2–$3.5 million compared to FIT and 10–34 QALYs lost with a cost increase of $2.2–$2.6 compared to colonoscopy) (Figure 3). Compared to sDNA-FIT, blood-based screening resulted in similar QALYs, but at higher costs. With 80% uptake, blood-based screening with the Epi proColon test resulted in slightly higher QALYs than FIT screening with 60% uptake. However, costs remained substantially higher.

Blood-based testing with 100% uptake, but only 60% adherence to follow-up colonoscopy after a positive test result, decreased QALYs considerably compared to 100% uptake with perfect adherence to follow-up testing (Figure 4 and Table 2). The cost-effectiveness of blood-based testing compared to FIT and sDNA-FIT was relatively insensitive to the imperfect follow-up assumption.

Probabilistic Sensitivity Analysis

In probabilistic sensitivity analysis, at a WTP of $100,000, blood-based screening was cost-effective compared to no screening for almost all (99.8%–100%) cost, disutility, and screening uptake combinations evaluated (Supplementary Figure 2). In 1.6%–10.0% and 0.1%–0.5% of the simulations, blood-based screening was cost-effective compared to sDNA-FIT and colonoscopy screening, respectively (Supplementary Figure 3). However, blood-based screening was never cost-effective compared to FIT. At higher WTPs, the probability that blood-based screening was cost-effective compared to FIT, sDNA-FIT, and colonoscopy increased. Even at a WTP of $150,000, blood-based screening was rarely cost-effective compared to FIT (0%–1.1%).

Discussion

Evaluating the cost-effectiveness of blood-based screening tests is a critical factor in determining the value of implementing such tests. In this study, we showed that a blood-based screening test with performance characteristics that meet the CMS coverage criteria is cost-effective compared to no screening. However, blood-based screening with these performance criteria was estimated to be less effective and more costly than the currently recommended FIT, sDNA-FIT, and colonoscopy screening strategies. Even if the uncertainty around model parameters was considered and combined with a 20-percentage-point-higher uptake, blood-based screening was rarely cost-effective. Although the Epi proColon and Shield tests, both of which are currently available, performed slightly better than a blood test that meets the CMS coverage criteria, FIT remained the cost-effective option.

At present, the sensitivities of various blood tests for the detection of CRC are similar to that of FIT. Nevertheless, the longer screening interval and the current inability of blood tests to detect precursor lesions are important drivers of its lack of cost-effectiveness compared to FIT. Moreover, the cost of a blood test is considerably higher than that of FIT. Performance characteristics of currently available blood tests are not yet able to offset the higher cost.

Prior studies have shown the importance of (advanced) adenoma sensitivity of noninvasive tests to improve the

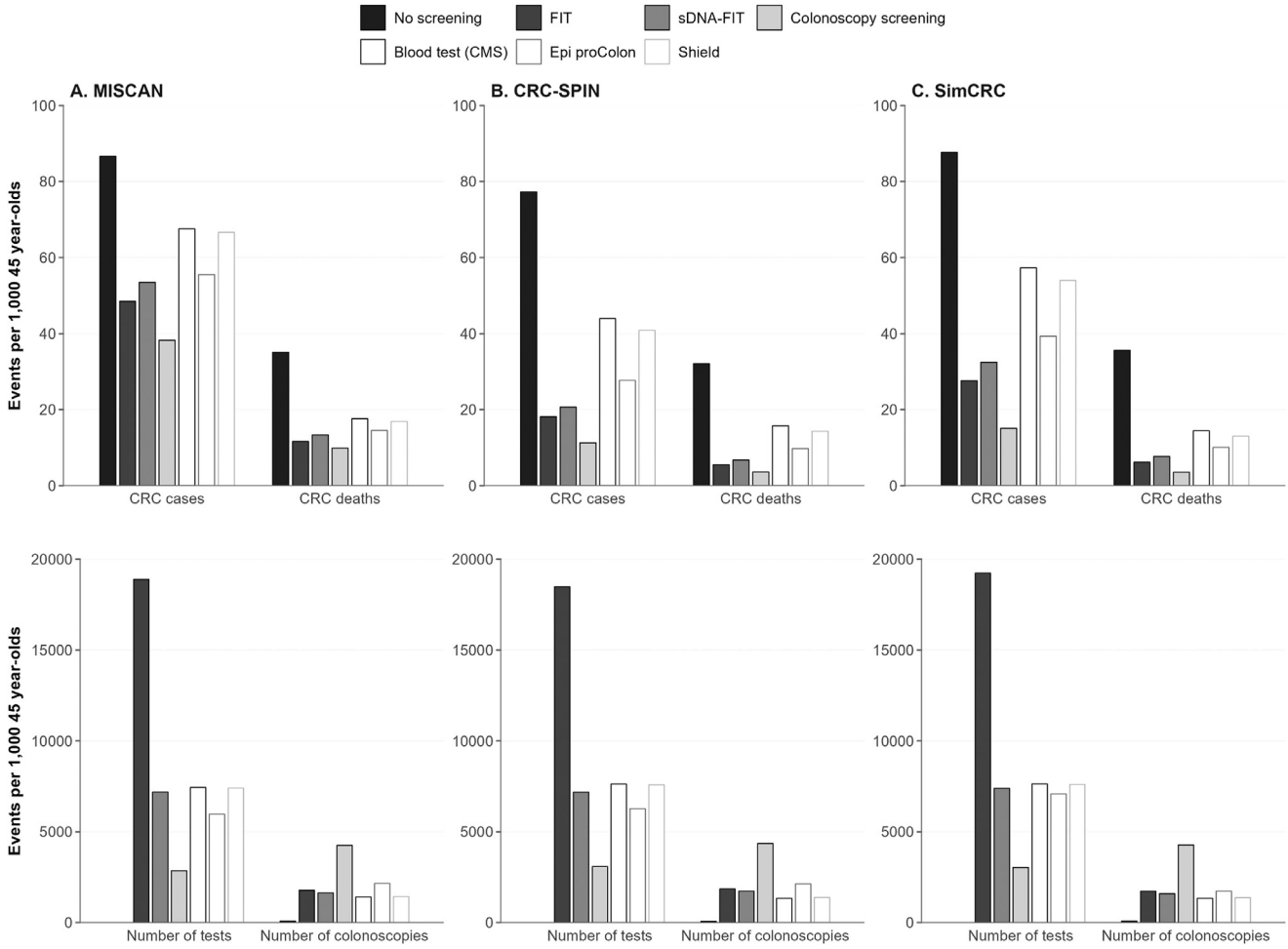

Figure 1. Number of CRC cases and deaths and number of tests and colonoscopies with different screening strategies.

balance between costs, burdens, and benefits.[27] For instance, a study compared FIT screening with a hypothetical test that had higher sensitivity for CRC but no sensitivity for adenomas.[28] The findings showed that this hypothetical test, despite having higher uptake rates, was not more effective and was more costly than FIT, even though the unit cost of the test was assumed to be equal to that of FIT. This result was primarily due to the nondetection of adenomas.

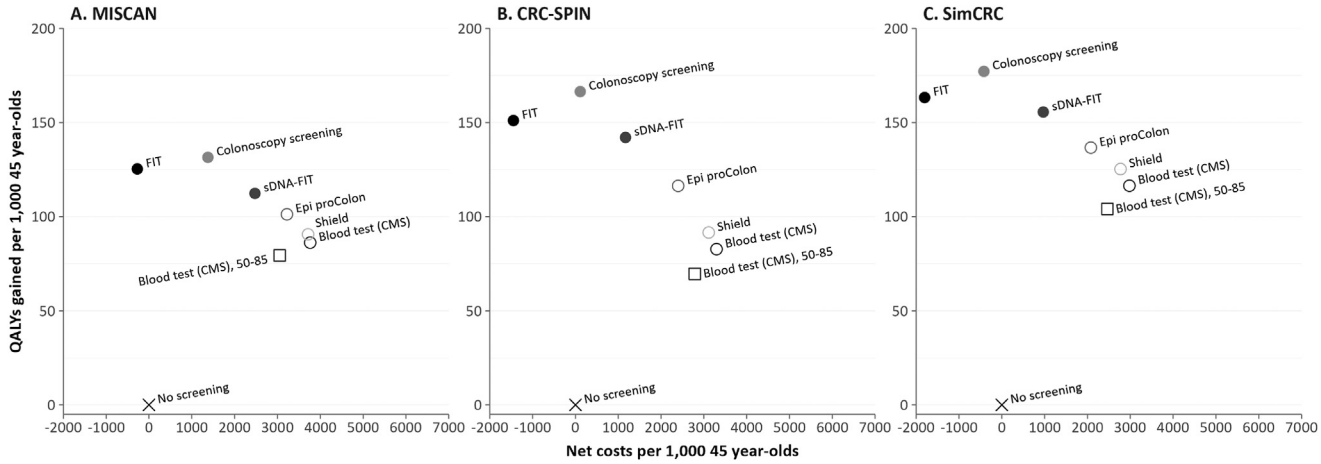

Figure 2. QALYs gained and net costs compared to no screening for a cohort of 45-year-olds with FIT, sDNA-FIT, and colonoscopy screening and different blood-based screening strategies. Costs are expressed in thousands (eg, 5000 is 5,000,000).

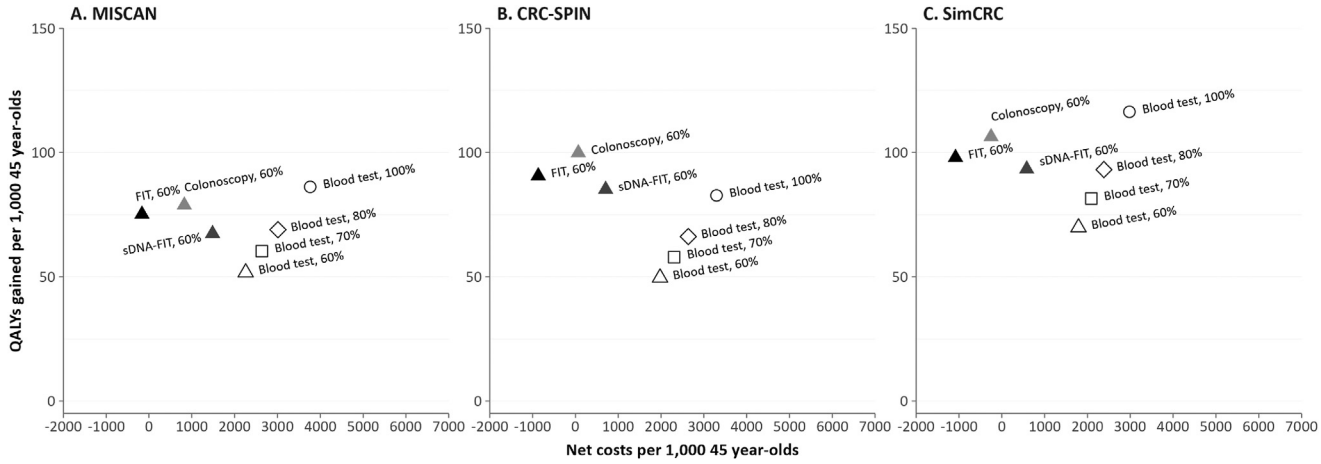

Figure 3. QALYs gained and net costs for a cohort of 45-year-olds with different uptake scenarios for FIT, sDNA-FIT, colonoscopy, and blood-based screening. Test characteristics of the blood test were based on the CMS coverage criteria. Costs are expressed in thousands (eg, 5000 is 5,000,000).

Another study explored under which conditions a biomarker test would be cost-effective, considering different performance characteristics.[29] At the highest performance characteristics considered (53% sensitivity for large adenomas, 100% sensitivity for CRC, and 100% specificity), the unit cost of a blood test could be at most 7 times higher than the unit cost of FIT to be considered cost-effective. This threshold could potentially double with a 20-percentage-point increase in uptake. In our study, the unit cost of the blood test far exceeds 20 times the costs of FIT (ie, $500 vs $23). Consequently, even with high performance characteristics or improved uptake, blood-based screening strategies will not be cost-effective.

Although the Epi proColon test has the lowest sensitivity to detect CRC, screening with this test resulted in slightly higher QALYs gained and CRC cases and deaths averted compared to the other blood tests. Due to the relatively low specificity for CRC of the Epi proColon test, a higher number of individuals are referred for a follow-up colonoscopy. Because the detection rate of adenomas was equal to the false positive rate in individuals without adenomas or cancer, 19.6% of simulated individuals with advanced adenomas underwent a colonoscopy by chance. The detection of advanced adenomas in these individuals contributed to the slightly improved results. Another beneficial effect of low specificity is that individuals without findings at their follow-up colonoscopy do not need to undergo expensive screening for at least 10 years. Hence, a test with low specificity effectively randomly assigns individuals into a colonoscopy-based screening program. This is favorable for cost-effectiveness because 1 colonoscopy is less costly than 3 blood-based screening tests.

Similar to FIT, a key advantage of blood-based screening tests over colonoscopy screening is that it is noninvasive, which potentially reduces patient discomfort and enhances screening uptake, leading to improved patient outcomes. Adler et al[7] reported that 97% of individuals who declined colonoscopy screening opted for a noninvasive test, with 83% choosing a blood test. In addition, our sensitivity analysis showed that even if a blood test were to increase

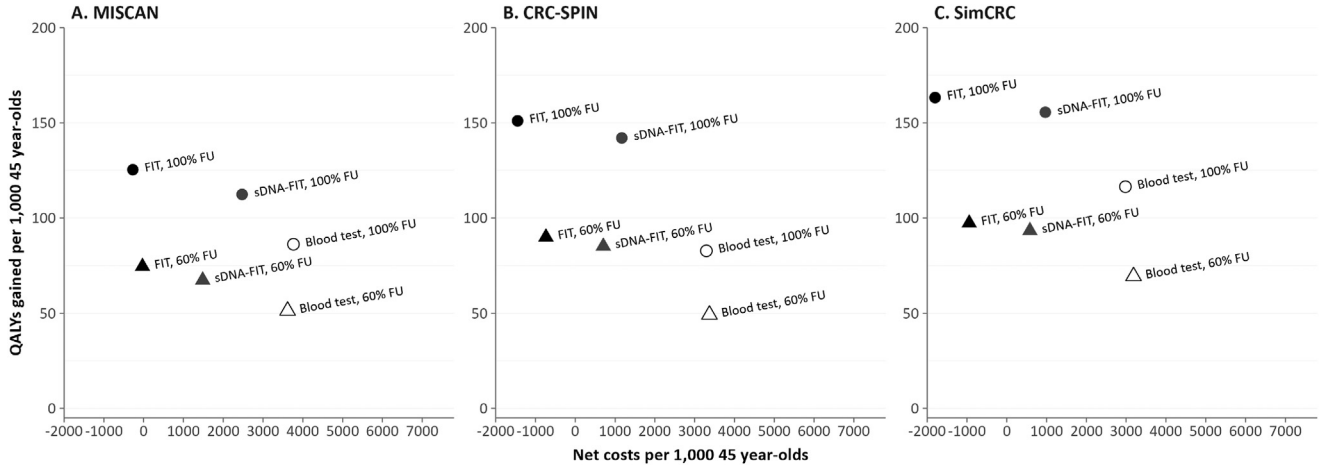

Figure 4. QALYs gained and costs for a cohort of 45-year-olds with imperfect adherence to follow-up (FU) colonoscopy (60%) with FIT, sDNA-FIT, and blood-based screening compared to perfect adherence to follow-up colonoscopy. Test characteristics of the blood test were based on the CMS coverage criteria. Costs are expressed in thousands (eg, 5000 is 5,000,000).

screening uptake from 60% to 80% or increase adherence to follow-up colonoscopy, it would still not be cost-effective compared to FIT screening at 60% uptake. People may argue that the comparison should be with no screening because the blood test is only meant for people not willing to undergo established tests. For individuals who are unwilling to undergo FIT or colonoscopy, annual blood-based screening has been shown to be cost-effective compared to alternatives.[21] However, substitution of a blood test for current alternatives cannot be ruled out, especially if the blood draw is performed at the same time that blood is drawn for other routine tests. Previous studies of septin 9 showed that when current alternatives are substituted for by blood-based screening, the effectiveness of screening will decrease.[8]

Another critical factor influencing screening effectiveness is completion of a follow-up colonoscopy after a positive (noncolonoscopy) test result. Studies have indicated low rates of follow-up colonoscopy after a positive FIT result,[30,31] which diminishes the overall effectiveness of a 2-stage noninvasive screening program. In addition, if the test is expensive, screening costs are increased considerably without adding significant benefit if patients do not receive follow-up colonoscopy after a positive test result. Our models show that a blood test meeting the CMS criteria is better than no screening, but the degree of benefit depends highly on the rate of adherence to blood testing and the rate of follow-up colonoscopy for positive test results. If those with a positive blood test result are more likely than those with a positive FIT result to undergo follow-up colonoscopy, blood-based screening has the potential to enhance its effectiveness compared to FIT screening.

Our results are consistent with previous studies that estimated the cost-effectiveness of blood-based screening. A similar study to ours showed that a blood test meeting CMS coverage criteria decreased life-years gained by $\geq$19 compared to stool-based strategies.[32] To achieve the same life-years gained as multitarget stool DNA and FIT screening strategies, advanced adenoma sensitivity of 30% and 15%, respectively, would be needed. Another study showed that a ^{m}SEPT9 blood-based screening test was cost-effective compared to no screening but was less effective than established alternatives, such as FIT and colonoscopy.[8]

Although other studies have evaluated the cost-effectiveness of blood-based screening, an important strength of this study is that we modeled imperfect screening scenarios and explored the threshold cost of a blood test to be cost-effective. Furthermore, we used comparative modeling and demonstrated robustness of the results. However, our work also has 3 noteworthy limitations. First, we assumed independence between repeat blood tests, but the degree of independence is unknown. Because blood-based tests rely on biomarkers, it may be that in some individuals, precursor lesions or CRC might never be found. For example, 18% of tumors do not have methylation of the *SEPT9* gene promoter.[33] The Epi proColon test relies on the detection of the methylated *SEPT9* gene and will therefore not detect CRC at any test in 18% of individuals. This independence assumption results in an optimistic bias that favors repeated testing for all modalities. Second, the disutility associated with a blood-based screening test was assumed to be equal to that of FIT. Individuals may experience less discomfort from blood testing because they do not have to sample their stool, thus reducing patient disutility. However, for some, the fear and anxiety associated with a blood draw could be large.[34] Given that our assumed disutility associated with blood testing is already very modest, this assumption will likely not affect the results substantially.

Furthermore, we did not consider any substitution effect in this study. As was indicated before, when substitution of blood-based screening for alternatives cannot be ruled out, the effectiveness of screening will be affected. Finally, we assumed 100% uptake to screening, follow-up colonoscopy, and surveillance in our base case analysis. Furthermore, in our differential uptake scenarios, we assumed either complete uptake or no uptake (ie, no screening) at all, which is not realistic. However, it is more realistic than assuming that people randomly adhere to screening. At present, there are limited data available to inform test-specific adherence in different phases of the screening process. As indicated by our sensitivity analysis, lower uptake will generally decrease the (cost-)effectiveness of screening.

When making a coverage decision, CMS evaluates whether there is sufficient evidence to support that a test is suitable for screening. Although this concept is valuable to ensure the use of effective tests, this study shows that blood-based CRC screening with CMS performance test characteristics could result in both a significant increase in costs and a loss of benefit. In an otherwise unscreened population, blood-based screening would be cost-effective. However, if those who would otherwise be screened with a different test are instead screened with a blood test, it could be problematic. Differences in effectiveness between blood testing and FIT or colonoscopy are considerable, so even low levels of substitution could result in lower effectiveness and higher costs. Before blood tests become widely available and disseminated, more research is needed to simultaneously define the conditions (ie, test characteristics, costs, and adherence) under which blood tests would be effective and cost-effective compared to other screening options. These conditions could inform more comprehensive coverage determinations.

In conclusion, CRC screening with blood tests is likely to be cost-effective compared to no screening. However, the current test performance characteristics are insufficient to justify their high costs compared with less expensive and more effective alternatives such as FIT, sDNA-FIT, and colonoscopy.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2024.02.012.

References

1. Siegel RL, Miller KD, Wagle NS, et al. Cancer statistics, 2023. CA Cancer J Clin 2023;73:17–48.

2. Lauby-Secretan B, Vilahur N, Bianchini F, et al. The IARC perspective on colorectal cancer screening. N Engl J Med 2018;378:1734–1740.
3. Wolf AMD, Fontham ETH, Church TR, et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. CA Cancer J Clin 2018;68:250–281.
4. Lin JS, Piper MA, Perdue LA, et al. Screening for colorectal cancer: updated evidence report and systematic review for the US Preventive Services Task Force. JAMA 2016;315:2576–2594.
5. Medina GG, McQueen A, Greisinger AJ, et al. What would make getting colorectal cancer screening easier? Perspectives from screeners and nonscreeners. Gastroenterol Res Pract 2012;2012:895807.
6. Gordon NP, Green BB. Factors associated with use and non-use of the fecal immunochemical test (FIT) kit for colorectal cancer screening in response to a 2012 outreach screening program: a survey study. BMC Public Health 2015;15:546.
7. Adler A, Geiger S, Keil A, et al. Improving compliance to colorectal cancer screening using blood and stool based tests in patients refusing screening colonoscopy in Germany. BMC Gastroenterol 2014;14:183.
8. Ladabaum U, Allen J, Wandell M, et al. Colorectal cancer screening with blood-based biomarkers: cost-effectiveness of methylated septin 9 DNA versus current strategies. Cancer Epidemiol Biomarkers Prev 2013;22:1567–1576.
9. Centers for Medicare & Medicaid Services. Screening for colorectal cancer - blood-based biomarker tests. Available at: https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&NCAId=299. Accessed June 1, 2023.
10. Knudsen AB, Rutter CM, Peterse EFP, et al. Colorectal cancer screening: an updated modeling study for the US Preventive Services Task Force. JAMA 2021;325:1998–2011.
11. Peterse EFP, Meester RGS, Siegel RL, et al. The impact of the rising colorectal cancer incidence in young adults on the optimal age to start screening: microsimulation analysis I to inform the American Cancer Society colorectal cancer screening guideline. Cancer 2018;124:2964–2973.
12. Zauber A, Knudsen A, Rutter CM, et al. Evaluating the benefits and harms of colorectal cancer screening strategies: a collaborative modeling approach. Rockville, MD: Agency for Healthcare Research and Quality, 2015.
13. Rutter CM, Ozik J, DeYoreo M, et al. Microsimulation model calibration using incremental mixture approximate Bayesian computation. Ann Appl Stat 2019;13:2189–2212.
14. Gupta S, Lieberman D, Anderson JC, et al. Recommendations for follow-up after colonoscopy and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. Gastrointest Endoscop 2020;91:463–485.
15. Lin JS, Perdue LA, Henrikson NB, et al. Screening for colorectal cancer: updated evidence report and systematic review for the US Preventive Services Task Force. JAMA 2021;325:1978–1998.
16. Schroy IPC, Coe A, Chen CA, et al. Prevalence of advanced colorectal neoplasia in white and black patients undergoing screening colonoscopy in a safety-net hospital. Ann Intern Med 2013;159:13–20.
17. Zhao S, Wang S, Pan P, et al. Magnitude, risk factors, and factors associated with adenoma miss rate of tandem colonoscopy: a systematic review and meta-analysis. Gastroenterology 2019;156:1661–1674.
18. FindLabTest.com. Epi proColon®, Septin 9 gene methylation detection in online lab tests stores. Available at: https://www.findlabtest.com/lab-test/general-wellness/epi-procolon-septin-9-gene-methylation-detection-labcorp-481160#:~:text=None%20Epi%20proColon%C2%AE%2C%20Septin,Blood%20Test)%20with%20price%20%24498.00. Accessed June 14, 2023.
19. Ladabaum U, Mannalithara A, Brill JV, et al. Contrasting effectiveness and cost-effectiveness of colorectal cancer screening under commercial insurance vs. Medicare. Am J Gastroenterol 2018;113:1836–1847.
20. Dunn A, Grosse SD, Zuvekas SH. Adjusting health expenditures for inflation: a review of measures for health services research in the United States. Health Serv Res 2018;53:175–196.
21. Peterse EFP, Meester RGS, de Jonge L, et al. Comparing the cost-effectiveness of innovative colorectal cancer screening tests. J Natl Cancer Inst 2021;113:154–161.
22. Johnson DA, Barclay RL, Mergener K, et al. Plasma Septin9 versus fecal immunochemical testing for colorectal cancer screening: a prospective multicenter study. PLoS One 2014;9(6):e98238.
23. Potter NT, Hurban P, White MN, et al. Validation of a real-time PCR–based qualitative assay for the detection of methylated *SEPT9* DNA in human plasma. Clin Chem 2014;60:1183–1191.
24. Guardant. Guardant Health presents additional information from ECLIPSE study at 2023 Digestive Disease Week on the performance of Shield™ blood test. Available at: https://investors.guardanthealth.com/press-releases/press-releases/2023/Guardant-Health-presents-additional-information-from-ECLIPSE-study-at-2023-Digestive-Disease-Week-on-the-performance-of-Shield-blood-test/default.aspx. Accessed May 31, 2023.
25. Smith RA, Andrews K, Brooks D, et al. Cancer screening in the United States, 2016: A review of current American Cancer Society guidelines and current issues in cancer screening. CA Cancer J Clin 2016;66:96–114.
26. Gies A, Niedermaier T, Gruner LF, et al. Fecal immunochemical tests detect screening participants with multiple advanced adenomas better than T1 colorectal cancers. Cancers (Basel) 2021;13(4):644.
27. Piscitello A, Carroll LN, Fransen S, et al. Differential impact of test performance characteristics on burden-to-benefit tradeoffs for blood-based colorectal cancer screening: a microsimulation analysis. J Med Screen 2023;30:175–183.
28. Haug U, Knudsen AB, Lansdorp-Vogelaar I, et al. Development of new non-invasive tests for colorectal cancer screening: the relevance of information on adenoma detection. Int J Cancer 2015;136:2864–2874.

29. Lansdorp-Vogelaar I, Goede SL, Bosch LJW, et al. Cost-effectiveness of high-performance biomarker tests vs fecal immunochemical test for noninvasive colorectal cancer screening. Clin Gastroenterol Hepatol 2018; 16:504–512.
30. Mohl JT, Ciemins EL, Miller-Wilson LA, et al. Rates of follow-up colonoscopy after a positive stool-based screening test result for colorectal cancer among health care organizations in the US, 2017–2020. JAMA Netw Open 2023;6(1):e2251384.
31. Issaka RB, Bell-Brown A, Kao J, et al. Barriers associated with inadequate follow-up of abnormal fecal immunochemical test results in a safety-net system: a mixed-methods analysis. Prev Med Rep 2022;28:101831.
32. Fendrick AM, Vahdat V, Chen JV, et al. Comparison of simulated outcomes between stool- and blood-based colorectal cancer screening tests. Popul Health Manag 2023;26:239–245.
33. Ahmed D, Danielsen SA, Aagesen TH, et al. A tissue-based comparative effectiveness analysis of biomarkers for early detection of colorectal tumors. Clin Transl Gastroenterol 2012;3(12):e27.
34. France CR, France JL, Himawan LK, et al. Fear is associated with attrition of first-time whole blood donors: a longitudinal examination of donor confidence and attitude as potential mediators. Transfusion 2021;61:3372–3380.

Received October 13, 2023. Accepted February 2, 2024.

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Conflicts of interest
The authors disclose no conflicts.

Funding
This research was supported by grant U01-CA253913 from the National Cancer Institute (NCI) as part of the Cancer Intervention and Surveillance Modeling Network. Additional funding was obtained through National Institutes of Health/NCI Cancer Center Support grant P30 CA008748 (to Ann G. Zauber and Anne I. Hahn). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. This research was completed with resources provided by the Laboratory Computing Resource Center at Argonne National Laboratory.

Data Availability
The data generated in this study are available within the article and its Supplementary Materials. Full documentation of the Cancer Intervention and Surveillance Modeling Network (CISNET) models used to produce the results presented in this study can be found at https://cisnet.cancer.gov/colorectal/profiles.html. Interested researchers can contact the authors directly for more insight into the CISNET models. Analytical code to compute aggregated results and produce figures can be made available upon request.