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Comparing a fecal immunochemical test and circulating tumor DNA blood test for colorectal cancer screening adherence

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Abstract

Background and Aim: Colorectal cancer (CRC) screening programs are most effective at reducing disease incidence and mortality through sustained screening participation. A novel blood test modality is being explored for CRC screening, but it is unclear whether it will provide sustained screening participation. This study aimed to investigate whether a circulating tumor DNA (ctDNA) blood test improved CRC screening re-participation when compared with a fecal immunochemical test (FIT) and to define the predictors of sustained CRC screening in an Australian population.

Methods: South Australians who initially participated in CRC screening using a ctDNA blood test (n = 36) or FIT (n = 547) were offered the same CRC screening test approximately 2 years later through an extended phase of a randomized controlled trial. Surveys collected demographic, psychosocial, and clinical information. Predictors of CRC screening re-participation were explored using chi-square, Wilcoxon tests, and logistic regression.

Results: Participants offered a second ctDNA blood test were equally likely to re-participate in CRC screening as those who completed a FIT in the first round and who were offered the same test (61% *vs* 66% re-participation respectively, P = 0.6). CRC fatalism, health activation, and self-efficacy were associated with repeated screening participation. Test awareness was predictive of repeated FIT-based CRC screening.

Conclusions: Targeted interventions to improve CRC screening awareness and increase patient health activation may improve CRC screening adherence. A ctDNA blood test may be a suitable CRC screening option to maintain CRC screening adherence in people who do not participate in screening with FIT.

Ethical approval: This study was approved by the Southern Adelaide Clinical Human Research Ethics Committee (#483.14).

Informed consent: Written and informed consent was obtained from all participants.

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Clinical trial registration: This trial was prospectively registered with the Australian and New Zealand Clinical Trials Registry (ACTRN #12615000972527).

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide.[1] Organized CRC screening programs that use the fecal immunochemical test (FIT) have been established in many countries over the world, with proven effectiveness at reducing CRC incidence and mortality.[2–4] While participation in CRC screening has increased in recent years, many screening programs are under-utilized, with approximately half of the eligible population choosing not to participate.[1,3] Repeated participation in CRC screening is equally effective as colonoscopy for detecting CRC.[5] Therefore, promotion of and improvements to long-term adherence to CRC screening can substantially improve program cost-effectiveness and save more lives.[6,7]

A major initial barrier to CRC screening participation is fecal aversion.[8–10] We have previously shown that one-time CRC screening participation can be improved in individuals reluctant to complete a FIT through offer of a circulating tumor DNA (ctDNA) blood test.[11] An individual's decision to participate in CRC screening has also been linked to differences in demographics, beliefs, and experiences,[12,13] but the overall effects of these attributes on CRC screening participation differ substantially between populations and studies,[13] and limited data are available on factors affecting longer term adherence in CRC screening. Defined participant and non-participant characteristics are needed so that targeted strategies can be developed and implemented to promote sustained CRC screening and creating lifetime screeners.

In Australia, approximately 77% of individuals re-participate in FIT-based CRC screening as part of the Australian National Bowel Cancer Screening Program (NBCSP).[1] However, it is not known whether participation is sustained in people reluctant to complete FIT but who are willing to participate in CRC screening with a novel blood test screening modality.

This study aimed to compare CRC screening re-participation rates in individuals offered a second screening round with FIT or ctDNA blood test, and further identify psychosocial predictors of repeat CRC screening participation in an Australian population, ahead of targeted intervention.

Methods

Study design and population. The study population comprised of participants enrolled in a randomized controlled trial conducted in 2016.[11] Invitees aged 50–74 years old were randomly selected from six South Australia regions from the Australian electoral roll. Invitees were offered a free CRC screening test with FIT; with the intervention arms including a ctDNA blood test offer upfront or 12 weeks later if the FIT was not completed. Invitees were informed that the accuracy of the blood test to detect CRC was similar to that of the FIT. CRC screening test participation was assessed at 24 weeks after the initial study invitation. A total of $n = 583$ participants who returned a negative CRC screening test in this first screening round and who had not otherwise withdrawn were mailed an invitation in 2018 to participate in a second CRC screening round using the same testing method that they had completed almost 2 years prior (FIT or ctDNA blood test). No opportunity was provided for invitees to cross-over to another test modality during the second CRC screening round. An advanced notification letter was sent to participants 2 weeks before each screening invitation to inform of the upcoming screening offer.[14,15] Non-participants were sent a reminder letter 6 weeks after invitation.[16] Participation rates for the second CRC screening round were determined after 12 weeks. Given this study's focus on CRC screening re-participation, individuals reporting that they had undergone recent or regular colonoscopy were excluded from analysis ($n = 16$).

Ethical approval was obtained from the Southern Adelaide Clinical Human Research Ethics Committee (reference #483.14). The trial was prospectively registered with the Australian and New Zealand Clinical Trials Registry (ACTRN #12615000972527). The study conducted in accordance with the Declaration of Helsinki. Written and informed consent was obtained from all participants.

Screening tests. Screening test kits, including an invitation letter, information sheet, option for withdrawing, and a consent form were mailed to the invitee's home address. Participants offered a FIT received two FIT sample collection tubes and sheets (OC-Sensor, Eiken Chemical Co., Japan), test completion instructions, and a reply-paid envelope for return of the completed test and forms to the laboratory (Flinders Centre for Innovation in Cancer, Bedford Park, South Australia) by mail. These invitees were instructed to collect a ~10 mg fecal sample from two independent bowel motions and return the samples within 10 days of collection of the final sample. Invitees were instructed to consult their primary care physician and not complete the FIT if they had experienced rectal bleeding at any time in the preceding month. Receipt of any completed FIT was classed as participation, with completed FITs analyzed for hemoglobin concentration as previously described.[17] Participants offered a ctDNA blood test received a blood test referral form and a list of blood collection center locations, with directions on how to contact a convenient center. Blood test participants had blood collected by phlebotomy into two K3 EDTA Vacuette tubes (Greiner Bio-One, Germany). Plasma was isolated from whole blood and stored at −80°C until couriered to Clinical Genomics Pty. Ltd. (North Ryde, New South Wales) for analysis of ctDNA biomarkers; methylated *BCAT1* and *IKZF1*. FIT and ctDNA blood test sample processing, analysis, and positivity thresholds were performed as previously described.[18] Test results were reported to participants and their primary care physician by mail. Participants with positive screening test results were advised to undergo colonoscopy.

Surveys. Four paper surveys were provided to the study population in a prospective manner. Each survey was provided alongside a reply-paid envelope for mail return. One survey was provided alongside the original test offer in 2016, which was to be completed before the participant's first test, reflecting their baseline attitudes towards CRC testing. The second survey was provided 24 weeks later, after all participants completed their first CRC screening round for this study. Participants received a third survey upon commencement of the second round of CRC screening; 22 months after the original study invitation. The fourth and final survey was provided 12 weeks after the second CRC screening round offer. Invitees were encouraged to complete the surveys regardless of test participation. Surveys 1 and 3 measured behavior and attitudes towards CRC testing, including previous experiences

with fecal and blood sampling, barriers to testing,[10,19] previous participation in CRC screening,[20] perceived risk of CRC,[21] perceptions about confidence to complete the screening requirements (self-efficacy),[22] perceived performance characteristics of the test (response efficacy), and family history of CRC.[21,23] Surveys 2 and 4 measured screening test acceptability[24] and reasons for non-participation.[25] All four surveys measured the health activation of respondents over the knowledge, self-efficacy, beliefs, actions, and locus of control domains using the Consumer Health Activation Index (CHAI).[26] CHAI items were subcategorized into Patient-Provider Engagement (representing items related to elements of shared care with a doctor) and Health-Self Management (encompassing items related to consumer-centered care such as looking for information and taking care of oneself).[27] Individuals who culturally identified as Australian, New Zealand, English, Welsh, Irish, and/or Scottish were collectively termed an Anglo-Celtic cultural identity for the purposes of analysis. Further details regarding the survey design and end-point assessments are described in the supporting information.

Statistical analysis. An intention-to-treat analysis was performed in R using tidyverse and gtsummary.[28,29] Sustained CRC screening participation variables were explored using the Pearson chi-square and Wilcoxon rank-sum tests for categorical and continuous variables, respectively, with Fisher's exact test employed where expected observations were $n < 5$. Longitudinal changes in health activation were explored using a Kruskal–Wallis ANOVA, followed by a post-hoc Wilcoxon rank sum test. Health activation before and after completing the first CRC screening test was compared in paired data using the Wilcoxon signed-rank test. Mosaic plots were created with vcd.[30] Logistic regression was used to determine the predictors of sustained CRC screening using the FIT, defined as completion of the FIT in the first round of CRC screening, followed by subsequent completion of another FIT test within the study period, as defined by either participation in CRC screening within this study, or a survey response indicating that a CRC screening test was completed through the NBCSP within 2 years. A small sample size prevented completion of this analysis for blood test participants. A *P*-value of ≤ 0.05 was considered significant.

Results

Colorectal cancer screening demographics. The study population and design are summarized in Figure 1. Participant sociodemographic characteristics are described in Table 1. A total of 373/567 (65.7%) of the eligible study population re-participated in CRC screening, with 351/531 (66.1%) participants completing a second FIT, and 22/36 (61.1%) participants completing a second ctDNA blood test. There was no significant difference between the type of CRC screening test (i.e. FIT or blood test) and re-participation status (Table 1, $P = 0.5$). Individuals who culturally identified as Australian, New Zealand, English, Welsh, Irish, and/or Scottish, herein termed Anglo-Celtic, participated in sustained CRC screening when compared with people identifying with other cultural backgrounds (Table 1, $P = 0.029$).

Test familiarity, efficacy, and health activation on sustained colorectal cancer screening. Individuals who had either previously heard of a FIT, or had previously completed a FIT before the initial screening round were significantly more likely to re-participate in FIT-based CRC screening when compared with individuals with less familiarity with FIT (Table 2, $P = 0.019$ and $P = 0.009$, respectively). Limited conclusions can be drawn from the ctDNA blood test group due to low numbers of participants with survey responses in this study arm (Table S1). Sustained CRC screening with either test was associated with CRC fatalism, high self-efficacy for completing their CRC screening test, and high test response efficacy (Table 2,

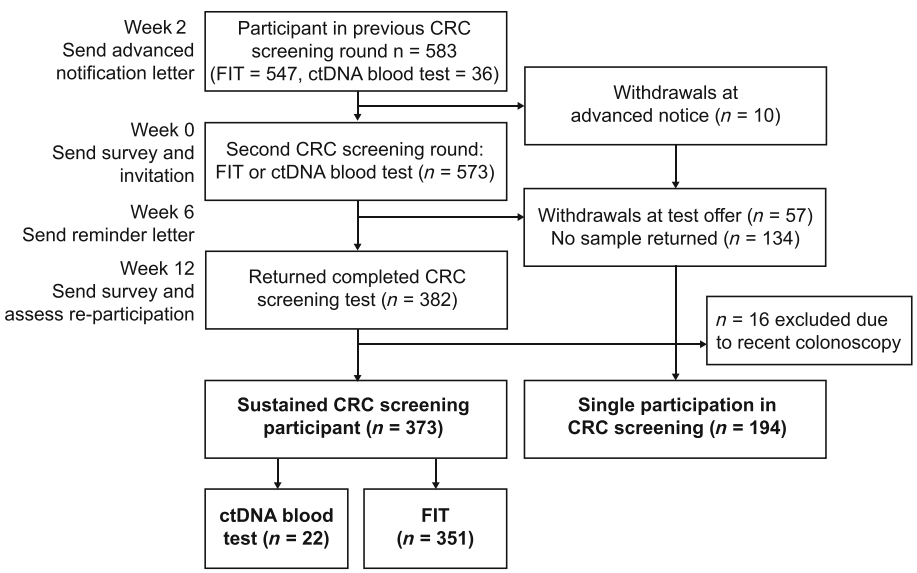


Figure 1 Flow diagram and study design. CRC, colorectal cancer; ctDNA, circulating tumor DNA; FIT, fecal immunochemical test.

Table 1 Study demographics by participation status in a second round of colorectal cancer screening

Characteristic	CRC screening participation status			
	N	Sustained	Single	*P*-value
		n = 373	*n* = 194	
First screening test completed in study, *n* (%)	567			0.5[†]
FIT	531	351 (66%)	180 (34%)	
ctDNA blood test	36	22 (61%)	14 (39%)	
Age at first CRC screening round (years), *n* (%)	566			0.054[†]
50-60	207	130 (63%)	77 (37%)	
61–70	255	164 (64%)	91 (36%)	
> 70	104	76 (76%)	25 (24%)	
Sex	567			0.3[†]
Male	262	167 (64%)	95 (36%)	
Female	305	206 (68%)	99 (32%)	
Socio-economic quintile, *n* (%)	567			0.5[†]
1 (Lowest)	74	48 (65%)	26 (35%)	
2	99	64 (65%)	35 (35%)	
3	81	57 (70%)	24 (30%)	
4	163	100 (61%)	63 (39%)	
5 (Highest)	150	104 (69%)	46 (31%)	
Health insurance status, *n* (%)	473			0.2[†]
Private	398	275 (69%)	123 (31%)	
None	75	58 (77%)	17 (23%)	
Education level, *n* (%)	466			0.085[†]
School	199	133 (67%)	66 (33%)	
Tertiary	267	197 (74%)	69 (26%)	
Marital status, *n* (%)	473			0.9[†]
Single, separated, or widowed	126	89 (71%)	37 (29%)	
Married or De Facto	347	243 (70%)	104 (30%)	
Country of birth, *n* (%)	454			0.4[†]
Australia	330	235 (71%)	95 (29%)	
Other	124	83 (67%)	41 (33%)	
Language, *n* (%)	472			0.6[†]
English only	417	295 (71%)	122 (29%)	
Multilingual	55	37 (67%)	18 (33%)	
Cultural identity, *n* (%)	423			**0.029**[†]
Anglo-Celtic	345	247 (72%)	98 (28%)	
Other	78	46 (59%)	32 (41%)	
Family history of CRC, *n* (%)	470			0.4[†]
First-degree relative	82	61 (74%)	21 (26%)	
Other/none	388	269 (69%)	119 (31%)	

Bold *P*-values indicates $P < 0.05$.

CRC, colorectal cancer; ctDNA, circulating tumor DNA; FIT, fecal immunochemical test; IQR, interquartile range; N, total respondents.

[†]Pearson's chi-squared test.

$P = 0.039$, $P < 0.001$, and $P = 0.040$, respectively). Sustained CRC screening participants reported significantly higher health activation after completing their first CRC screening test (Fig. 2a, $P = 0.033$). Sustained CRC screening participants also reported consistently higher patient-provider engagement scores when compared with single CRC screening participants; even during the first screening round in which all respondents participated in CRC screening (Fig. S1, $P < 0.05$ for all observations).

Barriers to sustained colorectal cancer screening. Individuals who re-participated in CRC screening using the FIT were significantly less likely to report fecal aversion (i.e. beliefs that the FIT was unhygienic, distasteful, or embarrassing) as their non-participant counterparts (Table 3, $P = 0.041$), and survey respondents who completed their first ctDNA blood test were more likely to report fecal aversion than respondents who completed their first FIT ($n = 78\%$ *vs* 36% respectively, $P < 0.001$).

Predictors of sustained colorectal cancer screening using the fecal immunochemical test. A total of 38 individuals who did not re-participate in the second round of CRC screening with FIT reported completing a CRC screening test offered through the NBCSP during the study window (Fig. 3a; 38/59 survey respondents or 38/180 total single-round

Table 2 Test familiarity and health activation on colorectal cancer screening re-participation

Characteristic	FIT participation				ctDNA blood test participation				Combined screeningtest participation			
	N	Sustained	Single	*P*-value	*N*	Sustained	Single	*P*-value	*N*	Sustained	Single	*P*-value
		n = 351	*n* = 180			*n* = 22	*n* = 14			*n* = 373	*n* = 194	
Test familiarity at first CRC screening offer, *n* (%)												
FIT	415			**0.019**[†]	5			N/A	420			**0.020**[†]
Heard of	397	280 (97%)	117 (92%)		5	3 (100%)	2 (100%)		402	283 (97%)	119 (92%)	
Not heard of	18	8 (3%)	10 (8%)		0	0 (0%)	0 (0%)		18	8 (3%)	10 (8%)	
Participation	410			**0.009**[†]	5			> 0.9[‡]	415			**0.007**[†]
Previously completed FIT	353	253 (89%)	100 (79%)		3	2 (67%)	1 (50%)		356	255 (89%)	101 (79%)	
Never completed FIT	57	31 (11%)	26 (21%)		2	1 (33%)	1 (50%)		59	32 (11%)	27 (21%)	
ctDNA blood test	413			0.2[†]	5			N/A	418			0.2[†]
Heard of	99	73 (26%)	26 (20%)		0	0 (0%)	0 (0%)		99	73 (25%)	26 (20%)	
Not heard of	314	212 (74%)	102 (80%)		5	3 (100%)	2 (100%)		319	215 (75%)	104 (80%)	
Attitudes towards CRC, *n* (%)												
Perceived risk	452			0.2[†]	19			0.7[‡]	471			0.3[†]
Below average	53	33 (10%)	20 (15%)		1	1 (7.1%)	0 (0%)		54	34 (10%)	20 (14%)	
Average	328	229 (72%)	99 (73%)		14	11 (79%)	3 (60%)		342	240 (73%)	102 (73%)	
Above average	71	55 (17%)	16 (12%)		4	2 (14%)	2 (40%)		75	57 (17%)	18 (13%)	
Fatalism	423			0.060[†]	16			0.5[‡]	439			**0.039**[†]
Low	275	188 (62%)	87 (72%)		12	8 (67%)	4 (100%)		287	196 (62%)	91 (73%)	
Medium/high	148	114 (38%)	34 (28%)		4	4 (33%)	0 (0%)		152	118 (38%)	34 (27%)	
CRC screening test characteristics, *n* (%)												
Self-efficacy, *n* (%)	455			< **0.001**[†]	19			N/A	474			< **0.001**[†]
Low/medium	50	24 (7.5%)	26 (19%)		0	0 (0%)	0 (0%)		50	24 (7.2%)	26 (18%)	
High	405	295 (92%)	110 (81%)		19	14 (100%)	5 (100%)		424	309 (93%)	115 (82%)	
Response efficacy, *n* (%)	445			**0.025**[†]	19			> 0.9[‡]	464			**0.040**[†]
Low/medium	19	9 (2.9%)	10 (7.6%)		1	1 (7.1%)	0 (0%)		20	10 (3.1%)	10 (7.3%)	
High	426	304 (97%)	122 (92%)		18	13 (93%)	5 (100%)		444	317 (97%)	127 (93%)	
Consumer Health Activation Index (CHAI; %); median (IQR)												
First screening round												
Before	409	76 (68, 83)	76 (68, 80)	0.2[§]	5	72 (50, 76)	72 (71, 73)	> 0.9[§]	414	76 (68, 82)	76 (69, 80)	0.2[§]
After	318	78 (70, 88)	74 (68, 80)	**0.041**[§]	21	76 (68, 78)	76 (74, 82)	0.6[§]	339	78 (70, 88)	74 (68, 80)	0.073[§]
Second screening round												
Before	314	78 (70, 84)	76 (69, 80)	0.3[§]	15	72 (64, 90)	80 (70, 89)	0.8[§]	329	78 (68, 84)	76 (68, 80)	0.2[§]
After	296	80 (70, 88)	76 (69, 80)	0.14[§]	18	74 (69, 91)	74 (69, 87)	> 0.9[§]	314	80 (70, 88)	75 (69, 80)	0.2[§]

Bold *P*-values indicates $P < 0.05$.

CRC, colorectal cancer; ctDNA, circulating tumor DNA; FIT, fecal immunochemical test; IQR, interquartile range; N, total respondents.

[†]Pearson's chi-squared test.

[‡]Fisher's exact test.

[§]Wilcoxon rank sum test. CRC.

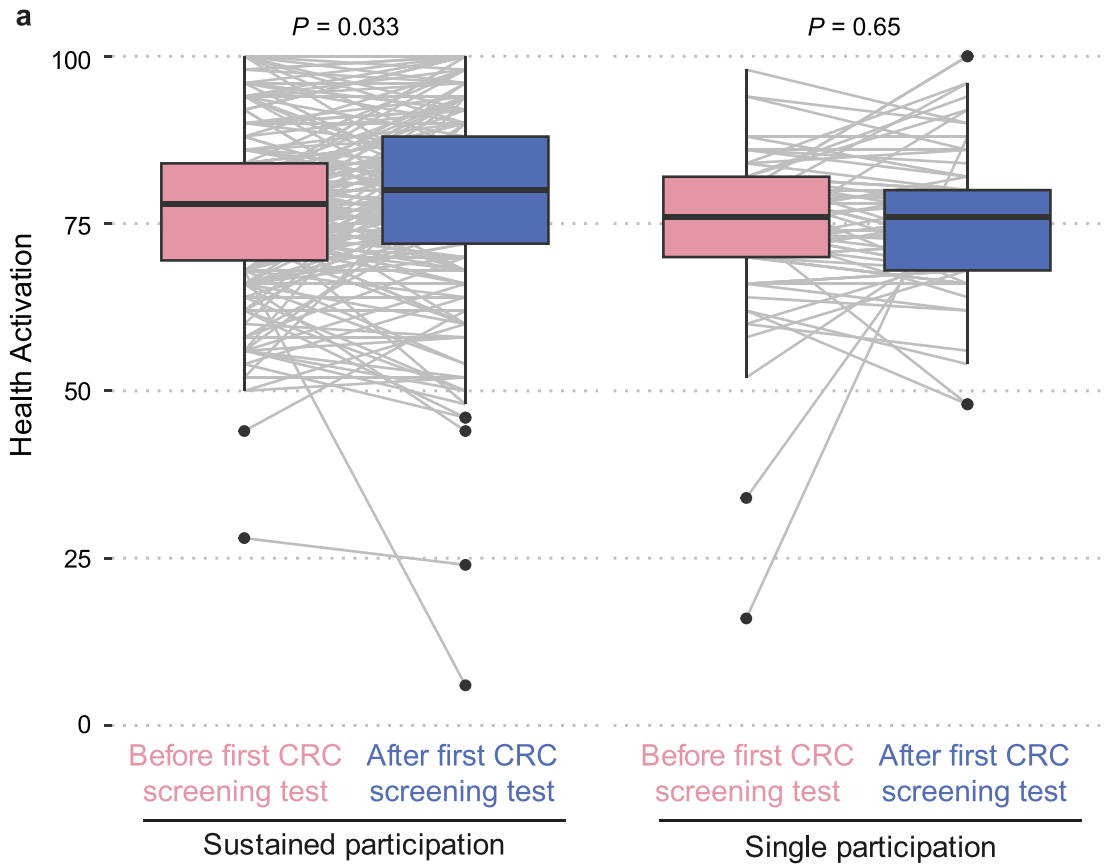


Figure 2 Health activation increases after colorectal cancer (CRC) screening participation but only for future sustained CRC screening participants. Paired Consumer Health Activation Index scores, collected before and after their first CRC screening test, for n = 208 individuals who re-participated in CRC screening ('Sustained participation'), and n = 73 individuals who did not re-participate in CRC screening ('Single participation').

participants). Sustained CRC screening participation with FIT was re-classified as completion of the FIT in the first CRC screening round, followed by completion of a subsequent CRC screening test within the study period (either through this study or through the NBSCP) in order to explore predictors of sustained CRC screening with FIT (n = 389). Individuals who have previously heard of the FIT, have previously completed a FIT before the first CRC screening round, or with high self-efficacy to complete the FIT were each more than twice as likely to participate in sustained CRC screening (Fig. 3b, P = 0.032, P = 0.02, and P = 0.003, respectively). Individuals aged > 70 years at the first offer were approximately twice as likely to participate in sustained CRC screening with FIT when compared with their 50- to 60-year-old counterparts (Fig. 3b, P = 0.021). Conversely, people with low CRC fatalism, and those who identify with a background other than Anglo-Celtic were approximately half as likely to re-participate in FIT-based CRC screening (Fig. 3b, P = 0.015 and P = 0.007, respectively).

Discussion

Sustained participation is essential for a successful CRC screening program. Understanding patterns of sustained participation in CRC screening enables identification of population groups who may be at risk of not participating ahead of targeted interventions. We observed a similar rate of sustained CRC screening participation between individuals completing a second ctDNA blood test and second FIT, and found that test awareness and self-efficacy predictive of sustained CRC screening with FIT. These findings extend our previous findings,[11,31] demonstrating that CRC screening using a ctDNA blood test promotes re-participation to the same extent as the FIT, and is a suitable strategy for individuals who do not wish to complete FIT, such as people with high fecal aversion or benign bleeding conditions.

Many studies have examined FIT screening participant behavior over multiple screening offers,[32–37] but this is the first study to our knowledge which examined sustained CRC screening with a blood test. Although the highest participation rates are found in screening programs which use the FIT,[3] previous research in an Australian cohort found that most survey respondents would prefer to participate in CRC screening with a blood test rather than the usual fecal sample.[38] In the current study, sustained participation did not differ between participants offered a blood test when compared with the FIT. This may be due to the composition of the blood test group, which was exclusively comprised of individuals who were reluctant to complete a FIT in the initial study offer.[11]

Table 3 Common screening barriers on colorectal cancer screening re-participation

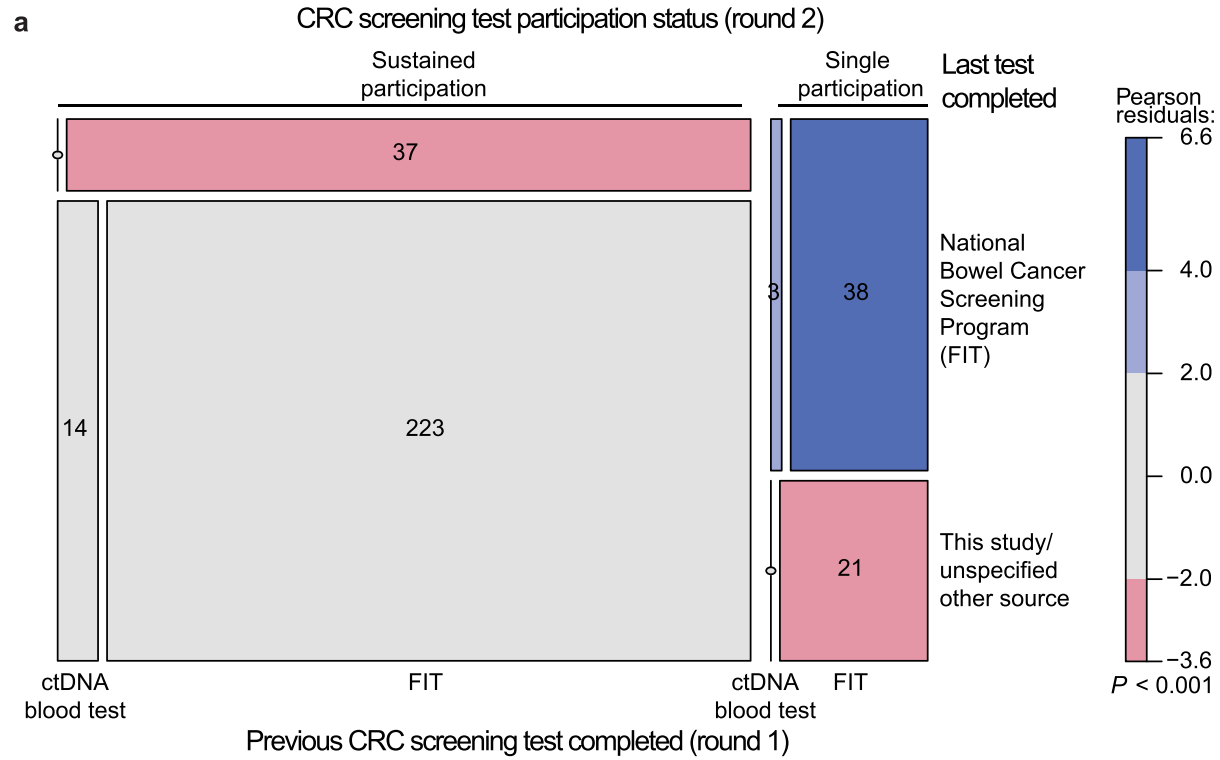
Characteristic	FIT participation				ctDNA blood test participation				Combined screeningtest participation			
	N	Sustained	Single	*P*-value	*N*	Sustained	Single	*P*-value	*N*	Sustained	Single	*P*-value
		n = 351	*n* = 180			*n* = 22	*n* = 14			*n* = 373	*n* = 194	
FIT												
Belief that the FIT is …												
Unhygienic, *n* (%)	442			0.7[†]	17			0.6[‡]	459			0.6[†]
Yes	58	42 (13%)	16 (12%)		6	5 (42%)	1 (20%)		64	47 (15%)	17 (13%)	
No	384	270 (87%)	114 (88%)		11	7 (58%)	4 (80%)		395	277 (85%)	118 (87%)	
Distasteful, *n* (%)	449			0.087[†]	18			> 0.9[‡]	467			0.087[†]
Yes	147	95 (30%)	52 (39%)		13	9 (69%)	4 (80%)		160	104 (32%)	56 (40%)	
No	302	219 (70%)	83 (61%)		5	4 (31%)	1 (20%)		307	223 (68%)	84 (60%)	
Embarrassing, *n* (%)	446			0.4[†]	18			> 0.9[‡]	464			0.4[†]
Yes	78	52 (16%)	26 (20%)		8	6 (46%)	2 (40%)		86	58 (18%)	28 (21%)	
No	368	264 (84%)	104 (80%)		10	7 (54%)	3 (60%)		378	271 (83%)	107 (79%)	
Fecal aversion, *n* (%)	454			**0.041[†]**	18			> 0.9^	472			**0.048[†]**
Present	165	106 (33%)	59 (43%)		14	10 (77%)	4 (80%)		179	116 (35%)	63 (45%)	
Absent	289	212 (67%)	77 (57%)		4	3 (23%)	1 (20%)		293	215 (65%)	78 (55%)	
Blood test												
Anxiety during blood taking, *n* (%)	455			0.6[†]	19			0.6[‡]	474			0.5[†]
Present	226	156 (49%)	70 (51%)		9	6 (43%)	3 (60%)		235	162 (49%)	73 (52%)	
Absent	229	163 (51%)	66 (49%)		10	8 (57%)	2 (40%)		239	171 (51%)	68 (48%)	
Needle-phobia, *n* (%)	454			0.3[†]	19			> 0.9[‡]	473			0.4[†]
Afraid of needles	100	66 (21%)	34 (25%)		2	2 (14%)	0 (0%)		102	68 (20%)	34 (24%)	
Not afraid of needles	354	253 (79%)	101 (75%)		17	12 (86%)	5 (100%)		371	265 (80%)	106 (76%)	

Bold *P*-values indicates $P < 0.05$.

CRC, colorectal cancer; ctDNA, circulating tumor DNA; FIT, fecal immunochemical test; IQR, interquartile range; N, total respondents.

[†]Pearson's chi-squared test.

[‡]Fisher's exact test.



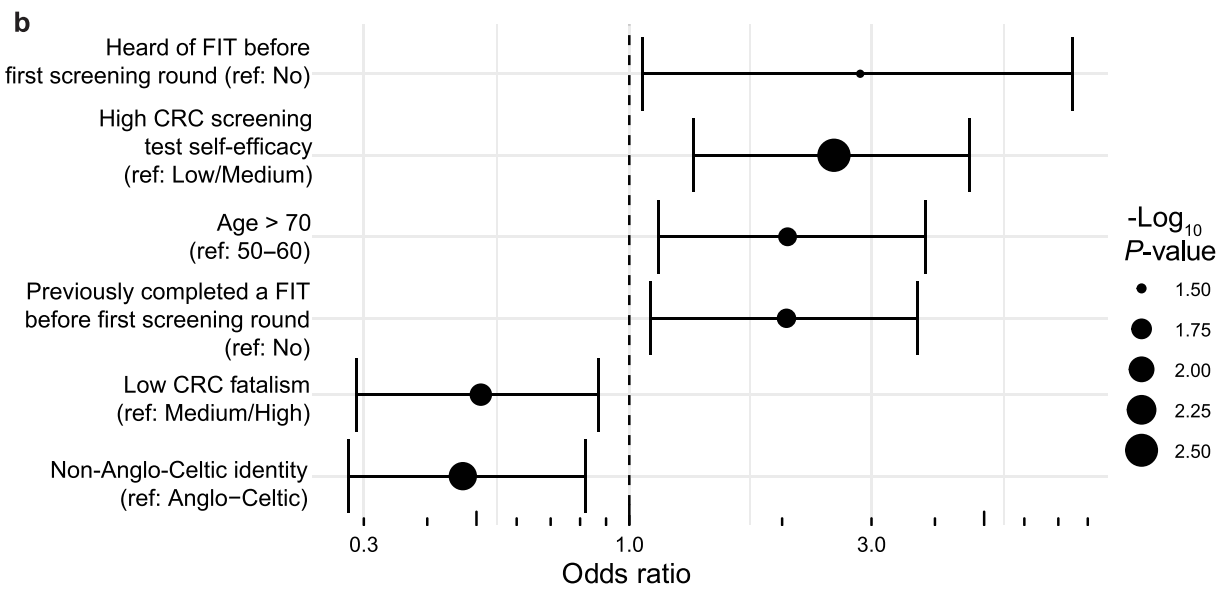


Figure 3 (a) Mosaic plot of colorectal cancer (CRC) screening round 2 re-participation status, test modality, and completion of a fecal immunochemical test (FIT) either offered through the Australian National Bowel Cancer Screening Program or this study for survey respondents. (b) Forest plot showing significant ($P < 0.05$) predictors of any sustained participation in CRC screening with the fecal immunochemical test (FIT), via completion of the first CRC screening round with the FIT, followed by completion of either a FIT offered through the current study or through the National Bowel Cancer Screening Program (n = 389 sustained CRC screening participants). ctDNA, circulating tumor DNA.

Test awareness is a well-described facilitator of CRC screening participation and adherence.[12,13] Accordingly, having previously heard of the FIT, and having prior experience completing a FIT were both predictors of sustained FIT-based CRC screening. This study is also the first to explore health activation in the context of sustained CRC screening. A validation of the CHAI for use in an older Australian population has been recently completed, and found that domains encompassed by the measure can be

adequately described by the retention of fewer items compared to the existing 10 items, and can be broken into two major subscales; patient-provider engagement and health services management.[27] We found that patient-provider engagement was consistently higher in sustained when compared with single-round CRC screening participants. Taken together, these data suggest that targeted interventions to improve awareness and activate participants, such as physician's recommendations, may be beneficial in improving CRC screening re-participation rates.

Dissatisfaction with FIT has been previously linked with a reduced likelihood of re-participation in CRC screening.[37,39] The relationship between fecal aversion and reduced CRC screening participation is well established.[9,12] Accordingly, we saw an association between fecal aversion and single-round CRC screening with FIT, highlighting the value of the ctDNA blood test as a suitable mechanism for improving CRC screening re-participation in individuals who do not complete FIT.

This study was not without limitations. Limited conclusions were drawn from the blood test cohort due to low sample size and survey completion rates, hampering insights into the psychosocial demographics of individuals offered a ctDNA blood test. Our sample size was calculated for the first round of CRC screening, and was powered to detect a participation difference between study arms. Another limitation relates to the lack of opportunity for previous screening participants to change their test modality in the second CRC screening round. We were unable to assess how CRC screening preferences changed with time, and were unable to determine whether participants who completed their first but not second CRC screening FIT would instead adopt repeated CRC screening with a blood test. We were unable to report on colonoscopy uptake or outcomes for those returning a positive screening test due to incomplete data, nor were we able to identify all individuals who completed a separate CRC screening test during our study due to limited survey responses, potentially resulting in underestimation of sustained FIT-based CRC screening. Finally, this study focused on CRC screening tests completed in an Australian population, in which participation in a centrally organized CRC screening program using the FIT is approximately 44%, and re-participation is approximately 77%[1]: Provision of our CRC screening test, in addition to those normally received by some of the study population as a part of a centrally organized screening program, may have resulted in testing offers serving as a deterrent rather than a facilitator of participation,[15] resulting in reduced re-participation. Regardless, this study has provided valuable pilot data highlighting that re-participation rates are comparable between participants offered FIT *versus* ctDNA blood test.

Strengths of this study include the focus on single-CRC screening participants, the longitudinal capture of health activation, and the applicability of the study to population-based organized screening programs.

This study is to our knowledge the first to show that re-participation in CRC screening does not significantly change in individuals who complete a FIT *versus* a ctDNA blood test. This data shows a reasonable uptake in CRC screening re-participation using a ctDNA blood test, highlighting its use as a potential CRC screening tool for targeting groups with low uptake of CRC screening using FIT. Further, this is the first study to demonstrate that health activation is predictive of CRC screening adherence in a general population. Targeted interventions to improve health activation, improve CRC screening awareness and self-efficacy, and personalize screening where FIT is inappropriate may all promote CRC screening adherence.

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Data availability statement. Deidentified participant data can be shared upon reasonable request.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Supplementary Methods.
Table S1. Survey completion rates by colorectal cancer screening test re-participation status.
Figure S1. Changes over time in health activation for **(a)** Patient-Provider Engagement and **(b)** Health Self-Management subdomains as measured using a variation of the Consumer Health Activation Index[7,11] in sustained vs. single-round CRC screening participants. Data was analyzed using Wilcoxon rank-sum tests. n; total survey respondents within each category, *; $P < 0.05$, ns; $P > 0.05$.