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Cost-effectiveness of blood-based colorectal cancer screening – a simulation model incorporating real-world longitudinal adherence

Elifnur Yay Donderici [a], Shaun P. Forbes [a], Nicole J. Zhang [a], Gregory Schafer[a], Victoria M. Raymond [a], Amar K. Das [a], Craig Eagle[a], AmirAli Talasaz [a] and William M. Grady [b]

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ABSTRACT

Objectives: Although U.S. Preventive Services Task Force (USPSTF) recommended CRC screenings are effective; patient reluctance reduces adherence. Most cost-effectiveness models assume perfect adherence, yet one-third of eligible individuals aren't current with CRC screening. Our study assesses the cost-effectiveness of Shield, an FDA-approved blood-based CRC screening test, using real-world adherence.
Methods: The CAN-SCREEN (Colorectal cANcer SCReening Economics and adherENce) model, a validated discrete-event simulation, evaluated clinical and economic outcomes of CRC screening under real-world adherence scenarios. We compared the Shield blood-based test administered every 3 years to no screening, considering it cost-effective if the incremental cost-effectiveness ratio (ICER) was under $100,000 per quality-adjusted life-year (QALY) gained.
Results: Shield increased QALYs by 154 and raised costs by $7.5 million per 1,000 individuals, with an ICER of $48,662 per QALY, meeting the $100,000/QALY threshold. Shield remained cost-effective up to a unit cost of $3,241 (at $100,000/QALY) and $4,942 (at $150,000/QALY). Sensitivity analyses confirmed cost-effectiveness with lower adherence to diagnostic colonoscopy (56.1%) and annual screenings.
Conclusion: The CAN-SCREEN model shows that Shield is cost-effective compared to no screening. Including real-world adherence improves accuracy in assessing screening strategies. Shield's noninvasive approach offers a promising, cost-effective way to increase adherence and reduce CRC mortality.

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Adherence; colorectal cancer; liquid biopsy; screening; simulation

1. Introduction

Colorectal Cancer (CRC) is one of the leading causes of cancer-related mortality globally, with estimated deaths of nearly 900,000 in 2018 [1]. Early detection and intervention have been proven critical to improving patient outcomes. The U.S. Preventive Services Task Force (USPSTF) recommends routine screening for CRC starting at age 45 for average-risk individuals, with screening colonoscopy every 10 years, or annual fecal immunochemistry testing (FIT) or fecal occult blood testing (FOBT), or multi-target stool DNA (mts-DNA) test every three years, among a few others [2]. Previous research has demonstrated reduced mortality through routine CRC screening though early cancer detection [3–12]; however, despite proven effectiveness, community outreach, and education efforts, screening adherence remains suboptimal, and is often limited by factors such as invasiveness, preparation requirements, and patient reluctance [13–16].

Most existing cost-effectiveness analysis models for CRC screening assume perfect adherence for all screening modalities and estimate the health economics impact within the US health systems, which is unrealistic and does not reflect real-world clinical practices [17]. The National Health Information Survey (NHIS) estimated that over 59% of adults are not up to date with their CRC screening, representing over 45 million Americans [18]. The impact of adherence on health outcomes of CRC screening has been demonstrated previously [19–21].

To evaluate the effectiveness of Shield versus no screening, one should follow the technical report of USPSTF's guidelines on colorectal cancer screening [2]. Given the variability in tests and procedures, comparing Shield directly to no screening helps focus on its specific benefits and limitations without the complexities of comparing it to other screening methods that have distinct features and costs [17]. Also, screening can prevent and treat colorectal cancer; yet it remains underutilized. The USPSTF highlights the importance of screening and the need to boost uptake regardless of screening approach by contrasting screening with no screening.

In this study, we evaluated the effectiveness and cost-effectiveness of FDA-approved blood-based CRC screening test (Shield [Guardant Health, Inc]) while implementing real-world adherence.

2. Methods

We performed a cost-effectiveness analysis using the validated CAN-SCREEN (Colorectal cANcer SCReening Economics and adherENce) model which utilizes real-world adherence scenarios to evaluate various CRC screening strategies per screened

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individual for ages 45–75, tracking them until death from CRC or other causes [20]. The model was constructed using Arena Version 16.20 by Rockwell Automation Technologies, Inc., integrated with Microsoft Excel.

2.1. Decision model

The details of CAN-SCREEN and the validation against the results with those from existing published models including those used to support USPSTF recommendations have been detailed in previous publication [20]. In brief, the CAN-SCREEN discrete-event simulation model compares the performance of various CRC screening methods against no screening. The simulation runs 4,000 trials for each cohort of 10,000 individuals, assessing outcomes such as life-years gained, number of colonoscopies, etc. The model's natural history component includes six health states: no lesion, non-advanced adenoma, advanced adenoma, asymptomatic CRC, symptomatic CRC, and death (Figure 1). It uses established parameters for adenoma initiation, growth, and transition to cancer stages, with age and sex influencing mortality rates. The longitudinal adherence component of the model assumes that individuals who adhere to screening in the first year will maintain the same adherence rate in subsequent screenings, while non-adherent individuals are offered screening annually with a gradually declining adherence rate. The model also presents results for full adherence model as part of a validation analysis.

2.2. Screening modalities

The cost-effectiveness analysis study assessed Shield, a blood-based test, administered every 3 years compared to no screening. Key clinical parameters and Shield test performance are summarized in Table 1. Individuals who tested positive on Shield underwent a follow-up diagnostic colonoscopy. Those with a false-positive result resumed their original screening schedule and modality 10 years after a negative follow-up diagnostic colonoscopy. Individuals with detected and removed adenomas were assumed to follow colonoscopy surveillance according to current US recommendations.

2.3. Cost data

Table 1 contains the cost assumptions used in this study. The study utilized the manufacturer's reported test cost of $1,495 to assess the cost-effectiveness of the Shield screening assay. Individuals who received positive results from Shield and those who had symptom-detected colorectal cancer incurred expenses for diagnostic colonoscopy. The medical costs for CRC were categorized into three clinically significant periods. The study examined the medical costs incurred within the first year after diagnosis. The mortality costs specifically considered the medical expenses in the last year of life for CRC patients who died from CRC, excluding those who died from other causes. The continuing care costs encompassed the care received throughout the intervening months. Finally, the study also included medical costs associated with colonoscopy complications which included serious gastrointestinal events such as gastrointestinal bleeding and perforation.

2.4. Cost-effectiveness analysis

Costs associated with screening, screening-related complications, and stage-specific CRC care were calculated from the perspective of the healthcare sector, encompassing both commercially reimbursed expenses and out-of-pocket payments. Costs were inflated to 2023 US dollars using the personal healthcare deflator price index [30]. The lifetime costs and

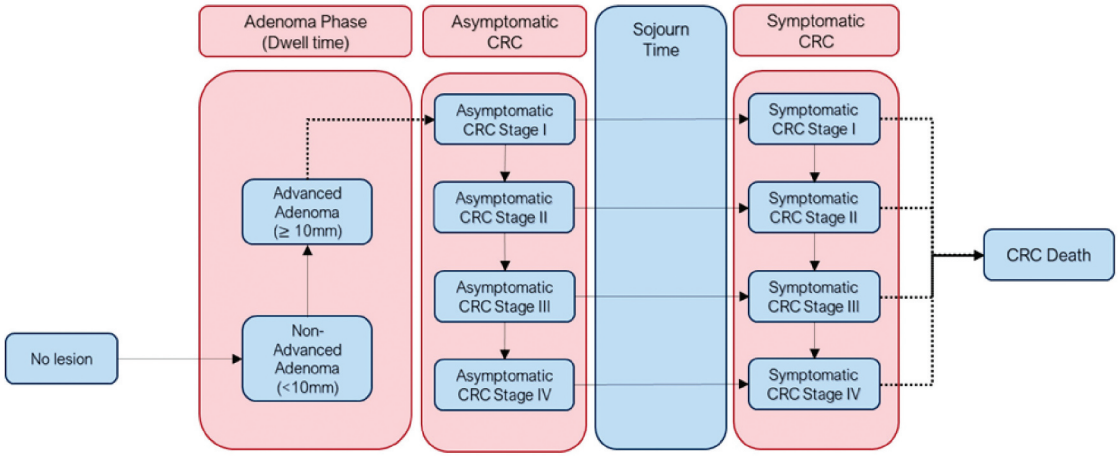

Figure 1. Conceptual model for the underlying natural history component of the CAN-SCREEN model (no screening arm).

Abbreviations: CAN-SCREEN, Colorectal cANcer SCReening Economics and adherence; CRC, colorectal cancer; mm, millimeter.

The natural history component consists of the following processes: 1. Adenoma initiation risk: Nonhomogeneous Poisson process based on age, sex, & tumor location (proximal/distal); 2. Adenoma growth: Continuous growth to 10 mm (advanced adenoma [AA]) that varies by tumor location while AA growth rate calibrated to be consistent with 2021 CISNET dwell times [17]; 3. Transition from AA to asymptomatic CRC: Calibrated logistic regression model dependent on age, sex, tumor location, and tumor size to be consistent with 2021CISNET dwell times [17]; 4. Asymptomatic stage progression: Calibrated rates to be consistent with 2021 CISNET sojourn times [17]; starting values for calibration were based on literature [22,23]; 5. Transition from asymptomatic CRC to symptomatic CRC: Calibrated constant transition rates to be consistent with CRC stage distribution (SEER 1975–1979) and 2021 CISNET sojourn times while the starting values for calibration used transition probabilities from literature [17]; 6. Symptomatic stage progression: Calibrated constant transition rate that increases by stage based on literature [23]; 7. CRC Death: Constant transition rate increasing by stage adjusted based on observed trends [24]. Model also allows for competing risks of background and screening (colonoscopy) related mortality.

Table 1. Test performance characteristics and cost assumptions used in this study.

Input Parameters	Value(s)	Standard Error	Reference
Adherence to Shield, %	90	3.00[a]	Assumption
Adherence to diagnostic colonoscopy, %	76.2	1.07	Corley et al 2017 [25] Jensen et al 2016 [26]
CRC Sensitivity, specificity, %			
Shield	83.00, 90.00	3.00[c], 3.00[c]	Chung et al 2024 [27]
Colonoscopy	91.00, 86.75	1.63[b], 3.47[b]	van den Puttelaar et al 2024 [11]
FIT	73.80, 96.40	5.36[b], 1.86[b]	van den Puttelaar et al 2024 [11]
mtsDNA	94.00, 91.00	3.32[b], 3.03[b]	van den Puttelaar et al 2024 [11]
AA Sensitivity, %			
Shield	13.0	2.00[c]	Chung et al 2024 [27]
Colonoscopy	91.0	3.06[b]	van den Puttelaar et al 2024 [11]
FIT	23.8	1.58[b]	van den Puttelaar et al 2024 [11]
mtsDNA	42.0	1.91[b]	van den Puttelaar et al 2024 [11]
Non-AA Sensitivity, %			
Shield	11.0	2.00[c]	Chung et al 2024 [27]
Colonoscopy	81.0	2.30[b]	van den Puttelaar et al 2024 [11]
FIT	7.6	0.48[b]	van den Puttelaar et al 2024 [11]
mtsDNA	15.0	0.69[b]	van den Puttelaar et al 2024 [11]
Screening testing interval, years			
Shield	3	-	Assumption
Colonoscopy	10	-	Knudsen et al 2016 [28]
FIT	1	-	Knudsen et al 2016 [28]
mtsDNA	3	-	Knudsen et al 2016 [28]
Test costs			
Colonoscopy	$1,980.00[d]		van den Puttelaar et al 2024 [11]
Colonoscopy + polypectomy	$3,486.07[d]		Assumption
FIT	$25.53[e]		van den Puttelaar et al 2024 [11]
Shield	$675.00[e], $1,495.00[d]		van den Puttelaar et al 2024 [11], GH Internal Data
mtsDNA	$550.00[e]		van den Puttelaar et al 2024 [11]
CRC Medical costs in first year[d]			
Stage I	$58,236.00		van den Puttelaar et al 2024 [11]
Stage II	$82,582.00		van den Puttelaar et al 2024 [11]
Stage III	$119,984.00		van den Puttelaar et al 2024 [11]
Stage IV	$178,295.00		van den Puttelaar et al 2024 [11]
CRC Medical costs in years between the first year and last year of life[d]			
Stage I	$5,993.00		van den Puttelaar et al 2024 [11]
Stage II	$6,969.00		van den Puttelaar et al 2024 [11]
Stage III	$10,783.00		van den Puttelaar et al 2024 [11]
Stage IV	$51,116.00		van den Puttelaar et al 2024 [11]
CRC Mortality costs[d]			
Stage I	$117,524.00		van den Puttelaar et al 2024 [11]
Stage II	$132,478.00		van den Puttelaar et al 2024 [11]
Stage III	$138,695.00		van den Puttelaar et al 2024 [11]
Stage IV	$174,407.00		van den Puttelaar et al 2024 [11]
Colonoscopy Complication Costs			
GI Bleeding	$50,558.28		HCUPNet [29]
Perforation	$129,038.61		HCUPNet [29]

Abbreviations: AA, advanced adenoma; CRC, colorectal cancer; FIT, fecal immunochemical test; GI, gastrointestinal; mtsDNA, multitarget stool DNA; PCRC, pre-clinical CRC.

Notes.

a) Not varied in full adherence model – assumed binomial distribution in longitudinal model.

b) Calculated by assuming a binomial distribution with 100 sample size and using this formula.

c) Assumption.

d) Costs inflation adjusted to 2023 dollars [30].

e) Test costs at 2021 dollars reported at a recent analysis from CISNET performed for the American Gastroenterological Association (AGA). These test costs are used for model validation of our ICER results derived from the full adherence CAN-SCREEN model.

quality-adjusted life-years (QALYs) were projected by the CAN-SCREEN longitudinal adherence model, applying a 3% annual discount rate.

We used the incremental cost-effectiveness ratio (ICER) to compare the cost per QALY gained. Shield was considered cost-effective if the ICER was below the US willingness-to-pay thresholds of $100,000 per QALY gained. Value-based pricing analysis was conducted to determine the maximum unit test cost at which Shield could be deemed cost-effective compared to no screening at $100,000 and $150,000 per QALY gained.

2.5. Model validation

We validated the model by comparing our ICER results derived from the full adherence model with a recent analysis from CISNET performed for the American Gastroenterological Association (AGA) [11], using costs associated with screening, screening-related complications, and stage-specific CRC care in 2021 US dollars. For the validation analysis, we used a cohort of 10,000 simulated individuals (with 4,000 replications) that began screening at 45.

2.6. Sensitivity analyses

We performed a sensitivity analysis to assess the impact of reducing follow-up diagnostic colonoscopy adherence from 76.2% to 56.1% for Shield based on an alternative literature [31]. We also conducted an additional sensitivity analysis to evaluate the outcomes when Shield was performed at a 1-year interval compared to the standard 3-year interval. The 1-year interval analysis was included to explore the potential benefits of more frequent testing on health outcomes and cost-effectiveness.

3. Results

3.1. Results from model validation using the full adherence model

Our model produces estimates for ICER that fall within the range of a recent analysis from CISNET performed for the AGA [11] (Table 2).

3.2. Longitudinal adherence model

Without screening, our model predicted that 1,000 individuals aged 45 lived an average of 15.269 QALYs and incurred approximately $6.3 thousand in CRC treatment costs (Table 3). Among these individuals, 71 would be diagnosed with CRC, and 29 would die from it. Shield with screening every 3 years showed a significant reduction in CRC cases and deaths compared to no screening: Shield averted 27 cases (when adjusting for decimal precision) and 13 deaths per 1,000. The number of lifetime colonoscopies required per 1,000 individuals was 1,053 and the number of noninvasive tests per 1,000 individuals was 5,140 over a lifetime.

Compared to no screening, Shield increased the number of QALYs by 154 per 1,000 individuals and raised costs by 7.5 million per 1,000. With an incremental cost of $48,662 per QALY gained, Shield was found to be cost-effective relative to no screening at $100,000 cost per QALY willingness-to-pay threshold. Furthermore, at a Shield unit cost of $3,241, the intervention results in a cost of $15,360 per person compared to no screening, yielding $100,000 per QALY gained. Similarly, with a unit cost of $4,942, the cost per person increases to $23,040 corresponding to $150,000 per QALY gained. This indicates that the unit cost of Shield can be as high as $3,241 and $4,942 to remain cost-effective at thresholds of $100,000 and $150,000 per QALY gained, respectively, while maintaining a consistent QALY gain of 0.1536 per person.

3.3. Sensitivity analyses

As shown in Table 4, reducing the adherence to diagnostic colonoscopy assumption from 76.2% to 56.1% did not provide a significant change in ICER of Shield when compared to no screening ($48,662/QALY vs $48,982/QALY, respectively). Also, Shield performed at 1-year interval had an incremental cost of $82,405 per QALY compared to no screening which is still cost-effective at thresholds of $100,000 and $150,000 per QALY gained.

4. Discussions

In this study, we compared the outcomes of Shield screening every 3 years against no screening using CAN-SCREEN model

Table 4. Sensitivity analyses of shield screening - impact of reduced diagnostic colonoscopy adherence and alternative screening intervals using longitudinal adherence CAN-SCREEN model.

Scenario	QALYs/ Person	Cost ($)/Person	Cost ($)/QALY Gained vs No screening
Diagnostic Colonoscopy Adherence			
76.2%	0.1536	$7,474.54	$48,661.85
56.1%	0.1509	$7,390.97	$48,982.21
Shield Screening Interval			
Triennial	0.1536	$7,474.54	$48,661.85
Annual	0.1700	$14,006.18	$82,405.39

Abbreviations: CAN-SCREEN, Colorectal cANcer SCReening Economics and adherence; CRC, colorectal cancer; QALY, quality-adjusted life-years.

Table 2. Validation of ICER results from the full adherence CAN-SCREEN model under the no-screening scenario, compared to the CISNET full adherence model analysis performed for the AGA (in 2021 USD).

Screening Modality	Screening Test Commercial Cost (2021 USD)	CAN-SCREEN Cost ($)/QALY Gained vs No screening	CISNET AGA Cost ($)/ QALY Gained vs No screening
FIT	$25.53	5,311	Dominating
mtsDNA	$550	17,656	6,200–22,000
CMS min BBT	$675	30,441	25,600–43,700
Shield	$675	29,476	22,200–41,000

Abbreviations: AGA, American Gastroenterological Association; BBT, blood-based test; CAN-SCREEN, Colorectal cANcer SCReening Economics and adherence; CISNET, Cancer Intervention and Surveillance Modeling Network; CMS, Centers for Medicare & Medicaid Services; FIT, fecal immunochemical test; mtsDNA, multitarget stool DNA; QALY, quality-adjusted life-years.

Table 3. Clinical and economic outcomes per 1,000 simulated patients using longitudinal adherence CAN-SCREEN model.

Intervention	Number of Tests	Number of Colonoscopies	CRC Cases	CRC Deaths	Life-Years	QALYs/ Person	Cost ($)/Person	Cost ($)/QALY Gained vs No screening
No screening	-	-	71	29	21024	15.269	$6,312.18	-
Shield	5140	1053	45	16	21192	15.423	$13,786.72	$48,662

Abbreviations: CAN-SCREEN, Colorectal cANcer SCReening Economics and adherence; CRC, colorectal cancer; QALY, quality-adjusted life-years.

and found that Shield significantly improved health outcomes and was cost-effective. To the best of our knowledge, CANSCREEN is the first simulation model for CRC screening that integrates longitudinal adherence and the test cost of $1,495 as reported by the manufacturer to evaluate the Shield screening assay.

Screening with Shield-reduced CRC incidence by 27 cases and prevented 13 CRC-related deaths per 1,000 individuals while also increasing QALYs by 154 per 1,000 individuals. Although the intervention raised healthcare costs by $7.5 million per 1,000 individuals, it resulted in a favorable incremental cost-effectiveness ratio of $48,662 per QALY gained, which is well within the commonly accepted cost-effectiveness threshold of $100,000/QALY [32]. Additionally, the cost-effectiveness of Shield remained robust even with lower adherence to follow-up colonoscopies, and annual screening also proved economically viable. Additionally, our analysis showed that Shield would still be cost-effective compared to no screening even if its price were as high as $3,241 per test at a $100,000 per QALY threshold. If the willingness-to-pay threshold is increased to $150,000 per QALY, the value-based price could go up to $4,942, indicating that Shield remains an acceptable value under different pricing conditions. These results underscore Shield as an effective and cost-efficient strategy for CRC prevention when compared to no screening.

While our study highlights the critical role of incorporating imperfect longitudinal adherence into simulation models, it remains essential to include scenarios with full adherence for comparative purposes across studies. Using the cost and test parameters published by van den Puttelaar et al., we performed an analysis and found that the ICER values from CANSCREEN are consistent with those produced by CISNET in previous AGA evaluations, even with the implausible assumption of complete adherence [11]. In particular, van den Puttelaar et al. evaluated the cost-effectiveness of triennial blood-based screening from ages 45 to 75 compared to no screening using three microsimulation models for colorectal cancer (MISCAN-Colon, CRC-SPIN, and SimCRC). For this study, the performance parameters of the hypothetical blood test were determined using Shield and CMS coverage criteria, at a commercial cost of $675 (2021 USD). The study indicated that a blood-based screening test with performance characteristics consistent with CMS coverage standards and Shield is more cost-effective than no screening. However, when compared to FIT, mtsDNA, and colonoscopy screenings, blood-based screening was not deemed cost-effective if full screening participation was assumed. In addition, Ladabaum et al., using the MOSAIC and Shield's recently announced list price of $1,495, found that for people who are determined not to get a screening colonoscopy or stool test, Shield is more cost-effective than not getting screened at all, given a high rate of follow-up after a colonoscopy [33].

Kisiel et al. utilized a validated microsimulation platform and found that triennial CRC screening with a blood-based test showed favorable outcomes when compared to no screening [34]. However, when directly compared to the non-invasive stool-based mtsDNA test, the blood-based screening's clinical and economic impacts were found to be less favorable, with the mtsDNA test demonstrating superior results. It is important to note that their model assumed varying levels of adherence to the blood-based test, starting at the published real-world adherence rate of 65.6% for mtsDNA. Adherence was then increased in relative 10% increments −72.2%, 78.7%, 85.3%, and 91.8%- culminating in a scenario of perfect (100%) adherence. The data informing initial adherence in this study aligns with those used for our longitudinal adherence scenario, which measures the proportion of patients adhering to a screening test within a specific follow-up period (e.g. 1 year). However, Kisiel et al. did not assume that patient participation in subsequent CRC screening rounds for patients who remain non-adherent often decreases over time.

Nascimento De Lima et al. also did not take imperfect adherence into account and assumed full adherence to both primary screening and follow-up colonoscopy across all screening regimens and intervals [35]. They found that administering a $500 blood test every 3 years, meeting CMS coverage criteria, resulted in a gain of 83–116 QALYs at a cost of $8,559–$9,413 per person. However, they concluded that while a triennial blood test meeting CMS's minimum performance criteria may be cost-effective compared to no screening, it is both more expensive and less effective than alternative strategies, such as decennial colonoscopy or annual fecal immunochemical testing (FIT). These findings, however, assume perfect adherence to both primary screening and follow-up procedures, an assumption that does not reflect real-world conditions. Therefore, the study may overestimate the cost-effectiveness and clinical value of existing screening methods such as colonoscopy and FIT while underestimating the potential benefits of a blood test in enhancing overall screening participation and accessibility.

Comparing Shield, a blood-based test, to no screening, is aligned with the methodology outlined in the USPSTF's modeling technical report on colorectal cancer screening [17]. The report highlights the challenge of doing a complete analysis that compares various CRC screening options with each other, mainly due to disparities in the quantities of non-colonoscopy tests and procedural discrepancies. Consequently, various screening methods are categorized into groups based on their common modality-specific properties. Therefore, given Shield's specific advantages and disadvantages as a novel blood-based modality, we similarly compared it with no screening.

In addition, comparing Shield to an unscreened population offers an effective way to enhance screening uptake and outcomes in real-world contexts, given the substantial deficiencies in adherence to current screening methods. This comparison provides valuable insights into Shield's potential to bridge this gap.

While previous research has examined the cost-effectiveness of blood-based screening, a strength of this study is that it considers the impact of longitudinal adherence on the cost-effectiveness of Shield using the manufacturer's market price of $1,495. However, our work has also limitations. Firstly, the study did not consider any potential substitution effect between screening modalities. As also stated by van den Puttelaar et al., if the possibility of using blood-based screening only as a substitute for other

methods and not increase overall population screening, it will have an impact on the current level of efficacy of the screening process [11]. Secondly, although being predicted to possibly account for up to 30% of instances of colorectal cancer, the CAN-SCREEEN model, like most models in the literature, ignores the serrated polyp route in the adenoma-carcinoma sequence due to a lack of published data and understanding of its natural history. Thirdly, the current lifetime risk of having CRC in the absence of screening in the US is uncertain, considering the increasing occurrence of CRC among younger persons [24]. Although our model's dwell time results align with those from CISNET, they may not fully capture the magnitude of this concerning phenomena.

5. Conclusions

Despite the availability of multiple CRC screening modalities, there remains a significant unmet need, with approximately one-third of the US population not being up to date with their CRC screenings [36]. Shield, a validated cost-effective blood-based CRC test, represents a promising new modality that aims to address this gap by maximizing adherence. Its non-invasive nature is likely to increase patient preference and participation.

Declaration of interest

E Yay Donderici, S Forbes, N Zhang, G Schafer, V Raymond, A Das, C Eagle, and AA Talasaz are employees of, and have stock ownership in, Guardant Health, Inc. WM Grady is a paid consultant for Guardant Health, Inc., Karius, Inc., and Diacarta, Inc. and receives research support from LucidDx Technologies. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Author contributions

E Yay Donderici, S Forbes, N Zhang, V Raymond and A Das were involved in the conception and design. All authors were involved in the interpretation of the data. E Yay Donderici drafted the manuscript. All authors revised it critically for intellectual content. Lastly, all authors read and gave approval of the final manuscript and agree to be accountable for all aspects of the work.

Data availability statement

The authors confirm that the data supporting the findings of this study are provided within the article itself and in the supplementary material of a prior study, reference [20].

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