



# Interval colorectal cancers after negative faecal immunochemical test in the New Zealand Bowel Screening Pilot

Kai Sheng Saw <sup>1</sup>, Kerry Sexton,<sup>2</sup> Paul Frankish,<sup>3</sup> Mike Hulme-Moir,<sup>4</sup> Ian Bissett,<sup>1</sup> Susan Parry<sup>2,5</sup>

**To cite:** Saw KS, Sexton K, Frankish P, *et al.* Interval colorectal cancers after negative faecal immunochemical test in the New Zealand Bowel Screening Pilot. *BMJ Open Gastroenterol* 2023;**10**:e001233. doi:10.1136/bmjgast-2023-001233

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/bmjgast-2023-001233>).

Received 8 August 2023  
Accepted 2 November 2023

## ABSTRACT

**Objective** Evaluate the diagnostic performance of faecal immunochemical test (FIT), identify risk factors for FIT-interval colorectal cancers (FIT-IC) and describe long-term outcomes of participants with colorectal cancers (CRC) in the New Zealand Bowel Screening Pilot (BSP).

**Design** From 2012 to 2017, the BSP offered eligible individuals, aged 50–74 years, biennial screening using a quantitative FIT with positivity threshold of 15 µg haemoglobin (Hb)/g faeces. Retrospective review of prospectively maintained data extracted from the BSP Register and New Zealand Cancer Registry identified any CRC reported in participants who returned a definitive FIT result. Further details were obtained from hospital records. FIT-ICs were primary CRC diagnosed within 24 months of a negative FIT. Factors associated with FIT-ICs were identified using logistic regression.

**Results** Of 387 215 individuals invited, 57.4% participated with 6.1% returning positive FIT results. Final analysis included 520 CRC, of which 111 (21.3%) met FIT-IC definition. Overall FIT sensitivity for CRC was 78.7% (95% CI=74.9% to 82.1%), specificity was 94.1% (95% CI=94.0% to 94.2%). In 78 (70.3%) participants with FIT-IC, faecal Hb was reported as undetectable. There were no significant associations between FIT-IC and age, sex, ethnicity and deprivation. FIT-ICs were significantly associated with proximal tumour location, late stage at diagnosis, high-grade tumour differentiation and subsequent round screens. Median follow-up time was 74 (2–124) months. FIT-IC had significantly poorer overall survival.

**Conclusion** FIT sensitivity in BSP compared favourably to published data. FIT-ICs were more likely to be proximal tumours with poor long-term outcomes. Further lowering of FIT threshold would have minimal impact on FIT-IC.

## INTRODUCTION

Colorectal cancer (CRC) screening has been shown to reduce CRC-related mortality through early detection and removal of tumours and precursor lesions.<sup>1</sup> Population screening programmes for CRC most commonly use the faecal immunochemical test (FIT) for haemoglobin (Hb).<sup>1</sup>

Australasia has the highest estimated age standardised incidence rate of CRC.<sup>2</sup> In New Zealand, CRC is the third most common

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Faecal immunochemical tests (FITs) are widely used internationally for detection of colorectal cancer. Different population and screening programme parameters can impact test performance. Pilot programmes provide important local data to inform national programmes.

## WHAT THIS STUDY ADDS

⇒ Most FIT interval cancers (single, OC-Sensor at positivity threshold of 15 µg Hb/g faeces) had undetectable faecal haemoglobin (f-Hb) levels at the time of screening and were more likely to be proximal tumours with poor long-term outcomes.  
⇒ There is lower participation in bowel screening for Māori and Pacific populations.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Lowering already low f-Hb positivity thresholds is unlikely to significantly reduce FIT-IC. New approaches are required to optimise identification of FIT-IC in population screening for CRC.  
⇒ Targeted interventions are required to improve participation of Pacific and Māori populations in bowel cancer screening.

cancer and second most common cause of cancer-related death.<sup>3 4</sup> Hence, in 2012, New Zealand launched an FIT (OC-Sensor) based Bowel Screening Pilot (BSP) to determine the feasibility of rolling out a national bowel screening programme.

Screening tests are not diagnostic tests and therefore all bowel cancer screening programmes will fail to detect disease in some individuals. The incidence of interval or ‘missed’ cancers is a key performance indicator informing FIT sensitivity for detection of CRC.<sup>5 6</sup> Faecal Hb (f-Hb) concentrations and, by extension, the diagnostic performance of FIT are affected by a number of variables, including age and sex. The majority of published FIT diagnostic performance data are from European cohorts and many



© Author(s) (or their employer(s)) 2023. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

## Correspondence to

Dr Kai Sheng Saw;  
kai.saw@auckland.ac.nz



questions remain regarding the transferability of FIT diagnostic performance data between different populations.<sup>6,7</sup> Analysing the impact of these variables in context can help optimise screening parameters to ensure that, within limits of available resource, predefined programme goals are met.<sup>7-9</sup>

The BSP represents the first systematic large-scale use of FIT in New Zealand. The aims of this study were therefore:

1. To evaluate the diagnostic performance of FIT for the detection of CRC in participants of the BSP.
2. To identify factors that are associated with increased likelihood of an FIT-interval CRC (FIT-IC) diagnosis compared with screen-detected CRC (SDCRC) diagnosis.
3. To describe the long-term outcomes for participants with CRC in the BSP.

## METHODS

The reporting of this observational cohort study conforms to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement.<sup>10</sup>

### The New Zealand Bowel Screening Pilot

The BSP was funded by the New Zealand Ministry of Health and conducted by the Waitemata District Health Board (WDHB) from January 2012 to December 2017. A single biennial quantitative FIT (OC-sensor, Eiken Chemical Co, Tokyo, Japan) was offered to all men and women aged 50–74 years who lived in the WDHB catchment area and were eligible for publicly funded healthcare. Individuals who had a colonoscopy within the last 5 years, were under colorectal polyp or CRC surveillance, were actively being treated for inflammatory bowel disease or were already referred for and awaiting colonic investigations due to presence of symptoms were advised not to participate.

Eligible participants were identified and managed through the BSP pathway using a purpose-built information system—the BSP Register. A pre-invitation letter was sent, followed by a kit containing a FIT specimen collection device, information leaflet, test instructions and a consent form. A prepaid first class return envelope was provided for participants to post their sample to one centralised accredited laboratory for analysis. Non-responders were followed up by a reminder letter and for priority population groups (Māori, Pacific peoples and individuals in the most deprived quintile of socioeconomic deprivation) by telephone.

FIT specimen handling, analysis and quality control were conducted and reported in line with guidelines for studies on FIT (see online supplemental appendix 1 for details).<sup>11</sup> Quantitative f-Hb concentrations for participants were prospectively recorded in the BSP Register but were identified to clinicians as positive or negative result only based on the predetermined positivity threshold of 15 µg Hb/g faeces.

Participants with negative FIT results were informed directly in writing. Participants with a positive FIT result were contacted by their general practitioner or a BSP nurse and offered a free of charge colonoscopy (and/or computed tomographic colonography if indicated) within 55 working days. Colonoscopy procedures were performed by experienced endoscopists with regular review of key performance indicators and unplanned post procedure admissions. Colonoscopy findings and histopathology results were electronically reported according to a standardised template and linked automatically to the BSP Register. All histopathological diagnoses of CRC in New Zealand were automatically registered with the New Zealand Cancer Registry (NZCR). Participants diagnosed with CRC were referred to a colorectal multi-disciplinary meeting to determine cancer management recommendations.

### Data sources

In May 2022, data were extracted from the NZCR for individuals who were diagnosed with CRC between 2012 and 2019. The resulting list of patients were matched with data in the BSP Register to ascertain participation in BSP and relevant screening history. This cross-referenced registry generated list was then further audited against individual WDHB electronic clinical records. Further data as indicated below were collected to complete the dataset required for planned analysis. Only primary colorectal adenocarcinomas were included. Due to a change in FIT positivity threshold in the BSP from 15 µg Hb/g faeces (75 ng Hb/mL buffer) to 40 µg Hb/g faeces (200 ng Hb/mL buffer) for the period of 1st July 2017 to 31st December 2017, CRCs identified in this time period were also excluded from analysis.

FIT-ICs were defined, in line with international convention, as CRC diagnosed after a negative FIT result but before the invitation of subsequent screening round. The remaining CRCs were classified as SDCRC.

In all identified CRC cases, the following variables were obtained from cross-referencing of registry data and further audited against clinical records: age at the time of FIT, sex, ethnicity, socioeconomic status, screening round, date of definitive FIT result, quantitative f-Hb level, histopathological confirmation of CRC diagnosis and CRC primary tumour location. Further data collected directly from clinical records included cancer stage at diagnosis, tumour characteristics including tumour differentiation grade, mucinous differentiation, presence of lymphovascular invasion, presence of perineural invasion, BRAF mutation or microsatellite instability (MSI), treatment intent, treatments received, date of last follow-up, disease recurrence status and survival status at last follow-up. Data on participation was provided by the Ministry of Health.

Socioeconomic status was classified based on NZDep2013 Index of Deprivation, an area-based measure of socioeconomic deprivation in New Zealand.<sup>12</sup> Primary tumour location was categorised as proximal (caecum to transverse colon) and distal (splenic flexure to rectum).

CRCs were staged according to the AJCC TNM eighth edition.<sup>13</sup> Tumour differentiation grade was categorised as low grade (well-differentiated/grade 1 and moderately differentiated/grade 2) and high grade (poorly/grade 3 and undifferentiated/grade 4).

### Statistical analysis

The primary outcome was the sensitivity and specificity of FIT for detection of CRC at BSP positivity threshold of 15 µg Hb/g faeces. FIT-IC proportions were calculated by dividing the number of FIT-IC by the sum of SDCRC plus FIT-IC and presented in percentages. Median follow-up for participants was calculated from date of definitive FIT result to death or considered censored at last follow-up.

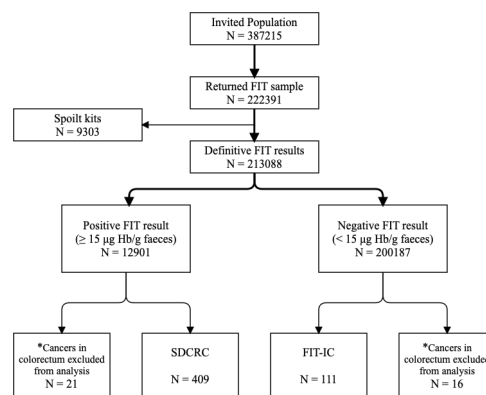
For description of categorical variables, frequency tables and percentages were used. For description of continuous variables, mean and medians were used. Missing values were excluded from analysis that compared between groups. Wilson's method for binomial distribution was used to calculate 95% CIs. Differences in proportions between categorical groups were evaluated for statistical significance using  $\chi^2$  test or Fisher's exact test. Univariate and multivariate logistic regression analysis was performed with FIT-IC as the outcome variable of interest. Kaplan-Meier curve and Cox proportional hazards models were used to assess overall survival and disease-free survival (DFS) between groups. Survival analyses were performed using the date of definitive FIT result as the start time to address potential time-related bias. Sensitivity analyses for survival were performed using landmark survival analyses and time-dependent Cox proportional hazards model. For landmark survival analyses, varying landmark times using the date of CRC diagnosis, date of treatment initiation and mean diagnosis time for FIT-IC cohort were used. For time-dependent Cox proportional hazards analysis, CRC diagnosis time and treatment initiation time were selected as time-dependent variables.

For exploratory analysis of FIT-IC proportions across a range of relevant f-Hb positivity thresholds, the numeric f-Hb concentration of each case was used to determine the number of cases with a positive and negative result at alternative cut-offs of 4, 10, 15, 20, 40, 60, 80, 100, 150 and 200 µg Hb/g faeces, respectively. This analysis was based on the assumption that all CRCs with measured f-Hb level above the exploratory positivity threshold would be diagnosed as an SDCRC and vice versa for FIT-IC.

P values < 0.05 were considered statistically significant. Analysis was conducted in R software V.4.2.2 (R Core Team, Vienna, Austria).

### Patient and public involvement

The BSP was implemented in association with consumer and professional consultation, particularly with regard to consideration of strategies to optimise ethnic-specific participation.<sup>14 15</sup> This study proposal was reviewed by the Auckland Health Research Ethics Committee, a



**Figure 1** Invited BSP participant study flow diagram.

\*Cancers in colorectum excluded—anal squamous cell carcinoma, neuroendocrine tumours, gastrointestinal stromal tumours, lymphoma, metastases to or malignant invasion into colorectum and duplicate registration for one FIT result due to synchronous CRC. BSP, New Zealand Bowel Screening Pilot; CRC, colorectal cancer; FIT, faecal immunochemical test; FIT-IC, FIT-interval colorectal cancer; SDCRC, screen-detected CRC.

panel comprising representatives of consumers of health services and the indigenous Māori people.

## RESULTS

The BSP invited 387 215 eligible individuals to participate, with 222 391 (57.4%) individuals returning a FIT kit. **Figure 1** shows the flow of invited BSP participants in the study.

Participation rate for women was 63.0% compared with 58.8% for men. Participation rate increased with increasing age. Those of Pacific ethnicity had the lowest participation rate (37.9%) followed by Māori (50.2%), Asian (53.8%) and European/other ethnicities (60.0%). Participation rate decreased with increasing socioeconomic deprivation. Initial screening rounds made up 54.5% of FIT results, with 45.5% results from two subsequent screening rounds.

At the f-Hb threshold of 15 µg Hb/g faeces (75 ng Hb/mL buffer), 12 901 (6.1%) returned FIT results were treated as a positive result. Prevalent round FIT positivity rate was significantly higher compared with subsequent round screens (7.0% vs 4.9%,  $p < 0.001$ ).

In total, 520 CRCs were identified and included in the final analysis, of which 111 met the definition of FIT-IC. In total, 46 (41.4%) FIT-ICs were detected within 12 months of a negative FIT and 65 (58.6%) were detected in between 12 and 24 months of a negative FIT. For 78 of the FIT-ICs (70.3%), there was no detectable f-Hb at the time of FIT screening (the lower limit of detection for the OC-Sensor assay analyser was 4 µg Hb/g).

Overall FIT sensitivity for CRC was 78.7% (95% CI 74.9% to 82.1%) with specificity of 94.1% (95% CI 94.0% to 94.2%). Positive predictive value for CRC was 3.1% (95% CI 2.9% to 3.3%), with negative predictive value


**Table 1** Cumulative incidence of interval colorectal cancer and FIT sensitivity by age, sex, ethnicity and screening round

	SDCRC	FIT-IC	Sensitivity (95% CI)	OR for FIT-IC	P value
All	409	111	78.7% (74.9% to 82.1%)		
Female	188	60	75.8% (70.1% to 80.7%)	1 (ref.)	
Male	221	51	81.3% (76.2% to 85.4%)	0.723 (0.474–1.101)	0.131
Age 50–54 years	41	14	74.5% (61.7% to 84.2%)	1.021* (0.990–1.055)	0.189
Age 55–59 years	47	9	83.9% (72.2% to 91.3%)		
Age 60–64 years	84	15	84.8% (76.5% to 90.6%)		
Age 65–69 years	107	27	79.9% (72.3% to 85.8%)		
Age 70–74 years	130	46	73.9% (66.9% to 79.8%)		
Māori	15	2	88.2% (65.7% to 96.7%)	1 (ref.)	
Pacific	9	5	64.3% (38.8% to 83.7%)	4.167 (0.730–33.643)	0.128
Other	329	98	77.0% (72.8% to 80.8%)	0.804 (0.165–5.863)	0.801
Asian	56	6	90.3% (80.5% to 95.5%)	2.234 (0.616–14.332)	0.291
Prevalent round	233	49	82.6% (77.7% to 86.6%)	1 (ref.)	
Subsequent rounds†	176	62	73.9% (68.0% to 79.1%)	1.675 (1.099–2.564)	0.017

\*OR with each year of increasing age.  
†Subsequent rounds include CRCs detected on participants second and third screening rounds due to small CRC numbers and shortened third screening round.  
CRC, colorectal cancer; FIT, faecal immunochemical test; FIT-IC, FIT-interval colorectal cancer.

of 99.9% (95% CI 99.9% to 99.9%). The overall FIT-IC proportion was 21.3% with an SDCRC to FIT-IC ratio of 3.7 to 1.0.

There were no significant differences on univariate regression analysis between FIT-IC and SDCRC by age, sex, ethnicity and socioeconomic deprivation (table 1). Although FIT-IC proportion was higher in subsequent round screens compared to prevalent round screens, the difference was not significant on multivariable analysis. There was no significant difference in proportion of interval cancers with undetectable f-Hb by screening

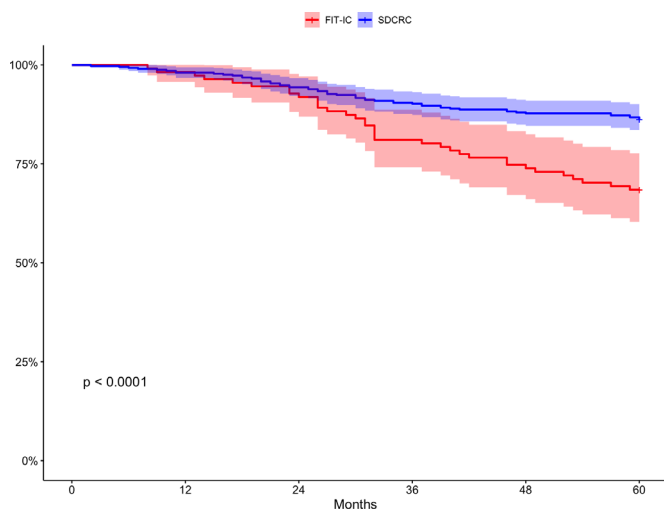
round (FIT-IC with undetectable f-Hb in prevalent round 69.4% vs subsequent round 71.0%).

Compared with SDCRC, FIT-ICs were more likely to be proximally located tumours, late stage (stages III and IV) at diagnosis with high grade tumour differentiation (table 2). Mean f-Hb values for the SDCRC cohort were higher for distal CRC compared with proximal CRC (146.4 µg Hb/g faeces vs 119.3 µg Hb/g faeces, respectively;  $p < 0.001$ ). On multivariate analysis adjusting for age, sex, ethnicity, socioeconomic deprivation, screening round, location of primary tumour, stage at diagnosis and

**Table 2** FIT-IC proportion by location of primary tumour, stage and tumour differentiation grade

	SDCRC	FIT-IC	FIT-IC proportion	Univariate p value
All cases	409	111	21.8%	
Primary tumour location				
Proximal	115 (28.1%)	52 (46.8%)	31.1%	<0.001
Distal	293 (71.6%)	56 (50.5%)	16.0%	
CRC stage at diagnosis				
Early stage (I, II)	291 (71.1%)	65 (58.6%)	18.3%	0.015
Late stage (III, IV)	114 (27.9%)	44 (39.6%)	27.8%	
Tumour differentiation grade				
Low grade	376 (91.9%)	87 (78.4%)	18.8%	0.017
High grade	29 (7.1%)	15 (13.5%)	34.1%	

One SDCRC and three FIT-ICs: unclear primary tumour location. Four SDCRCs and two FIT-ICs: incomplete CRC stage information. Four SDCRCs and nine FIT-ICs: incomplete tumour grade information.  
CRC, colorectal cancer; FIT, faecal immunochemical test; FIT-IC, FIT-interval colorectal cancer; SDCRC, screen-detected CRC.



**Figure 2** Kaplan-Meier curve for overall survival of all participants with CRC at 5 years from FIT. CRC, colorectal cancer; f-Hb, faecal haemoglobin; FIT, faecal immunochemical test; FIT-IC, FIT-interval colorectal cancer; SDCRC, screen-detected CRC.

tumour differentiation grade, only location of primary tumour retained a statistically significant association with FIT-IC.

The median follow-up time for all patients with CRC was 74 months (range 2–124 months). There was a significantly higher 5-year overall survival for SDCRC compared with FIT-IC, with divergence of survival becoming apparent at 24 months from FIT result (figure 2). FIT-IC group had 2.4 times higher unadjusted all-cause mortality compared with SDCRC group at 5 years (31.5% (22.3%–39.7%) vs 13.7% (10.3%–17.0%),  $p < 0.001$ ). A similar improved DFS for SDCRC at 5 years was observed (SDCRC 83.1% (79.5%–86.8%) vs FIT-IC 64.9% (56.6%–74.4%),  $p < 0.001$ ).

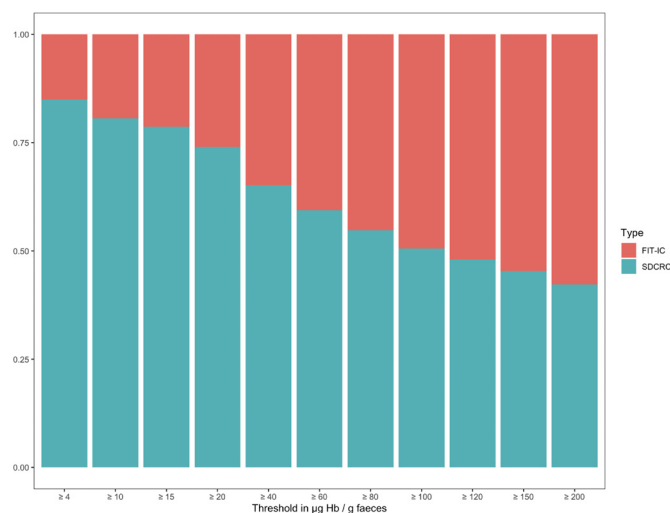
Sensitivity analyses with various landmark times for survival analysis to account for time-related biases also showed significant survival advantage in favour of SDCRC group. There was no significant difference in survival between SDCRC and FIT-IC when stratified by stage at diagnosis on multivariate survival analysis. In keeping with the greater proportion of stage IV CRC in this group, FIT-ICs were less likely to be suitable for curative intent management than SDCRC (79.3% vs 94.1%,  $p < 0.001$ ).

### Exploratory analysis at different positivity thresholds

Exploratory analysis across a range of relevant f-Hb positivity thresholds showed an expected increase in FIT-IC proportions at higher f-Hb thresholds (figure 3). Projected FIT-IC proportions were 15.0% at threshold of  $4 \mu\text{g Hb/g}$  faeces and 34.8% at threshold of  $40 \mu\text{g Hb/g}$  faeces with further increase to 51.9% at threshold of  $120 \mu\text{g Hb/g}$  faeces.

## DISCUSSION

The present study assessed the diagnostic accuracy of the OC-Sensor FIT in the BSP using a positivity threshold



**Figure 3** Exploratory analysis with proportion of SDCRC to FIT-IC by various f-Hb thresholds. F-Hb, faecal haemoglobin; FIT, faecal immunochemical test; FIT-IC, FIT-interval colorectal cancer; SDCRC, screen-detected colorectal cancer.

of  $15 \mu\text{g Hb/g}$  faeces. The overall sensitivity, specificity, positive predictive value and negative predictive value, including initial and subsequent rounds, were 78.7%, 94.1%, 3.1% and 99.9%, respectively. Patients with a FIT-IC made up 21.3% of the patients with CRC. More than 70% of the FIT-ICs had undetectable levels of f-Hb. Primary tumour location in the proximal colon, advanced cancer stage at diagnosis and a high tumour differentiation grade were all associated with FIT-IC. Those with a FIT-IC had poorer overall survival.

Despite high age standardised incidence rates of CRC in New Zealand, the diagnostic performance of FIT for CRC detection in the BSP compares favourably with findings from a meta-analysis of 17 studies reporting on FIT-IC.<sup>6</sup> This meta-analysis included a heterogeneous mix of screening programme settings and reported a pooled SDCRC to FIT-IC ratio of 2.6 to 1.0, which is estimated to represent an FIT sensitivity of 71.9%.<sup>6</sup> Tran *et al* reported FIT sensitivity estimate of 86.8% for a Belgian cohort with several screening programme parameters that are more directly comparable with the BSP.<sup>16</sup> FIT-IC comparison between cohorts can be complicated due to variation in reported metrics. Different screening programme parameters (eg, f-Hb positivity threshold, screening age range) and underlying CRC epidemiology can also influence observed FIT-IC. Hence, caution is required when comparing FIT-IC between different screening programmes.

There were no observed significant associations between FIT-IC proportion and age or sex in the BSP. While some FIT-based screening programmes have different positivity thresholds for men and women, it is worth noting that a number of meta-analyses have not demonstrated a significant association between FIT sensitivity or FIT-IC rates and sex.<sup>6,9,17,18</sup> While there was a trend towards increasing FIT-IC proportions for older



participants in the BSP and other cohorts, this did not reach statistical significance.<sup>19,20</sup> Differences in a country's population composition and disease incidence can limit transferability of findings regarding FIT performance. This highlights the important role pilot programmes can play in populations for whom screening is proposed. It is then possible to tailor screening programme parameters to meet local contexts, priorities and resources.<sup>7,21</sup>

Similar to findings in the BSP, other international cohorts have reported significantly higher FIT-IC proportions in subsequent screening rounds.<sup>22,23</sup> The effect of screening round in the BSP was no longer significant on multivariate regression, suggesting that other confounding factors such as age and location of primary lesion may be crucial in explaining this observation as suggested by Zorzi *et al.*<sup>22</sup>

Consistent with many other studies, FIT-IC identified in the BSP are significantly more likely to be proximal colon cancers.<sup>16,19,24</sup> Similar to those reported by Selby *et al.*, BSP data demonstrated that f-Hb levels were significantly lower for proximal colon cancers, possibly explaining in part the higher proportion of FIT-IC in the proximal colon.<sup>25</sup> One proposed explanation for lower f-Hb levels in proximal colonic lesions is related to longer colonic transit time leading to greater f-Hb degradation.<sup>7,26</sup> It has also been proposed that non-polypoid tumours that bleed less are more commonly identified in the proximal colon, hence the association with a lower probability of detection by f-Hb-based tests.<sup>16,27,28</sup> This effect is further compounded by the fact that sessile serrated lesions, which can account for 15%–30% of sporadic CRC, are more common in the proximal colon.<sup>28–30</sup>

Many FIT-IC analyses have demonstrated that FIT-ICs are more likely to be diagnosed at a more advanced cancer stage.<sup>16,19,24</sup> This observation could be partly explained by the delayed diagnosis and stage progression of truly missed CRCs at the time of FIT testing. FIT-IC stage distribution in the BSP was comparable to an unscreened cohort in New Zealand.<sup>31,32</sup> Another possible explanation for this association would be the existence of a subgroup of newly arising tumours with inherently 'aggressive' tumour biology that progressed rapidly and presented as late stage at diagnosis.

A strength of this study was the use of data generated from cross-reference of two prospectively maintained registries, augmented by auditing against individual hospital records to ensure data accuracy. While this study of the BSP represents the first detailed analysis on the diagnostic performance of FIT for CRC screening in New Zealand, several limitations need to be acknowledged.

FIT diagnostic performance measures in this study were estimated using number of SDCRC and FIT-IC. The true number of CRCs in all FIT-tested participants is unknown as not all CRCs missed at the time of FIT screening would have been diagnosed within the conventionally defined 24-month time interval. This can lead to overestimation of FIT sensitivity. Given FIT-IC figures reflect both CRC truly missed at the time of FIT screening and newly

arising CRC not present at the time of FIT screening, there is also the possibility of underestimating FIT sensitivity.<sup>5</sup> While imperfect, this method of estimating FIT diagnostic performance remains a practical approach to monitoring an important aspect of FIT-based population screening.

The retrospective nature of some elements of data collection in this study limited analysis of a number of factors that may be associated with increased likelihood of FIT-IC such as BRAF mutation and MSI status. Exploratory analysis by van der Vlugt *et al* has demonstrated striking molecular profile differences between FIT-IC and SDCRC.<sup>33</sup> While CRC molecular profiles are routinely measured now, this was not the situation during the BSP.

The survival analysis should be interpreted with caution. While long-term outcomes are important programme goals for CRC screening, survival analyses are limited by numerous confounders that can be difficult to quantify and adjust for, such as tumour biology and individual risk factors.

A further limitation of this study is the variable participation rate between subgroups of eligible participants. While BSP participation rates are above the recommended acceptable minimum uptake of 45%, participation is inequitable across different ethnic and socioeconomic subgroups.<sup>5</sup> Caution is required when interpreting overall findings in the context of these underscreened subgroups and when extrapolating findings outside a single centre. While not a problem unique to New Zealand, efforts to improve participation in underscreened population groups are underway to reduce these inequities.<sup>34</sup>

The present study found that less than a third of the patients with FIT-IC could have been identified even by lowering the FIT threshold to any detectable f-Hb value. FIT-IC analyses in other cohorts have similarly demonstrated that the majority of FIT-ICs had f-Hb values below the predetermined low f-Hb positivity threshold.<sup>19,35</sup> In recent publications exploring the role of FIT in assessment of symptomatic patients, the sensitivity of FIT for CRC detection was also not 100% even when positivity thresholds were set at the lower limits of detection of various FIT assay-analyser platforms.<sup>36,37</sup> The practical implications of a disproportionate loss of specificity and increase in test positivity with ever lower f-Hb positivity thresholds is well documented.<sup>16,20,38,39</sup> Efforts to improve neoplasia detection in FIT-based screening may be more productive if pivoted towards developing more comprehensive risk-stratified screening strategies or enhancing FIT-based technology.<sup>28,39,40</sup>

In conclusion, FIT diagnostic performance in the BSP as evidenced by FIT-IC rates compared favourably to existing meta-analysis. Patients with FIT-IC are more likely to present with more advanced CRC and experience poorer outcomes. The majority of FIT-IC had no detectable f-Hb at the preceding FIT, so, even with lower f-Hb positivity thresholds, FIT-IC proportion will remain significant in FIT-based population screening

programmes. Further understanding of the tumour biology of both CRC groups, those present at FIT screen but with no detectable f-Hb and those that rapidly develop between screens, is needed. This information could lead to the development of novel screening strategies with the potential to reduce the FIT-IC rate.

#### Author affiliations

<sup>1</sup>Department of Surgery, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand

<sup>2</sup>National Screening Unit, New Zealand Ministry of Health, Wellington, New Zealand

<sup>3</sup>Department of Gastroenterology, Te Whatu Ora – Health New Zealand Waitemata, Takapuna, New Zealand

<sup>4</sup>Department of Surgery, Te Whatu Ora – Health New Zealand Waitemata, Takapuna, New Zealand

<sup>5</sup>Department of Medicine, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand

**Contributors** KSS: conceptualisation; data curation; formal analysis; project administration; and writing—original draft preparation, review and editing. KS: conceptualisation; investigation; data curation; formal analysis; and writing—review and editing. PF: conceptualisation; investigation; and writing—review and editing. MH-M: conceptualisation; investigation; and writing—review and editing. IB: conceptualisation; formal analysis; writing—original draft preparation, review and editing; and supervision. SP: conceptualisation; investigation; formal analysis; writing—review and editing; and supervision. IB is the guarantor of the article.

**Funding** KSS's research is funded through the New Zealand Health Research Council Clinical Research and Training Fellowship.

**Competing interests** None declared.

**Patient consent for publication** Not applicable.

**Ethics approval** This study involves human participants and was approved by the Auckland Health Research Ethics Committee (reference AH23729). Participants gave informed consent to participate in the study before taking part.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data may be obtained from a third party and are not publicly available. Requests for deidentified data need to be made through the National Screening Unit as data release is subject to approval to ensure respectful use, particularly for indigenous peoples.

**Supplemental material** This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

#### ORCID iD

Kai Sheng Saw <http://orcid.org/0000-0001-9621-1993>

#### REFERENCES

- Shaukat A, Levin TR. Current and future colorectal cancer screening strategies. *Nat Rev Gastroenterol Hepatol* 2022;19:551.
- Sharma R, Abbasi-Kangevari M, Abd-Rabu R. Global, regional, and national burden of colorectal cancer and its risk factors, 1990-2019: a systematic analysis for the global burden of disease study 2019. *Lancet Gastroenterol Hepatol* 2022;7:S2468-1253(22)00044-9:627-47..
- New Zealand Ministry of Health. Cancer: New registrations and deaths 2013. . 2016 Available: <https://www.health.govt.nz/publication/cancer-new-registrations-and-deaths-2013>
- Te Whatu Ora Health New Zealand. New cancer registrations 2020. . 2022 Available: <https://www.tewhatauora.govt.nz/our-health-system/data-and-statistics/new-cancer-registrations-2020/#new-cancer-registrations-2020-files>
- Moss S, Ancelle-Park R, Brenner H, *et al*. International agency for research on C. European guidelines for quality assurance in colorectal cancer screening and diagnosis. First edition—evaluation and interpretation of screening outcomes. *Endoscopy* 2012;44 Suppl 3:SE49-64.
- Wieten E, Schreuders EH, Grobbee EJ, *et al*. Incidence of Faecal occult blood test interval cancers in population-based colorectal cancer screening: a systematic review and meta-analysis. *Gut* 2019;68:873-81.
- Fraser CG, Rubeca T, Rapi S, *et al*. Faecal Haemoglobin concentrations vary with sex and age, but data are not transferable across geography for colorectal cancer screening. *Clin Chem Lab Med* 2014;52:1211-6.
- Symonds EL, Osborne JM, Cole SR, *et al*. Factors affecting Faecal Immunochemical test positive rates: demographic, pathological, behavioural and environmental variables. *J Med Screen* 2015;22:187-93.
- Selby K, Levine EH, Doan C, *et al*. Effect of sex, age, and positivity threshold on fecal Immunochemical test accuracy: A systematic review and meta-analysis. *Gastroenterology* 2019;157:1494-505.
- Elm E von, Altman DG, Egger M, *et al*. The strengthening of reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ* 2007;335:806-8.
- Fraser CG, Allison JE, Young GP, *et al*. A standard for Faecal Immunochemical tests for Haemoglobin evaluation reporting (FITTER). *Ann Clin Biochem* 2014;51(Pt 2):301-2.
- Atkinson J, Salmond C, Crampton P. *NZDep2013 index of deprivation*. Wellington: Department of Public Health, University of Otago, 2014.
- Amin MB, Greene FL, Edge SB, *et al*. "The eighth edition AJCC cancer staging manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging". *CA Cancer J Clin* 2017;67:93-9.
- Bartholomew K, Zhou L, Crengle S, *et al*. A targeted promotional DVD fails to improve Maori and Pacific participation rates in the New Zealand bowel screening pilot: results from a pseudo-randomised controlled trial. *BMC Public Health* 2019;19:1245.
- Sandiford P, Buckley A, Holdsworth D, *et al*. Reducing ethnic inequalities in bowel screening participation in New Zealand: A randomised controlled trial of telephone follow-up for non-respondents. *J Med Screen* 2019;26:139-46.
- Tran TN, Peeters M, Hoeck S, *et al*. "Optimizing the colorectal cancer screening programme using Faecal Immunochemical test (FIT) in Flanders, Belgium from the "interval cancer" perspective". *Br J Cancer* 2022;126:1091-9.
- Ribbing Wilén H, Saraste D, Blom J. Gender-specific cut-off levels in colorectal cancer screening with fecal Immunochemical test: A population-based study of colonoscopy findings and costs. *J Med Screen* 2021;28:439-47.
- Sarkeala T, Färkkilä M, Anttila A, *et al*. Piloting gender-oriented colorectal cancer screening with a Faecal Immunochemical test: population-based Registry study from Finland. *BMJ Open* 2021;11:e046667.
- Portillo I, Arana-Arri E, Idigoras I, *et al*. Colorectal and interval cancers of the colorectal cancer screening program in the Basque country (Spain). *World J Gastroenterol* 2017;23:2731-42.
- Toes-Zoutendijk E, Kooyker AI, Dekker E, *et al*. Incidence of interval colorectal cancer after negative results from first-round fecal Immunochemical screening tests, by cutoff value and participant sex and age. *Clin Gastroenterol Hepatol* 2020;18:1493-500.
- Heinävaara S, Gini A, Sarkeala T, *et al*. Optimizing screening with Faecal Immunochemical test for both sexes - cost-effectiveness analysis from Finland. *Prev Med* 2022;157:106990.
- Zorzi M, Hassan C, Capodaglio G, *et al*. Divergent long-term detection rates of proximal and distal advanced Neoplasia in fecal Immunochemical test screening programs: A retrospective cohort study. *Ann Intern Med* 2018;169:602-9.
- Breekveldt ECH, Toes-Zoutendijk E, van de Schootbrugge-Vandermeer HJ, *et al*. Factors associated with interval colorectal cancer after negative FIT: results of two screening rounds in the Dutch FIT-based CRC screening program. *Int J Cancer* 2023;152:1536-46.

- 24 van der Vlugt M, Grobbee EJ, Bossuyt PMM, *et al.* Interval colorectal cancer incidence among subjects undergoing multiple rounds of fecal Immunochemical testing. *Gastroenterology* 2017;153:439–47.
- 25 Selby K, Jensen CD, Lee JK, *et al.* Influence of varying quantitative fecal Immunochemical test positivity thresholds on colorectal cancer detection: A community-based cohort study. *Ann Intern Med* 2018;169:439–47.
- 26 Doubeni CA, Levin TR. In screening for colorectal cancer, is the FIT right for the right side of the colon *Ann Intern Med* 2018;169:650–1.
- 27 Chiu H-M, Lin J-T, Chen C-C, *et al.* Prevalence and characteristics of Nonpolypoid colorectal Neoplasm in an asymptomatic and average-risk Chinese population. *Clin Gastroenterol Hepatol* 2009;7:463–70.
- 28 Chang L-C, Shun C-T, Hsu W-F, *et al.* Fecal Immunochemical test detects Sessile Serrated adenomas and polyps with a low level of sensitivity. *Clin Gastroenterol Hepatol* 2017;15:872–9.
- 29 Cubiella J, Castro I, Hernandez V, *et al.* Characteristics of adenomas detected by fecal Immunochemical test in colorectal cancer screening. *Cancer Epidemiol Biomarkers Prev* 2014;23:1884–92.
- 30 Brenner H, Niedermaier T, Chen H. Strong Subsite-specific variation in detecting advanced adenomas by fecal Immunochemical testing for hemoglobin. *Int J Cancer* 2017;140:2015–22.
- 31 Sharples KJ, Firth MJ, Hinder VA, *et al.* The New Zealand PIPER project: colorectal cancer survival according to Rurality, Ethnicity and socioeconomic deprivation—results from a retrospective cohort study. *N Z Med J* 2018;131:24–39.
- 32 Al Hinai K, Fischer J, Al Mamari A, *et al.* Improved stage and survival for patients in the Aotearoa New Zealand colorectal cancer screening program 2012–2019. *ANZ J Surg* June 7, 2023.
- 33 van der Vlugt M, Carvalho B, Fliers J, *et al.* Missed colorectal cancers in a fecal Immunochemical test-based screening program: molecular profiling of interval Carcinomas. *World J Gastrointest Oncol* 2022;14:2195–207.
- 34 de Klerk CM, Gupta S, Dekker E, *et al.* “Expert working group ‘coalition to reduce inequities in colorectal cancer screening’ of the world Endoscopy O. socioeconomic and ethnic inequities within organised colorectal cancer screening programmes worldwide”. *Gut* 2018;67:679–87.
- 35 Digby J, Fraser CG, Carey FA, *et al.* Interval cancers using a quantitative Faecal Immunochemical test (FIT) for Haemoglobin when colonoscopy capacity is limited. *J Med Screen* 2016;23:130–4.
- 36 D’Souza N, Georgiou Delisle T, Chen M, *et al.* Faecal Immunochemical test is superior to symptoms in predicting pathology in patients with suspected colorectal cancer symptoms referred on a 2Ww pathway: a diagnostic accuracy study. *Gut* 2021;70:1130–8.
- 37 Saw KS, Liu C, Xu W, *et al.* Faecal Immunochemical test to triage patients with possible colorectal cancer symptoms: meta-analysis. *Br J Surg* 2022;109:644.
- 38 Toes-Zoutendijk E, van Leerdam ME, Dekker E, *et al.* Real-time monitoring of results during first year of Dutch colorectal cancer screening program and optimization by altering fecal Immunochemical test cut-off levels. *Gastroenterology* 2017;152:767–75.
- 39 van de Veerdonk W, Hoeck S, Peeters M, *et al.* Towards risk-stratified colorectal cancer screening. adding risk factors to the fecal Immunochemical test: evidence, evolution and expectations. *Prev Med* 2019;126:105746.
- 40 Wisse PHA, de Klaver W, van Wifferen F, *et al.* The Multitarget fecal Immunochemical test versus the fecal Immunochemical test for programmatic colorectal cancer screening: a cross-sectional intervention study with paired design. *BMC Cancer* 2022;22:1299.