Digestive Diseases and Sciences
https://doi.org/10.1007/s10620-024-08466-x

ORIGINAL ARTICLE

Accuracy, Acceptability, and Application: Fecal Immunochemical Tests for Early Detection of Advanced Neoplasia in Colonoscopy-Based Surveillance

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Received: 6 March 2024 / Accepted: 23 April 2024

Abstract

Background The fecal immunochemical test (FIT) is widely used in colorectal cancer (CRC) screening, but limited data exist for its application in individuals at above-average risk for CRC who complete surveillance colonoscopies.

Aim To assess the accuracy, acceptability, and effectiveness of FIT in the interval between surveillance colonoscopies, for predicting advanced neoplasia (advanced adenoma or CRC) at the next colonoscopy.

Methods Individuals enrolled in an Australian surveillance program were included. Diagnostic accuracy was determined for 614 individuals completing a two-sample FIT (OC-Sensor) ≤ 3 months preceding surveillance colonoscopy. 386 Individuals were surveyed to assess acceptability of interval FIT. Additionally, a retrospective analysis was performed on 7331 individuals offered interval FIT between colonoscopies, where a positive FIT (≥ 20 µg hemoglobin/g feces) triggered an early colonoscopy. Associations between interval FIT results and advanced neoplasia were determined using regression analysis.

Results FIT detected CRC and advanced adenoma with sensitivities of 60.0% (3/5) and 27.1% (35/129), respectively. Most (89.1%, 344/386) survey respondents preferred completing interval FIT every 1–2 years. The detection rate of interval FIT for advanced neoplasia decreased with increasing FIT completion. Individuals returning a positive FIT had a higher risk of advanced neoplasia than those who did not complete FIT. Positive interval FIT reduced time-to-diagnosis for CRC and advanced adenoma by a median of 30 and 20 months, respectively.

Conclusion Interval FIT was well accepted and enabled earlier detection of advanced neoplasia in individuals at above-average risk of CRC. Given that interval FIT predicts advanced neoplasia, it may be used to personalize surveillance colonoscopy intervals.

Keywords Colonoscopy · Fecal immunochemical test · Colorectal cancer · Acceptability · Surveillance · Diagnostic accuracy

Background

Colorectal cancer (CRC) is a significant cause of cancer-related deaths [1]. Given that most CRC cases develop from pre-cancerous lesions, colonoscopy reduces CRC incidence [2] and mortality [3] through early detection and treatment of pre-cancerous neoplasia and CRC. Ongoing surveillance colonoscopies at varying frequencies are recommended for individuals at above-average risk for CRC due to personal history of colorectal neoplasia or family history of CRC [4–7]. Such surveillance constitutes a substantial burden for both patients and endoscopy services [8], yet most surveillance colonoscopies do not result in a finding of advanced neoplasia (advanced adenoma or CRC) [9, 10].

The fecal immunochemical test (FIT) is widely used in CRC screening programs for individuals at average risk to determine those that should undergo colonoscopy, based on the presence of fecal hemoglobin (Hb) above a set threshold [11]. In a previous study [12], we demonstrated that a FIT

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Published online: 16 May 2024

can detect advanced neoplasia early when offered yearly in the interval between surveillance colonoscopies for individuals at above-average risk of CRC. Use of an 'interval FIT' may therefore allow further prioritization or postponement of surveillance colonoscopy, identifying lesions early and reducing unnecessary pressure on healthcare resources [13–18]. However, the accuracy, acceptability, and preferred frequency of interval FIT have not been established in a clinical setting where individuals are undergoing regular surveillance colonoscopy. This study aimed to characterize the role of interval FIT for early detection of advanced neoplasia in a colonoscopy-based CRC surveillance program through assessing (i) diagnostic accuracy, (ii) consumer acceptability, and (iii) clinical utility of interval FIT for detection of advanced neoplasia when completed between surveillance colonoscopies.

Methods

Study Design and Population

Both longitudinal and cross-sectional analyses were performed on data collected from individuals ≥ 18 years old, at an above-average risk for CRC, who were enrolled within the Southern Cooperative Program for the Prevention of Colorectal Cancer (SCOOP) colonoscopy surveillance program [19]. Within this program, individuals with a personal history of colorectal neoplasia or significant family history of CRC undergo surveillance colonoscopy at intervals following guidelines from the National Health and Medical Research Council [4, 20]. Colonoscopies are conducted in hospitals within the Southern Adelaide Local Health Network in South Australia. As part of the research program, individuals are invited to participate with FIT as frequently as every year, or just prior to colonoscopy, as well as completing surveys for patient-reported outcomes. These research studies provided opportunity to assess the accuracy and application of FIT in the surveillance population. Analysis was restricted to those who were typically undergoing three to 5 yearly surveillance colonoscopies. Those who were potentially at high risk of CRC (inflammatory bowel disease, known or suspected familial colorectal syndrome, and/or a prior history of CRC) were excluded from analysis. Data from poor quality colonoscopies were also excluded.

Diagnostic Accuracy of FIT

To establish the sensitivity of FIT for advanced neoplasia within this population, individuals scheduled for surveillance colonoscopy (between September 2018 and September 2022) were invited to complete a two-sample FIT (OC-Sensor, Eiken Chemical Company, Tokyo, Japan) within 3 months prior to colonoscopy and before commencing bowel preparation. The result of the FIT did not change the timing of the colonoscopy procedure, and the colonoscopy was conducted without knowledge of the FIT results.

Acceptability of Interval FIT

To assess acceptability of interval FIT, 800 individuals who had previously been offered at least one FIT (regardless of completion status) and who had completed at least one colonoscopy were randomly invited for survey participation in December 2018, as previously described [21]. The primary outcome assessed was preferred frequency for interval FIT. Secondary outcomes included perceived satisfaction with FIT and colonoscopy, and comfortability with different CRC surveillance protocols (Supplementary Methods).

Clinical Application of Interval FIT

To assess program performance of interval FIT for detection of advanced neoplasia, a retrospective analysis was conducted to measure interval FIT participation rates, positivity rates, and the risk for advanced neoplasia at the subsequent colonoscopy. Individuals who had undergone at least one prior colonoscopy were invited by mail to complete a two-sample FIT (OC-Sensor, Eiken Chemical Company, Tokyo, Japan) 1y after colonoscopy. Further rounds were provided at ≥ 1 yearly intervals up until 1 year before their next surveillance colonoscopy recommended date (FIT sent between July 2008 and July 2020), with data analyzed for up to four rounds of FIT completion. Individuals with a positive FIT result (≥ 20 µg Hb/g feces in either sample) were scheduled for a colonoscopy earlier than their recommended surveillance interval. Individuals with negative FIT results or not returning a FIT underwent their guideline-recommended scheduled colonoscopy. Participants with surveillance colonoscopy intervals ≥ 10 years were excluded from analysis as their colonoscopy interval was inconsistent with the guidelines in use at the time of this study. Individuals were categorized by FIT completion status (only colonoscopy/no FIT; at least one FIT and colonoscopy), and further sub-categorized based on binary FIT result and the number of FIT rounds completed between surveillance colonoscopies.

FIT Offer and Analysis

Participants received an invitation letter, instructions, two sample collection devices, and a reply-paid envelope. Participants were instructed to collect ~ 10 mg fecal samples from two different bowel motions, and mail completed tests to the Bowel Health Services Laboratory, South Australia. Completed FITs were stored at 4 °C upon arrival and underwent quantitative Hb analysis within 14 days of first sample

collection using the OC-Sensor DIANA analyzer. FIT results were deemed positive when either sample contained ≥ 20 µg Hb/g feces.

Assessment of Outcomes at Colonoscopy

Colonoscopy and histopathology results were obtained from hospital records. All lesions found at colonoscopy were resected and retrieved for histopathological analysis. Advanced neoplasia included any diagnosis of CRC or advanced adenoma, including advanced conventional adenoma (adenoma ≥ 10 mm in size, and/or with villous change, high-grade dysplasia, and/or ≥ 5 tubular adenomas [20]), or high-risk sessile serrated lesions (≥ 10 mm size and/or with dysplasia and/or a traditional sessile serrated adenoma). All other neoplasia were considered non-advanced. Neoplasia classification was based on the most advanced lesion found at colonoscopy. Quality measures including caecal intubation distance (verified by endoscopic photos of the caecum) and bowel preparation score (using Boston Bowel Preparation Scale) were obtained from colonoscopy reports.

Statistical Analyses

Data were analyzed using Stata 16 (Statacorp LP, College Station, Texas), R 4.3.1, and Jamovi 2.3. p values < 0.05 were considered statistically significant. Participant characteristics and survey responses were summarized using descriptive and analytic statistics.

The diagnostic accuracy study was conducted following the Standards for Reporting of Diagnostic Accuracy Studies (STARD) guidelines [22]. Outcome assessments and diagnostic accuracy assessments (sensitivity, specificity, positive and negative predictive values, and area under receiver operating curve) are detailed within **2.6.**

Supplementary Methods

For the acceptability study, multivariable logistic regression analyses were used to determine socio-demographic and clinical factors associated with respondents' FIT timing preference. The first analysis examined whether preferences for the timing of interval FIT matched the frequency that the interval FITs were provided within the surveillance program. A second analysis compared preferences for annual versus biennial interval FIT. Predictor variables included within the multivariable analyses were age, sex, socio-economic status (SES; where participants' home postcodes were converted into socio-economic deciles as per Index of Relative Socio-economic Advantage and Disadvantage [23]), family history of CRC, private hospital insurance coverage, number of prior colonoscopies, surveillance colonoscopy interval length, and number of interval FITs completed within the program. Odds ratios (OR) with 95% confidence intervals (CI) were generated as an estimate of effect size.

For assessment of the interval FIT program to detect advanced neoplasia, competing-risk regression was used to assess the association between FIT result and advanced neoplasia found at colonoscopy [24]. Time-to-event was defined as the time between the most recent prior colonoscopy to the diagnosis of advanced neoplasia. A cumulative index function over time was generated based on the cumulative incidence rates of advanced neoplasia and competing non-advanced neoplasia. Sub-distribution hazard ratio (SHR) and 95% CI were estimated from competing-risk regression analysis. Confounders including age, sex, previous colonoscopy findings, and any family history of CRC were included in the final adjusted model. The competing-risk regression analysis was performed at two levels; first, incorporating all eligible participants in the study period; and second, based on the pathology of the prior colonoscopy, categorized as no neoplasia, non-advanced neoplasia, or advanced neoplasia.

Results

Diagnostic Accuracy of FIT

614 Participants were included in the diagnostic accuracy analysis (Fig. 1). The mean [± standard deviation (SD)] age was 65.1 (± 9.7) years, and 48.9% were female. Participants completed FIT a median of 7.0 [interquartile range (IQR), 5.0–9.0] days prior to surveillance colonoscopy. FIT detected 3/5 CRC cases (sensitivity 60.0%) and 35/129 advanced adenoma (sensitivity 27.1%, Supplemental Table 1). The sensitivity of FIT was highest in advanced adenomas containing high-grade dysplasia (50%), and with ≥ 5 tubular adenomas (47.1%). The specificity of FIT for advanced neoplasia was 86.6% (Supplemental Table 1).

Acceptability of Interval FIT

392 Individuals completed the survey; median age 65 years, 50.3% female. Respondents' characteristics are presented in Supplemental Table 2. Most respondents were satisfied with undergoing CRC surveillance, with 87.9% (334/380) of participants being satisfied with their most recent FIT and 80.2% (304/379) satisfied with their most recent colonoscopy. Overall, 89.1% (344/386) of respondents preferred to complete an interval FIT every 2 years or less. People aged ≥ 65 years (OR 2.18, 95% CI 1.05–4.54; $p = 0.04$) and those who had completed more prior FITs (OR 1.23, 95% CI 1.02–1.47; $p = 0.03$) were significantly more likely to prefer an interval FIT offered at a frequency matching what they were already receiving (1–2 yearly), while those who had more prior colonoscopies (OR 0.81, 95% CI 0.65–0.99;

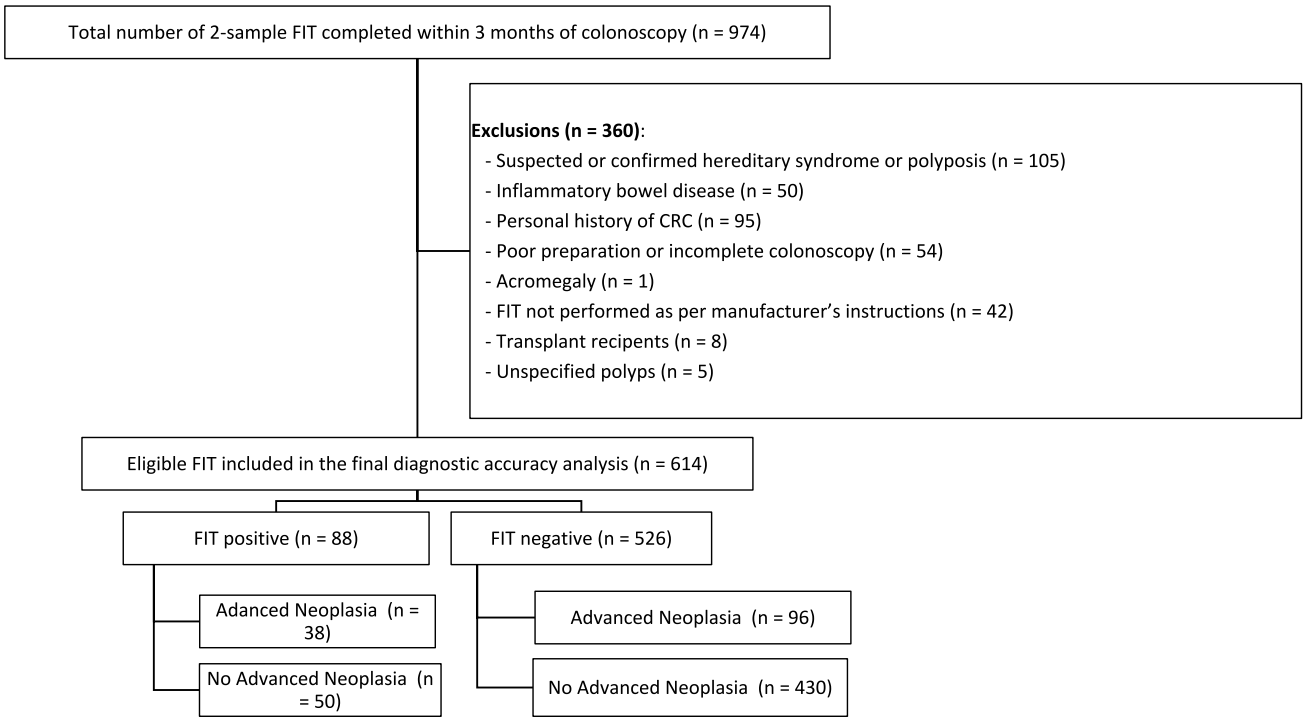

Fig. 1 STARD diagram for the diagnostic accuracy study; FIT, faecal immunochemical test. FIT positivity was defined as ≥ 20 µg haemoglobin/g faeces

$p = 0.042$) and those with private health insurance (OR 0.47, 95% CI 0.65–0.99; $p = 0.042$) were less likely to prefer more frequent yearly interval FIT compared to biennial FIT (Supplemental Table 3). When considering a potential change to surveillance, 67.6% of respondents were comfortable with yearly FIT in addition to 5 yearly surveillance colonoscopy, compared to only 13.3% being comfortable with the idea of colonoscopy without FIT (Supplemental Table 4).

Application of Interval FIT

Interval FIT Demographics

The interval FIT program analysis included 7331 individuals at above-average risk of CRC, representing 9737 pairs of colonoscopies (prior and follow-on), with 38,424 years of total analysis time at risk (Fig. 2). The mean (± SD) age of individuals was 62.7 (± 9.7) years and 51% were female. Individuals had a median of one prior colonoscopy (range 1–12). 6270 (64.4%) Surveillance colonoscopies were performed on people with a personal history of adenoma without a family history of CRC (post-polypectomy population), while 3467 (35.6%) procedures were performed on individuals with a family history of CRC, with or without a personal history of adenoma (family history population). The median time from prior colonoscopy to the last completed FIT and from the last completed FIT to the follow-on colonoscopy was 2.1 (IQR 1.1–3.1) and 1.6 (IQR 0.8–2.2) years, respectively (Table 1).

Interval FIT Participation and FIT Positivity Rate

The participation rate was 78.6% (7654/9737 intervals) for at least 1 interval FIT completion, 52.8% for 2 FITs (4044/7654), 40.9% for 3 FITs (1653/4044), and 40.8% for 4 FITs (674/1653). The first interval FIT result was negative in 88.6% (6782/7654) of individuals, and the cumulative (program-level) FIT positivity rate was 18.1% (1388/7654). FIT positivity within each round of completed interval FIT ranged from 24.2% (of those that were only provided with one round of FIT) to 7.3% (of those that were provided with four rounds of FIT, Table 1).

Interval FIT Colonoscopy Outcomes and Time-to-Diagnosis

CRC was diagnosed in 18/9737 (0.2%) colonoscopies, and advanced adenoma in 989/9737 (10.2%) colonoscopies, with an overall incidence of 10.4% for advanced neoplasia. Most of the colonoscopies (89.6%) did not have any finding of advanced neoplasia, with almost half (49.4%, 4814/9737) having no neoplastic findings (Table 2).

The median time between the FIT and the next colonoscopy was 1.8 years (IQR 0.6–2.2 years) for people offered only 1 of FIT and 1.1 years (IQR 0.8–1.9 years)

Table 1 Demographic and clinical characteristics of participants ($n=7331$) undergoing surveillance colonoscopies ($n=9737$ colonoscopy pairs) by interval FIT status

FIT status	No completion of FIT, only colonoscopy (*n*, %)	Completion of at least 1 FIT (*n*, %)	Completion of at least 2 FIT (*n*, %)	Completion of at least 3 FIT (*n*, %)	Completion of at least 4 FIT 4 (*n*, %)	*p* value
N (%)	2083 (21.4)	3610 (37.08)	2391 (24.56)	979 (10.05)	674 (6.92)	
FIT result						
Always negative	NA	2738 (75.8)	2034 (85.1)	868 (88.7)	625 (92.7)	**< 0.001**
At least 1 positive	NA	872 (24.2)	357 (14.9)	111 (11.3)	49 (7.3)	
Sex						
Male	1050 (50.4)	1868 (51.8)	1118 (46.8)	409 (41.9)	324 (48.1)	**< 0.001**
Female	1033 (49.6)	1742 (48.3)	1273 (53.2)	570 (58.2)	350 (51.9)	
Age (years [median, IQR])	60.6 (53.2, 68.2)	65.1 (57.8, 70.8)	65.3 (58.6, 70.7)	64.7 (58.4, 70.1)	64.0 (57.3, 69.5)	**< 0.001**
Socio-economic status*						
Low	695 (33.4)	1257 (34.9)	799 (33.5)	332 (33.9)	244 (36.2)	0.571
Medium	812 (39.0)	1363 (37.8)	959 (40.2)	371 (37.9)	262 (38.9)	
High	576 (27.7)	983 (27.3)	630 (26.4)	276 (28.2)	168 (24.9)	
Any family history of CRC						
No	1319 (63.3)	2578 (71.4)	1548 (64.7)	509 (52.0)	316 (46.9)	**< 0.001**
Yes	764 (36.7)	1032 (28.6)	843 (35.3)	470 (48.0)	358 (53.1)	
Pathology in prior colonoscopy						
No neoplasia	774 (37.2)	963 (26.7)	922 (38.6)	548 (56.0)	438 (65.0)	**< 0.001**
Non-advanced neoplasia	837 (40.2)	1536 (42.6)	1006 (42.1)	413 (42.2)	233 (34.6)	
Advanced adenoma	472 (22.7)	1111 (30.8)	463 (19.4)	18 (1.8)	3 (0.5)	
Polypectomy at prior colonoscopy						
Yes	1404 (67.4)	2772 (76.8)	1559 (65.2)	490 (50.1)	289 (42.9)	
No	679 (32.6)	838 (23.2)	832 (34.8)	489 (50.0)	385 (57.1)	
Number of prior colonoscopies prior to the interval (median IQR)	1 (1, 2)	1 (1, 2)	1 (1, 2)	1 (1, 2)	1 (1, 2)	**< 0.001**
Pathology in follow-up colonoscopy						
No neoplasia	1028 (49.4)	1692 (46.9)	1172 (49.0)	510 (52.1)	412 (61.1)	**< 0.001**
Non-advanced neoplasia	851 (40.9)	1498 (41.5)	969 (40.5)	379 (38.7)	219 (32.5)	
Advanced adenoma	197 (9.5)	413 (11.4)	248 (10.4)	88 (9.0)	43 (6.4)	
CRC	7 (0.3)	7 (0.2)	2 (0.1)	2 (0.2)	0 (0.0)	
Time (years) between prior colonoscopy to last FIT (median, IQR); range	NA	1.11 (1.0, 1.5) range (0.8–4.1)	3.7 (2.0, 3.1) range (1.6–4.6)	3.1 (3.0, 4.0) range (2.1–5.2)	4.1 (4.0, 4.4) range (3.0–5.4)	**< 0.001**
Time between last FIT to follow-on colonoscopy (median, IQR) in years; range	NA	1.8 (0.6, 2.2) range (0.1–4.9)	1.3 (0.8, 2.1) range (0.1–4.9)	1.8 (0.9, 2.3) range (0.1–4.6)	1.1 (0.8, 1.9) range (0.1–4.0)	**< 0.001**

Table 1 (continued)

FIT status	No completion of FIT, only colonoscopy (*n*, %)	Completion of at least 1 FIT (*n*, %)	Completion of at least 2 FIT (*n*, %)	Completion of at least 3 FIT (*n*, %)	Completion of at least 4 FIT 4 (*n*, %)	*p* value
Median surveillance interval (median, IQR) in years; range	3.7 (3.0, 5.2) range (1.2–8.8)	3.0 (2.1, 3.6) range (1.1–6.9)	3.9 (3.1, 5.2) range (2.0–7.4)	5.1 (4.8, 5.6) range (3.0–8.2)	5.2 (5.0, 6.1) range (4.0–8.2)	**< 0.001**

CRC colorectal cancer, *FIT* fecal immunochemical test, *IQR* interquartile range, *NA* not applicable

*Socio-economic status has been categorized into three groups as low (1–3), medium (4–6) and high (7–10). Bold font denotes statistically significant ($p < 0.05$) associations

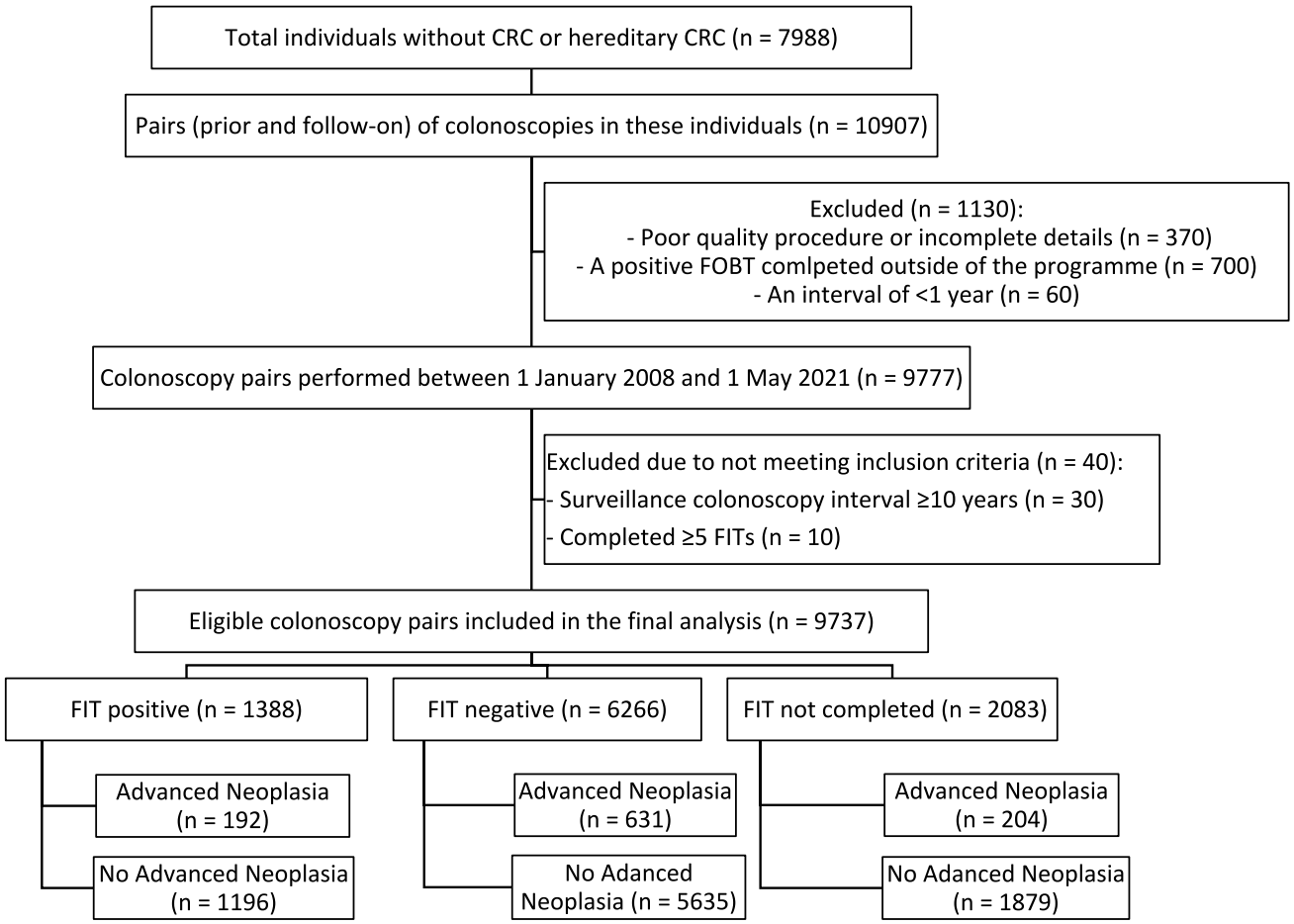

Fig. 2 STARD diagram for interval FIT study. CRC, colorectal Cancer; FIT, faecal immunochemical test

between the fourth FIT and colonoscopy for people offered 4 FITs. The cumulative sensitivity of interval FIT was comparable to that within the diagnostic accuracy study at 54.5% and 21.1% for CRC and advanced adenoma, respectively. Sensitivity for advanced adenoma was highest in individuals who completed only 1 FIT at 29.8% (Supplemental Table 5). Interval FIT positive predictive value (PPV) was highest in individuals completed only 1 FIT and decreased as the number of completed FITs increased (Supplemental Table 5). Participants with a positive interval FIT received their colonoscopy a median of 22 months earlier than their scheduled surveillance. Time-to-diagnosis for CRC and advanced adenoma was reduced by a median of 30 and 20 months, respectively (Supplemental Fig. 1). Four out of 11 CRC cases (36.4%) were diagnosed in individuals testing positive on their first interval FIT. A further 2 cases (18.2%) were detected after a positive interval FIT result was preceded by at

Table 2 Surveillance colonoscopy findings by interval FIT status

	N (%)	No neoplasia, *n* (%)	Non-advanced neoplasia, *n* (%)	Advanced adenoma, *n* (%)			CRC, *n* (%)
				All, *n* (%)	Advanced conventional adenoma, *n* (%)	High-risk sessile serrated lesions, *n* (%)	
n	9737	4814 (49.4)	3916 (40.2)	989 (10.2)	699 (7.2)	290 (3.0)	18 (0.18)
FIT completion status							
No FIT (only colonoscopy)	2083	1028 (49.4)	851 (40.9)	197 (9.5)	142 (6.8)	55 (2.6)	7 (0.3)
1 Negative FIT	2738	1303 (47.6)	1142 41.7)	290 (10.6)	178 (6.5)	112 (4.1)	3 (0.1)
2 Negative FITs	2034	999 (49.1)	817 (40.2)	217 10.7)	151 (7.4)	66 (3.2)	1 (0.1)
3 Negative FITs	868	449 (51.7)	339 (39.1)	79 (9.1)	58 (6.7)	21 (2.4)	1 (0.1)
≥ 4 Negative FITs	625	379 (60.6)	207 (33.1)	39 (6.2)	23 (3.7)	16 (2.6)	0 (0.0)
Positive FIT without any prior negative FIT	872	389 (44.6)	356 (40.8)	123 (14.1)	110 (12.6)	13 (1.5)	4 (0.5)
Positive FIT after 1 negative FIT	357	173 (48.5)	152 (42.6)	31 (8.7)	26 (7.3)	5 (1.4)	1 (0.3)
Positive FIT after 2 negative FITs	111	61 (54.9)	40 (36.0)	9 (8.1)	8 (7.2)	1 (0.9)	1 (0.9)
Positive FIT after ≥ 3 negative FITs	49	33 (67.4)	12 (24.5)	4 (8.2)	3 (6.1)	1 (2.0)	0 (0.0)

N total number of observations, *CRC* colorectal cancer, *FIT* fecal immunochemical test

least one negative interval FIT, and the remaining 5 cases (45.5%) were detected at the surveillance colonoscopy as scheduled. All CRC cases were diagnosed prior to stage IV (Supplemental Fig. 2). Participants who completed only 1 FIT and returning a positive result had the largest reduction in time-to-colonoscopy (Supplemental Fig. 1). There were 7 CRC cases that were detected at surveillance after non-participation of interval FIT.

Risk of Advanced Neoplasia by Interval FIT Status

The incidence of advanced neoplasia was highest among individuals who returned a positive interval FIT without having returned any previous negative FITs (SHR 2.62, 95% CI 2.13–3.22; $p < 0.001$) and lowest in individuals returning 4 or more negative FITs ($p < 0.001$). Incidence of advanced neoplasia did not significantly differ in individuals who returned a positive FIT after one or more negative interval FITs when compared with individuals in the no FIT group (Table 3, $p < 0.001$). Individuals aged ≥ 75 years (SHR 1.53, 95% CI 1.04–2.25; $p < 0.001$), and those with a prior diagnosis of either non-advanced neoplasia or advanced adenoma (SHR 2.24, 95% CI 1.83–2.74; $p < 0.001$) were also independent predictors of advanced neoplasia at next colonoscopy. These associations were not different when the analysis was stratified by the previous colonoscopy finding (Supplemental Table 6), when limited to those who returned only one FIT (Supplemental Fig. 3).

Discussion

FIT is widely used in CRC screening. However, its accuracy, acceptability, and effectiveness in cohorts that are above-average risk for CRC and undergoing regular surveillance colonoscopy, to detect either missed or rapidly growing colorectal lesions, are not well investigated. This study examined the diagnostic accuracy, consumer acceptability, and the role of interval FIT in the context of surveillance colonoscopy using a large cohort of individuals above average risk for CRC based in Australia. These data show that FIT results indicate risk of finding advanced neoplasia at colonoscopy, that it is well accepted by individuals undergoing surveillance colonoscopy, and that interval FIT could be used as a tool for risk stratification and triage for colonoscopy investigations in an above-average risk population.

Advanced neoplasia encompasses a spectrum of disease, with a generally slow progression from adenoma to CRC [25]. FIT has high diagnostic accuracy in CRC screening, where lesions are frequently found at advanced stages. In contrast, our CRC surveillance cohort has low prevalence of CRC and advanced adenoma, where CRC cases within the cohort were diagnosed early, and where most pre-cancerous neoplasia were mainly identified as advanced based on size; before lesions developed high-risk features such as a villous change and/or high-grade dysplasia. Accordingly, significant variability was observed in sensitivity values when advanced adenoma features were considered individually, with a sensitivity of 50% for conventional adenomas with high-grade dysplasia, 32% for ≥ 10 mm conventional adenomas, and just

Table 3 Association between interval FIT status and risk of advanced neoplasia at the subsequent colonoscopy

Variables	SHR* (95% CI)	*p* value
Interval FIT completion status		
FIT not done	1.00 (reference)	
1 Negative FIT	1.11 (0.92, 1.33)	0.25
2 Negative FITs	1.03 (0.85, 1.24)	0.77
3 Negative FITs	0.79 (0.61, 1.03)	0.08
≥ 4 Negative FITs	0.54 (0.39, 0.76)	**< 0.001**
Positive FIT without any prior negative FIT	2.61 (2.07, 3.30)	**< 0.001**
Positive FIT after 1 negative FITs	1.25 (0.86, 1.84)	0.24
Positive FIT after 2 negative FITs	1.15 (0.61, 2.16)	0.66
Positive FIT after ≥ 3 negative FITs	0.95 (0.36, 2.53)	0.93
Age (years)		
< 50	1.00 (Reference)	
50–54	0.78 (0.55, 1.10)	0.16
55–59	1.09 (0.82, 1.46)	0.54
60–64	1.30 (0.98, 171)	0.06
65–69	1.23 (0.93, 1.61)	0.14
70–74	1.29 (0.98, 1.70)	0.06
≥ 75	1.55 (1.13, 2.13)	**0.01**
Sex		
Female	1.00 (Reference)	
Male	1.03 (0.91, 1.17)	0.63
Socio-economic status		
Low	1.00 (Reference)	
Medium	1.03 (0.89, 1.19)	0.68
High	1.05 (0.89, 1.23)	0.55
Any family history of CRC		
No	1.00 (Reference)	
Yes	0.95 (0.82, 1.11)	0.59
Colonoscopy finding at prior colonoscopy		
No neoplasia	1.00 (Reference)	
Non-advanced neoplasia	1.44 (1.23, 1.69)	**< 0.001**
Advanced adenoma	1.92 (1.59, 2.32)	**< 0.001**

*SHR, Sub-distribution hazard ratio from the competing-risk regression analysis. Bold font denotes statistically significant ($p < 0.05$) predictors. Data shown reflects $n = 9737$ colonoscopy pairs

16% for high-risk sessile serrated lesions, consistent with previous findings [26, 27]. We observed a FIT sensitivity of 60.0% for CRC and 27.1% for advanced adenoma. This FIT sensitivity was lower than other studies, but may be related to different types of FIT, different positivity thresholds [12], and different risk of patients for advanced neoplasia, or different number of prior surveillance colonoscopies [13]. These findings highlight the relationship between FIT accuracy and the high-risk features of advanced adenoma, and therefore the importance of considering alternative biomarkers or predictive models suitable for all advanced features.

Interval FITs provided between surveillance colonoscopies were well accepted and most participants preferred to do a FIT every 1 or 2 years, along with colonoscopy surveillance every 5 years. Consistent with previous findings [28], more participants were comfortable with surveillance strategies incorporating an interval FIT than those without, with just 13.3% of participants comfortable with surveillance encompassing only colonoscopy, despite this being the recommendation in Australian surveillance guidelines. These findings indicate that patients are accepting of interval FIT when used to supplement their regular colonoscopy surveillance, compared to our previous work that showed poor acceptance of FIT as a stand-alone surveillance tool [21].

While the surveillance cohort had a low rate of CRC and advanced adenoma, positive FITs resulted in a reduction in time-to-diagnostic of CRC and advanced adenoma by 30 and 20 months, respectively, which is consistent with previous work that used Insure a brush-sampling FIT [12]. Advanced conventional adenomas were more prevalent than high-risk sessile serrated lesions and were also detected more frequently by interval FIT. Risk of advanced neoplasia was highest in individuals who had at least one positive FIT, independent of prior colonoscopy finding. The first interval FIT had the highest detection rate for advanced neoplasia, which may reflect detection of lesions missed at the previous colonoscopy. While risk of advanced neoplasia decreased with multiple negative FITs completed within the interval, the last interval FIT completed before colonoscopy still resulted in detection of 6.4% advanced neoplasia, suggesting earlier detection of rapidly growing cancerous lesions.

Considering the high acceptability and effectiveness of FIT predicting advanced neoplasia, incorporating it into colonoscopy surveillance guidelines may enable the diagnosis of missed or rapidly growing lesions. FIT has already been incorporated into risk prediction models applicable to screening populations and triaging individuals with symptoms [29, 30]. These models have demonstrated improved diagnostic performance, resulting in increased detection of advanced adenomas [29] and CRC [30]. Although colonoscopy surveillance is well known to decrease the risk of advanced lesions compared with not undergoing surveillance [2], the ability to identify high-risk individuals through FIT could contribute to more targeted screening strategies, optimizing the use of colonoscopy resources, and improving patient outcomes.

One potential approach may involve sending two rounds of FITs: one early in the interval to identify missed or rapidly growing lesions, and another at 1 year prior to the scheduled colonoscopy to establish the possibility to extend the interval for surveillance colonoscopy where resources are limited. These approaches have cost and quality of life implications; costs in bringing forward colonoscopies in those who test positive for FIT but have nothing found at colonoscopy and

savings for extending surveillance intervals after negative FIT, with associated anxiety and fear of cancer. Further economic analysis to establish the cost effectiveness of utilizing interval FIT as a surveillance tool for CRC and advanced adenoma is warranted. This will examine the effect on cost, survival, and quality of life outcomes for those who undergo surveillance colonoscopy with interval FIT that includes the cost of negative colonoscopy after a positive interval FIT and benefits of early detection with FIT one year after colonoscopy (due to missed CRC at previous colonoscopy). The further potential for quantitative utilization of absolute fecal hemoglobin levels to predict the risk of advanced neoplasia and personalize surveillance colonoscopy intervals requires further investigation [31].

There are several strengths of this study. Our diagnostic accuracy study was performed in a double-blinded manner and reported for each type of advanced neoplasia found at the next colonoscopy; notably including high-risk sessile serrated lesions, which are poorly detected by FIT and frequently excluded from diagnostic accuracy studies. Our assessment of interval FIT in a large surveillance cohort analyzed FIT within each participant, across multiple surveillance intervals, allowing us to characterize the effectiveness of interval FIT within each round, and based on previous colonoscopy findings. However, one limitation was that not everyone in the program had the opportunity to complete an equal number of FITs, and this may result in a reporting as well as self-selection bias. As most participants were undergoing post-polypectomy surveillance, there were the scarcity of CRC and advanced adenoma cases, leading to less robust results reflected by the wide 95% CIs around sensitivity and positive predictive values, emphasizing caution in interpreting our findings. A limitation for the acceptability assessments was that survey participants may have been undergoing surveillance for a longer duration compared to those offered interval FIT, as they had completed a median of two prior colonoscopies compared to one in the interval FIT study. As the number of prior colonoscopies was one of the predictors of acceptability, the finding should be interpreted with caution for the overall cohort.

Conclusions

Interval FIT was well accepted and enabled earlier detection of many advanced neoplastic lesions in individuals at above-average risk of CRC. The cumulative detection rate and PPV of FIT were highest in people completed only the first FIT, and multiple rounds of negative FIT predicted a lower risk of advanced neoplasia compared to non-participants in interval FIT surveillance. Interval FIT results are predictive of advanced neoplasia and may be used as a risk stratification tool to personalize surveillance colonoscopy intervals.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10620-024-08466-x.

Author's contribution MMW, MD, JMW, GPY and ELS contributed to study conceptualisation. MMW, MD, NB, GPY, JMW, CC, PB, RJF, and ELS contributed to study design. GPY and ELS acquired the funding. ELS oversaw the overall project. All authors contributed to scientific supervision of the project. GLL, GPY and ES did the data collection. MMW and MD did the data analysis. GLL contributed to visualisation of data. MMW, MD, and ELS did the data interpretation, with critical review from all other authors. MMW and MD wrote the first draft of the manuscript. All authors contributed to writing, critical review, and editing of the manuscript. MMW and MD did the literature search. MMW, MD, GLL, and ELS accessed and verified the data. All authors had final responsibility for the decision to submit for publication.

Funding Open Access funding enabled and organized by CAUL and its Member Institutions. This study was funded by a Flinders Foundation and the Cancer Council SA's Beat Cancer Grant. MMW was supported by the National Health and Medical Research Council (NHMRC) Investigator Grant (#2009050).

Declarations

Conflict of interest Authors GPY and ELS have previously received funding and consumables for investigator-led studies from Eiken Chemical Company (Japan). ELS is a member of a committee to standardize the analysis of FIT samples.

Ethical approval The study was approved by the Southern Adelaide Human Research Ethics Committee (Approval Number #422.13 and #330.17 for participants offered FIT and surveys, respectively). Studies were registered with the Australian and New Zealand Clinical Trials Registry (ACTRN #12618001406291 and #12618001277235, respectively). Written informed consent was provided from participants accompanying return of completed FIT and surveys.

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