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ORIGINAL ARTICLE

Estimate of Increase in Colorectal Cancer Diagnoses with Expansion of Fecal Immunochemical Testing in an Urban Safety-Net Population

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Abstract

Background Fecal immunochemical test (FIT) is less effective in detecting advanced adenomas (AA) than colonoscopy. Increase in FIT for colorectal cancer (CRC) screening may lead to an increased number of undetected AAs which may develop into future CRCs.

Aim We determined the potential impact of FIT expansion on missed AAs and future CRC diagnoses in an urban, tertiary-care, safety-net hospital.

Methods CRC and AA diagnoses were identified in patients undergoing colonoscopy for average-risk CRC screening or positive FIT between 2017 and 2019 at Boston Medical Center. Poisson regression modeling was used to estimate the frequency of AAs per year by age group using data from 2017 to 2019, assuming average outpatient volume and proportion of screening colonoscopies. Total number of patients who received FIT was extrapolated from those who underwent colonoscopy for positive FIT. We estimated AAs per year if 'one-time' FIT was used for screening in 75% and 100% of the population and subtracted this from the estimated AAs per year under the Poisson model to determine missed AAs. We used previously described, age and gender specific estimates of the annual progression of AA to CRC.

Results The estimated number of CRCs detected per year is 4.6/1785 males and 4.6/2086 females screened. With 75% FIT expansion, we estimate an additional 3.5 (95% CI 1.3, 9.5) and 2.2 (95% CI 0.64, 7.6) CRCs; with 100% FIT expansion, we estimate an additional 7.4 (95% CI 3.7, 14.9) and 4.2 (95% CI 1.7, 10.5) CRCs, in 5 years, in males and females, respectively.

Conclusion Expansion of FIT may substantially increase CRC incidence.

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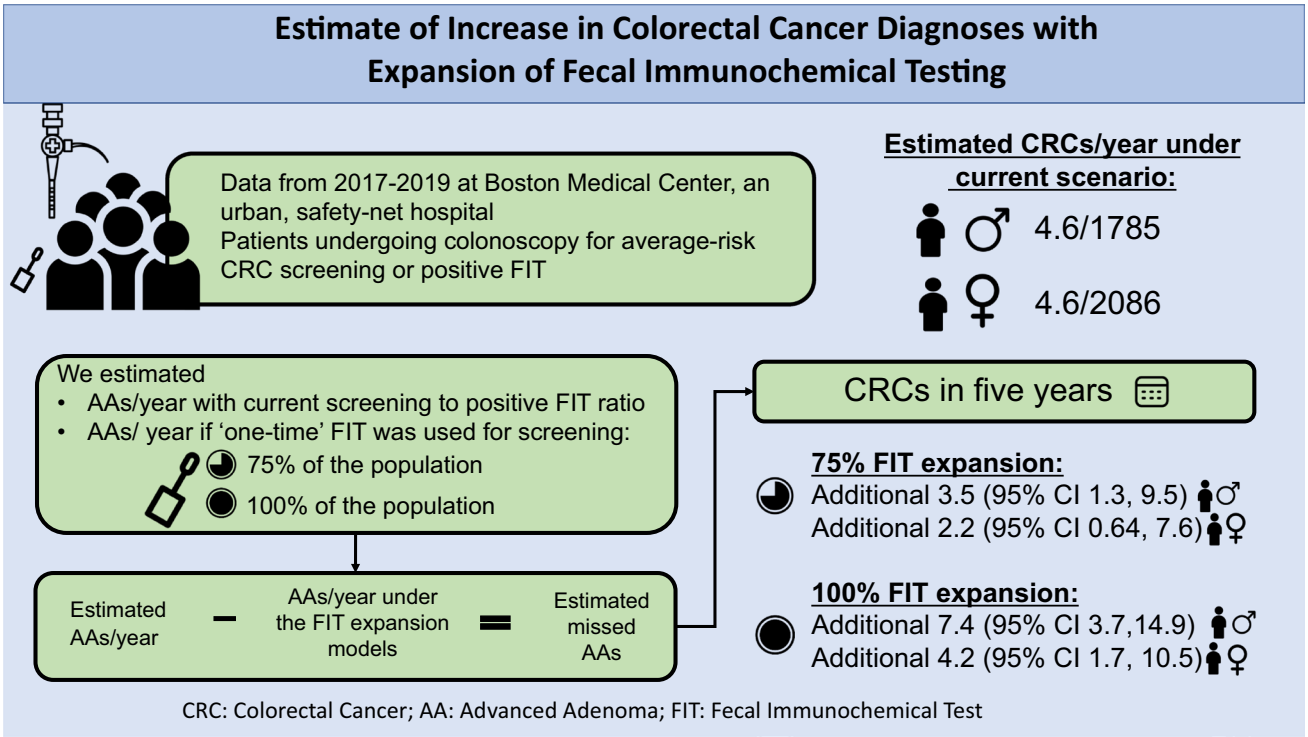
Graphical Abstract



Keywords Colorectal cancer screening · Fecal immunochemical test · Advanced adenoma · Prediction model · Screening

Abbreviations

FIT	Fecal immunochemical test
AA	Advanced adenoma
CRC	Colorectal cancer

Colorectal cancer (CRC) is the third leading cause of cancer in the United States [1]. Screening for CRC is effective in preventing cancer deaths as it can lead to detection of early-stage, potentially curable CRC [2, 3]. Colonoscopy and fecal immunochemical testing (FIT) are recommended methods for screening [3, 4]. In addition to CRC detection, colonoscopy serves as a colon cancer prevention test by detection and removal of advanced adenomas (AAs), which are precursors to CRC. In contrast, FIT has good performance for detection of CRCs but not detection of AAs [5]. The estimated sensitivity of AA detection by FIT ranges is approximately 20–30% [4].

While colonoscopy is the gold standard for CRC screening and prevention in the US, use of non-invasive tests like FIT play an important role in expanding CRC screening. This is particularly true in the wake of the COVID-19 pandemic, which led to temporary cessation of outpatient colonoscopy procedures and widespread disruption in CRC screening and diagnoses [6–9]. To mitigate this disruption, many centers actively expanded access to FIT as primary CRC screening [10]. At our center, FIT has been routinely offered to expand colorectal screening even prior to the COVID-19 pandemic, in part to offset capacity constraints for screening colonoscopy.

As FIT is less effective in detecting AAs, increased FIT administration may lead to an increased number of undetected AAs which may develop into CRCs in the future, thereby paradoxically increasing CRC diagnoses. We determined the potential impact of FIT expansion on missed AAs and future CRC diagnoses in the patient population in an urban, tertiary-care, safety-net hospital.

Methods

Data Source and Study Inclusion/Exclusion Criteria

We created a database of outpatient colonoscopies performed at Boston Medical Center, Boston, MA from 2017 to 2019 by combining data from reimbursement records (Visiquate Inc, Santa Rosa, CA), endoscopy procedural data (Provation, Minneapolis, MN), and pathology reports

[11]. We first used Current Procedural Terminology (CPT) codes recorded for reimbursement to exclude colonoscopies of decompression, hemorrhoidal band ligation, endoscopic ultrasound, stent placement, balloon dilation, or foreign body removal. The complete list of included and excluded CPT codes is provided in Supplementary Table 1. We merged this dataset with indications for colonoscopy as reported in Provation. Colonoscopies performed for indications of average-risk CRC screening or positive FIT were included in this study. The demographics of patients between 45 and 79 years attending primary care is shown in supplementary Table 2.

We identified AAs and CRCs by combining data on polyp size from Provation and polyp histology from pathology reports. AA was defined as an adenoma ≥ 10 mm in size, adenoma with tubulovillous/villous histology, adenoma with high-grade dysplasia, per the recommendations of the US Multi-Society Task Force (USMSTF) on Colorectal Cancer [12]. We used reporting systems within Provation to determine individuals who had polyps ≥ 10 mm. Using a natural language search we identified pathology reports with the key words of "tubulovillous," "villous," "dysplasia," "dysplastic," "carcinoma," "cancer," "adenocarcinoma," and "high-grade" to identify individuals with AA or CRC. These terms were chosen as they are pre-selected by consensus by our pathology colleagues for standardized reporting of colon pathology at our institution. Each pathology record with the above words was reviewed by one of the authors to exclude pathology that did not meet AA criteria. (For example, those that said "negative for adenocarcinoma").

To validate our database creation strategy and the accuracy of AA and CRCs diagnoses, we reviewed charts of all individuals who underwent colonoscopy for the first 2 months of 2017–2019. Our strategy correctly identified AA vs 'not AA' 99.5% of the time and CRC at all times. Finally, as the rate of adenoma to carcinoma progression has been described in individuals > 55 years old, and we had very few individuals > 80 years old, we restricted the analysis to individuals between the ages of 55 and 80 [13].

Statistical Analysis

Expected Number of Yearly Colonoscopies and CRC Screening Tests

The expected number of colonoscopies performed per year by age and indication was determined by averaging the data from 2017 to 2019. We determined the expected number of individuals undergoing CRC screening per year by adding the expected number of colonoscopies performed for CRC screening and the expected number of FIT tests performed per year. To determine the expected number of FIT tests performed per year, we assumed that 7% of individuals undergoing FIT have a positive test result [5], and all FIT-positive individuals are linked to a subsequent colonoscopy. Our center has a robust FIT program, which utilizes patient navigators to ensure return of FIT and linkage of positive FIT to colonoscopy. In the study period, 88.5% individuals with positive FIT either received a colonoscopy or had a documented reason for not receiving one through our center (including external colonoscopy or patient declined).

Estimation of Expected Number of AAs Detected per Year by Age and Gender

AA rate varies by age and gender and is higher in males and with increasing age [14]. We stratified our population by gender and previously described age groups (55–59 years, 60–64 years, 65–69 years, 70–74 years, and 75–79 years) [13]. We used Poisson regression modeling to estimate the frequency of AAs per year by age group using data from 2017 to 2019, assuming average outpatient volume and proportion of screening colonoscopies.

Estimation of Missed AAs with FIT Expansion

As the current estimated use of FIT as the primary method for CRC screening at our center is ~ 50%, we created two models with FIT expansion to 75% and 100% of the population > 55 years old eligible for CRC screening. We assumed that the expected number of individuals undergoing CRC screening tests per year is constant. We estimated AAs detected in these two models using age- and gender-specific AA detection rates in individuals undergoing screening colonoscopies and colonoscopies for positive FIT. The calculations of AA detection for positive FIT are based on the reported performance of single-application FIT. (The effect of serial annual FIT over 5 years on AA detection rate has not been reported). To estimate the number of missed AAs, we subtracted the estimated AAs detected per year under the FIT expansion models from the estimated AAs detected per year under the Poisson model.

Estimate of Progression of Missed AAs to CRC with Expanded FIT Strategy in Population > 55 Years of Age

We used age and gender specific estimates of the annual progression of AA to CRC as previously determined by Brenner et al. [13]. We calculated the cumulative risk of developing CRC in 5 years in each age and gender specific group as 1 − exp (5*rate of annual progression), conditional on not dying from other causes [13]. We multiplied the cumulative risk of developing CRC in 5 years to the age and gender specific missed adenomas estimate to determine predicted new CRCs in 5 years. The 95% confidence interval was calculated by the formula $\hat{p} = \hat{p} + 1.96$ sq rt $[(\hat{p}*(1-\hat{p})/n]$ where

$\hat{p}$ is the point estimate and n is the total number of persons screened.

Statistical analysis was performed using Excel 365 (Redmond, WA) and SAS (version 9.4, Cary, NC).

Results

Baseline Characteristics

We identified 6018 colonoscopies performed in the age group 55–80 years, for CRC screening and follow up for positive FIT between 2017 and 2019. Of these, we estimated that 414 (7%) were performed for follow up of positive FIT. During this period, 4257 (41%) colonoscopies were also performed for the same indications in individuals between the age of 45 and 55 years; these were not included in the analyses. Of these, 97% individuals were between 50 and 55 years. In the study period, colonoscopies were not recommended in CRC screening guidelines for individuals between the age of 45 and 49. We noted that 'screening for CRC' was the referring indication or listed as an indication by the endoscopist for many individuals in this age group, when they had a normal colonoscopy for a symptomatic indication such as hematochezia as in practice this would serve as the first colonoscopy for CRC screening. Table 1 shows the AA detection rate by age, gender, and indication.

Expected Number of Yearly Colonoscopies and FIT Tests

Table 2 shows the expected number of colonoscopies per year by indication, expected number of FIT tests per year, and the expected number of individuals undergoing CRC screening by gender. Based on data from 2017 to 2019, it is estimated that 1785 males and 2086 females will undergo screening for CRC per year. If there is no expansion of FIT testing beyond baseline levels, an estimated 946 males (53%) and 1059 (51%) females will undergo FIT testing. This is lines with the current practice at our center, where FIT is offered as the first line CRC screening test in addition colonoscopy to eligible patients attending primary care clinics. Our FIT program has patient navigators to ensure return of FIT and linkage of positive FIT to colonoscopy. Other CRC screening tests like CT colonoscopy, flexible sigmoidoscopy and multitarget DNA tests are rarely used.

Estimated AA Detection and Missed AAs in FIT Expansion Models

Table 3 shows an estimate of AAs detected and missed, by gender, if FIT testing is expanded to 75% and 100% of the eligible population. With 75% FIT expansion, there would be 21 and 14 missed AAs in males and females, respectively, which is equivalent to one missed AA each for every 85 males and every 153 females screened. With 100% FIT expansion, there would be 46 and 29 missed

Table 1 Number of colonoscopies performed between 2017 and 2019 for CRC screening and positive FIT, advanced adenomas detected, and advanced adenoma detection rate by age, gender, and indication

Age group	Screening for CRC			Positive FIT		
	Colonoscopies	Advanced adenomas detected	Advanced adenoma detection rate	Colonoscopies	Advanced adenomas detected	Advanced adenoma detection rate
Males						
55–59	841	52	6.2	55	15	27.3
60–64	845	53	6.3	60	20	33.3
65–69	512	52	10.2	35	9	25.7
70–74	226	25	11.1	32	5	15.6
75–79	94	6	6.4	13	7	53.8
Total	2518	188	7.5	195	56	28.7
Females						
55–59	922	27	2.9	53	11	20.8
60–64	1082	40	3.7	56	7	12.5
65–69	636	33	5.2	49	3	6.1
70–74	347	14	4.0	38	5	13.2
75–79	99	2	2.0	23	2	8.7
Total	3086	116	3.8	219	28	12.8

CRC colorectal cancer, *FIT* fecal immunochemical test

Table 2 Expected number of colonoscopies per year (by indication), expected number of FIT tests per year and the expected number of persons undergoing CRC screening, by gender

Age group	No. of colonoscopies per year	Proportion of screening colonoscopies to colonoscopies for positive FIT	Expected screening colonoscopies per year	Expected colonoscopies for positive FIT per year	FIT + rate[a]	Expected no. of FIT tests per year	Expected no. of persons undergoing CRC screening per year[b]
Males							
55–59	299	0.94	281	18	7.0%	256	537
60–64	302	0.93	281	21	7.0%	302	583
65–69	182	0.94	171	11	7.0%	156	327
70–74	86	0.87	75	11	7.0%	160	235
75–79	36	0.86	31	5	7.0%	72	103
Total	905		839	66		946	1785
Females							
55–59	325	0.94	306	20	7.0%	279	584
60–64	379	0.95	360	19	7.0%	271	631
65–69	228	0.93	212	16	7.0%	228	440
70–74	128	0.91	116	12	7.0%	165	281
75–79	41	0.8	33	8	7.0%	117	150
Total	1101		1027	74		1059	2086

FIT fecal immunochemical test; *CRC* colorectal cancer

[a]FIT + rate is based on prior literature and was used to estimate expected number of individuals undergoing FIT test per year [5]

[b]Expected number of individuals undergoing CRC screening per year was determined by adding expected number of screening colonoscopies and FIT tests per year

AAs in males and females, respectively, equivalent to one missed AA each for every 39 males and 72 females screened.

Expected Number of CRCs in 5 Years Due to Progression of Missed AAs with FIT Expansion

Table 4 shows estimates of the number of additional CRCs that would be detected in 5 years using previously calculated AA to CRC transition rates for age group and gender. With 75% FIT expansion, we estimate an additional 3.5 (95% CI 1.3, 9.5) and 2.2 (95% CI 0.64, 7.6) CRCs in 5 years in males and females, respectively, which is equivalent to one additional CRC diagnosis in 5 years for every 510 males and 948 females screened. With FIT expansion to 100%, we estimate an additional 7.4 (95% CI 3 0.7, 14.9) and 4.2 (95% CI 1.7, 10.5) CRCs in 5 years in males and females, respectively, which is equivalent to one additional CRC diagnosis in 5 years for every 241 males and 497 females screened. These CRC diagnoses are in addition the estimated number of CRCs detected in our population per year without FIT expansion (4.6 out of 1785 males and 4.6 out of 2086 females screened).

Discussion

FIT is a non-invasive, inexpensive, easy to administer and well-accepted stool recommended and widely used for CRC screening. It has excellent performance in CRC detection but not in detection of AAs [5]. Expansion of 'one-time' (and not serial) FIT, to replace colonoscopy as the modality for CRC screening, in theory, will lead to missed AAs which can progress to CRCs. Conversely, expansion of FIT can also lead to increase in CRC screening uptake and thus improvement of CRC outcomes [4, 13]. Understanding this tradeoff is important in designing CRC screening programs. In this observational study, we estimate the number of missed AAs and potential increase in number of CRCs in 5 years, in our patient population, assuming the screening population is relatively constant every year. We also estimate the number of missed AAs and the potential increase in the number of CRCs in 5 years, in our patient population.

Our results suggest that expansion of 'one-time' FIT may substantially increase the CRC incidence. If all 3871 individuals eligible for CRC screening receive FIT (100% expansion), we estimated 2–3 times higher number of

Table 3 Estimate of AAs detected and missed, by gender, if FIT testing is expanded to 75% and 100% of the eligible population

Males											
FIT expansion to 75%											
Age group	Individuals undergoing CRC screening per year[a]	Individuals undergoing FIT test per year	Expected number of individuals that are FIT + [b]	Average AA detection rate in FIT + individuals[c]	Expected number of AAs in FIT + individuals	Individuals undergoing screening colonoscopies per year	Average AA detection rate in individuals undergoing screening colonoscopies	Expected number of AAs in individuals undergoing screening colonoscopies	Total expected number of AAs[d]	Expected number of AAs without FIT expansion[e]	Missed AAs[f]
55–59	537	403	28	28.7	8.1	134	7.5	10.1	18.2	22.2	4.1
60–64	583	437	31	28.7	8.8	146	7.5	10.9	19.7	24.5	4.8
65–69	327	245	17	28.7	4.9	82	7.5	6.1	11.1	20.1	9.0
70–74	235	176	12	28.7	3.5	59	7.5	4.4	7.9	10.1	2.2
75–79	103	77	5	28.7	1.6	26	7.5	1.9	3.5	4.5	1.1
Total	1785	1339	94		26.9	446		33.5	60.4	81.5	21.1
FIT expansion to 100%											
Age group	Individuals undergoing CRC screening per year[a]	Individuals undergoing FIT test per year	Expected number of individuals that are FIT + [b]	Average AA detection rate in FIT + individuals[c]	Expected number of AAs in FIT + individuals	Individuals undergoing screening colonoscopies per year	Average AA detection rate in individuals undergoing screening colonoscopies	Expected number of AAs in individuals undergoing screening colonoscopies	Total expected number of AAs[d]	Expected number of AAs without FIT expansion[e]	Missed AAs[f]
55–59	537	537	38	28.7	10.8	0	7.5	–	10.8	22.2	11.4
60–64	583	583	41	28.7	11.7	0	7.5	–	11.7	24.5	12.8
65–69	327	327	23	28.7	6.6	0	7.5	–	6.6	20.1	13.5
70–74	235	235	16	28.7	4.7	0	7.5	–	4.7	10.1	5.4
75–79	103	103	7	28.7	2.1	0	7.5	–	2.1	4.5	2.5
Total	1785	1785	125		35.9	0		–	35.9	81.5	45.6
Females											
FIT expansion to 75%											
Age group	Individuals undergoing CRC screening per year[a]	Individuals undergoing FIT test per year	Expected number of individuals that are FIT + [b]	Average AA detection rate in FIT + individuals[c]	Expected number of AAs in FIT + individuals	Individuals undergoing screening colonoscopies per year	Average AA detection rate in individuals undergoing screening colonoscopies	Expected number of AAs in individuals undergoing screening colonoscopies	Total expected number of AAs[d]	Expected number of AAs without FIT expansion[e]	Missed AAs[f]
55–59	584	438	31	12.8	3.9	146	3.8	5.5	9.5	13.2	3.8

Table 3 (continued)

Females

FIT expansion to 75%

Age group	Individuals undergoing CRC screening per year[a]	Individuals undergoing FIT test per year	Expected number of individuals that are FIT + [b]	Average AA detection rate in FIT + individuals[c]	Expected number of AAs in FIT + individuals	Individuals undergoing screening colonoscopies per year	Average AA detection rate in individuals undergoing screening colonoscopies	Expected number of AAs in individuals undergoing screening colonoscopies	Total expected number of AAs[d]	Expected number of AAs without FIT expansion[e]	Missed AAs[f]
60–64	631	473	33	12.8	4.2	158	3.8	6.0	10.2	15.6	5.3
65–69	440	330	23	12.8	3.0	110	3.8	4.2	7.1	11.7	4.6
70–74	281	211	15	12.8	1.9	70	3.8	2.7	4.6	5.7	1.2
75–79	150	112	8	12.8	1.0	37	3.8	1.4	2.4	1.3	−1.2
Total	2086	1564	110		14.0	521		19.8	33.8	47.5	13.6

FIT expansion to 100%

Age group	Individuals undergoing CRC screening per year[a]	Individuals undergoing FIT test per year	Expected number of individuals that are FIT + [b]	Average AA detection rate in FIT + individuals[c]	Expected number of AAs in FIT + individuals	Individuals undergoing screening colonoscopies per year	Average AA detection rate in individuals undergoing screening colonoscopies	Expected number of AAs in individuals undergoing screening colonoscopies	Total expected number of AAs[d]	Expected number of AAs without FIT expansion[e]	Missed AAs[f]
55–59	584	584	41	12.8	5.2	0	3.8	–	5.2	13.2	8.0
60–64	631	631	44	12.8	5.7	0	3.8	–	5.7	15.6	9.9
65–69	440	440	31	12.8	3.9	0	3.8	–	3.9	11.7	7.7
70–74	281	281	20	12.8	2.5	0	3.8	–	2.5	5.7	3.2
75–79	150	150	11	12.8	1.3	0	3.8	–	1.3	1.3	−0.1
Total	2086	2086	146		18.7	0		–	18.7	47.5	28.8

[a]This is as per estimates shown in Table 2

[b]This is calculated assuming 7% of FIT tests are positive [5]

[c]This is as per AA detection rates shown in table

[d]This is estimated by adding expected number of AAs in FIT positive individuals and those undering screening colonoscpies

[e]This has been determined by the Poisson model fitted with data from 2017 to 2019

[f]This is the difference between expected AAs detected without FIT expansion and with FIT expansion

Table 4 Estimated annual transition of advanced adenoma and cumulative risk of developing colorectal cancer in 5 years

	Age group	Annual transition to CRC in %[a]	Cumulative risk of developing CRC in 5 years in %	75% FIT expansion		100% FIT expansion	
				Missed AAs	Additional CRCs detected in 5 years	Missed AAs	Additional CRCs detected in 5 years
Males	55–59	2.6	12.2	4.1	0.5	11.4	1.4
	60–64	3.1	14.4	4.8	0.7	12.8	1.8
	65–69	3.8	17.3	9.0	1.6	13.5	2.3
	70–74	5.1	22.5	2.2	0.5	5.4	1.2
	75–79	5.2	22.9	1.1	0.2	2.5	0.6
Total					**3.5**		**7.4**
					(95% CI 1.3,9.5)		(95% CI 3.7,14.9)
Females	55–59	2.5	11.8	3.8	0.4	8.0	0.9
	60–64	2.7	12.6	5.3	0.7	9.9	1.3
	65–69	3.8	17.3	4.6	0.8	7.7	1.3
	70–74	5.0	22.1	1.2	0.3	3.2	0.7
	75–79	5.6	24.4	−1.2	0.0	−0.1	0.0
Total					**2.2**		**4.2**
					(95% CI 0.64,7.6)		(95% CI 1.7,10.5)

AA advanced adenoma, *CRC* colorectal cancer, *FIT* fecal immunohistochemical test

[a]Annual transition rates of AA to CRC have previously been calculated by Brenner et al. [13]

incident CRC per year in 5 years (additional 7.3 CRCs per year for males and 4.6 CRCs per year for females). Given this projected increase in CRC cases, we will need to continue to further adjust and study our approach to CRC screening, particularly if any further decrease in endoscopic capacity occurs.

The results of this study are specific to our patient population, but the methodology used can be applied to other populations to generate population-specific estimates. Our patient population is a relatively younger, urban, mid-size, safety-net population. We estimated that approximately 50% of the population received FIT as the screening modality prior to the COVID-19 pandemic, which is higher than the average proportion of CRC screening in the US [15]. Each center's estimate will depend on the population at risk. We stratified our population by well-defined and well-studies categories of race and gender. However, we were unable to stratify further by race/ethnicity due lack of robust prior data on rates of AA and CRC and due to heterogeneity in report of race/ethnicity in our population.

There is limited evidence to suggest how serial FIT testing may impact the detection of AAs. US guidelines recommend annual FIT testing to improve detection of both AAs and CRC but acknowledge that long-term comparative data to other screening modalities is lacking. Most studies assessing FIT test characteristics were for a one-time test, with the gold-standard comparator being colonoscopy and/or clinical follow-up [4]. Incorporating serial FIT data (was it available) into our models would likely result in at least a modest decrease in our estimates of missed AAs, and subsequently 5-year CRC incidence [16]. Patient adherence to continued yearly FIT testing is inconsistent and ranges widely from 1 to 54% [17], which can also contribute to difficulty in estimating CRC outcomes. To what extent this might be offset by real-world limitations of serial FIT testing including annual compliance and linkage to colonoscopy in a timely manner is unknown.

There are several limitations to our study. Our calculations of AA detection for positive FIT are based on the reported performance of single-application FIT, but the effect of serial annual FIT over 5 years on AA detection rate is not known. We used the age- and gender-specific AA detection rates in our individuals undergoing screening colonoscopy and colonoscopy for positive FIT to determine the estimated number of AAs under each model. While specific to our population, the age- and gender-specific AA rates are like those described by Brenner et al. [13]. Age- and gender-specific AA rates in FIT-positive individuals have not been described. Our pooled AA rates appear to be similar to published gender specific estimates [18, 19]. We restricted our population to those over age 55, as the rate of AA to CRC progression has not been described in the population < 55 years. The estimated number of FIT tests performed per year was extrapolated from the assumption that 7% of individuals undergoing FIT test positive [5], and all FIT-positive individuals are linked to colonoscopy. Failure to include individuals with advanced serrated lesions due to the lack of modeling data on rates of progression

may have resulted in an underestimation of projected cancer cases. Finally, our study focuses on proportions of FIT and colonoscopy for CRC screening but does not consider the newer multitarget stool DNA tests [20] as they are not commonly used at our center.

In summary, our findings highlight that expanding FIT to the majority of the eligible average-risk screening population may result in a substantial number of missed AAs, with risk of progression to additional CRC diagnoses within 5 years if counteractive measures are not taken. Further studies will be necessary to determine the impact of expanded FIT testing on incident CRC, and to identify the optimal balance of FIT and colonoscopy for CRC screening to reach the highest proportion of the population without increasing missed AAs and progression to CRC.

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Author's contribution Conceptualization: AM, PCS; Methodology: AM, HJC; Formal analysis: AM, HJC; Data curation: JJC, HSA, ECC, AN, AT, AM; Writing original draft: JJC, HSA; Writing-review and editing: all authors; Supervision: AM.

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Declarations

Conflict of interest The authors have no conflicts of interest pertaining to this manuscript. In the last 24 months, A. Mohanty has received research support from Gilead, served on an advisory board for Gilead and has been the principal investigator for clinical trials conducted by Intercept, Inventiva and Novo Nordisk. *Disclosure* The authors did not receive any assistance with manuscript preparation.

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